Enzymatic and Chemical Synthesis of Polyesters and Polycarbonates Derived from LTartaric Acid and Synthesis of Polycaprolactones Initiated by Cavitands

Ruizhi Wu
University of South Florida

Follow this and additional works at: https://digitalcommons.usf.edu/etd

Part of the American Studies Commons

Scholar Commons Citation

This Dissertation is brought to you for free and open access by the USF Graduate Theses and Dissertations at Digital Commons @ University of South Florida. It has been accepted for inclusion in USF Tampa Graduate Theses and Dissertations by an authorized administrator of Digital Commons @ University of South Florida. For more information, please contact digitalcommons@usf.edu.
Enzymatic and Chemical Synthesis of Polyesters and Polycarbonates Derived from L-Tartaric Acid and Synthesis of Polycaprolactones Initiated by Cavitands

by

Ruizhi Wu

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctoral of Philosophy Department of Chemistry College of Arts and Sciences University of South Florida

Major Professor: Kirpal S. Bisht, Ph.D
Julie P. Harmon, Ph.D.
Abdul Malik, Ph.D.
Li-June Ming, Ph.D.

Date of Approval:
Tuesday, April 7, 2009

Keywords: caprolactone, cycliccarbonate, biodegradable, hydrophilic, multiarm polymer

© Copyright 2009, Ruizhi Wu
ACKNOWLEDGMENTS

I would like to express my deepest thanks to Dr Kirpal S. Bisht, my major professor, for teaching me not only to be a better chemist but more importantly, for leading me to a successful future. For his time and effort on my research and behalf I will always to be grateful. I would like to thank my committee members Dr. Julie P. Harmon, Dr. Edward Turos, Dr. Abdul Malik and Dr. Li-June Ming for their helpful discussions and advises of my research.

I am grateful of all of my current and former colleagues for their assistance and support. First and foremost, my former colleagues post-doctor Dr. Talal Al-azemi who encourage me and help go through a lot of struggle in research. Also I would like to thank my lab mate Pasha M. Khan who study with me in my whole Ph. D. research, my former lab mate Jason A. Carr, Eric E. Dueo and Surbhi Bhatt who trained and supported me at the beginning of my graduate research life, Sumedh Parulekar, Kirti Muppalla, Meghanath Gali and Ali who work with me in the same lab. Last but not the least I wish to acknowledge all my friends for the lighter moment I share with them. Thanks Department of Chemistry and University of South Florida for allowing me to carry out my research projects successfully.

Finally, I am at loss of words to express my love to my family. Thanks my parents and my sister for their supporting to my graduate research aboard. I wish and hope I could share my future success with them.
# TABLE OF CONTENTS

LIST OF TABLES  iii

LIST OF FIGURES  iv

LIST OF SCHEMES  viii

LIST OF ABBREVIATIONS  ix

ABSTRACT  xi

## CHAPTER 1: SYNTHESIS OF POLYESTERS AND POLYCARBONATE VIA RING-OPENING POLYMERIZATION  1

1.1 Introduction of ring-opening polymerization  1
1.2 Enzyme-catalyzed ring-opening polymerization  5
1.3 Polycarbonates and their application  9
1.4 Polyester and their application  15
1.5 References  20

## CHAPTER 2: FUNCTIONALIZED POLYCARBONATE DERIVED FROM TARTARIC ACID- ENZYMATIC RING-OPENING POLYMERIZATION OF A SEVEN-MEMBERED CYCLIC CARBONATE  27

2.1 Introduction  27
2.2 Synthesis of 7 member cyclic carbonate monomer (ITC)  31
2.3 Polymerization of ITC using four different enzyme catalysts  34
2.4 The kinetics study of polymerization of ITC catalyzed by Novozyme-435  36
2.5 Polymer NMR characterization  42
2.6 Deprotection of the ketal groups of poly(ITC)  46
2.7 Thermal analysis of poly(ITC)  51
2.8 Conclusions  52
2.9 Experiment  53
2.10 References  58
CHAPTER 3: ONE-SHOT BLOCK COPOLYMERIZATION OF A FUNCTIONAL SEVEN-MEMBERED CYCLIC CARBONATE DERIVED FROM L-TARTARIC ACID WITH ε-CAPROLACTONE

3.1 Introduction 62
3.2 Bulk homopolymerization of ITC 65
3.3 Copolymerization of ITC and CL. 74
3.4 NMR characterization of copolymers. 78
3.5 Deprotection of ketal groups of copolymer 88
3.6 Thermal analysis of copolymers of ITC 91
3.7 Conclusion 93
3.8 Experiment 94
3.9 References 97

CHAPTER 4: SPATIALLY DIRECTIONAL MULTIARM POLY (ε-CAPROLACTONE) BASED ON RESORCIN[4]ARENE CAVITAND CORE

4.1 Introduction 102
4.2 Synthesis of Tetrol Resorcin[4]arenes Initiator Cores 105
4.3 Synthesis and Characterization of Tetra-Arm Poly(ε-caprolactone)s 107
4.4 Thermal Properties 115
4.5 Crystallization Behaviors 118
4.6 Conclusions 121
4.7 Experiment 122
4.8 References 128

CHAPTER 5: CONCLUSION AND FUTURE APPLICATION 133

ABOUT THE AUTHOR 135
LIST OF TABLES

Table 1.1. Difference catalyst using in ring-opening polymerization 2
Table 1.2. Polymerization of difference size of cyclic carbonate 11
Table 1.3. Enthalpy and entropy of ROP for selected lactones (298 K) 18
Table 2.1. Enzymatic ring-opening polymerization of monomer (3) in bulk at 80 °C. 35
Table 2.2. Deprotection of ketal groups of poly(ITC) 46
Table 3.1 Ring-opening polymerization of ITC monomer in bulk at 120 °C 67
Table 3.2. Sn(Oct)$_2$ catalyzed ring-opening co-polymerizations of ITC and ε-CL 77
Table 3.3. Removal of the acetonide groups from copolymer 88
Table 4.1. Polymerization of ε-CL with of resorcin[4]arene 2c and 3c 108
LIST OF FIGURES

Figure 1.1. The life cycle of polylactide

Figure 2.1. $^1$H NMR (250 MHz, CDCl$_3$) spectrum of (5S, 6S)-Dimethyl 5,6-O-isopropylidene-1,3-dioxepin-2-one (ITC, 3).

Figure 2.2. $^{13}$CNMR (62.9 MHz, CDCl$_3$) spectrum of (5S, 6S)-Dimethyl 5,6-O-isopropylidene-1,3-dioxepin-2-one (ITC, 3).

Figure 2.3. Percent monomer conversion of (3) as a function of time (h) for Novozyme-435 catalyzed ring-opening polymerization at 80 °C in bulk for 48h.

Figure 2.4. Number-average molecular weight and weight distribution as a function of monomer conversion for Novozyme-435 catalyzed ring opening polymerization at 80 °C in bulk for 48h.

Figure 2.5. First-order kinetic plot for Novozyme-435 catalyzed ROP of ITC monomer at 80 °C for 48h.

Figure 2.6. $^1$H NMR (500 MHz, CDCl$_3$) spectrum of the polycarbonate obtained from the Novozyme-435 catalyzed ROP of monomer (3) in bulk at 80 °C for 48h.

Figure 2.7. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of the polycarbonate obtained from the Novozyme-435 catalyzed ROP of monomer (3) in bulk at 80 °C for 48h.

Figure 2.8. $^1$H-$^{13}$C HMQC-NMR (250 MHz, CDCl$_3$) spectra of Poly(ITC).

Figure 2.9. $^1$H NMR (500MHz, DMSO-$d_6$) spectra of Poly(ITC); (a) before de-protection [Table 2-2, entry 1]. (b) After de-protection [Table 2-2, entry 5].

Figure 2.10. $^{13}$C NMR (100 MHz, DMSO-$d_6$) spectra of Poly(ITC); (a) before de-protection [Table 2-2, entry 1]. (b) After de-protection [Table 2-2, entry 5].
Figure 2.11. GPC chromatograms of Poly(ITC); (a) before de-protection ($M_n = 15500 \text{ g/mol}$) [Table 2-2, entry 1]. (b) After de-protection ($M_n = 12500 \text{ g/mol}$) [Table 2-2, entry 4].

Figure 3.1. $^1H$ and $^{13}C$ NMR spectra of poly(ITC) obtained by Sn(Oct)$_2$-catalyzed ROP in bulk at 120 °C for 12 h [Table 3-1, entry 3]

Figure 3.2. $^1H$-$^1H$ COSY-NMR (500 MHz, CDCl$_3$) spectrum of Poly(ITC) [Table 3-1, entry 3].

Figure 3.3. $^1H$-$^{13}C$ HSQC-NMR (500 MHz, CDCl$_3$) spectrum of Poly(ITC) [Table 3-1, entry 3].

Figure 3.4. Percent monomer conversion of (3) as a function of time (h) for Sn(Oct)$_2$ catalyzed ring-opening polymerization at 120 °C in bulk for 12h.

Figure 3.5. Number-average molecular weight and weight distribution as a function of monomer conversion for Sn(Oct)$_2$ catalyzed ring opening polymerization at 120 °C in bulk for 12h.

Figure 3.6. Plot of ln([M]$_0$/[M]) as function of polymerization time (h) for Sn(Oct)$_2$ catalyzed ROP of ITC monomer in bulk at 120 °C.

Figure 3.7. GPC chromatograms ROP of ITC with ε-CL in bulk at 120 °C for 12 h (M/I =200): (a) Catalyzed by Sn(Oct)$_2$. (b) Catalyzed by ZnEt$_2$-H$_2$O.

Figure 3.8. $^1H$ NMR spectra (500 MHz, CDCl$_3$) of poly(ITC-block-CL) [Table 2, entry 4], obtained by Sn(Oct)$_2$-catalyzed ROP in bulk at 120 °C for 12 h.

Figure 3.9. $^{13}C$ NMR spectra (500 MHz, CDCl$_3$) of poly(ITC-block-CL) [Table 3-2, entry 4], obtained by Sn(Oct)$_2$-catalyzed ROP in bulk at 120 °C for 12 h.

Figure 3.10. $^1H$-$^{13}C$ HSQC-NMR (500 MHz, CDCl$_3$) spectrum of Poly(ITC-block-CL) [Table 3-2, entry 4].

Figure 3.11. $^1H$-$^1H$ COSY-NMR (500 MHz, CDCl$_3$) spectrum of Poly(ITC-block-CL) [Table 3-2, entry 4].
Figure 3.12. $^1$H NMR (250 MHz, CDCl$_3$) spectra for various reaction time of Sn(Oct)$_2$-catalyzed $^1$H NMR (250 MHz, CDCl$_3$) spectra for various reaction time of Sn(Oct)$_2$-catalyzed copolymerization of ITC monomer with ε-caprolactone (ε-CL) at 120 °C in bulk [1:1 feed ratio].

Figure 3.13. Plot of monomer conversion (%) as a function of reaction time (min) for Sn(Oct)$_2$-catalyzed copolymerization of ITC monomer (■) with ε-caprolactone (●) at 120 °C in bulk [1:1 feed ratio].

Figure 3.14. Mechanism of stannous octanoate-catalyzed block polymerization of ε-CL and ITC:

Figure 3.15. GPC chromatograms of poly[ITC-block-CL] at different reaction times catalyzed by Sn(Oct)$_2$ at 120 °C in bulk

Figure 3.16. $^1$H-NMR spectrum (500 MHz, DMSO-$d_6$) of Poly[ITC-block-CL] after deprotection [Table 3-3, entry 4].

Figure 3.17. $^{13}$C-NMR (125 MHz, DMSO-$d_6$) spectra of Poly[ITC-block-CL] after de-protection [Table 3-3, entry 4].

Figure 3.18. DSC thermogram of poly(44%ITC)-block-poly(56% ε-CL) (Table 3-2, entry 4)

Figure 4.1. Representative GPC chromatograms for 2cSPL [Table 4-1, entry 1-4].

Figure 4.2. Representative GPC chromatograms for 3cSPL [Table 4-1, entry 5-8].

Figure 4.3. $^1$H-NMR (500 MHz, CDCl$_3$) spectrum of 2cSPL$_{40}$ [Table 4-1, entry 1].

Figure 4.4. $^{13}$C-NMR (500 MHz, CDCl$_3$) spectrum of directional-polycaprolactone based on initiator 2c [Table 4-1, entry 1] catalyzed by Sn(Oct)$_2$ at 120 °C.

Figure 4.5. Dept135-NMR (500 MHz, CDCl$_3$) spectrum of directional-polycaprolactone based on initiator 2c [Table 4-1, entry 1] catalyzed by Sn(Oct)$_2$ at 120 °C.

