Melt Polymerization of Lactide Using Biocompatible Materials

Thesis

Presented in Partial Fulfillment of the Requirements for the Degree Master of Science in the Graduate School of The Ohio State University

By

Tamara L. Beilke, B.S.
Graduate Program in Chemistry

The Ohio State University

2010

Thesis Committee:
Professor Malcolm Chisholm, Advisor
Professor James A. Cowan
ABSTRACT

In this study, L-lactide was polymerized using various simple metal oxides and carbonates, as well as several over-the-counter health supplements to compare their activities towards ROP of lactide against that of the popularly used tin octanoate, Sn(Oct)$_2$. The resulting polymer obtained from each catalyst was examined by means of mass spectrometry and gel permeation chromatography to determine its molecular weight and polydispersity index (PDI). $^1$H NMR and homonuclear decoupling NMR was also used to determine the microstructure of the resultant polymer, as well as to confirm the end groups.

From the studies, it was found that CaO and the Goldline $^\text{®}$ Pink Bismuth tablets are able to convert the lactide to polylactide in high conversions (>90%) in 65 hours, which was similar to the tin octanoate. The PDI values obtained for these two catalysts were extremely narrow, 1.70 and 1.27 respectively, indicating a nicely controlled polymerization despite long reaction times. The molecular weights were comparable to tin octanoate, as determined by GPC and MALDI. Future studies on the polymerizations can determine whether these catalysts will be viable replacements for the more toxic tin octanoate.
DEDICATION

This work is dedicated to my parents, Mark and Lou Ann Klotzbach, and my husband, Michael Beilke
ACKNOWLEDGEMENTS

Getting any type of graduate degree is a group effort, and that is certainly the case for this graduate degree.

First and foremost, I would like to thank Dr. Chisholm for guiding me through this research project. The wisdom and constructive criticism that was shared with me has helped me to grow and mature as a chemist and student. I am also very grateful for his sincere support as I chose to turn to a career in education.

I would also like to thank my group members for all of their guidance as I learned my way around a synthetic chemistry lab. I am grateful to Dr. Ruaraidh McIntosh for getting me started in the lab and teaching me proper synthetic techniques. Dr. Yang Li provided the expertise to obtain the GPC data for this study. Alex Bernard collected the SEM images for the samples shown. Chandrani Chatterjee and Kittisak Choojun graciously and patiently answered all of my questions about running experiments and interpreting data. I would also like to thank all of my group members for all of their food they have shared with me over the last three years!

Lastly, thank you to the Ohio State University and the Chemistry Department for providing me with the opportunity to study here and for all the financial support during my time here.
VITA

2007 – 2010…………………………Graduate Teaching Assistant/Research Assistant
The Ohio State University, Columbus, OH

2003 – 2007…………………………Bachelor of Science in Chemistry,
Saint Louis University, Saint Louis, MO

Publications

Applications ; Tim Zhao, Ed.; Academic Press, 2009, p 179

through electrodes.” Journal of Material Chemistry. 18, 667-674.

microenvironment for enzyme immobilization at electrodes by hydrophobically
modifying chitosan and Nafion polymers.” Journal of Membrane Science. 311, 81-
88.

modification of chitosan and Nafion on transport properties, ion-exchange capacities,
and enzyme immobilization.” Journal of Membrane Science. 282, 276-283.

Fields of Study

Major Field: Chemistry
TABLE OF CONTENTS

Abstract ............................................................................................................................... ii

Dedication .......................................................................................................................... iii

Acknowledgements .......................................................................................................... iv

Vita ...................................................................................................................................... v

Table of Contents ............................................................................................................... vi

List of Schemes .................................................................................................................. viii

List of Figures .................................................................................................................... ix

List of Abbreviations .......................................................................................................... xiii

Chapter 1 ............................................................................................................................. 1

1.1. Introduction .............................................................................................................. 1

1.1.1. Biodegradable Polymers .............................................................................. 1

1.1.2. Polylactide .................................................................................................... 2

1.1.3. Stereochemistry of the polymers .............................................................. 4

1.1.4. Mechanism for ROP ............................................................................... 7

1.1.5. Catalysts for ROP .................................................................................. 10

1.2. Objectives ............................................................................................................. 14

Chapter 2 ........................................................................................................................... 16

2.1. Previous work on these catalysts ................................................................. 16

2.2. Techniques for Polymer Characterization ................................................ 18
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2.1. Nuclear Magnetic Resonance Spectroscopy – $^1$H and Homonuclear Decoupling</td>
<td>18</td>
</tr>
<tr>
<td>2.2.2. Gel Permeation Chromatography</td>
<td>19</td>
</tr>
<tr>
<td>2.2.3. Matrix Assisted Laser Desorption Ionization – Time of Flight Mass Spectrometry</td>
<td>20</td>
</tr>
<tr>
<td>2.3. Experimental</td>
<td>21</td>
</tr>
<tr>
<td>2.4. Results and Discussion</td>
<td>22</td>
</tr>
<tr>
<td>2.5. Conclusions</td>
<td>60</td>
</tr>
<tr>
<td>2.6. Future Considerations</td>
<td>61</td>
</tr>
<tr>
<td>Bibliography</td>
<td>62</td>
</tr>
</tbody>
</table>
LIST OF SCHEMES

Scheme 1. Formation of lactide from natural resources..................................................... 3

Scheme 2. Initiation and propagation mechanisms for ring-opening polymerization ....... 8

Scheme 3. Side reactions for the ring-opening polymerization ......................................... 9

Scheme 4. Proposed mechanisms for the conversion of Sn(Oct)$_2$ to the initiating species,
where R = H, alkyl ............................................................................................................ 11
LIST OF FIGURES

Figure 1. Comparison of fossil fuel usage during the production of one kilogram of polymer.......................................................... 4

Figure 2. Stereoisomers of Lactide ................................................................. 5

Figure 3. Microstructures of polylactide .............................................................. 6

Figure 4. Structure of tin(II) bis(2-ethylhexanoate) .............................................. 10

Figure 5. Structure of Coates’ [(BD1)ZnOPr³]₂ complex ........................................ 12

Figure 6. Hillmeyer and Tollman's zinc catalyst for ROP, where R = tBu, Me ........ 12

Figure 7. Structure of {HB(3-Bu'pz)₃}MgOEt ................................................................. 13

Figure 8. Crystal structure of [LO¹]CaN(SiMe₃)₂, where LO¹ = 4-tert-butyl-2,5-bis(morpholinomethyl)phenoxy)................................................. 14

Figure 9. Structure of bismuth subsalicylate ...................................................... 17

Figure 10. Homodecoupled ¹H NMR spectra of methine proton region of PLAs having various tacticities ................................................................. 19

Figure 11. MALDI-TOF of poly(L-LA) obtained from polymerizations using Sn(Oct)₂ as the catalyst ................................................................. 24