Figure 4.6. $^1$H-NMR (500 MHz, CDCl$_3$) spectrum of 3cSPL$_{40}$ [Table 4-1, entry 5] catalyzed by Sn(Oct)$_2$ at 120 °C.
Figure 4.7. DSC thermograms of polycaprolactones 116
Figure 4.8. TGA thermograms of polycaprolactones 117
Figure 4.9. WAXS diffractograms overly of LPCL, 2cSPL$_{200}$ and 3cSPL$_{200}$. 120
**LIST OF SCHEMES**

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.</td>
<td>Ring-opening polymerization of lactones catalyzed by organometallic species [M] in presence of nucleophiles (Nu).</td>
<td>4</td>
</tr>
<tr>
<td>1.2.</td>
<td>Ring-opening polymerization of lactones by the “coordination–insertion” mechanism.</td>
<td>4</td>
</tr>
<tr>
<td>1.3.</td>
<td>Ring opening polymerization of varied ring-sized lactone</td>
<td>5</td>
</tr>
<tr>
<td>1.4.</td>
<td>Mechanism of enzymatic ring-opening polymerization.</td>
<td>7</td>
</tr>
<tr>
<td>2.1.</td>
<td>Enzymatic polymerization of monomer (3) in bulk at 80 °C</td>
<td>30</td>
</tr>
<tr>
<td>2.2.</td>
<td>Synthesis of seven-member cyclic carbonate monomer from L-Tartaric acid</td>
<td>31</td>
</tr>
<tr>
<td>3.1.</td>
<td>Ring-opening polymerization of ITC monomer in bulk at 120 °C</td>
<td>65</td>
</tr>
<tr>
<td>3.2.</td>
<td>Ring-opening copolymerization of ITC with ε-CL catalyzed by Sn(Oct)$_2$ at 120 °C for 12h in bulk.</td>
<td>75</td>
</tr>
<tr>
<td>3.3.</td>
<td>Deprotection of the acetonide groups from copolymer</td>
<td>88</td>
</tr>
<tr>
<td>4.1.</td>
<td>Synthesis of tetrahydroxy resorcinarenes initiator cores</td>
<td>105</td>
</tr>
<tr>
<td>4.2.</td>
<td>Synthesis of directional polycarpolactone based on resorcin[4]arenes 2c and 3c</td>
<td>107</td>
</tr>
</tbody>
</table>
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AK</td>
<td>Pseudomonas fluorescens</td>
</tr>
<tr>
<td>CDCl₃</td>
<td>Deuterated chloroform</td>
</tr>
<tr>
<td>DMP</td>
<td>2,2-Dimethoxypropane</td>
</tr>
<tr>
<td>DMSO-d₆</td>
<td>Deuterated dimethyl sulfoxide</td>
</tr>
<tr>
<td>DSC</td>
<td>Differential scanning calorimetry</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>GPC</td>
<td>Gel Permeation Chromatography</td>
</tr>
<tr>
<td>Hₘ</td>
<td>Enthalpy of melting</td>
</tr>
<tr>
<td>ITC</td>
<td>(5S,6S)- Dimethyl 5,6- isopropylidene-1,3-dioxepin-2-one</td>
</tr>
<tr>
<td>Kₚₚₚ</td>
<td>Apparent rate constant</td>
</tr>
<tr>
<td>LAH</td>
<td>Lithium Aluminum Hydride</td>
</tr>
<tr>
<td>MBC</td>
<td>5-Methyl-5-benzzyloxy carbonyl-1,3-dioxan-2-one</td>
</tr>
<tr>
<td>Mₙ</td>
<td>Number-average molecular weight</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>Novozyme435</td>
<td>Candida antarctica</td>
</tr>
<tr>
<td>PCL</td>
<td>Poly (ε-caprolactone)</td>
</tr>
<tr>
<td>PDI</td>
<td>Polydispersity Index</td>
</tr>
<tr>
<td>PLA</td>
<td>Polylactide</td>
</tr>
<tr>
<td>PPL</td>
<td>Porcine pancreatic lipase</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>PS-30</td>
<td>Pseudomonas cepacia</td>
</tr>
<tr>
<td>ROP</td>
<td>Ring-Opening Polymerization</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>PTSA</td>
<td>Para Toluene Sulfonic Acid</td>
</tr>
<tr>
<td>$T_g$</td>
<td>Glass transition temperature</td>
</tr>
<tr>
<td>$T_m$</td>
<td>Melting temperature</td>
</tr>
<tr>
<td>TGA</td>
<td>Thermogravimetric</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>$X_c$</td>
<td>Percent crystallinity</td>
</tr>
<tr>
<td>WAXS</td>
<td>Wide-angle X-ray scattering</td>
</tr>
</tbody>
</table>
Enzymatic and Chemical Synthesis of Polyesters and Polycarbonates Derived from L-Tartaric Acid and Synthesis of Polycaprolactones Initiated by Cavitands

Ruizhi Wu

ABSTRACT

Due to the excellent properties of biodegradability and biocompatibility, aliphatic polycarbonate and polyesters are very promising either as biomaterials or as environmentally friendly materials to address growing ecological concerns. The first chapter describes an overview of ring-opening polymerization, enzymatic polymerization and their application on the polymerization of cyclic carbonate and lactones.

The second chapter describes the synthesis of enantiomerically pure functional polycarbonate from a novel seven-membered-cyclic carbonate (5S, 6S)-Dimethyl 5,6-isopropylidene-1,3-dioxepin-2-one (ITC) derived from naturally occurring L-tartaric acid. The monomer was synthesized in three steps and screened for polymerization with four commercially available lipases.

Block co-polymerization of ITC with ε-caprolactone in ‘one-shot feeding’ is reported in the third chapter. It is the first report of ‘one-shot’ block copolymerization of ε-caprolactone with a cyclic carbonate monomer. The deprotection of the ketal groups resulted in copolymers containing free hydroxy groups in the polymer backbone.
In chapter four, star-shaped poly(ε-caprolactone)’s (PCL) series based on two tetra-
hydroxy resorcinarenes initiators were reported. These polymers were synthesized by the
ring-opening polymerization. The data suggest that the initiator core directed the PCL-
arms toward more interactions resulting in increasing in the rigidity of star-polymers
compare to linear-PCL.
CHAPTER 1
SYNTHESIS OF POLYESTERS AND POLYCARBONATE VIA RING-OPENING POLYMERIZATION

1.1 Introduction of ring-opening polymerization.

Not like the vinyl polymerization and polycondensation which have already been broadly applied in both scientific and industrial fields, the systematic study of ring-opening polymerization has only 50 years history.\textsuperscript{1,2} But so far, ring-opening polymerization has been playing more and more important roles in industrial applications such as engineering thermoplastics and elastoplastics. Ring-opening polymerization can introduce functional groups into polymer back bone chain which is difficult for vinyl polymerization, for example, ether, ester, amide and carbonate etc. Even most ring-opening polymerization product can be obtained by polycondensation, ring-opening polymerization is more controllable than polycondensation. First, two functional group must be equivalent to prepare high molecular weight polymer in polycondensation, which is automatically achieved in ring-opening polymerization. Secondly, molecular weight and polydispersity ratio is easier to be controlled in ring-opening polymerization since ring-opening polymerization is going through living polymerization mechanism but polycondensation is step-polymerization. And because of the same reason mentioned before, block copolymerization is more possible and controllable in ring-opening
polymerization than polycondensation. Last but not the least, the ring-opening polymerization of cyclic monomers is more efficient as no leaving group is involved while efficient removal of the condensate is required to shift the equilibrium to the polymerization in polycondensation.

A wide variety of ring-opening polymerization have been successfully carried out in the presence of different kinds of initiators and catalysts according to cationic, anionic, coordination and enzymatic mechanisms. The examples of the polymerization initiators and catalysts are shown in Tables 1.1.

### Tables 1.1 Difference catalyst using in ring-opening polymerization

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Mechanism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$OSO$_2$CF$_3$</td>
<td>Cationic polymerization</td>
<td>[3]</td>
</tr>
<tr>
<td>HOSO$_2$CF$_3$</td>
<td>Cationic polymerization</td>
<td>[4]</td>
</tr>
<tr>
<td>BF$_3$·OEt$_2$</td>
<td>Lewis acids</td>
<td>[3]</td>
</tr>
<tr>
<td>SnCl$_4$</td>
<td>Lewis acids</td>
<td>[4]</td>
</tr>
<tr>
<td>SbCl$_5$</td>
<td>Lewis acids</td>
<td>[5]</td>
</tr>
<tr>
<td>TiCl$_4$</td>
<td>Lewis acids</td>
<td>[6]</td>
</tr>
<tr>
<td>CH$_3$I</td>
<td>Lewis acids</td>
<td>[3]</td>
</tr>
<tr>
<td>C$_6$H$_5$CH$_2$Br</td>
<td>Lewis acids</td>
<td>[3]</td>
</tr>
<tr>
<td>CH$_2$=CHCH$_2$I</td>
<td>Lewis acids</td>
<td>[3]</td>
</tr>
<tr>
<td>I$_2$</td>
<td>Lewis acids</td>
<td>[3]</td>
</tr>
<tr>
<td>Bu$_{4-n}$SnCl$_n$</td>
<td>Lewis acids</td>
<td>[7]</td>
</tr>
<tr>
<td>Catalyst</td>
<td>Mechanism</td>
<td>Reference</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>K$_2$CO$_3$</td>
<td>Anionic polymerization</td>
<td>[8]</td>
</tr>
<tr>
<td>$t$-BuOK</td>
<td>Anionic polymerization</td>
<td>[9]</td>
</tr>
<tr>
<td>$s$-BuLi</td>
<td>Anionic polymerization</td>
<td>[10]</td>
</tr>
<tr>
<td>Bu$_2$Mg</td>
<td>Anionic polymerization</td>
<td>[11]</td>
</tr>
<tr>
<td>NaH</td>
<td>Anionic polymerization</td>
<td>[8]</td>
</tr>
<tr>
<td>CH$_3$COOK+18-crown-6 ether</td>
<td>Anionic polymerization</td>
<td>[8]</td>
</tr>
<tr>
<td>4-(dimethylamino) pyridine (DMAP)</td>
<td>Anionic polymerization</td>
<td>[12]</td>
</tr>
<tr>
<td>Quinuclidine</td>
<td>Anionic polymerization</td>
<td>[12]</td>
</tr>
<tr>
<td>1,4-diazabicyclo[2.2.2]octane (DABCO)</td>
<td>Anionic polymerization</td>
<td>[12]</td>
</tr>
<tr>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene(DBU)</td>
<td>Anionic polymerization</td>
<td>[12]</td>
</tr>
<tr>
<td>Samarium complex</td>
<td>Anionic polymerization</td>
<td>[13]</td>
</tr>
<tr>
<td>Rare earth chloride (Y, La, Pr, Nd, Dy)</td>
<td>Anionic polymerization</td>
<td>[14-17]</td>
</tr>
<tr>
<td>Bu$_2$SnO</td>
<td>Coordination polymerization</td>
<td>[8]</td>
</tr>
<tr>
<td>Bu$_2$Sn(OCH$_3$)$_2$</td>
<td>Coordination polymerization</td>
<td>[11]</td>
</tr>
<tr>
<td>SnOct$_5$</td>
<td>Coordination polymerization</td>
<td>[8]</td>
</tr>
<tr>
<td>BuSnCl$_3$</td>
<td>Coordination polymerization</td>
<td>[18]</td>
</tr>
<tr>
<td>Al(OsBu)$_3$</td>
<td>Coordination polymerization</td>
<td>[10]</td>
</tr>
<tr>
<td>Al(O$^3$Pr)$_3$</td>
<td>Coordination polymerization</td>
<td>[8]</td>
</tr>
<tr>
<td>Al(Et)$_{3-x}$(OR)$_x$</td>
<td>Coordination polymerization</td>
<td>[19]</td>
</tr>
<tr>
<td>Al[O(CH$_3$PhNO$_2$)$<em>x$(Et)$</em>{3-2x}$]</td>
<td>Coordination polymerization</td>
<td>[19]</td>
</tr>
<tr>
<td>Aluminoxanes (methyl and isobutyl)(MAO, IBAO)</td>
<td>Coordination polymerization</td>
<td>[20]</td>
</tr>
</tbody>
</table>
The ROP proceeds mainly via two major polymerization mechanisms depending on what organometallics is used. Some of them acts as catalysts, and activate the monomer by complexation with the carbonyl group (Scheme 1.1). Polymerization is then initiated by any nucleophile, e.g., water or alcohol, present in the polymerization medium as impurities or as compound added on purpose. In the second mechanism, the organometallic plays the role of initiator and the polymerization proceeds through an ‘insertion–coordination’ mechanism (Scheme 1.2). Metal alkoxides are typical initiators, which first coordinates the carbonyl of the monomer, followed by the cleavage of the acyl–oxygen bond of the monomer and simultaneous insertion into the metal alkoxide bond.
Scheme 1.1  Ring-opening polymerization of lactones catalyzed by organometallic species [M] in presence of nucleophiles (Nu).

Scheme 1.2  Ring-opening polymerization of lactones by the “coordination–insertion” mechanism.
1.2 Enzyme-catalyzed ring-opening polymerization

Enzyme is a powerful catalyst of ring-opening polymerization, especially the production and chemical recycling of green and sustainable polymers. It can be applied to the synthesis of biodegradable aliphatic polyesters, polycarbonates, polythioesters, polyphosphates, and polysiloxane. Also, enzymes will provide versatile synthetic tools for regio- and enantioselective polymerizations.

About 20 years ago, Lipase-catalyzed polymerization was discovered by using the hydrolase enzyme. Most of the early studies were generally carried out at room temperature. But recently it was found that enzyme can be acting in organic medium at a high temperature. This has led to developing a new field of enzyme-catalyzed polymerization. The pioneering work of Klibanov and coworkers implied that the enzyme-catalyzed reactions become novel and valuable tools in the field of both synthetic organic chemistry and polymer chemistry\textsuperscript{31, 32}. Not only can the dry lipase withstand heating at 90–120°C for many hours, but it exhibits a high catalytic activity at that temperature\textsuperscript{31-36}.

\begin{center}
\[
\begin{array}{c}
\text{m=2: } \beta\text{-PL} \\
\text{m=3: } \gamma\text{-BL} \\
\text{m=4: } \delta\text{-VL} \\
\text{m=5: } \varepsilon\text{-CL} \\
\text{m=10: UDL} \\
\text{m=11: DDL} \\
\text{m=14: PDL}
\end{array}
\end{center}

\begin{center}
\[
\begin{array}{c}
\text{m=2: Poly(3HP)} \\
\text{m=3: Poly(4HB)} \\
\text{m=4: Poly(5HV)} \\
\text{m=5: PCL} \\
\text{m=10: Poly(UDL)} \\
\text{m=11: Poly(DDL)} \\
\text{m=14: Poly(VDL)}
\end{array}
\end{center}

Scheme 1.3 Ring Opening Polymerization of Varied Ring-sized Lactone.
Two independent groups, Uyama and Kobayashi \textit{et al.}\textsuperscript{37,38} and Knani \textit{et al.}\textsuperscript{39}, have both reported the lipase-catalyzed ring-opening polymerization of lactones in 1993. This invention has led to a quick development of enzyme-catalyzed polymerization as a novel methodology of polymer synthesis. Small to large-sized (4- to 16-membered) lactones were found to be polymerized in a lipase-catalyzed ring-opening fashion, though their polymerizability varied according to ring size as well as enzyme origin (Scheme 1.3)\textsuperscript{52}. These lactones could be polymerized by conventional chemical catalysts; however, there are some characteristic features in the lipase-catalyzed polymerization profiles. The large-sized lactones were efficiently polymerized by lipase. On the other hand, when using conventional anionic catalysts, the polymerizability of these large-sized lactones was much lower than that of the medium-sized \(\varepsilon\)-caprolactone (\(\varepsilon\)-CL) due to the lower ring strain. In general, similar to chemical catalysts, the lipase-catalyzed ROP of lactones gives both higher molecular weights and higher monomer conversions than the condensation polymerization of hydroxyacids\textsuperscript{53}. In organic media, interesting cyclic oligomers are mainly produced\textsuperscript{54}. ROP of \(\gamma\)-BL, which is usually a problem by traditional techniques, is oligomerized in the presence of porcine pancreas and \textit{Pseudomonas capacia}\textsuperscript{55}. As a rule, large-size lactones react faster than the smaller ones, which is the reverse of what is observed for chemical ROP\textsuperscript{56}. Actually, the rate-determining step in enzymatic polymerization is the formation of a lactone–lipase complex, which is more favorable for more hydrophobic largesized lactones. ROP takes place according to an “activated monomer” mechanism (Scheme 1.4)\textsuperscript{57}. The key step is the reaction of lipase with the lactone with formation of an acyl–enzyme intermediate, which further reacts with water, alcohols, or hydroxyl end-capped chains during either the initiation or the
propagation step. Most recent insights into the mechanism of lipase-catalyzed ROP of lactones are discussed in details in the review written by S. Kobayashi\textsuperscript{58}.

**Activation**

\[
\begin{align*}
&\text{(CH}_2\text{)}_m \quad \text{m=2-15} \\
&\text{EM} + \text{ROH} \quad \text{Lipase} \quad \text{OH} \\
&\text{Enzyme-activated monomer (EM)}
\end{align*}
\]

**Initiation**

\[
\text{EM} + \text{ROH} \quad \text{Lipase} \quad \text{OH} \\
\]

**Propagation**

\[
\text{EM} + \text{R} \left[\text{O} - \text{(CH}_2\text{)}_m\right]_n \text{OH} \quad \text{Lipase} \quad \text{OH} \\
\]

**Scheme 1.4** Mechanism of enzymatic ring-opening polymerization.

The seven-membered unsubstituted lactone ε-CL is the most extensively studied with respect to lipase-catalyzed ring-opening polymerization. ε-CL is quickly polymerized by various lipases of different origin. Among them, lipase CA appears as the most effective for the polymerization of ε-CL\textsuperscript{59,60}, and under appropriate conditions PCL with a molecular weight (\(M_n\)) greater than 47,000 was produced\textsuperscript{61}. A rapidly increasing
number of publications now exist that showcase the potential of in *vitro* enzyme catalysis to provide a wide range of polymer structures\(^{33-51}\).
1.3 Polycarbonates and their application

The polycarbonates are versatile materials because of their good temperature, impact resistance and optical properties. They have wide application in house-wares as well as laboratories and in industry. They have also been even applied in hospitals for various medical purposes. Most of the applied polycarbonates are usually aromatic polycarbonate. Recently the poly(aliphatic carbonate) is getting more and more attention from polymer chemists because it has better biodegradability and biocompatibility. In 1932, Carothers et al. first synthesized poly (trimethylene carbonate) from thermal polymerization of 1,3-dioxan-2-one (TMC). Since then a number of polycarbonates have been synthesized through ring opening polymerization using anionic, cationic, and coordination catalysts. In recent years, the enzyme-catalyzed synthesis of polycarbonate and its copolymer has been reported in which no undesirable decarboxylation occurred.

The chemistry of cyclic carbonates, which has been explored since the 1930s, has come to be a rich area of research within the past 20 years. Two main approaches for the use of cyclic carbonates have been investigated. Brunelle and the research group from General Electric have focussed on the synthesis of aromatic cyclic carbonate oligomers and their applications in the preparation of bisphenol A polycarbonates, copolymers, and composites\(^{62}\). At the same time Kricheldorf, Ho¨cker and Heitz groups\(^{63}\), from Germany and Endo\(^{64}\) from Japan have been exploring aliphatic cyclic carbonates as useful monomers for the preparation of polycarbonates as well as copolymers with other heterocyclic monomers\(^{65}\).

Synthetic biodegradable polymers have become interesting materials for a variety of biomedical applications. In those fields homopolymers and copolymers of five-
(1,3-dioxolan-2-ones) and six-membered carbonates (1,3-dioxan-2-ones) with cyclic esters (lactones and lactides) have been found to be good materials because of their biocompatibility, low toxicity and biodegradability.

Much of the interest in ring-opening polymerizations stems from the fact that the polymers formed may have lower densities than the monomers from which they are derived (volume expansion may accompany polymerization)\(^\text{64, 66–68}\). This is in marked contrast with conventional polymerizations, which invariably involve a net volume contraction. Such polymerizations are therefore of particular interest in adhesive, molding filling, and other applications where volume contraction is undesirable. In relation to this, besides expandable spiroorthocarbonates known since the 1970s\(^\text{69, 70}\), cyclic carbonates (six- and seven-membered) also polymerize with volume expansion in which the degree of density reduction may reach 10% as was recently found by Endo \textit{et al.}\(^\text{71,72}\).

The ability of cyclic carbonate monomers to undergo ring-opening polymerization depends on both thermodynamic and kinetic factors. The size of a ring and its strain as well as the kind and number of substituents determine the reaction enthalpy and entropy. Medium size rings (six- and seven-membered), because of relatively small ring strain, have low enthalpies of ring opening (polymerize with moderate exotherms) and their polymerization carried out under equilibrating conditions does not proceed for 100% conversion and a relatively significant amount of cyclic monomer as well as oligomeric cycles are usually present in the post-reaction mixture\(^\text{73–75}\). The polymerization of oligomeric aromatic cyclic carbonates of larger size is known to be entropy driven\(^\text{62}\).
A wide variety of cyclic carbonate monomers have been successfully used for ring-opening polymerization carried out in the presence of different kinds of initiators and catalysts according to cationic, anionic, coordination and enzymatic mechanisms. This includes monomers with both small and larger size molecules. Representative examples of the monomers are shown in Tables 1.2.

**Table 1.2 Polymerization of different size of cyclic carbonate**

<table>
<thead>
<tr>
<th>Monomer</th>
<th>Polymer</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Monomer 1" /></td>
<td><img src="image2" alt="Polymer 1" /></td>
<td>15</td>
</tr>
<tr>
<td>R=H, CH₃</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R₁=R₂=H</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>R₁=H, R₂=CH₃</td>
<td></td>
<td>76</td>
</tr>
<tr>
<td>R₁=H, R₂=C₄H₉</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>R₁=R₂=CH₃</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>R₁=R₂=C₂H₅</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>R₁=Ph, R₂=CH₃</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>R₁=Ph, R₂=CH₃</td>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>
Table 1.2 Polymerization of difference size of cyclic carbonate (continued)

<table>
<thead>
<tr>
<th>Monomer</th>
<th>Polymer</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>R_1=Ph, R_2=C_2H_5</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>R_1=R_2=Ph</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>R_1=C_2H_5, R_2=CH_2OSi(CH_3)_3</td>
<td></td>
<td>77</td>
</tr>
<tr>
<td>R_1=C_2H_5, R_2=CH_2OC(O)NPh</td>
<td></td>
<td>77</td>
</tr>
<tr>
<td>R_1=C_2H_5, R_2=CH_2OCH_2CH=CH_2</td>
<td></td>
<td>77</td>
</tr>
<tr>
<td>R_1=CH_3, R_2=CN</td>
<td></td>
<td>78</td>
</tr>
<tr>
<td>R_1=CH_3, R_2=COOCH_3</td>
<td></td>
<td>79</td>
</tr>
<tr>
<td>R_1=C_2H_5, R_2=CH_2OC(O)CH_3</td>
<td></td>
<td>79</td>
</tr>
<tr>
<td>R_1=CH_3, R_2=CH_2OC(O)CH_3</td>
<td></td>
<td>79</td>
</tr>
<tr>
<td>R_1=R_2=CH_2</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>R_1=R_2=CH_2OCH_2OCH_3</td>
<td></td>
<td>81</td>
</tr>
<tr>
<td>R_1=R_2=CH_2OC(CH_3)_2OCH_3</td>
<td></td>
<td>82</td>
</tr>
<tr>
<td>R_1=R_2=</td>
<td></td>
<td>12</td>
</tr>
</tbody>
</table>
Table 1.2 Polymerization of difference size of cyclic carbonate (continued)

<table>
<thead>
<tr>
<th>Monomer</th>
<th>Polymer</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Monomer" /></td>
<td><img src="image2" alt="Polymer" /></td>
<td>83</td>
</tr>
<tr>
<td>R=H, CH₃</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image3" alt="Monomer" /></td>
<td><img src="image4" alt="Polymer" /></td>
<td>84</td>
</tr>
<tr>
<td>R₁= NHCO₂CH₂Ph, R₂=CH₃</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image5" alt="Monomer" /></td>
<td><img src="image6" alt="Polymer" /></td>
<td>85</td>
</tr>
<tr>
<td>X=4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image7" alt="Monomer" /></td>
<td><img src="image8" alt="Polymer" /></td>
<td>86</td>
</tr>
<tr>
<td>X=6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image9" alt="Monomer" /></td>
<td><img src="image10" alt="Polymer" /></td>
<td>87</td>
</tr>
<tr>
<td>X=10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1.2 Polymerization of difference size of cyclic carbonate (continued)

<table>
<thead>
<tr>
<th>Monomer</th>
<th>Polymer</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Monomer Image" /></td>
<td><img src="image2" alt="Polymer Image" /></td>
<td>55</td>
</tr>
<tr>
<td><img src="image3" alt="Monomer Image" /></td>
<td><img src="image4" alt="Polymer Image" /></td>
<td>53</td>
</tr>
</tbody>
</table>
1.4 Polyesters and their application

The modern materials age that we are now in is marked by the plastic revolution in the last half of the 20th century. It would be difficult to imagine life without them. Their manufacture is a growth industry with worldwide production exceeding 150 million tons per year. However, concerns are now arising about their environmental footprint and in particular the impact of resource and energy utilization and disposal. These concerns have spurred investigations into the development of renewable, biodegradable and biocompatible polymers; of these, aliphatic polyesters are promising sustainable alternatives to commodity plastics such as polypropylene.

The most commercially viable material to date is polylactide (PLA), produced by the ring opening polymerization of lactide, which itself derives from biomass such as corn or wheat. Polylactide has good mechanical and physical properties and therefore is suitable for use in disposable consumer articles as well as fibre applications, a key advantage being its hydrolysis to lactic acid, a metabolite in the carboxylic acid cycle. The success of polylactide highlights the commercial and environmental potential for plastics sourced from plants, with renewable life cycles and which are carbon neutral (Fig. 1.1).89
PLA is currently manufactured on a large scale in the US and by smaller enterprises in the EU and Japan. The applications for polylactide are enhanced by its biocompatibility and its ability to be absorbed and degraded in vivo; furthermore, it is an FDA approved substance for use in therapy. It has been used for some time in biomedical applications such as sutures, stents, dental implants, vascular grafts, bone screws and pins. It has also been investigated as a vector for drug delivery, for example in the long-term
delivery of antimicrobial drugs, contraceptives and prostate cancer treatments. PLA has been widely used in the field of tissue engineering as a scaffold material to support cell and tissue growth.

The polymerization of lactides and lactones by the ring-opening polyaddition process is free of these limitations and is thus preferred for their synthesis with tailor-made properties. High molecular weight polyesters can be easily prepared under mild conditions from lactones of different ring-size, substituted or not by functional groups. A broad range of anionic, cationic and coordinative initiators or catalysts have been reported for the ROP. Generally speaking, ionic (non-bulky ion pairs and free ions) initiators are much reactive and, in case of polyesters, are responsible for detrimental inter- and intra-molecular transesterification reactions lowering the molecular weight and broadening the molecular weight distribution of the polymer. Many organometallic derivatives of metals with d-orbitals of a favourable energy, such as Al, Sn, Nd, Y, Yb, Sm, La, Fe, Zn, Zr, Ca, Ti and Mg, are imparting control to the polymerization in contrast to their anionic counter-part. In the more favourable cases, the ring-opening polymerization of lactones and lactides is a living/controlled process that leads to polyesters of narrow molecular weight distribution with a molecular weight predetermined by the monomer-to-initiator molar ratio.

The ring opening polymerization of lactones is an attractive method to synthesize aliphatic polyesters because it enables living polymerizations to be conducted and therefore provides a route to tightly control the polymers’ physical properties and polydispersity indices. The thermodynamic driving force for the polymerization is the relief of ring strain, which enables the entropy, unfavorable in all polymerizations, to be
overcome. A range of simple lactones of varying ring size and strain have been investigated, as shown in Table 1.3.  

**Table 1.3** Enthalpy and entropy of ROP for selected lactones (298 K)

<table>
<thead>
<tr>
<th>Ring Size</th>
<th>Name of the Monomer</th>
<th>$\Delta H$/kJ mol$^{-1}$</th>
<th>$\Delta S$/J mol$^{-1}$•K$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ -Propiolactone</td>
<td>-82.3</td>
<td>-74$^a$</td>
</tr>
<tr>
<td></td>
<td>$\gamma$ -Butyrolactone</td>
<td>5.1</td>
<td>-29.9$^a$</td>
</tr>
<tr>
<td></td>
<td>$\delta$ -Valerolactone</td>
<td>-27.4</td>
<td>-65.0$^a$</td>
</tr>
<tr>
<td></td>
<td>$\varepsilon$ -Caprolactone</td>
<td>-28.8</td>
<td>-53.9$^a$</td>
</tr>
<tr>
<td></td>
<td>Lactide</td>
<td>-22.9</td>
<td>-25.0$^b$</td>
</tr>
</tbody>
</table>

$a$: [Monomer] = 10 M, conducted in liquid monomer  
$b$: [Monomer] = 1 M, conducted in solution
Among the wide variety of aliphatic polyesters, PLA and PLGA polymers are the most used materials for drug delivery due to their fast and adjustable degradation rate. The sharp increase of the patents number in this field in the early 90s coincides with the clinical success and commercialization of Lupron Depot, the first parenteral sustained-release formulation using PLA, which was approved in 1989\textsuperscript{96}.

High volumes of PLA are produced under the name Natureworks\textsuperscript{TM} by the joint venture between Dow and Cargill in a plant built in North America with a capacity of 0.14 million tones/year\textsuperscript{97}, mainly for commodity market. Besides, there are four established suppliers of GMP-grade PLA (PLA which complies with the Good Manufacturing Practice regulations (GMP) promulgated by the European Agency for the Evaluation of Medicinal Products) and PLGA: Purac (Purasorb\textsuperscript{TM}), Birmingham Polymers (Lactel\textsuperscript{TM}), Boehringer Ingelheim (Resomer\textsuperscript{TM}) and Alkermes (Medisorb\textsuperscript{TM}). Other newer suppliers and smaller manufacturers are also catering the local niche markets worldwide.