Figure 12. ¹H NMR spectrum of polylactide sample obtained from polymerization using Sn(Oct)₂ as the catalyst (CDCl₃, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled ¹H NMR of the same sample. .................. 25
Figure 13. $^1$H NMR spectrum of polylactide sample obtained from polymerization using CaO as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample. .......................... 27

Figure 14. MALDI-TOF of poly(L-LA) obtained from polymerizations using CaO as the catalyst ............................................................................................................................... 28

Figure 15. GPC chromatogram of poly(lactide) obtained from the polymerization using CaO as the catalyst (CHCl$_3$ solvent) .......................................................................................................................... 29

Figure 16. MALDI-TOF of poly(L-LA) as obtained from using BaO as the catalyst. (a) Whole scale. (b) Selected region where polymerization leads to cycles. (c) Selected region where polymerization leads to chains .............................................................................................. 31

Figure 17. $^1$H NMR spectrum of polylactide sample obtained from polymerization using BaO as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample. ....................... 32

Figure 18. GPC chromatogram of poly(lactide) obtained from the polymerization using BaO as the catalyst (CHCl$_3$ solvent) .......................................................................................................................... 33

Figure 19. MALDI-TOF of poly(L-LA) obtained from polymerizations using MgO as the catalyst .......................................................................................................................... 35

Figure 20. $^1$H NMR spectrum of polylactide sample obtained from polymerization using MgO as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample. .......................... 36

Figure 21. MALDI-TOF of poly(L-LA) obtained from polymerizations using ZnO as the catalyst .......................................................................................................................... 37
Figure 22. $^1$H NMR spectrum of polylactide sample obtained from polymerization using ZnO as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample. ......................... 38

Figure 23. GPC chromatogram of poly(lactide) obtained from the polymerization using ZnO the catalyst (CHCl$_3$ solvent)........................................................................................................................................... 39

Figure 24. MALDI-TOF of poly(L-LA) obtained from polymerizations using CaCO$_3$ as the catalyst. (a) Whole spectrum. (b) Selected region, where the reaction produces cycles. (c) Selected region where the reaction produces chains ..................................... 42

Figure 25. $^1$H NMR spectrum of polylactide sample obtained from polymerization using CaCO$_3$ as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample. ......................... 43

Figure 26. SEM of CaCO$_3$ crystals before use in a polymerization reaction........................... 44

Figure 27. SEM of CaCO$_3$ crystals after use in a polymerization reaction............................. 44

Figure 28. MALDI-TOF of poly(L-LA) obtained from polymerizations using MgCO$_3$ as a catalyst. (a) Whole region. (b) Selected region, where the reaction produces cycles. (c) Selected region where the reaction produces chains. ................................................. 46

Figure 29. $^1$H NMR spectrum of polylactide sample obtained from polymerization using MgCO$_3$ as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample. ......................... 47

Figure 30. MALDI-TOF of poly(L-LA) obtained from polymerizations using Rolaids® as the catalyst. (a) Whole scale. (b) Selected region................................................................. 49
Figure 31. $^1$H NMR spectrum of polylactide sample obtained from polymerization using Rolaids® as the catalyst (CDCl$_3$, 400MHz). Insert (a) shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample. .................................................... 50

Figure 32. GPC chromatogram of poly(lactide) obtained from the polymerization using Rolaids® tablets the catalyst (CHCl$_3$ solvent) ................................................................... 51

Figure 33. MALDI-TOF spectrum of poly(L-LA) obtained using calcium hydroxyapatite as the catalyst. (a) Whole scale. (b) Selected region......................................................... 53

Figure 34. $^1$H NMR spectrum of polylactide sample obtained from polymerization using calcium hydroxyapatite as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample ...... 54

Figure 35. SEM of HA crystals before use in polymerization of lactide ......................... 55

Figure 36. SEM of HA after use in a polymerization of lactide ...................................... 55

Figure 37. MALDI-TOF of Poly(L-LA) obtained from polymerizations using Goldline® Pink Bismuth tablets.......................................................................................................... 57

Figure 38. $^1$H NMR spectrum of polylactide sample obtained from polymerization using Goldline® Pink Bismuth tablets as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample................................................................................................................................ 58

Figure 39. GPC chromatogram of poly(lactide) obtained from the polymerization using Goldline® Pink Bismuth tablets the catalyst (CHCl$_3$ solvent)................................. 59
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>β-diiminate</td>
</tr>
<tr>
<td>$^1$H</td>
<td>Proton-1</td>
</tr>
<tr>
<td>$^{13}$C</td>
<td>Carbon-13</td>
</tr>
<tr>
<td>GPC</td>
<td>Gel permeation chromatography</td>
</tr>
<tr>
<td>HA</td>
<td>Calcium hydroxyapatite</td>
</tr>
<tr>
<td>L-LA</td>
<td>L-Lactide</td>
</tr>
<tr>
<td>MALDI-TOF</td>
<td>Matrix assisted laser desorption ionization – time of flight</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>PLA</td>
<td>Polylactide</td>
</tr>
<tr>
<td>ROP</td>
<td>Ring-opening polymerization</td>
</tr>
<tr>
<td>Sn(Oct)$_2$</td>
<td>Tin(II) bis(2-ethylhexanoate)</td>
</tr>
<tr>
<td>$T_g$</td>
<td>Glass transition temperature</td>
</tr>
</tbody>
</table>
CHAPTER 1

1.1. INTRODUCTION

1.1.1. Biodegradable Polymers

Plastics are synthetic materials which are used for packaging, building materials, and other types of consumables. Common plastics in daily use are typically made from petroleum based monomer feedstocks. For example, packaging materials used for consumable products are often made from polyolefins like polystyrene and polyethylene. These plastics have succeeded as commercial necessities because of their incredible stability.\(^1\) They are able to resist natural degradation processes like hydrolysis and enzymatic digestion.

Fossil fuels are used as both the feedstock and the energy source for the production of many synthetic polymers. Recent reports suggest that the reserve to production ratio for oil in the world is just over 40 years, meaning that should production continue at the same rate as it is currently, oil reserves will last 40 years.\(^2\) With such a grim outlook on the oil reserves, it has become increasingly pertinent to find ways to reduce fossil fuel usage for energy and oil-based product usage.