For the time being, tin octoate and alkoxides were the most widely used organometallic mediators for the ring-opening polymerization of lactones even if novel powerful and interesting metal free catalytic systems are emerging as valuable alternatives.
1.5 References:

1. Comprehensive Polymer Science; Allen, G.; Berington, J. C., Eds.; Pergamon: 
2. Ivin, K. J.; Saegusa, T. Ring-Opening Polymerization; Elsevier Applied Science: 
   London, 1984; Chapter 1.
   A32, 1847
   33, 2193
   43
14. Huang, Q. H.; Shen, Z. Q.; Zhang, Y. F.; Shen, Y. Q.; Shen, L. F.; Yuan, H. Z.; 


23
48. Uyama, H.; *Kobunshi Ronbunshu*, **2001**, 58, 382
64. Takata, T.; Endo, T.; Luch, R. M.; Expanding monomers, 1992, 142.


CHAPTER 2

Functionalized Polycarbonate Derived from Tartaric Acid- Enzymatic Ring-Opening Polymerization of a Seven-Membered Cyclic Carbonate

2.1 Introduction

Polymers from renewable resources, which are biodegradable and biocompatible, have been an attractive area of research. The uncertainty and price fluctuations in the petroleum-based raw materials coupled together to the problems of the polymeric solid waste accumulation demands development of biodegradable polymers from renewable resources. In recent years, many carbohydrates and amino acids based polymers have been reported in the literature.\textsuperscript{1,2} The utility of the biocompatible polymers is also highlighted in biomedicine for degradable scaffoldings and drug delivery applications. Of the different natural resources, carbohydrates because of their natural abundance and functional diversity stand out as highly convenient raw material and carbohydrate based polymers have been extensively reported in literature.

L-tartaric acid, a widely available and relatively inexpensive natural resource from a large variety of fruits, has been extensively utilized in organic synthesis as a source of chirality but its use in polymers has been somewhat limited.\textsuperscript{3} L-tartaric acid has been used in synthesis of polyamide,\textsuperscript{4} polyesters,\textsuperscript{5} polyurethanes,\textsuperscript{6} and polycarbonate.\textsuperscript{7} The incorporation of tartaric acid or its derivative in degradable
polymers has been through condensation polymerization, which is limited by the removal of the condensate, i.e., water or alcohol; efficient removal of the condensate is required to shift the equilibrium to the polymerization. The ring opening polymerization (ROP) of cyclic monomers is more efficient as no leaving group is involved and unlike condensation polymerization, can be performed at much lower temperature and is hence energy efficient. It has been previously reported that compared to polycondensation, the ROP of lactones led to formation of higher molecular weight polyesters and higher monomer conversion. For example, poly(butylenes succinate) (PBS) prepared by ROP of cyclic(butylenes-succinate) oligomer had $M_w$ of 130,000 g/mol, which was about 3 times that of the PBS prepared by direct condensation of the two monomers. However, prior to this report there are no reports of a cyclic monomer derived from tartaric acid suitable for ROP.

Aliphatic polycarbonates have attracted much attention in the last two decades because of their biodegradability, biocompatibility, and nontoxicity. It is well-known that incorporation of hydrophilic functional groups enhances the biodegradability of the polymers and synthesis of polycarbonates having hydroxy, amine, and carboxyl pendent functional groups has been reported. Water soluble poly(hydroxyalkylene carbonate)s and the polycarbonate based on 1,4:3,6-dihydrohexitols and L-tartaric acid derivatives are examples, which are reported to exhibit high biodegradability in vitro and in vivo hydrolysis. Five- and six-membered cyclic carbonate monomers have been polymerized via ring-opening polymerization. The polymerization of five-membered cyclic carbonate usually is associated with extensive decarboxylation resulting in undesirable ether linkages.
of six-membered cyclic carbonate and its derivatives proceeds with minimal decarboxylation in the polymer chain, and therefore, they are the most studied and have been polymerized by anionic, cationic, and enzymatic catalysts.\textsuperscript{11-13} Although aliphatic ring-opening polymerization of larger ring size carbonates have been demonstrated in the literature,\textsuperscript{15-16} there are only a few examples of polymerization of a seven-membered cyclic carbonates. The most studied seven-membered cyclic carbonate monomer, 1,3-dioxepan-2-one (7CC), has been polymerized by both anionic and cationic catalysts.\textsuperscript{15a,b} The interest in the seven membered cyclic carbonate stems from its higher polymerizability compared to smaller size ring carbonates.\textsuperscript{15(a,b), 16a} Many copolymers of 7CC have been synthesized such as poly(7CC-co-δ-VL), poly(7CC-co-ε-CL), and polt(TOX-co-7CC-OTM).\textsuperscript{17}

Enzymes are versatile catalysts with demonstrated ability to carry out a wide range of transformation such as the polymerization of large ring systems which are otherwise difficult to polymerize by conventional catalysis.\textsuperscript{11(a,b)-12} Ring opening polymerization of cyclic carbonates has also been studied and the polymerization is known to proceed without any decarboxylation. Our earlier results on lipase catalyzed polymerization of 5-methyl-5-benzyloxy carbonyl-1,3-dioxan-2-one (MBC) and 5-methyl-5-carboxyl-1,3-dioxan-2-one (MCC) led to formation of first example of pendant carboxyl group polycarbonates. Random copolymers of trimethylene carbonate (TMC) were also synthesized with MBC and MCC using lipase catalyzed ROP. Polymerization of cyclic dicarbonates, cyclobis(hexamethylene carbonate) (CHMC) and cyclobis(diethylene glycol carbonate) (CDGC) and their copolymerization with caprolactone (CL) and dodecanolactone (DDL) have also been carried out using lipase
catalyzed ROP. However, there is no report in the literature of enzymatic ring-opening polymerization of cyclic monocarbonates larger than six.

In this chapter we report the synthesis and enzymatic ring-opening polymerization of a new optically pure functional seven-membered carbonate monomer derived from naturally occurring L-tartaric acid. As an extension of our ongoing search efforts on biodegradable polymer synthesis based on renewable resources, the novel polycarbonate containing pendant hydroxyl group has now been synthesized from \((5S,6S)\)-Dimethyl 5,6-O-isopropylidene-1,3-dioxepin-2-one (ITC, 3) by lipase catalyzed ROP. The monomer was synthesized in three steps starting from L-tartaric acid. Together with the use of renewable resources the utilization of the enzyme-catalyzed ROP brings a “green-chemistry” appeal to this report. Various commercially available lipases were screened to polymerize the monomer at 80 °C. The polymerization was investigated through the relationship between reaction time, monomer conversion, molecular weight, and molecular weight distribution. Deprotection of the ketal groups resulted in optically active polycarbonate with free hydroxyl groups in the polymer backbone. (Scheme 2.1)

**Scheme 2.1** Enzymatic polymerization of monomer (3) in bulk at 80 °C.
2.2 Synthesis of 7 member cyclic carbonate monomer (ITC)

Enantiomerically pure seven membered-cyclic carbonate monomer, dimethyl 5,6-O-isopropylidene-1,3-dioxepin-2-one (ITC, 3) was prepared from L-tartaric acid in three steps (Scheme 2.2). The commercially available L-tartaric acid was converted to the ketal diester, 1 upon reaction with dimethoxy propane in methanol. The methyl diester groups in 1 were reduced using LAH to the diol 2. The cyclic carbonate synthesis attempted through reaction of 2 with ethyl chloroformate resulted in low yield; however when triphosgene was used in presence of pyridine in THF good yield was obtained (57% yield). The ITC monomer was recrystallized from hexane: dichloromethane (1:10) to yield colorless crystals; mp 75 °C, [α]_D^20 =+84.79°. The ¹H- and ¹³C- NMR spectra were used to establish the molecular structure of ITC and no resonances due to the compound 2 or the oligomeric structures were detected (Figures 2.1 and 2.2). The absence of any diastereotopic resonances in its ¹³C- NNMR spectrum suggests a complete preservation of its absolute stereochemistry. The acetonide dimethyl hydrogens (H-3) were observed at 1.43 ppm; the repeat unit methylenes (H-1_α,β), owing to their diastereotopic relationship, were observed as 4.31 and 4.29 ppm; the methine (H-2) were at 4.01 ppm. The high resolution mass measurement confirmed its structure as dimethyl 5,6-O-isopropylidene-1,3-dioxepin-2-one (HRESIMS m/z [M+H]^+: Calcd. for C₈H₁₃O₅: 189.07630. Found 189.07593).

Scheme 2.2 Synthesis of seven-member cyclic carbonate monomer from L-Tartaric acid:
(i) DMP, cat. PTSA, MeOH, and cyclohexane, azeotrope; (ii) LAH 0 °C in ether; (iii) Triphosgene, pyridine, THF, 0 °C.

Figure 2.1 $^1$H NMR (250 MHz, CDCl$_3$) spectrum of (5S, 6S)-Dimethyl 5,6-\textit{O}isopropylidene-1,3-dioxepin-2-one (ITC, 3).
Figure 2.2 $^{13}$C NMR (62.9 MHz, CDCl$_3$) spectrum of (5$S$, 6$S$)-Dimethyl 5,6-O-isopropylidene-1,3-dioxepin-2-one (ITC, 3).
2.3 Polymerization of ITC using four different enzyme catalysts

Initial screening of four commercially available lipases from different sources for their ability to polymerize the ITC monomer (3) showed considerable variation in monomer conversion and molecular weight. Table 2.1 summarizes the results obtained for the enzymatic polymerizations screen at 80 °C in bulk. Lipase from *Candida antarctica* (CAL-B immobilized on acrylic resin- Novozyme435), *Pseudomonas fluorescens* (AK), and *Pseudomonas cepacia* (PS-30) accepted ITC as substrate, porcine pancreatic lipase (PPL) however showed no reactivity and the monomer was recovered at the end of the polymerization. Lipase AK showed the highest monomer conversion, though, with low molecular weights polymers, $M_n = 1800-2300$ g/mol and polydispersities of 1.5-1.6. Lipase PS-30 showed 72% monomer conversion with moderate $M_n = 9500$ after 24 h. With Novozyme-435, 88% monomer conversion was obtained after 24h for ROP of the monomer with high number-average molecular weight, $M_n = 15500$ g/mol and polydispersity of 1.7. We previously reported that Novozym-435 showed the best result for ROP of cyclic carbonates and the screening results in the present study indicated that it is the best lipase to carry out the polymerization of ITC. Therefore, in this study, the ring opening polymerization of the cyclic carbonate monomer ITC was further investigated using 50 wt % of the Novozym-435 at 80 °C in bulk. Since the role of water as initiator in lipase catalyzed ROP reactions has been established in all cases, Novozym-435 was dried overnight in vacuo at 50 °C prior to use to limit the amount of water. Importantly, no polymerization was observed under the same conditions in the absence of the lipase or when a thermally deactivated lipase was used, which indicates the ROP of ITC was catalyzed by the lipase.
### Table 2.1 Enzymatic Ring-Opening Polymerization of Monomer (3) in bulk at 80 °C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lipase $^a$</th>
<th>Time (h)</th>
<th>Conversion $^b$ (%)</th>
<th>$M_n$ $^c$ (g/mol)</th>
<th>$M_w/M_n$ $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Novozyme-435</td>
<td>12</td>
<td>51</td>
<td>10000</td>
<td>1.8</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>24</td>
<td>88</td>
<td>15500</td>
<td>1.7</td>
</tr>
<tr>
<td>3</td>
<td>AK</td>
<td>12</td>
<td>80</td>
<td>1800</td>
<td>1.6</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>24</td>
<td>97</td>
<td>2300</td>
<td>1.5</td>
</tr>
<tr>
<td>5</td>
<td>PS</td>
<td>12</td>
<td>40</td>
<td>5500</td>
<td>1.7</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>24</td>
<td>72</td>
<td>9500</td>
<td>1.6</td>
</tr>
<tr>
<td>7</td>
<td>PPL</td>
<td>12</td>
<td>NR $^d$</td>
<td>NA $^e$</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>24</td>
<td>NR</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>


$^b$ Determined from $^1$HNMR.

$^c$ Determined from GPC.

$^d$ no reaction (monomer recovered).

$^e$ not applicable.
2.4 The kinetics study of polymerization of ITC catalyzed by Novozyme-435

To examine the kinetics of the polymerization, the relationship between reaction time, monomer conversion, molecular weight, and molecular weight distribution were investigated for Novozyme-435 polymerization of ITC. In Figure 2.3 percent monomer conversion as a function of reaction time is plotted. Unlike the sharp increase in monomer conversion observed in enzymatic polymerization the ITC monomer conversion increased steadily during the polymerization. This was attributed to the relatively high melting point of the ITC monomer (75 °C), which is close to polymerization temperature (80 °C). Similar polymerization behavior was observed previously in the enzymatic polymerization of 5-methyl-5-benzyloxy carbonyl-1,3-dioxan-2-one (MBC), which has melting point of 73 °C. The ITC monomer conversion reached 88% in 24h and increased slightly to 91% at 48 h. The slow increase in monomer conversion, from 88% - 91%, in 24h was attributed to the increased viscosity in the bulk polymerization. With increasing monomer conversion, especially in bulk polymerization, the increased viscosity of the reaction mixture limit the monomer access to the lipase active site. We have observed similar phenomenon during bulk polymerization of MBC. The role of increased reaction viscosity in limiting the monomer conversion has been investigated and addition of solvent to the polymerization has shown to increase the monomer conversion. 20
Figure 2.3 Percent monomer conversion of (3) as a function of time (h) for Novozyme-435 catalyzed ring-opening polymerization at 80 °C in bulk for 48h.

Figure 2.4 shows number average molecular weight ($M_n$) and polydispersity index (PDI) of the polymer as a function of the percent monomer conversion. The absolute molecular weight of the ITC polymer was measured using $^1$H-NMR, upon quantification of the end groups and polymer repeat units, and compared to those measured by GPC calibrated with polystyrene standards. Similar molecular weights were obtained using both methods; e.g., $M_n$ 16000 g/mol by $^1$H-NMR and 15500 g/mol by GPC. Therefore, in this study, further measurements were obtained using the more convenient GPC method. In Figure 2.4, the number-average molecular weight ($M_n$) of the polymer showed linear increase with percent monomer conversion, suggesting a fast
initiation process and in which the propagating reactive centers are non-terminating. Such a mechanism is typically associated with the enzymatic polymerization.\textsuperscript{12} The enzymatic polymerization of cyclic monomers is believed to proceed via formation of an enzyme-activated-monomer (EAM) complex, the rate determining step. In absence of an added nucleophile, the small amounts of water in both the lipase and the substrate initiate the polymerization. After this water is consumed, the nucleophilic attack by the terminal hydroxyl group leads to chain propagation. However, it is difficult to precisely determine the water content of the lipase available for the chain initiation; equilibrium exists between the 'free water' and the 'bound essential water', required for the activity of the lipase. In this study, the lipase and the substrate were always dried in a drying pistol over P\textsubscript{2}O\textsubscript{5}, at 50 °C/0.1 mm Hg; 15 h prior to use in the polymerization.
Figure 2.4. Number-average molecular weight (●) and weight distribution (▲) as a function of monomer conversion for Novozym-435 catalyzed ring opening polymerization at 80 °C in bulk for 48h.