Likewise, consumable products made of ‘immortal materials’ are ending up in the landfill after only a short lifetime. While recycling has been in effect for decades, recycling only accounts for 30% of the plastics which are thrown away.\(^3\) At the same time, plastics can only be recycled so many times before they are no longer suitable for
consumer products because successive melt/recasting cycles diminish the physical properties.\(^3\)

For this reason, researchers have been turning towards developing polymers which are capable of breaking down under conditions present in a landfill or compost. These polymers will be suitable for short lifetimes, and ideally will be made from renewable resources. There are two types of standards which are used to describe the ability for the polymer to break down: biodegradable and compostable. Biodegradable polymers are polymers which break down from a naturally occurring micro-organism like bacteria or fungi.\(^3\) Compostable plastics are those which degrade into CO\(_2\), water, inorganic materials, and biomass at the same rate as other compostable materials but leave no toxic residue behind.\(^3\)

There are many naturally occurring biodegradable polymers which are derived from plants, such as cellulose, starch, proteins, and rubber.\(^1\) Other types of biodegradable polymers are made synthetically from plant derived feedstock. In this type of biodegradable polymer, the monomer is derived from some component of the plant material. Lactic acid, which is used for polylactide (PLA), is made from the fermentation of glucose, maltose and dextrose from potatoes or sucrose from cane or beet sugar.\(^4\) PLA polymer is capable of being fully broken down back to water and CO\(_2\) by enzymatic processes.\(^5\)

1.1.2. Polylactide

Polylactide has gained increasing attention in recent years as being a viable competitor in the plastics industry.\(^5-9\) NatureWorks, LLC is the major producer of commercial polylactide in the United States, with production of 140,000 metric tons per
year. They are credited with making the first commodity polymer which is made entirely from renewable resources, e.g. corn, and using wind energy as their power source so that their manufacturing process is carbon neutral. In Scheme 1, the formation of lactide begins with the reaction of carbon dioxide with water, two readily available and inexpensive materials.

\[
\begin{align*}
\text{CO}_2 + \text{H}_2\text{O} & \rightarrow \text{HO} - \text{O} - \text{O} \rightarrow \text{H}_2\text{O} \\
\text{HO} - \text{O} - \text{OH} & \rightarrow \text{HO} - \text{O} - \text{OH} \\
\text{O} - \text{O} & \rightarrow \text{HO} - \text{O} - \text{OH} \\
\text{CH}_3 & \rightarrow \text{HO} - \text{O} - \text{OH} \\
\text{CH}_3 & \rightarrow \text{HO} - \text{O} - \text{OH}
\end{align*}
\]

Scheme 1. Formation of lactide from natural resources

Figure 1 compares the amounts of fossil fuels used in the production process of one kilogram of polymer, starting with the processing of raw material, polymerization and ending with the polymer pellet. It does not account for processing the polymer into materials, recycling, or the breakdown. The graph also shows that the first generation polylactide technology, which is labeled PLA 1, has allowed reductions of fossil fuel usage of 25-55% compared to its competitors. With the use of renewable wind energy, it is expected that future polylactide technologies will show even greater reductions.
Biodegradable polymers like polylactide are useful for a variety of practical applications. They are ideal for one-time-use packages, such as food wrappings and water bottles, which are often not recycled because of lack of availability. They break down into harmless byproducts which are naturally metabolized by the body, so they are also ideal for use as sutures, stints, and other biomedical applications. A major benefit to these products is that as the polymer degrades and the body heals, the load is transferred slowly from the device back to the body. Not only does this prevent a second surgery to remove the device, but it also reduces the need for rehabilitative therapy.\textsuperscript{13}

1.1.3. Stereochemistry of the polymers

Physical properties of the polymers, including melting temperature, toughness, and rate of degradation, are dictated by the physical composition and stereochemistry of the polymer.\textsuperscript{14} Polymers which have stereoregularity will be able to form crystalline polymers, whereas highly random polymers will form amorphous materials with low a $T_g$.\textsuperscript{15,16} Monomers with stereogenic centers allow for unique microstructures which can
provide fine tuning of the physical properties. Lactide contains two stereogenic centers and has three forms, L-(R,R), D-(S,S), and meso-(S,R), shown in Figure 2.

![Stereoisomers of Lactide](image)

Figure 2. Stereoisomers of Lactide

The possible microstructures of polylactide are shown in Figure 3. When either pure L- or D-lactide is polymerized, the polymer is predominately isotactic, meaning all the methyl groups face in the same direction and the methine centers are either (SSSS)$_n$ or (RRRR)$_n$ along the chain. Syndiotactic polymers, which can form using meso-lactide, are those which have perfectly alternating methyl groups, or RSRS methine carbons. Heterotactic polymers are repeating RRSS or SSRR units and are formed using rac-lactide. Stereoblock polymers have a large block of R followed by a large block of S, indicating that the propagation of one stereoisomer is kinetically more favorable. Once one stereoisomer runs out, the second is polymerized. A second possibility for the formation of the stereoblock polymers is that during propagation, a mistake is made which is then propagated. Stereocomplexes can also comprise an equal mixture of isotactic poly(L-lactide) and poly(D-lactide) chains.

NMR is a viable technique for determining the stereochemistry of the polymers. Work by Kricheldorf suggests that $^1$H and $^{13}$C NMR can detect the stereochemistry to the
tetrad level, meaning the proton being examined is affected by one neighboring unit to the left and two neighboring units to the right on the polymer chain.\textsuperscript{15} Using this technique, one can determine the microstructure of the polymer very precisely, which may give information about the mechanism of polymerization.

Figure 3. Microstructures of polylactide

The stereochemistry of the polymer can be controlled by two mechanisms. Enantiomorphic site control is the mechanism by which the stereochemistry of the catalyst dictates the stereochemistry of the inserted monomer. Spassky and coworkers
developed a chiral aluminum catalyst, (R)-(SalBinap)-AlOCH$_3$, which is capable of selectively polymerizing L-lactide over D-lactide in a ratio of 20:1.\textsuperscript{14} Chain-end control is the mechanism by which the last inserted monomer will dictate the stereochemistry of the next monomer insertion. The two mechanisms lead to different types of polymers. Chain end control propagates a mistake in the chain, whereas the enantiomorphic site control corrects the mistake. Studies by Chisholm and coworkers show that many factors, such as the chirality of the ancillary ligands and end group as well as the solvent contribute in a complex way to the mechanism which controls the stereochemistry.\textsuperscript{18}

1.1.4. Mechanism for ROP

Lactide is a cyclic monomer with two carbonyl groups which are allow it to be polymerized via a variety of mechanisms, such as anionic, coordination-insertion, or by organic catalysts, such as nucleophilic carbenes.\textsuperscript{19} Anionic ring opening polymerization (ROP) occurs by attack of the anionic initiator on the carbonyl carbon, resulting in acyl-oxygen bond cleavage. Organic catalysts such as nucleophilic N-heterocyclic carbenes can attack the carbonyl carbon to initiate ROP. On the other hand, the mechanism for initiation can also occur by the coordination insertion method as shown in Scheme 2. The monomer first coordinates to the metal center, and the nucleophilic initiating group on the metal center attacks the carbonyl bond. The ring is cleaved at the acyl-oxygen bond, rather than the alkyl-oxygen bond, which has been clearly established by studying the end groups by NMR.\textsuperscript{20-23} A new alkoxide bond is formed which then participates in further propagation. Catalysts which adhere to this mechanism are most commonly studied for ROP of lactide because they allow for the greatest variation in stereoselectivity due to ligand design.
**Initiation by Coordination/Insertion**

\[
\text{Initiation by Coordination/Insertion}
\]

\[
\text{Propagation (Ring-opening Polymerization)}
\]