Figure 2.4, the polydispersity index (PDI) increased from 1.4 to 1.8 with increasing monomer conversion to 50%, suggesting new chain initiation events along with chain propagation. Interestingly, beyond 50% monomer conversion, the PDI remained unchanged (within experimental error) with increasing polymer molecular weight suggesting no new initiation events and only chain propagation. Although, the transesterification reactions among polymer chains have been observed during the lipase catalyzed polyesters synthesis, the linear increase in $M_n$ with percentage monomer conversion (Figure 2.4) indicates that the chain transfer reactions occurring during the polymerization were minimal.
Figure 2.5 show plot of $-\ln([M]/[M]_0)$ as a function of reaction time. $[M]_0$ is the initial monomer concentration, and $[M]$ is the monomer concentration at the given polymerization time ($t$). The monomer conversions were calculated from the $^1$HNMR spectra. The correlation coefficients ($R^2$) of 0.973 from linear regression analysis show linearity, which suggests that Novozym-435 catalyzed ROP of ITC monomer, followed first-order rate law. This indicates that throughout the chain propagation the number of growing chains is constant and termination is low. These results support that ROP catalyzed by Novozym-435 show characteristic of non-terminating chain polymerization. Similar behaviors of lipase catalyzed ROP were reported in the literature.\textsuperscript{20, 22} The apparent rate constant ($K_{\text{app}}$) for the polymerization was found to be $5.29 \times 10^{-2}$ h\textsuperscript{-1} from the slope of Figure 2.5 using the equation $K_{\text{app}} = d(-\ln([M]/[M]_0)/dt$.\textsuperscript{22}
Figure 2.5 First-order kinetic plot for Novozyme-435 catalyzed ROP of ITC monomer at 80 °C for 48h.
2.5  Polymer NMR Characterization

The structure of the polymer was confirmed by $^1$H (Figure 2.6) and $^{13}$C NMR (Figure 2.7). The optical rotation measurement for the polymer was $[\alpha]_D^{20} = +77.8$. The absence of any diastereotopic resonances in its $^{13}$C-NNMR spectrum suggests a complete preservation of its absolute stereochemistry. The peak assignments were based on comparison with NMR spectra of the monomer, DEPT-135, two dimensional $^1$H-$^1$H COSY and $^1$H-$^{13}$C HMQC experiments for the polymer (Figure 2.8).

Figure 2.6 show the $^1$H-NMR for the polymer obtained by Novozyme-435 catalyzed polymerization along with peaks assignment (Table 2.1, entry 2). The acetonide dimethyl hydrogens (H-3) were observed at 1.43 ppm; the repeat unit methylenes (H-1a,b), owing to their diastereotopic relationship, were observed as 4.61 and 4.25 ppm; the methine (H-2) were at 4.25 ppm. The insert in Figure 2.6 shows expanded low intensity signal at 3.68 ppm, assigned to the hydroxymethylene end-group hydrogens for the CHCH$_2$OH; the signal appear as doublet of doublet with $J = 10$ Hz and 5 Hz. For molecular weight calculations the degree of polymerization was determined from the area under the repeat unit methylenes and methines (H-1 and H-2, 4.61 and 4.25 ppm) resonances and the end group CH$_2$OH resonance (3.68 ppm). The absolute molecular weight of the polymer calculated from the end-group analyses was 15980 g/mol ($M_n$) which is in good agreement with the number average molecular weight ($M_n$) determined from the GPC [15500 g/mol, Table 2.1, entry 2]. $^{13}$C-NMR spectrum of poly(ITC) is shown in Figure 2.7, apart from the major peaks which are for the main resonances of the polymer repeating units, low intensities resonances was also observed which are characteristic of the end group carbons. The low intensity carbon resonances at 64.8 ppm
confirmed the presence of end-group hydroxy methylene carbon (-CH$_2$OH). The presence of hydroxyl end-group is in agreement with the well established enzymatic polymerization mechanism of cyclic esters and carbonates.$^{11-12}$

Figure 2.6. $^1$H NMR (500 MHz, CDCl$_3$) spectrum of the polycarbonate obtained from the Novozyme-435 catalyzed ROP of monomer (3) in bulk at 80 °C for 48h.
Figure 2.7. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of the polycarbonate obtained from the Novozyme-435 catalyzed ROP of monomer (3) in bulk at 80 °C for 48h.
Figure 2.8. $^1$H-$^{13}$C HMQC-NMR (250 MHz, CDCl$_3$) spectra of Poly(ITC).
2.6 Deprotection of the ketal groups of poly(ITC)

An important aspect of this work is to introduce functional groups in the polymer backbone, which is expected to enhance the biodegradability of the polymer and could be utilized in post-polymer modification. Biodegradable polymers having pendant hydroxyl groups are of particular importance as these are capable of forming prodrug formulations through a covalent link to the bioactive compounds. A covalent prodrug is advantageous as it is capable of precise loading and the release of the active compound can be controlled through choice of the proper covalent bond and length of the linker. Also, availability of the pendant groups provides opportunity for post polymerization modifications for modulating the hydrophilicity, physical properties, and biodegradability of the polymer.

Table 2.2 Deprotection of ketal groups of poly(ITC)*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (min)</th>
<th>Conversion a (%)</th>
<th>Yield b (%)</th>
<th>$M_n$ d (g/mol)</th>
<th>$M_w/M_n$ d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>15500</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(15980)e</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>43</td>
<td>95</td>
<td>13500</td>
<td>1.7</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>65</td>
<td>93</td>
<td>13000</td>
<td>1.8</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>91</td>
<td>92</td>
<td>12500</td>
<td>1.8</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>99</td>
<td>88</td>
<td>10000</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(10570)e</td>
<td></td>
</tr>
</tbody>
</table>

*CH$_2$Cl$_2$/CF$_3$COOH/H$_2$O at room temperature (see experimental section). a Determined from $^1$HNMR. b isolated after precipitation in methanol. d Determined from GPC. e Calculated from $^3$HNMR.
Trifluoroacetic acid has been used as an efficient deprotecting agent for the removal of the ketal groups in polycarbonates with minimal degradation in the polymer chain.\textsuperscript{19} Table 2.2 shows the results obtained for the deprotection of the ketal groups in various reaction times for poly(ITC). The $M_n$ of polymer before the deprotection is 15500 with PDI of 1.7. After 5 minutes reaction time 43\% removal of the ketal groups was observed; calculated from the new resonance at 3.6 ppm (\text{-CH\textsubscript{-}OH}), and broad peak at 5 ppm (\text{-OH}) in its $^1$H-NMR spectrum (\textbf{Figure 2.9}). In 15 minutes, the conversion reached 91\% ($M_n$ = 12500 g/ mol) with slight increase in PDI from 1.7 to 1.8. A complete removal of the acetonide protecting groups was achieved after 20 minutes with increase in the polydisperisty to 2.0 and $M_n$ of 10000 g/mol, suggesting minimal degradation of the polymer backbone. In \textbf{Figure 2.10} the absence of resonance at 28 ppm of the methyl carbons from acetonide groups also proves that the ketal group is removed. \textbf{Figure 2.11} shows GPC traces for the poly(ITC) before and after acetonide deprotection. The unimodal nature of the CPC trace confirms minimal degradation of the polymer backbone. The longer retention time of deprotected poly(ITC) trace is primarily due to the molecular weight loss from removal of acetonide protecting groups. The specific rotation ($\left[\alpha\right]_D^{20}$) of poly(ITC) before and after deprotection is $+$ 77.8 (c = 1, CH$_2$Cl$_2$) and $+$56.0 (c = 1, EtOH), respectively.
Figure 2.9. $^1$H NMR (500MHz, DMSO-$d_6$) spectra of Poly(ITC); (a) before de-protection [Table 2.2, entry 1]. (b) After de-protection [Table 2.2, entry 5].
Figure 2.10 $^{13}$C NMR (100 MHz, DMSO-$d_6$) spectra of Poly(ITC); (a) before de-protection [Table 2.2, entry 1]. (b) After de-protection [Table 2.2, entry 5].
Figure 2.11 GPC chromatograms of Poly(ITC); (a) before de-protection ($M_n = 15500$ g/mol) [Table 2.2, entry 1]. (b) After de-protection ($M_n = 12500$ g/mol) [Table 2.2, entry 4].
2.7 Thermal Analysis.

The thermal properties of the polymers before and after deprotection were examined by DSC analyses under helium atmosphere. The samples were scanned from -100 to 300 °C in rate of 10°C/min. The glass transition temperature \((T_g)\) was not observed for poly(ITC), however, sharp melting temperature \((T_m)\) peak was observed at 58.79 °C with heat of enthalpy \(\Delta H_f = 62.72 \text{ J/g}\). The DSC thermogram of the deprotected poly(ITC) is very comparable to the protected polymer. De-protected poly(ITC) shows \(T_m\) of 60.09 °C and \(\Delta H_f = 69.73 \text{ J/g}\). The slight increase in the \(T_m\) indicated that the crystallinity of free hydroxy polymer is slightly higher. Similar to that of the protected polymer, a \(T_g\) was not found.

![](image)

Figure 2.12 DSC chromatograms of Poly(ITC); (a) before de-protection \((M_n = 15500 \text{ g/mol})\) [Table 2.2, entry 1]. (b) After de-protection \((M_n = 12500 \text{ g/mol})\) [Table 2.2, entry 4].
2.8 Conclusions

Synthesis of a new seven-membered cyclic carbonate monomer (ITC) derived from L-tartaric acid and its enzymatic polymerization is reported. Four commercially available lipases were screened for the polymerization of monomer (ITC) in bulk at 80 °C. Immobilized *Candida antarctica* lipase -B (Novozym-435) was found to be the most efficient catalyst to carry out the ROP of ITC. The relationship between reaction time, monomer conversion, molecular weight, and weight distribution were investigated for Novozyme-435 catalyze the polymerization. NMR examination of the polymers revealed hydroxy end groups. The deprotection of the ketal groups using trifluoroacetic acid offered polycarbonate with pendant hydroxy groups with minimal degradation in the polymer chain. The presence of hydroxy groups is expected to enhance the biodegradability, and the hydrophilicity of the polymers. Physical, chemical, and biodegradation evolution are currently underway in our laboratories.
2.9 Experiment

Materials. All reagents were used without further purification unless otherwise are specified. L-tartaric acid (99%), p-Toluenesulfonic acid (98.5%) and Triphosgene were purchased from the Aldrich Chemical Company. 2,2-Dimethoxypropane, Triethylamine (99%) and Lithium aluminium hydride (95%) were purchased from Acros Chemical Co. Diethyl ether and tetrahydrofuran (THF) were dried over Na before use. Porcine pancreatic lipase (PPL) Type II Crude (activity = 61 units/mg protein) was purchased from Sigma Chemical Co. Lipase PS-30 from Pseudomonas cepacia (20,000 units/g), and Lipase AK were obtained from Amano Enzymes Co., Ltd. The carrier fixed lipase Novozym 435 (from Candida antarctica, fraction B; specified activity at pH 7.0 is 10,000 units/g) was a gift from Novo Nordisk Inc.

Measurements. Molecular weights were measured by gel permeation chromatography (GPC) using a Shimadzu HPLC system equipped with a model LC-10ADvp pump, model SIL-10A auto injector, model RID-10A refractive index detector (RI), model SPD-10AV UV-Vis detector, and waters HR 4E styrage column. CHCl₃ (HPLC grade) was used as an eluent at a flow rate of 1.0 mL/min. The sample concentration and injection volumes were 0.5 % (w/v) and 100 µL, respectively. EzChrome Elite (Scientific Software Inc.) was used to calculate molecular weights based on a calibration curve generated by narrow molecular weight distribution polystyrene standards (5.00 x 10², 8.00 x 10², 2.10 x 10³, 4.00 x 10³, 9.00 x 10³, 1.90 x 10⁴, 5.00 x 10⁴, 9.26 x 10⁴, 2.33 x 10⁵, and 3.00 x 10⁵ g/mol, Perkin-Elmer). ¹H- and ¹³C-NMR
spectra were recorded on a Bruker DPX-250, Varian inova-400 and 500 spectrometers. Sample concentrations were about 10% (w/v) in CDCl$_3$ containing 1% TMS as an internal reference. Monomer conversions were calculated from $^1$H-NMR spectra upon integration of area of peaks for -2CH$_3$ of the monomer at 1.38 ppm and for the polymer at 1.43 ppm. The degree of polymerization (DP) calculated from the $^1$HNMR spectrum by determining the area under the repeat unit methylenes and methines (H-1 and H-2, 4.63 and 4.25 ppm) resonances and the end group CH$_3$OH resonance (3.68 ppm) were in good agreement with the molecular weight obtained using GPC.

Optical rotations were measured on an Autopol IV (Rudolph Instruments) automated polarimeter at 20 °C in CHCl$_3$/MeOH at a concentration of 1.0. Thermal analyses were preformed on a Dupont DSC 2920 TA instrument attached to a Thermal Analyst 2000 TA instrument computer. Indium was used as the standard for the temperature calibration and the analyses were made under constant stream of nitrogen with a heating rate 10 °C/min and cooling rate of 40 °C/min.