Scheme 2. Initiation and propagation mechanisms for ring-opening polymerization

Side reactions may occur that result in variation in the molecular weight from chain to chain, as shown in Scheme 3. Inter-chain transesterification is the process by which the metal alkoxide of one chain attacks the carbonyl of another growing chain instead of inserting a monomer.\(^5\) Intra-chain transesterification can also occur in which a sufficiently long chain backbites on itself.\(^5\) This process results in the formation of cycles of various lengths. Chain transfer occurs by having water or alcohol present. In this case, the polymer chain is eliminated from the metal center and transferred onto the alcohol or water, where it remains dormant at a constant molecular weight while the
metal center continues to propagate a new polymer chain. Subsequent chain transfer leads to reactivation of the dormant chain toward propagation.

Chain transfer is often a beneficial side reaction and used to control the molecular weight of the polymer. Living polymerizations are those in which the polymer grows as long as there is monomer present, and with the addition of a transfer agent such as an alcohol, the lengths of the chains can be controlled. Each alcohol grows a polymer chain, and if the rate of exchange between transfer agents is more rapid than the rate of ring enchainment, then a narrow polydispersity (narrow molecular weight distribution) is maintained.

**Interchain Transesterification**

\[ \text{P = propagation polymer} \]

\[ \text{Scheme 3. Side reactions for the ring-opening polymerization} \]

**Intrachain Transesterification**

\[ \text{Chain Transfer} \]

\[ \text{LM−OP} + \text{LM′−OP} \rightarrow \text{LM−OP} + \text{LM′−OP} \]
1.1.5. Catalysts for ROP

ROP of lactide has been studied using various transition metal, lanthanide and main group metal initiators. Ring opening polymerization is achieved most often using a catalyst in the form of LM-X, where L is an inert ligand set, M is the metal center, and X is the initiating group. The initiating group must be sufficiently nucleophilic in order to attack the carbonyl bond, with the most commonly studied X groups being the alkoxides, carbonates and oxides. For industrial applications, the polymerization is best done in a melt, without any solvent present. With solvent present, side reactions become more prevalent.

The most widely used industrial catalyst for the polymerization of polylactide is tin(II) bis(2-ethylhexanoate), or Sn(Oct)$_2$. This catalyst is highly active even in the presence of water and oxygen and has good solubility in molten lactide. Melt polymerizations with Sn(Oct)$_2$ have yields at 94% for low monomer: initiator ratios of 10:1 and for larger ratios of 200:1 in short reaction times. Sn(Oct)$_2$ does not cause a significant amount of racemization, showing pure poly(L-lactide) when L-lactide is polymerized. The structure of Sn(Oct)$_2$ is shown in Figure 4.

![Figure 4. Structure of tin(II) bis(2-ethylhexanoate)](image)

The mechanism for initiation by Sn(Oct)$_2$ is not well understood, but studies by Kricheldorf and coworkers show that there is a small amount of octanoate end groups in
the polymer in addition to -CH-OH end groups from the hydrolysis of alkoxide-initiated polymers.\textsuperscript{25} For all studied monomer:initiator ratios, the amount of octanoate end groups was significantly smaller than the amount of alcohol end groups, suggesting that the Sn-alkoxide species is the more reactive initiator. Scheme 4 shows the alkoxide may be formed by coordination of a protic species (water or alcohol) with the loss of octanoic acid. The protic species may also participate in chain transfer, as shown in Equation 3, which results in lower molecular weight polymers.\textsuperscript{5}

\[
\begin{align*}
\text{Sn(Oct)}_2 + \text{ROH} & \rightleftharpoons (\text{RO})\text{Sn(Oct)}_2 & \text{Eq. 1} \\
\text{Sn(Oct)}_2 + \text{ROH} & \rightleftharpoons (\text{RO})\text{Sn(Oct)} + \text{OctH} & \text{Eq. 2} \\
\text{RO-(lactide)}_n\text{-Sn(Oct)} + \text{ROH} & \rightleftharpoons (\text{RO})\text{Sn(Oct)} + \text{RO-(lactide)}_n\text{-H} & \text{Eq. 3}
\end{align*}
\]

Scheme 4. Proposed mechanisms for the conversion of Sn(Oct)\textsubscript{2} to the initiating species, where R = H, alkyl

Calcium, magnesium and zinc are commonly studied metals for the ROP of lactide. They are biocompatible metals, which make them ideal for making the polylactide for biomedical applications. Because of their reactivity, the alkaline earth metals are more unstable, and require rigorous working conditions absent of water or oxygen. Many researchers have been working on the development of ligand sets which offer protection from the inhibiting side reactions that can plague the polymerization process. Calcium has been found to be the most reactive metal, while zinc is least reactive of the three.\textsuperscript{26}

Coates and coworkers have reported using the β-diiminate (BDI-H) ligand for use in the stabilization of magnesium and zinc.\textsuperscript{17} Their complexes have 95% conversion in
20 minutes. The complex shown in Figure 5 is reported to have great stereoselectivity, producing heterotactic PLA from rac-LA, and syndiotactic PLA from meso-LA.\textsuperscript{27}

![Figure 5. Structure of Coates’ [(BDI)ZnOPr\textsuperscript{i}]\textsubscript{2} complex](image)

Hillmeyer and Tolman have studied a zinc complex which is able to polymerize lactide up to 1500 equivalents in 18 minutes with 93% conversion.\textsuperscript{6} The dimeric zinc compound is shown in Figure 6. Early successful magnesium complexes to be reported for the ROP of lactide include the trispyrazolylborate magnesium alkoxide complexes studied by Chisholm and coworkers, shown in Figure 7.\textsuperscript{28}

![Figure 6. Hillmeyer and Tollman's zinc catalyst for ROP, where R = tBu, Me](image)
There are fewer studies on the use of calcium in ROP of lactide. Calcium is the most abundant metal in the human body, making it one of the most suitable metals for use in biological applications. Early studies using calcium show that it requires high temperatures and living polymerizations were rare, but Feijan and coworkers have shown the use of bis(tetrahydrofuran)calcium bis[bis(trimethylsilyl)amide] in the presence of excess isopropyl alcohol gives a fast and controlled polymerization of lactide.\textsuperscript{23} The addition of the alcohol results in the \textit{in-situ} formation of a calcium-isopropoxide bond which initiates the ring opening of the lactide. A disadvantage regarding these complexes is their elevated sensitivity towards air and moisture, requiring the use of the glovebox for polymerization reactions.