**Synthesis of Dimethyl 2,3-O-isopropylidene-L-tartrate (1).**\textsuperscript{7b} In 100mL two-neck round-bottom flask, L-tartaric acid(1) (0.034mol, 5g) and p-toluenesulfonic acid monohydrate (0.21mmol, 0.04g) was added into a solution of 2,2-dimethoxypropane(0.077mol, 9.5ml, 8.05g) in methanol (2mL). Mixture was refluxed for about 1h until the solid dissolved and a dark-red homogeneous solution was observed. Additional 2,2 dimethoxypropane (0.039mol, 4.8mL, 4.1g) and cyclohexane(20mL) were then added and heated to reflux to remove acetone-cyclohexane and cyclohexane-methanol azeotropes. After the removal of the azeotropes was completed, another 1mL of
2,2-dimethoxypropane was added into the reaction, and the mixture was reflux for 15 minute. After the mixture cooled to room temperature, potassium carbonate (0.2g) was added. The mixture was stirred until the dark-red solution changed to yellow color. The potassium carbonate solid was filtered and the volatile solvent was evaporated under vacuum. The product was collected from chromatography on silica gel eluted with 30% ethyl acetate/hexanes. A pale yellow oil, bp 120–122°C (8mmHg), (0.030mol, 6.52g, 89%); \([\alpha]_D^{20} = -49.18\) (c=1.0, MeOH). \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta=4.73\) (s, 2H, 2OCHCO), \(3.74\) (s, 6H, 2OCH\(_3\)), \(1.41\) (s, 6H, 2CH\(_3\)). \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)): \(\delta=25.9, 52.4, 76.6, 113.5, 169.7\)

**Synthesis of 2,3-Di-O-isopropylidene-L-threitol (2).**\(^{7b}\) In a 1L three-neck flask, lithium aluminum hydride (0.048mol, 1.8g) was carefully added to ice-cold diethyl ether (50mL). The mixture was stirred for 30 minutes and a solution of dimethyl 2,3-O-isopropylidene-L-tartrate (6g, 0.028mol) in diethyl ether (20mL) was added dropwise over 2h while the reaction flask was maintained in an ice bath and under nitrogen atmosphere. After the addition was complete, the mixture was stirred and heated to reflux for 4 hours. Reaction mixture was then cautiously quenched by water (1.8mL), 4N sodium hydroxide solution (1.8mL), and water (5.4mL) in an ice bath. Then the mixture was stirred until all the gray color LAH has disappeared. The mixture was filtered on a Büchner funnel and the precipitated solid was extracted with THF in a Soxhlet apparatus. The extracted solution was dried by anhydrous magnesium sulfate and filtered, and volatile material was removed under reduced pressure. The residue was purified by chromatography on silica gel using 80% ethyl acetate/hexanes as eluent to afford the
product. A pale yellow oil, bp 96-98°C (8mmHg), (0.02mol, 3.22g, 71%); \([\alpha]_D^{20} = +10.98^\circ \) (MeOH, c=0.5); \(^1\)HNMR (250 MHz, CDCl\(_3\)) \(\delta: 1.42 \text{ (s, 6 H, } 2\text{CH}_3), 3.73 \text{ (m, 6 H, } 2\text{CH}_2+2\text{OH}), 3.94 \text{ (m, 2 H, } 2\text{CH}); \(^{13}\)CNMR (62.5 MHz, CDCl\(_3\)) \(\delta: 26.7, 62.1, 78.3, 109.1\)

Synthesis of (5S, 6S)-Dimethyl 5,6-O-isopropylidene-1,3-dioxepin-2-one (ITC, 3). Triphosgene (0.01mol, 2.97g) was dissolved in dry THF (100mL) and the solution is added dropwise to a mixture of 2,3-Di-O-isopropylidene-L-Threitol (0.02mol, 3.24g) and Pyridine (0.0633mol, 4.99g) dissolved in 200 mL tetrahydrofuran (THF) at 0 °C over a period of 30 minutes. The reaction mixture was stirred at room temperature for 6 hours. Precipitated Pyridine hydrochloride was filtered off, and the filtrate was concentrated under reduced pressure. The product was purified by chromatography on silica gel using 20% ethyl acetate/hexanes as a solvent mixture. White solid, mp 75 °C (0.0114 mol, 2.14g, 57%); \([\alpha]_D^{20} = +84.79^\circ \) (CH\(_2\)Cl\(_2\), c=1); HRMS \(m/z [M+H]^+\). Calcd for C\(_8\)H\(_{13}\)O\(_5\): 189.07630. Found 189.07593; \(^1\)H NMR (CDCl\(_3\)) \(\delta: 1.38 \text{ (s, 6 H, } 2\text{CH}_3), 4.04 \text{ (m, 2H, } -\text{CH-O}), 4.29 \text{ (dd, 5 and 12.5 Hz, 4H, } -\text{CH}_2\text{-O}); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta: 26.9, 67.7, 75.7, 110.7, 154.4\).

General Procedure for the Enzymatic Polymerization. All reactions were carried out in bulk. The lipase was dried (in a drying pistol over P\(_2\)O\(_5\), at 50 °C/0.1 mm Hg; 15 h) in 6 mL sample vials. In a glove bag, maintained under nitrogen atmosphere, the monomer was transferred to a 6 mL reaction vial and the pre-weighed enzyme (94 mg/mmol of carbonate) was added. The reaction vial was capped with a
rubber septum and placed in a constant temperature oil bath maintained at 60°C for predetermined times. Reactions were terminated by dissolution of the contents of the reaction vial in chloroform and removal of the enzyme (insoluble) by filtration (glass fritted filter, medium pore porosity). The filtrates were combined, solvents were removed in vacuo and the crude products were analyzed by proton ($^1$H) NMR and gel permeation chromatography (GPC). Polymers were purified by precipitation in methanol.

**General procedure for the removal of Isopropylidene protective groups.** Polymer (100mg) was dissolved in 1 mL of CH$_2$Cl$_2$. Then 1 mL CF$_3$COOH (80%) was added into the CH$_2$Cl$_2$. After stirring at room temperature for a predetermined time, the resulting solution was poured into 10mL iced cold methanol. The polymer was collected by vacuum filtration, and dried in a vacuum.
2.10 References


CHAPTER 3

One-Shot Block Copolymerization of a Functional Seven-Membered Cyclic Carbonate Derived from L-Tartaric Acid with \(\varepsilon\)-Caprolactone

3.1 Introduction

Biodegradable polymers have gained increasing interest in the past two decades. Many research groups around the world have devoted their efforts to the development of new biodegradable materials and to explore their potential applications especially in biomedical field. The diversity of the application of biodegradable polymer requires the development of a wide range of biomaterials. Copolymerization of two different monomers or more is an effective method of altering the properties of polymers. In last chapter we have talked about the enzymatic homopolymerization of ITC. To modify the properties of the new polymer, we decided to study on the copolymer of ITC.

Polyesters such as poly(\(\varepsilon\)-caprolactone) and polylactide find many applications as homopolymers and copolymers in biomedical and pharmaceutical fields.\(^1\) Copolymers of \(\varepsilon\)-caprolactone with carbonates provide opportunities for development of interesting biomaterial for their biocompatibility and bioresorbability. Because the ester bonds are more sensitive to hydrolysis than carbonates, the copolymerization of \(\varepsilon\)-caprolactone with carbonates enables tuning of the physical properties of the copolymers and thereby facilitates access to the tailor-made biopolymers. However, when a mixture
of two monomers is subjected to polymerization, usually a random copolymer or mixture of two homopolymer is formed. While copolymerization of two monomers results mostly in random copolymers, formation of block polymer has also been reported. The most common method for preparing block polymers is through the sequential addition of the monomers that polymerize via living or controlled polymerization mechanism.\(^2\) Also, an interesting approach to block copolymer synthesis known as “one-shot feeding”, in which the two monomers are fed together, has also been described.\(^3,4\) The one-shot feeding methodology is advantageous as the process is much simpler compared to the sequential monomer feeding. However, only a few examples of one-shot block polymerization are available primarily because the polymerization rates of the two monomers must be significantly different. Dissimilar monomers that have very different reactivities or are polymerized by fundamentally different chemistries (e.g., ATRP, cationic or anionic ROP, and free radical polymerization) have only been reported. For example, there have been no reports of one-shot block copolymerization of cyclic carbonates or lactones, which polymerize following similar chemistries.

Six-membered cyclic carbonates have been widely used in polycarbonate synthesis via ROP because their polymerization proceeds with minimal decarboxylation, which leads to ether linkages along the polymer chain; the five-membered cyclic carbonate ROP results in extensive decarboxylation.\(^11\) Seven-membered cyclic carbonates exhibit higher polymerizability, but there are only a few examples reported in the literature.\(^12\) The seven-membered cyclic carbonate monomer 1,3-dioxepan-2-one (7CC) has been polymerized by both anionic and cationic catalysts, and its copolymerization with trioxane, \(\delta\)-aleralactone, and \(\epsilon\)-caprolactone has also been
In chapter 2 we have reported the synthesis and enzymatic polymerization of a new seven-membered functional carbonate monomer, (5S,6S)-dimethyl 5,6-isopropylidene-1,3-dioxepin-2-one (ITC), from naturally occurring L-tartaric acid. In this chapter the ROP of ITC, derived from naturally occurring L-tartaric acid, by stannous octanoate, Sn(Oct)$_2$, triisopropoxide aluminum, Al(OiPr)$_3$, and diethylzinc monohydrate, ZnEt$_2$-H$_2$O, is reported. The polymerization of the monomer ITC was studied through the relationship between reaction time, monomer conversion, molecular weight, and molecular weight distribution. Copolymerization of ITC with $\varepsilon$-caprolactone was also investigated, and diblock copolymers with different feed ratios were synthesized, importantly in oneshot feeding. This, to best of our knowledge, is the first report of one-shot block polymerization of a lactone and a cyclic carbonate monomer. The homo- and copolymers were characterized by detailed spectral and thermal analyses.
3.2 Bulk Homopolymerization of ITC.

Three catalysts: stannous octanoate, [Sn(Oct)$_2$], triisopropoxide aluminum, Al(OiPr)$_3$, and diethyl zinc monohydrate, ZnEt$_2$-H$_2$O, were tested as catalysts for the ring-opening polymerization of the monomer (ITC, 3). The screening polymerizations were investigated in bulk at 120 °C for 12 h. (Scheme 3.1) The monomer-to-catalyst ratio (M/C) was varied to test the efficiency of the catalysts.

![Scheme 3.1 Ring-Opening Polymerization of ITC monomer in Bulk at 120 °C](image)

Stannous octanoate [Sn(Oct)$_2$] is the most often used catalyst/initiator system for the polymerization of lactones and cyclic carbonates. It is the catalyst of choice for ROP for its low cost, low toxicity, and high efficiency and yields almost complete monomer conversions even at high monomer to catalyst ratios. Sn(Oct)$_2$ itself, however, does not contain a reactive alkoxide group, but it has been shown that alcohols (ROH) or residual water in the polymerization system can act as co-initiators, in which at least one octanoate group is substituted in a rapid equilibrium to form a Sn-alkoxide group. The Sn-alkoxide is the true initiator of the ring-opening polymerization process. We have previously reported on the synthesis and physical properties of optically enriched...
polyesters, based on (R+S)-4-ethyl-ε-caprolactone and (R+S)-4-methyl-ε-caprolactone prepared using SnOct₂ as a catalyst/initiator system.²⁰

Table 3.1 shows the results obtained of the screening experiment. Both Sn(Oct)₂, and ZnEt₂-H₂O catalysts show 100% monomer conversion in 24 hours calculated from the area of the ketal methyl resonances in the ¹H NMR spectra of monomer and the polymer appearing at 1.38 and 1.43 ppm, respectively. The monomer conversions for the polymerizations catalyzed by Al(OiPr)₃ were lower than those with Sn(Oct)₂ and ZnEt₂-H₂O. The number-average molecular weight (Mₙ) was dependent upon the catalytic system used; generally higher molecular weight polymers were obtained with Sn(Oct)₂. As expected, at higher M/C ratios (entries 3, 6, and 9) the higher Mₙ poly(ITC) was synthesized. The polydispersity index (PDI), for all M/C ratios, ranged between 1.4 and 1.6. In general, Sn(Oct)₂-catalyzed polymerizations had the highest Mₙ and monomer conversion at all M/C ratio used; therefore, it was chosen for further investigation of the homopolymerization of ITC.
Table 3.1 Ring-Opening Polymerization of ITC monomer in Bulk at 120 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>M/C a</th>
<th>Conversion (%) b</th>
<th>$M_n^c$ (g/mol)</th>
<th>$M_n^d$ (g/mol)</th>
<th>$M_w/M_n^d$</th>
<th>$M_w/M_n^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sn(Oct)$_2$</td>
<td>50</td>
<td>100</td>
<td>9400</td>
<td>9000</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>100</td>
<td>100</td>
<td>18800</td>
<td>15500</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>200</td>
<td>100</td>
<td>37600</td>
<td>26000</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>ZnEt$_2$-H$_2$O</td>
<td>50</td>
<td>100</td>
<td>9400</td>
<td>7500</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>100</td>
<td>100</td>
<td>18800</td>
<td>13500</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>200</td>
<td>100</td>
<td>37600</td>
<td>20500</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Al(O$i^i$Pr)$_3$</td>
<td>50</td>
<td>74</td>
<td>6960</td>
<td>5500</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>100</td>
<td>75</td>
<td>14100</td>
<td>11200</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>200</td>
<td>72</td>
<td>27100</td>
<td>16500</td>
<td>1.6</td>
<td></td>
</tr>
</tbody>
</table>

a Monomer/catalyst ratio (mol/mol) = 200. b Calculated from $^1$HNMR. c Theoretical $M_n$ calculated using the monomer conversion. d Determined from GPC.

The structure of the poly(ITC) synthesized by Sn(Oct)$_2$- catalyzed ROP was analyzed from its $^1$H and $^{13}$C NMR (Figure 3.1) spectral data. The optical rotation measurement for the polymer was $[\alpha]_D^{20} = +77.8$. The absence of any diastereotopic resonances in its $^{13}$C NMR spectrum suggested complete retention of its absolute stereochemistry. The covalent character of Sn(Oct)$_2$ catalyst, which catalyzed the polymerization through an insertion-type mechanism, is responsible for preservation of the stereochemistry which has previously been demonstrated in the preparation of optically pure poly(L-lactide). However, the mechanism is still controversial, and several pathways of Sn(Oct)$_2$ initiated ROP have been proposed in the literature. The most common include co-initiation with hydroxy groups (e.g., H$_2$O, alcohol) through
monomer insertion-type mechanisms; in bulk polymerization adventitious hydroxy impurity (H₂O) is believed to be the co-initiator.

**Figure 3.1.** $^1$H and $^{13}$C NMR spectra of poly(ITC) obtained by Sn(Oct)$_2$-catalyzed ROP in bulk at 120 °C for 12 h [Table 3.1, entry 3].

The assignments in **Figure 3.1** were based on comparison with NMR spectra of the monomer, two-dimensional $^1$H-$^1$H COSY (**Figure 3.2**) and $^1$H-$^{13}$C HSQC (**Figure 3.3**) experiments for the polymer. The acetonide dimethyl hydrogens (H-8) were observed at 1.43 ppm; the repeat unit methylenes (H-6), owing to their diastereotopic relationship, were observed as 4.51 and 4.20 ppm; the methine (H-7) was at 4.20 ppm.
End groups H-6', H-6'', and H-7' were observed at 3.72, 4.0, and 3.82 ppm, respectively. The end-group assignments were confirmed from the respective $^1$H-$^{13}$C correlations observed in the HSQC experiment. Interestingly, in the HSQC experiment, the resonance at 3.82 (2H) correlated to two carbons, confirming that both H7' resonances were overlapping. No proton resonances were found around 3.5 ppm for the ether linkages, which indicated that no decarboxylation in the main chain occurred during the polymerization. In the 13C NMR spectrum, the acetonide carbon (C-8) was at 28.7 ppm, the C-6 was at 67.5 ppm, and the C-7 was at 77.2 ppm. The end-group carbons C-6' and C-7' were at 64.8 and 75.4 ppm, respectively.
Figure 3.2 $^1$H-$^1$H COSY-NMR (500 MHz, CDCl$_3$) spectrum of Poly(ITC) [Table 3.1, entry 3].

Figure 3.3 $^1$H-$^{13}$C HSQC-NMR (500 MHz, CDCl$_3$) spectrum of Poly(ITC) [Table 3.1, entry 3].

Figure 3.4 shows monomer conversion as a function of the reaction time for Sn(Oct)$_2$-catalyzed polymerization of ITC at 120 °C in bulk (M/C=200). The conversion increased linearly with time and reached 89% by 4 hours; after 6 hours all of the ITC monomer was consumed. The relationship among numberaverage molecular weight ($M_n$), molecular weight distribution (PDI), and monomer conversion is plotted in Figure 3.5. The molecular weight increased linearly with monomer conversion. The correlation coefficient ($R^2$) of 0.99 from the regression analysis of the number-average molecular weight.
weight versus percent monomer conversion suggests that no transfer reaction occurred during the course of polymerization. Poly(ITC) of $M_n=26000$ g/mol was isolated after 12 hours. The $[\alpha]_D^{20}=+77.8$ suggested formation of an optically pure polymer and that there is no racemization of the monomer occurred during the polymerization. The polydispersity index (PDI) ranged from 1.3 to 1.5, which was within experimental error. The narrow molecular weight distribution advocates absence of chain initiation and transfer reactions occurring after 23% monomer conversion and that the main event is chain propagation.

![Graph showing percent monomer conversion vs reaction time](image)

**Figure 3.4** Percent monomer conversion of (3) as a function of time (h) for Sn(Oct)$_2$ catalyzed ring-opening polymerization at 120 °C in bulk for 12h.
**Figure 3.5** Number-average molecular weight and weight distribution as a function of monomer conversion for Sn(Oct)$_2$ catalyzed ring opening polymerization at 120 °C in bulk for 12h.

In **Figure 3.6** the ln([M]$_0$/[M]) is plotted as a function of polymerization time (t), where [M]$_0$ is the initial concentration of the monomer and [M] is the monomer concentration at a given polymerization time (t). Analysis of the graph by regression analysis ($R^2=0.9933$) suggested a first-order rate law for Sn(Oct)$_2$-catalyzed polymerization of ITC in bulk at 120 °C. These results are in agreement with general ROP mechanism of nonterminating chain polymerization. The apparent rate constant of propagation step ($K_{app}$) of $1.05 \times 10^3$ s$^{-1}$ was calculated from the slope of the regression line using the equation $K_{app} = \frac{d(-\ln[M]/[M]_0)}{dt}$.21
Figure 3.6. Plot of \(\ln([M]_0/[M])\) as function of polymerization time (h) for Sn(Oct)\(_2\) catalyzed ROP of ITC monomer in bulk at 120 °C.
3.3 Copolymerization of ITC and CL.

The complexity and the broad array of potential applications of biodegradable materials require polymers with varieties of properties. Degradable polyesters based on lactone monomers, such as L-lactide and ε-caprolactone are increasingly being considered as environmentally friendly materials. Copolymerization of two or more monomers is one of the most versatile methods for tailoring material properties by changing the composition of the copolymer. Our continuous efforts to develop new biodegradable polymers\textsuperscript{22} led us to explore the copolymerization of ITC monomer with ε-caprolactone, which is efficient and easy method to tune up the properties of a polymer.

Sn(Oct)$_2$, ZnEt$_2$-H$_2$O, and Al(OiPr)$_3$ were screened for the copolymerization of ITC with CL in 50:50 feed ratio in bulk at 120 °C for 12 h. The M/C mole ratios of 1/200 were used for the copolymerization. The copolymers were analyzed by NMR and GPC. The $^1$H NMR spectra of the crude products from copolymerization conducted using Sn(Oct)$_2$ and ZnEt$_2$-H$_2$O were similar; however, GPC chromatograms of ZnEt$_2$-H$_2$O catalyzed copolymerization showed a bimodal distribution indicating the formation of two homopolymers (Figure 3.7b). In contrast, Sn(Oct)$_2$-catalyzed copolymerization showed a unimodal distribution indicating the formation of a copolymer (Figure 3.7a). The $^1$H NMR spectrum of the copolymerization catalyzed by Al(OiPr)$_3$ showed only the formation of poly(ε-CL), leaving the ITC monomer unreacted. This result is supported by the low reactivity of Al(OiPr)$_3$ catalyst toward ITC monomer as observed in ITC homopolymerization screening, which showed percent monomer conversion lower seventies after 24 hours (Table 3.1, entries 7-9). A detailed investigation of the copolymerization of ITC with ε-CL was, therefore, undertaken catalyzed by Sn(Oct)$_2$. 

75
Copolymerization of ITC and $\varepsilon$-CL was first carried out by Sn(Oct)$_2$ in bulk at 120 °C for 12 h as shown in Scheme 3.2, and the results are summarized in Table 3.2.

![Figure 3.7 GPC chromatograms ROP of ITC with $\varepsilon$-CL in bulk at 120 °C for 12 h (M/I =200): (a) Catalyzed by Sn(Oct)$_2$. (b) Catalyzed by ZnEt$_2$-H$_2$O.](image)

It can be seen from Table 3.2 that Sn(Oct)$_2$ can efficiently initiate the copolymerization of ITC and $\varepsilon$-CL as single-component catalyst at 120 °C. The copolymer was obtained in 92% isolated yield after 12 h, when the feeding molar ratio of the monomers is 50:50 under the conditions reported in Table 3.2 (entry 4). All the
copolymers obtained in Table 3.2 had a unimodal molecular weight distribution with polydispersity index ranging from 1.4 to 1.6, indicating the polymers obtained were pure copolymers without homopolymers of \( \varepsilon \)-caprolactone and ITC. A GPC curve for the copolymer obtained at the molar monomer feed ratio of 50:50 is shown in Figure 3.7a as an example. In general, high yields (>87%) were obtained upon precipitation of the copolymer from methanol. The number-average molecular weights \((M_n)\) were in the range of 23000 - 26000 g/mol. Copolymer molar composition revealed that incorporation of ITC monomer was less than that in the monomer feed after 12 h of polymerization reaction. Analyses of the crude polymerization mixture suggested that lost ITC monomer may be in the lower molecular weight fraction. The copolymerization of the optically pure ITC monomer with \( \varepsilon \)-caprolactone, a nonchiral monomer, was evident as the specific rotation decreased with decreasing ITC content in the copolymers.
Table 3.2. Sn(Oct)$_2$ catalyzed Ring-Opening Co-polymerizations of ITC and ε-CL

<table>
<thead>
<tr>
<th>Entry</th>
<th>Monomer feed ratio $^a$</th>
<th>Copolymer molar composition $^b$</th>
<th>Yield $^c$</th>
<th>$M_n$ $^d$</th>
<th>PDI $^d$</th>
<th>$T_m$ $^e$</th>
<th>$ΔH_m$ $^e$</th>
<th>$[α]_D^{20}$ $^f$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100:0</td>
<td>[ITC:CL]</td>
<td>87</td>
<td>24000</td>
<td>1.6</td>
<td>58.8</td>
<td>62.85</td>
<td>+ 77.8</td>
</tr>
<tr>
<td>2</td>
<td>90:10</td>
<td>[ITC:CL]</td>
<td>88</td>
<td>23000</td>
<td>1.6</td>
<td>57.0</td>
<td>68.11</td>
<td>+ 62.5</td>
</tr>
<tr>
<td>3</td>
<td>70:30</td>
<td>[ITC:CL]</td>
<td>91</td>
<td>24000</td>
<td>1.6</td>
<td>56.5</td>
<td>64.96</td>
<td>+ 47.9</td>
</tr>
<tr>
<td>4</td>
<td>50:50</td>
<td>[ITC:CL]</td>
<td>92</td>
<td>24000</td>
<td>1.6</td>
<td>54.6</td>
<td>60.23</td>
<td>+ 33.8</td>
</tr>
<tr>
<td>5</td>
<td>30:70</td>
<td>[ITC:CL]</td>
<td>92</td>
<td>25000</td>
<td>1.5</td>
<td>54.1</td>
<td>59.27</td>
<td>+ 19.3</td>
</tr>
<tr>
<td>6</td>
<td>10:90</td>
<td>[ITC:CL]</td>
<td>95</td>
<td>26000</td>
<td>1.4</td>
<td>52.7</td>
<td>56.27</td>
<td>+ 3.3</td>
</tr>
<tr>
<td>7</td>
<td>0:100</td>
<td>[ITC:CL]</td>
<td>95</td>
<td>26000</td>
<td>1.4</td>
<td>52.7</td>
<td>57.1</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Reactions were carried out in bulk for 12h at 120 °C using monomer/catalyst mole ratio (M/C) = 200. $^b$Monomer feed ratio in mol/mol. $^c$Calculated from $^1$H-NMR spectrum. $^d$Insoluble portion in methanol. $^e$Determined from GPC. $^f$Measured from DSC. $^g$Specific rotation measured in CH$_2$Cl$_2$ (c =1.0).
3.4 NMR Characterization of Copolymers.

The copolymers were characterized by detailed analyses of the $^1$H NMR, $^{13}$C NMR, $^1$H-$^1$H COSY, and $^1$H-$^{13}$C HSQC and by comparison with the respective homopolymers spectra. For example, the structure of the poly(ITC-co-CL) synthesized by ROP of an equimolar amount of ITC and $\epsilon$-CL and catalyzed by Sn(Oct)$_2$ was analyzed by $^1$H and $^{13}$C NMR spectra shown in Figure 3.8 and Figure 3.9, respectively.

**Figure 3.8** $^1$H NMR spectra (500 MHz, CDCl$_3$) of poly(ITC-block-CL) [Table 3-2, entry 4], obtained by Sn(Oct)$_2$-catalyzed ROP in bulk at 120 °C for 12 h. The inset in the figure shows a comparison of the data before and after acetylation.
Figure 3.9. $^{13}$C NMR spectra (500 MHz, CDCl$_3$) of poly(ITC-block-CL) [Table 3.2, entry 4], obtained by Sn(Oct)$_2$-catalyzed ROP in bulk at 120 °C for 12 h. The inset in the figure shows a comparison of the data before and after acetylation.

The copolymer molar compositions were calculated from relative peak area of the H1 (-COCH$_2$- at 2.32 ppm) and H6 resonances (-OCH$_2$- at 4.17 and 4.50 ppm) in the $^1$H NMR spectrum for ε-CL and ITC repeat units, respectively (Figure 3.8). The diastereotopic protons (H6$_a$,b) were observed at 4.17 and 4.50 ppm; the assignments were based on $^1$H-$^{13}$C correlation HSQC experiment (Figure 3.10).
The proton resonances belonging to the acetone methyl (H8) in ITC and H3 of e-CL repeat unit (-CH2-) overlapped at 1.43 ppm. Upon comparison to the 1H NMR spectrum of the poly(ITC), the low-intensity resonances in the 1H NMR spectrum of the copolymer at 3.72, 3.82, and 4.0 ppm were assigned to H6' (-CH2OH), H7' (-CHO-), and H6'' (-CH2OCOO), respectively, of the ITC block (insert in Figure 3.8). The presence of the free hydroxy end groups is in agreement with previous reports that -O-Sn-R end groups undergo exchange reaction with octanoic acid released from Sn(Oct)2, resulting in hydroxy end groups. Alternatively, the hydroxyl end groups can also be generated upon precipitation in methanol; a similar observation was made during precipitation of poly(L-
The resonances of the methyleneoxy hydrogens (pCL-CH₂-OCOO-pITC) belonging to the CL-ITC link were observed at 3.66 ppm (H-5'', CL-ITC) and at 4.28 and 4.36 ppm (H6'''', pCL-OCOO-CH₂- pITC). The ¹H-¹H COSY experiment (Figure 3.11) was used to confirm the CL-ITC link assignments in the copolymer (Table 3.2, entry 4), which showed coupling of H-5'' to H-4'' and the H-6''' to the H-7'''. Importantly, no proton resonances were found around 3.5 ppm (ether linkage) in either the homopolymer [poly(ITC)] or the copolymers, which indicate that no decarboxylation in the main chain occurred during the copolymerization.¹¹ In order to confirm the end-group assignment, the copolymer was subjected to acetylation of the hydroxyl end group, and the ¹H NMR spectra before and after acetylation are shown in Figure 3.8 (inset). The new acetate group resonance was observed at 1.98 ppm (s, CH₃CO), and its integral suggested that only one acetate group was attached, confirming only one hydroxy end group in the copolymer (HOOC-pCL-pITC-OH). A careful comparison of the data before and after acetylation was used to confirm the assignments in the ¹H NMR. Importantly, only the H-1' was deshielded to 4.1 ppm, suggesting an acetate formation at C-1'. As expected, the resonances arising from the CL-ITC link were unaffected by the end-group acetylation.
Figure 3.11. \(^1\)H-\(^1\)H COSY-NMR (500 MHz, CDCl\(_3\)) spectrum of Poly(ITC-block-CL) [Table 3.2, entry 4].