In addition, calcium complexes are plagued with poor control over the polymerizations and broad polydispersities, but researchers have tried to tackle that problem by developing novel ligands to stabilize the reactivity of the calcium center.\textsuperscript{29} Carpentier and coworkers have shown that a bis(morpholinomethyl)phenoxy calcium complex is capable of large-scale polymerization of lactide, where upwards of 1000 equivalents of lactide are polymerized in a living fashion.\textsuperscript{30} The crystal structure of the calcium catalyst is shown in Figure 8.

![Figure 7. Structure of \{HB(3-Bu\textsuperscript{t}pz\}_3\}MgOEt](image-url)
Figure 8. Crystal structure of \([LO^1]\text{CaN(SiMe}_3\text{)}_2\), where \(LO^1 = 4\text{-}\text{tert-butyl-2,5-bis(morpholinomethyl)phenoxy}\)

1.2. OBJECTIVES

After polymerization, the polymer product often contains trace amounts of the metal catalyst because of the difficulty in removing the catalyst. Since many of the polymers are being developed for applications to biomedical and pharmaceutical fields, even trace amounts of potentially toxic materials pose a problem. Catalysts made from biocompatible metals like calcium, magnesium and zinc are preferable, because these metals are inherently required for various functions in the body. While catalysts for ring-opening polymerization in the form of LM-OR are ideal as single site catalysts, there are two potential problems for their commercial use: (i) they generally require the use of organic solvents, which creates a problem of hazardous waste disposal, and (ii) it is generally unknown how the body will respond to the ligand system (L) during metabolism. The ligand sets are usually bulky organic groups which provide great stability for the catalyst, but the long term affects of their exposure has not been studied.
Therefore, this study investigates the ability of known compounds which are currently used for medicinal or biological purposes to function as initiators in ring opening polymerization reactions with lactide.
CHAPTER 2

2.1. PREVIOUS WORK ON THESE CATALYSTS

Kricheldorf and coworkers have previously studied metal oxides and metal carbonates for use as catalysts for lactide ring opening polymerization, specifically focusing on the amount of racemization that they cause during ROP, as determined by optical activity studies.\textsuperscript{31} Their study found that with increasing basicity of the catalyst, the more racemization occurred, which was reportedly due to the initial deprotonation of the lactide monomer. They report that metal carbonates, including CaCO\textsubscript{3}, cause significant racemization, but also note that CaCO\textsubscript{3} is inactive as a catalyst up to 180\degree C, where it gets 11% yield.

In this study, L-lactide is polymerized in a melt using various simple metal oxides and carbonates, including several commercially available over-the-counter medicines and supplements, which contain possible ROP initiating species. There is a larger focus on determining the end groups of the polymers as well as the possible molecular weight distribution, using a variety of techniques such as mass spectrometry and gel permeation chromatography (GPC). The stereochemistry of the resultant polymers was determined using homonuclear decoupling proton NMR. The results are compared to the current commercially used catalyst, Sn(Oct)\textsubscript{2} to determine the viability of using a less toxic material for mass production of polylactide polymers.
Three of the catalysts used in this study are compounds which are available as over the counter medicines and supplements. Rolaids®, a commonly used calcium supplement as well as antacid, is comprised of calcium carbonate and magnesium hydroxide. Goldline® Pink Bismuth, a generic form of the more well known Pepto-bismol®, is comprised of bismuth subsalicylate. Previous studies using bismuth salts, such as bismuth hexanoate and bismuth subsalicylate, for homo- and co-polymerizations of lactide with glycolide have shown promising results as an active catalyst relative to Sn(Oct)$_2$.$^{32-35}$ Such results by Kricheldorf and Rost have demonstrated that the bismuth subsalicylate, while being slower in initiation, has advantages in lower toxicity as well as in less blocky copolymerizations.$^{36}$ The structure of bismuth subsalicylate is shown in Figure 9. Lastly, calcium hydroxyapatite (HA), with a chemical formula of Ca$_{10}$(PO$_4$)$_6$(OH)$_2$, is sold commercially as a calcium supplement. HA has been studied in the polymerization of lactide by using it as a support off of which the lactide is grown.$^{37}$

![Figure 9. Structure of bismuth subsalicylate](image-url)
2.2. TECHNIQUES FOR POLYMER CHARACTERIZATION

2.2.1. Nuclear Magnetic Resonance Spectroscopy – $^1$H and Homonuclear Decoupling

Nuclear magnetic resonance spectroscopy utilizes a magnetic field and radio frequency pulse to interact with atomic nuclei due to the presence of a nuclear magnetism which comes about from having an odd number of protons and/or an odd number of electrons. NMR is a useful technique for characterization of organic molecules because it shows a unique pattern based on structural characteristics, revealing both the number of nuclei present as well as information about its environment. The homonuclear decoupling experiment allows for the effects of the nearest neighboring atoms to be eliminated so that only a selected region may be studied. From the literature, many studies have been done to precisely characterize the methine proton signal on polylactide as the tacticity is changed. $^{14,17,38}$ Shown in Figure 10, as the methyl protons are irradiated, the signal is a perfect singlet for isotactic polylactide, but is a much more complex pattern for atactic. The five different peaks in the atactic polymer are due to the five possible unique tetrad combinations that can arise from rac-lactide polymerization – $iii$, $iis$, $sii$, $isi$, and $sis$, where $i$ indicates an isotactic junction, and $s$ indicates a syndiotactic junction. $^{39}$ The information gained from these NMR experiments allow for the tendency for “mistakes” that occur during polymerization to be quantified, as well as for the determination of the selectivity of the catalyst to be determined.
Figure 10. Homodecoupled $^1$H NMR spectra of methine proton region of PLAs having various tacticities

2.2.2. Gel Permeation Chromatography

Gel permeation chromatography (GPC) is used for determining the mass distribution of the polymer chains. It is a type of size exclusion chromatography which separates out the chains based on size. GPC is comprised of a column filled with beads with pores of various sizes, through which solvent can flow. Polymers with large molecular weights are unable to fit into the pores, and so they pass more quickly through the column. Polymers with small molecular weights are able to travel through the pores, and so they have longer retention times. The detector of the GPC can be a variety of instruments, such as infrared spectrometer or mass spectrometer, which are useful for further characterization of the polymers upon elution. The detector used in this study was
a differential refractometer, which measured the refractive index as the sample is eluted. The relationship between molecular weight and elution volume, or retention time, is determined using a calibration curve of polystyrene standards.

The average molecular weight of the polymers is determined several ways, considering different aspects of the polymer character. The number average molecular weight, or $M_n$, is given as follows

$$M_n = \frac{\sum n_i M_i}{\sum n_i}$$

This expression gives the average weight over the total number of chains. The weight-average molecular weight, or $M_w$, is given as follows

$$M_w = \frac{\sum n_i M_i^2}{\sum n_i M_i}$$

In this expression, the molecular weight is determined as a “weighted” averaged such that longer chains account for a larger portion of the total weight of the polymer.

2.2.3. Matrix Assisted Laser Desorption Ionization – Time of Flight Mass Spectrometry

MALDI-TOF is used for the determination of the molecular weight of the polymer. MALDI-TOF is a soft ionization technique which does not cause fragmentation of the compounds under the laser, making it an ideal technique for studying the molecular weight of polymers. The laser ionizes a matrix, which is used to absorb the energy and protect the sample. The matrix then transfers the proton (or sodium) to the sample. The time of flight (TOF) detector measures the time it takes for the ion to reach the detector, which gives information about the size of the ion. The speed of the ions is proportional
to the square of the m/z value, so by measuring the time for the ion to reach the detector, the mass of the ion can be determined.

2.3. EXPERIMENTAL

The melt polymerizations were carried out at various monomer to catalyst ratios, 100:1, 50:1, and 25:1. MgO, CaO, BaO, ZnO, MgCO$_3$, CaCO$_3$, and Sn(Oct)$_2$ are all available from Sigma Aldrich. Calcium hydroxyapatite, Goldline® Pink Bismuth tablets, and Rolaids® are all available at local pharmacies and health food stores. Solid catalysts were ground in mortar and pestle before use to ensure the largest surface area. The monomer and catalyst were mixed in a 5 mL glass ampule and the ampule was sealed under vacuum. The reaction ampule was then heated in an oil bath to 130°C for 65 hours. Upon completion, the ampules were opened, and a $^1$H NMR was taken of the contents in order to determine the percent conversion. The polymers were then dissolved with chloroform in order to remove them from the vessel and collected by precipitating them out of the chloroform using excess methanol. The polymers were dried in a vacuum oven overnight before further characterization was carried out.

The polymers were characterized by $^1$H and homonuclear decoupling NMR using a Bruker DPX-400 spectrometer operating at 400 MHz. The peaks were referenced against chloroform-$d$ at 7.24 ppm for $^1$H NMR. Gel permeation chromatography was carried out at 40°C using a Waters Breeze system equipped with a Waters 2415 Refractive index detector and a set of two columns, Waters Styragel HR-2 and HR-4 (7.8 x 300 mm). CHCl$_3$ was used as the mobile phase at 1.0 mL/min. The sample concentration was 1.0% and the injection volume was 100 µL. The calibration curve was made with three polystyrene standards covering the molecular weight range from 1320 to
3.15 x 10^6 Daltons. The data was analyzed using the Breeze 2 software from Waters, using a correcting coefficient to convert from polystyrene to polylactide,

\[ M_a(\text{exp}) = X \cdot M_a(GPC), \]

where \( X = 0.58 \pm 0.05 \) for poly(L,D-LA).^{40}

Matrix assisted laser desorption/ionization time-of-flight mass spectroscopy (MALDI-TOF/MS) analysis was performed on a Bruker Microflex mass spectrometer provided by a grant from the Ohio BioProducts Innovation Center. The spectrometer was operated in a linear, positive ion mode. Laser power was used at a threshold level required to generate a signal. The accelerating voltage was 28 kV. Dithranol was used as the matrix. The matrix and sample were mixed in equal amounts in CHCl₃, and spotted on the target plate.

Scanning electron micrographs were obtained for samples using a JEOL JSM-5500 scanning electron microscope. Images were obtained for samples prior to use in polymerization reactions as well as after. The catalyst was collected by filtration after dissolving the polymer in chloroform and dried.

2.4. RESULTS AND DISCUSSION

Tin octanoate was used as a benchmark to polymerize polylactide. In this study, Sn(Oct)₂ polymerized lactide to a 95.9% conversion in 65 hours. From MALDI-TOF, the structure of the polymer was determined to be low molecular weight cycles, as shown in Figure 11. The production of cycles may have been due to an extended reaction period, where the polymer began to back-bite on itself, undergoing the process of intrachain transesterification which was shown previously in Scheme 3. It is also evident from the MALDI that transesterification is complete, because the peaks are separated by 72 mass units, which is one half of a lactide monomer. The ^1H NMR characterization of the
polymer shows there are no end groups present, which corresponds to the observation of cycles in MALDI. Homonuclear decoupling, as shown in Figure 12, on the methine protons results in a singlet, which indicates that epimerization has not taken place, which is consistent with results reported regarding polymerizations using tin octanoate. The polymer is isotactic in nature, with all the methyl groups facing in the same direction. GPC shows that the molecular weight distribution of the polymer is very broad, with a PDI of 2.47 ($M_n = 11,954$ Daltons, $M_w = 29,643$ Daltons).
Figure 11. MALDI-TOF of poly(L-LA) obtained from polymerizations using Sn(Oct)$_2$ as the catalyst.
Figure 12. $^1$H NMR spectrum of polylactide sample obtained from polymerization using Sn(Oct)$_2$ as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample.
Calcium oxide was able to polymerize L-lactide to 93.5% conversion at a monomer:catalyst ratio of 50:1. Epimerization is not evident, as the methine peak is reduced to a singlet during the homonuclear decoupling experiment, shown in Figure 13. End groups are not present in the $^1$H NMR, which further indicate the presence of cycles. MALDI-TOF, shown in Figure 14, indicated that low molecular weight cycles with no end groups being evident. Transesterification was complete. The polylactide sample was characterized by GPC, and found to have a PDI of 1.70 ($M_n = 10,863$ Daltons, $M_w = 18,480$ Daltons).

Barium oxide polymerized lactide in 94.5% yield at 130°C for 65 hours at a monomer to catalyst ratio of 25:1. MALDI-TOF was used to characterize the polymer and it shows that there is a bimodal distribution, as shown in Figure 16. The first, lower molecular weight mode is cycles no end group present. Cycles were likely formed when the chains reached a significant length and began backbiting, thus eliminating smaller cycles. The second, higher molecular weight mode is chains. The end groups were found to be hydroxide and a proton. Transesterification is evident in both modes because the peaks are separated by 72 mass units, or one half of a lactide monomer. The slight height difference between adjacent peaks may indicate that transesterification is not complete for this system. Upon irradiation of the methyl protons, the methine peak is reduced to a singlet, shown in Figure 17. Epimerization is not present, and the product is poly(L-lactide). From the GPC, the PDI was found to be 1.44 ($M_n = 3095$ Daltons, $M_w = 4449$ Daltons).
Figure 13. $^1$H NMR spectrum of polylactide sample obtained from polymerization using CaO as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample.
Figure 14. MALDI-TOF of poly(L-LA) obtained from polymerizations using CaO as the catalyst.
Figure 15. GPC chromatogram of poly(lactide) obtained from the polymerization using CaO as the catalyst (CHCl₃ solvent)
a) 

b) 

(C_{3}H_{4}O_{2})_{n}-H^{+} 

n=19
1371.6

n=21
1443.1
1516.0
1587.8
n=23
1660.2
1733.8
Figure 16. MALDI-TOF of poly(L-LA) as obtained from using BaO as the catalyst. (a) Whole scale. (b) Selected region where polymerization leads to cycles. (c) Selected region where polymerization leads to chains.
Figure 17. $^1$H NMR spectrum of polylactide sample obtained from polymerization using BaO as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample.
Figure 18. GPC chromatogram of poly(lactide) obtained from the polymerization using BaO as the catalyst (CHCl₃ solvent)
Magnesium oxide polymerized L-lactide to 91.7% conversion at a monomer to catalyst ratio of 25:1 in 65 hours. MALDI-TOF, in Figure 19, gives that the polymer is low molecular weight cycles. From the homonuclear decoupling NMR in Figure 20, epimerization does not occur, as the methine peak is reduced down to a singlet. Also, end groups are not elucidated from the NMR experiments, affirming the presence of cycles. By GPC, the PDI of the polymer was found to be 2.23 ($M_n = 7072$ Daltons, $M_w = 15,757$ Daltons).

Zinc oxide polymerized lactide to 62.6% yield in 65 hours using a monomer to catalyst ratio of 50:1. The polymer obtained was very hard and was easily precipitated out of methanol. From MALDI analysis, it was found that the polymer was made of lower molecular weight cycles, as shown in Figure 21. Efforts to determine higher molecular weight chains were unsuccessful by MALDI. Homonuclear decoupling NMR showed the methine peak reduced down to a sharp singlet, indicating no epimerization had occurred as shown in Figure 22. From GPC analysis, the PDI was found to be 2.94 ($M_n = 14,216$ Daltons, $M_w = 41,812$ Daltons). The chromatogram in Figure 23 showed a broad curve, which is the cause of the large PDI value.
Figure 19. MALDI-TOF of poly(L-LA) obtained from polymerizations using MgO as the catalyst.
Figure 20. $^1$H NMR spectrum of polylactide sample obtained from polymerization using MgO as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample.
Figure 21. MALDI-TOF of poly(L-LA) obtained from polymerizations using ZnO as the catalyst.
Figure 22. $^1$H NMR spectrum of polylactide sample obtained from polymerization using ZnO as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample.
Figure 23. GPC chromatogram of poly(lactide) obtained from the polymerization using ZnO the catalyst (CHCl₃ solvent)
Calcium carbonate polymerized L-lactide to 78.5% conversion. Epimerization was not present. The MALDI-TOF, given in Figure 24, indicates a bimodal distribution. The polymers undergo transesterification, shown by the peak separation of 72 mass units. The first, lower molecular weight mode is cycles, where no end group is evident. The second, higher molecular weight, mode is chains, with the end groups being water and a sodium or potassium ion. From the MALDI analysis, the polymer is comprised mostly of chains, which indicates that cycle formation is slow compared to the propagation of the polymer. GPC gives a PDI of 1.33 (Mn = 3646 Daltons, Mw = 4858 Daltons). $^1$H NMR indicates the presence of end groups in Figure 25, confirming the polymer is made up predominantly of chains. The homonuclear decoupling experiment indicates that the polymer is isotactic, while there may have been mistakes along the chain which are indicated by the imperfect quartet at 5.15 ppm, as well as having a broader singlet from the proton irradiation. In an effort to determine whether the polymer had grown on the surface of the calcium carbonate crystals, SEM images were taken before and after the polymerization. From Figure 26 and Figure 27, there is no significant growth of polymer material on the crystals.

Magnesium carbonate polymerized L-lactide to 88.5% conversion. The MALDI gave a bimodal distribution as shown in Figure 28, where the first mode is made up of cycles and the second mode is made up of chains. Unlike calcium carbonate, it is seen from the intensity of each mode that the polymer is made up predominantly of cycles. GPC analysis gives the PDI to be 1.89 (Mn = 5207 Daltons, and Mw = 9833 Daltons).
a) m/z 1000
Intensity

b) m/z 800
Intensity

(C₃H₄O₂)₊⁻H⁺
(C₃H₄O₂)₊⁻H⁺

793.14
864.98
937.93
1009.5
1080.6
1153.9
1224.3
1407.9
1479.7
1552.2
1623.8
1522.2
1600.0
Figure 24. MALDI-TOF of poly(L-LA) obtained from polymerizations using CaCO₃ as the catalyst. (a) Whole spectrum. (b) Selected region, where the reaction produces cycles. (c) Selected region where the reaction produces chains.
Figure 25. $^1$H NMR spectrum of polylactide sample obtained from polymerization using CaCO$_3$ as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample.
Figure 26. SEM of CaCO$_3$ crystals before use in a polymerization reaction

Figure 27. SEM of CaCO$_3$ crystals after use in a polymerization reaction
a) 

b) 

$\text{(C}_3\text{H}_4\text{O}_2)_n\cdot\text{H}^+$

$\text{m/z} 1000 - 4000$

Intensity

$\text{m/z} 1200 - 2200$

Intensity

$\text{m/z} 1082.8, 1227.0, 1370.7, 1515.3, 1660.8, 1805.0, 1949.0, 2093.0, 2236.2$

$\text{n} = 17, 21, 29$
Figure 28. MALDI-TOF of poly(L-LA) obtained from polymerizations using MgCO$_3$ as a catalyst. (a) Whole region. (b) Selected region, where the reaction produces cycles. (c) Selected region where the reaction produces chains.
Figure 29. $^1$H NMR spectrum of polylactide sample obtained from polymerization using MgCO$_3$ as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample.
Each Rolaids® tablet is a mixture of 40% calcium carbonate, 7% magnesium hydroxide, and 53% inactive filler ingredients. Rolaids® polymerized polylactide up to 75.9% conversion over 65 hours as determined by $^1$H NMR. The polymer obtained was a light brown material. The MALDI-TOF shows two modes are present as displayed in Figure 30, where the more intense mode corresponds to the sodiated ion and the less intense mode is the potassiated mode. The end groups are found to be a hydroxide and a proton, indicating that water is involved in the polymerization process. Both modes show that intramolecular transesterification is occurring, as the peaks are separated by 72 mass units.

From the $^1$H NMR, the end groups were confirmed to be a hydroxide and a proton. The multiplet at 4.32 ppm is due to the methine proton on the end lactide unit. It is shifted upfield relative to other methine protons because the end group is a carboxylic acid, while in the middle of the polymer chain it is an ether junction. The methyl peaks of the lactide end group show up as a doublet at 1.47 ppm. Using homonuclear decoupling NMR, the methyl protons were irradiated at 1.56 ppm. The insert (a) on Figure 31 shows that upon irradiation of the methyl protons, the multiplet reduces down to a singlet, indicative of an isotactic polymer. From GPC analysis, the PDI of the polymer sample was found to be 1.21 (Mn = 2131 Daltons, Mw = 2576 Daltons). The narrow curve shown in Figure 32 indicates that the polymer had a narrow molecular weight range.
Figure 30. MALDI-TOF of poly(L-LA) obtained from polymerizations using Rolaids® as the catalyst. (a) Whole scale. (b) Selected region.
Figure 31. $^1$H NMR spectrum of polylactide sample obtained from polymerization using Rolaids® as the catalyst (CDCl$_3$, 400MHz). Insert (a) shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample.
Figure 32. GPC chromatogram of poly(lactide) obtained from the polymerization using Rolaids® tablets the catalyst (CHCl₃ solvent)
Calcium hydroxyapatite, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, polymerized L-lactide less actively, with a 29.7% conversion when the monomer to catalyst ratio was 25:1. The MALDI analysis shows a bimodal distribution of peaks which arises from having either $\text{K}^+$ or $\text{Na}^+$ as the counter ion. The end groups are a hydroxide and a proton. The effects of incomplete transesterification are most evident in this sample, with peaks alternating in height much more prominently. GPC analysis could not be obtained for this sample. The end groups were also visible by $^1\text{H}$ NMR, with the peak assignments as shown in Figure 34.

Recently it was shown that polylactide could be grown onto porous calcium hydroxyapatite, making a hybrid of the two materials which they suggested as a more stable artificial bone material. In an effort to determine whether this current study had produced a similar effect on the hydroxyapatite, SEM imaging was used to study the physical structure before and after polymerization. As shown in Figure 35 and Figure 36, it can be seen that the likelihood of any polymer growth on the hydroxyapatite crystals is very low. The low percent conversion is also a likely reason to not see a significant amount of growth.
Figure 33. MALDI-TOF spectrum of poly(L-LA) obtained using calcium hydroxyapatite as the catalyst.  (a) Whole scale.  (b) Selected region.
Figure 34. $^1$H NMR spectrum of polylactide sample obtained from polymerization using calcium hydroxyapatite as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample.
Figure 35. SEM of HA crystals before use in polymerization of lactide

Figure 36. SEM of HA after use in a polymerization of lactide
Goldline® Pink bismuth tablets polymerized L-lactide up to 98.3% conversion over 65 hours. From MALDI analysis, polymer was determined to be comprised of lower molecular weight cycles. The polymer was characterized by 1H NMR, showing there were no end groups present. The methine proton peak was reduced down to a singlet during homonuclear decoupling NMR, as shown in Figure 38, indicating that epimerization did not take place during the reaction. According to GPC analysis, the PDI was 1.27 ($M_n = 14,712$ Daltons, $M_w = 18,688$ Daltons). Due to the large discrepancy in the molecular weight as determined by MALDI and GPC, it was concluded that there may have been a combination of higher molecular weight chains as well as lower molecular weight cycles present. All attempts to determine any higher molecular weight chains by MALDI were unsuccessful.
Figure 37. MALDI-TOF of Poly(L-LA) obtained from polymerizations using Goldline® Pink Bismuth tablets

$\left(\text{C}_3\text{H}_4\text{O}_2\right)_n\text{-H}^+$

Intensities and m/z values:
- m/z 800
- 1800
- Intensity
- 794.63
- 867.44
- 938.81
- 1011.8
- 1083.1
- 1155.3
- 1228.0
- 1315.5
- 1444.3
- 1515.8
- 1589.5
- 1658.9
- 1732.2
- 1805.3
Figure 38. $^1$H NMR spectrum of polylactide sample obtained from polymerization using Goldline® Pink Bismuth tablets as the catalyst (CDCl$_3$, RT 400MHz). The inserted figure shows the methine resonance in the homonuclear decoupled $^1$H NMR of the same sample.
Figure 39. GPC chromatogram of poly(lactide) obtained from the polymerization using Goldline® Pink Bismuth tablets the catalyst (CHCl₃ solvent)
2.5. CONCLUSIONS

From this study, it was found that potential catalysts such as the Goldline® Pink Bismuth tablets, made from bismuth subsilicate, and calcium oxide were the most successful catalysts for replacing the tin octanoate in industrial scale polymerization of lactide. The Goldline® Pink Bismuth tablets showed the highest percent conversions over the time period tested, and gave similar molecular weight results as the tin octanoate in terms of mass spectrometry and GPC. The PDI of the polymer produced by the Goldline® Pink Bismuth tablets was very narrow, 1.27, while the PDI of the polymer produced by Sn(Oct)$_2$ was 2.47, indicating a much more controlled molecular weight by the bismuth catalyst. Calcium oxide produces a high molecular weight polymer with narrow PDI.

Several catalysts were shown to be completely unsuitable for use in ROP of lactide. Calcium hydroxyapatite had the lowest percent conversions of all the catalysts, despite reports in literature of successful polymerizations. This may be due to the type of surface area that the hydroxyapatite has in the health supplement form as opposed to the more porous surface areas which are obtained from other sources of hydroxyapatite. Also, calcium carbonate showed polymerization activity towards the polymerization of lactide, but the molecular weight was so low that it was often difficult to precipitate the polymer out of chloroform solution. This was similarly true for the MgCO$_3$, BaO, and Rolaids samples.
2.6. FUTURE CONSIDERATIONS

For this project, the polymerizations were completed in 65 hour trials. This allowed many samples to come nearly to completion, while some samples were so slow that they did not reach completion. This also allowed sufficient time for several samples to begin undergoing a back-biting process to produce predominantly cycles. While the long polymerization times were useful for determining the ability of each catalyst to achieve high percent conversions and degree of epimerization, it is necessary to determine next if tranesterification is due to the long reaction times, or if it is a characteristic of the catalyst, and whether or not these catalysts are able to produce higher molecular weight chains on shorter time scales. The kinetic studies will be important to determine which catalyst may be able to exceed the activity of tin octanoate.

Also of interest will be to determine how the catalysts perform in a large scale melt polymerization. The purpose of this research is to determine a catalyst for use in industrial applications, so determining the ability for the bismuth tablets and calcium oxide to function successfully in monomer to catalyst ratios exceeding 10,000:1 will be of interest.
BIBLIOGRAPHY


(6) Williams, C. K.; Breyfogle, L. E.; Choi, S. K.; Nam, W.; Young; Hillmeyer, M. A.; Tolman, W. B. *Journal of the American Chemical Society* 2003, 125, 11350-11359.


(14) Ovitt, T. M.; Coates, G. W. *Journal of the American Chemical Society* 2002, 124, 1316-


(36) Kricheldorf, H. R.; Rost, S. Biomacromolecules 2005, 6, 1345-1352.

(37) Zhongkui Hong; Xueyu Qiu; Jingru Sun; Mingxiao Deng; Xuesi Chen; Xiabin Jing

Polymer 2004, 45, 6699-6706.


(40) Save, M.; Schappacher, M.; le; Soum, A. Macromolecular Chemistry and Physics 2002, 203, 889 - 899.