The \(^{13}\)C NMR spectrum of the copolymer [Table 3.2, entry 4] along with peak assignments is shown in Figure 3.9, and it did not contain resonances expected of the diad and triad sequences originating from a random copolymer, which suggests formation of AB block copolymers. The high-intensity peaks were assigned to the poly(\(\varepsilon\)-CL) and poly(ITC) resonances. The low-intensity peaks were assigned to the end groups and the
PCL-PITC link carbons. The PCL end groups C-1’ (-CH₂COOH) and C-9’ (-COOH) were observed at 32.8 and 177.0 ppm, respectively. The resonance at 62.8 ppm was assigned to the C-5″ (-CH₂O) of the PCL-PITC link. The poly(ITC) end group hydroxymethylene (C-6′) was observed at 64.8 ppm, and the C-7′ was at 75.2 ppm. The carbonate carbonyl (C-10′) linking the CL and ITC block was observed at 155.0 ppm. Interestingly, the C-6″ and C-6‴ carbons were observed at 66.3 and 67.2 ppm, owing to their proximity to the end group or the PCL-PITC link. The 13C NMR spectrum of the acetylated copolymer [Table 3.2, entry 4] was also acquired, and a comparison of the data before and after acetylation is included in Figure 3.9 (inset). The 13C NMR spectrum after acetylation showed a new peak at 17.0 ppm for the acetate methyl, and the C-6′ (-CH₂OCOCH₃) resonance was shifted downfield to 67.4 ppm. The downfield shift only in the resonance position of C-6′ confirmed the structure of the block copolymer and that only one hydroxy end group was present. The AB block copolymer structure was thus established and was in line with observation of only unimodal peaks in the GPC analyses.

Formation of the block copolymers is traditionally accomplished through sequential addition of monomers such that the prepolymer from the first monomer initiates polymerization of the second monomer, and inter- and intrachain transfer reaction are kept to a minimum. For example, polymerization of ε-caprolactone with DXO²³ and lactide²⁴ has been reported employing the sequential monomer addition strategy. In an interesting approach Saegusa et al.⁵ were first to report a unique one-shot block copolymerization, which involves successive polymerizations of each of two monomers that are fed simultaneously.
To understand the mechanism, copolymerization of ITC and ε-CL by Sn(Oct)$_2$ was further investigated. The progress of the copolymerization of equimolar amount of ITC and ε-CL was carefully monitored using $^1$H NMR spectra collected at predetermined time intervals, and it could be observed that the rate of polymerization of ε-CL was much higher than that of ITC. A stacked plot of $^1$H NMR spectra acquired during the copolymerization process is shown in Figure 3.12.

![Figure 3.12](image) $^1$H NMR (250 MHz, CDCl$_3$) spectra for various reaction time of Sn(Oct)$_2$-catalyzed copolymerization of ITC monomer with ε-caprolactone (ε-CL) at 120 °C in bulk [1:1 feed ratio].

The diastereomeric H-6 resonances in ITC monomer are observed as a multiplet centered at 4.3 ppm, and the H-1 in ε-CL monomer were observed at 2.6 ppm. The formation of the poly(ε-CL) prepolymer can be seen with emergence of a new H-1
resonance (a triplet) at 2.2 ppm, while the poly(ITC) formation results in a new H-6 resonance at 4.4 ppm. In the first 60 min, ε-CL conversion reached >98%, but none of ITC monomers had been consumed; in 80 min, ε-CL was completely consumed and ITC conversion was <10% (Figure 9). Clearly, ε-CL was polymerized first, and the polymerization of ITC was initiated only after all of the ε-CL monomer had been consumed (Figure 3.13). This proposed copolymerization mechanism in Figure 3.14 is supported by the NMR analyses of the reaction mixture and the structure of the AB block copolymer formed.

Figure 3.13 Plot of monomer conversion (%) as a function of reaction time (min) for Sn(Oct)$_2$-catalyzed copolymerization of ITC monomer (■) with ε-caprolactone (●) at 120 °C in bulk [1:1 feed ratio].
Figure 3.15 shows GPC curves during the copolymerization of ITC and ε-CL at predetermined time intervals. The GPC curves were unimodal, and the polymer molecular weight increased with monomer conversion. Importantly, the GPC curves continue to be unimodal and molecular weight increases even after the consumption of ε-CL was complete (Figure 3.13). For the synthesis of block copolymers it is required that chain transfer reactions do not occur during the polymerization. The polydispersity index of the copolymerization remained unchanged, within experimental error, throughout the course of the copolymerization, suggesting no chain transfer reactions took place. At the polymerization temperature of 120 °C it has been reported that no transesterification reactions occurred during stannous octanoate-catalyzed ring-opening polymerization of DL-lactide.25

![Figure 3.15](image)

**Figure 3.15.** GPC curves during the copolymerization of ITC and ε-CL at predetermined time intervals.

**Figure 3.14.** Mechanism of stannous octanoate-catalyzed block polymerization of ε-CL and ITC: (i) formation of stannous octanoate initiator, (ii) coordination/insertion/polymerization of ε-CL, (iii) coordination/insertion/polymerization of ITC to result in AB block copolymer, (iv) formation of the hydroxy end group.
Figure 3.15 GPC chromatograms of poly[ITC-block-CL] at different reaction times catalyzed by Sn(Oct)$_2$ at 120 °C in bulk (M/C = 200): (a) $M_n = 1700$ g/mol, PDI = 1.5. (b) $M_n = 6400$ g/mol, PDI = 1.6. (c) $M_n = 13000$ g/mol, PDI = 1.6.

The copolymerization of ITC with $\varepsilon$-CL catalyzed by Sn(Oct)$_2$ at 120 °C, therefore, resulted in formation of AB block copolymer, poly($\varepsilon$-CL)-block-poly(ITC), in which the poly($\varepsilon$-CL) prepolymer from the fast reacting monomer, $\varepsilon$-CL, initiated the ROP of the slow reacting ITC monomer. This is the first example, to the best of our knowledge, of the one-shot block polymerization of $\varepsilon$-CL with a carbonate monomer.
3.5 De-protection of Ketal Groups.

PCL is an important biodegradable synthetic polymer; however, the slow biodegradation rate of PCL due to its hydrophobic nature limits its applications. Introducing hydroxy functional groups in the polymer backbone is expected to enhance PCL hydrophilicity, physical properties, and biodegradability.

![Scheme 3.3 Deprotection of the acetonide groups from copolymer](image)

**Table 3.3 Removal of the acetonide groups**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (min)</th>
<th>Conversion (^a) (%)</th>
<th>Yield (^b) (%)</th>
<th>(M_n) (^c) (g/mol)</th>
<th>PDI (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td>24000</td>
<td>1.6</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>51</td>
<td>89</td>
<td>22500</td>
<td>1.7</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>79</td>
<td>87</td>
<td>22000</td>
<td>1.8</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>99</td>
<td>83</td>
<td>21000</td>
<td>1.9</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>100</td>
<td>75</td>
<td>18000</td>
<td>2.2</td>
</tr>
</tbody>
</table>

\(^a\) CH\(_2\)Cl\(_2\)/CF\(_3\)COOH/H\(_2\)O at room temperature (see experimental section). \(^b\) Calculated from \(^1\)H NMR. \(^c\) Insoluble portion in methanol. \(^c\) Determined from GPC.

Trifluoroacetic acid has been utilized as an efficient deprotecting reagent for the acetonide group of polymers containing carbonate and ester groups in the main chain with minimal degradation.\(^{15}\) The copolymer in **Table 3.2**, entry 4 was chosen as a model
to perform the deprotection. **Table 3.3** summarizes the results obtained for the deprotection in various reaction times. The $M_n$ of the copolymer before deprotection was 24000 g/mol and PDI of 1.6. After 5 min reaction time 51% of the isopropylidene protective were removed, the $M_n$ dropped to 22500, which was mainly due to the loss of acetonide groups. The conversion was calculated from the new resonance at 3.7 ppm of the methine hydrogens (-CH-OH) in the $^1$H NMR spectrum (**Figure 3.16**). After 15 min reaction 99% deprotection was achieved ($M_n = 21000$ g/mol) with slight increase in PDI to 1.9, which indicated minimal degradation of the polymer chain. At 20 min reaction time, complete removal of the ketal group was achieved with increase in PDI to 2.2. In **Figure 3.17** the absence of resonance at 28 ppm of the methyl carbons from acetonide groups also proves that the ketal group is removed. The specific rotation ([α]$_{D}^{20}$) of poly(44%ITC)-block-poly(56% ε-CL) before and after deprotection is +33.8 (CH$_2$Cl$_2$, c = 1) and +10.9 (EtOH, c = 1), respectively.

**Figure 3.16.** $^1$H-NMR spectrum (500 MHz, DMSO-$d_6$) of Poly[ITC-block-CL] after deprotection [*Table 3.3*, entry 4].
Figure 3.17 $^{13}$C-NMR (125 MHz, DMSO-$d_6$) spectra of Poly[ITC-block-CL] after de-protection [Table 3.3, entry 4].
3.6 Thermal Analysis of Copolymers of ITC.

The thermal analyses of synthesized polymers were carried out using DSC. The samples were scanned from -100 to +300 °C at a rate of 10 °C/min under a nitrogen atmosphere. Two glass transition temperatures ($T_g$) were observed for poly(44%ITC)-block-poly(56% ε-CL) (Table 3.2, entry 4) at -59.1 and -37.2 °C for the polyCL and the polyITC block, respectively, confirming the diblock nature of the copolymers (Figure 3.18). PCL is reported to have a $T_g$ of -60 °C and $T_m$ of 60 °C.\textsuperscript{26} The DSC thermogram also showed a sharp exothermic peak ($T_m$) for the poly[44%ITC-block-56%CL] at 54.6 °C with meting enthalpy ($\Delta H_m$) of 60.23 J/g. The melting temperature ($T_m$) of PCL ($M_n$ 24000 g/mol; PDI = 1.4; Table 3.2, entry 7) is found to be 52.7 °C, which is lower than the reported $T_m$ value of 60 °C for a similar $M_n$ PCL.\textsuperscript{26} In general, $T_m$ and melting enthalpy ($\Delta H_m$) values in Table 3.2 decrease with decreasing ITC monomer content in the feed ratio. Interestingly, only one melting temperature was observed for the AB block copolymers, which was because of the overlapping melting transitions of poly(ITC), $T_m = 58.8$ °C, and poly(CL), $T_m = 52.7$- 60 °C.
After deprotection, the $T_m$ and $\Delta H_m$ of poly[44%ITC-block-56%CL] increased to 59.4 °C from 54.6 °C and 78.84 from 60.23 J/g, respectively. The $\Delta H_m$ increased by 30% after the deprotection, which indicates higher crystallinity of the free hydroxy copolymer.
3.7 Conclusion

Enantiomerically pure seven-membered cyclic carbonate (ITC) synthesized from naturally occurring L-tartaric acid in three steps was investigated for its polymerization and copolymerization with \( \varepsilon \)-CL. From three catalysts, namely stannous octanoate \([\text{Sn}(\text{Oct})_2]\), triisopropoxide aluminum \([\text{Al}(\text{OiPr})_3]\), and diethylzinc monohydrate \((\text{ZnEt}_2\cdot\text{H}_2\text{O})\) screened for the polymerization of the monomer ITC, \(\text{Sn}(\text{Oct})_2\) was found to be the most efficient catalyst. The homopolymerization of ITC catalyzed by \(\text{Sn}(\text{Oct})_2\) followed a first-order rate law. The results are in agreement with the general mechanism of the ROP of a nonterminating chain polymerization. Optically active copolymers with various feed ratios were synthesized by the ring-opening copolymerization of ITC with \( \varepsilon \)-CL catalyzed by \(\text{Sn}(\text{Oct})_2\) at 120 °C for 12 h, in bulk. Detailed investigation of the copolymers revealed them to be AB block copolymers. It is the first report of “one-shot feeding” block copolymer synthesis of \( \varepsilon \)-caprolactone by ring-opening polymerization with a cyclic carbonate monomer. The deprotection of the ketal groups using trifluoroacetic acid offered poly[ITC-block-CL] with pendant hydroxy groups with minimal degradation in the polymer chain. Physical, chemical, and biodegradation evaluations are currently underway in our laboratories.
3.8 Experiment

Materials. All reagents were used without further purification unless specified otherwise. Stannous 2-ethylhexanoate (stannous octanoate, 95%), triisopropoxide aluminum, Al(O’Pr)₃, diethylzinc monohydrate, ZnEt₂-H₂O were purchased from the Aldrich Chemical Co. Diethyl ether and tetrahydrofuran (THF) were dried over pressed Na metal before use.

Measurements. Molecular weights were measured by gel permeation chromatography (GPC) using a Shimadzu HPLC system equipped with a model LC-10ADvp pump, model SIL-10A autoinjector, model RID-10A refractive index detector (RI), model SPD-10AV UV-vis detector, and Waters HR 4E styrage column. CHCl₃ (HPLC grade) was used as an eluent at a flow rate of 1.0 mL/min. The sample concentration and injection volumes were 0.5% (w/v) and 100 µL, respectively. EzChrome Elite (Scientific Software Inc.) was used to calculate molecular weights based on a calibration curve generated by narrow molecular weight distribution polystyrene standards (5.00 × 10², 8.00 × 10², 2.10 × 10³, 4.00 × 10³, 9.00 × 10³, 1.90 × 10⁴, 5.00 × 10⁴, 9.26 × 10⁴, 2.33 × 10⁵, and 3.00 × 10⁵ g/mol, Perkin-Elmer). ¹H and ¹³C NMR spectra were recorded using a Bruker DPX-250 as well as Varian Inova- 400 and -500 spectrometers. Sample concentrations were about 10% (w/v) in CDCl₃ containing 1% TMS as an internal reference.

Monomer conversions were calculated from ¹H NMR spectra upon integration of area of peaks for -2CH₃ of the monomer at 1.38 ppm and for the polymer at 1.43 ppm.
The degree of polymerization (DP) calculated from the \(^1\)H NMR spectrum by determining the area under the repeat unit resonances and the end group \(CH_2OH\) resonance were in good agreement with the molecular weight obtained using GPC.

Optical rotations were measured on an Autopol IV (Rudolph Instruments) automated polarimeter at 20 °C in CHCl₃ or MeOH at a concentration of 1.0. Thermal analyses were performed on a Dupont DSC 2920 TA Instruments attached to a Thermal Analyst 2000 TA Instruments computer. Indium was used as the standard for the temperature calibration, and the analyses were made under constant stream of nitrogen with a heating rate 10 °C/min and cooling rate of 40 °C/min.

**General Procedure for the Homopolymerization.** In a nitrogen atmosphere, ITC (11.6 mmol, 2 g) was charged into dry freshly silanized 15 mL glass Schlenk tubes, and \(5 \times 10^{-3}\) mol of stannous octanoate (2% dry toluene solution) per mole of total monomer was added as a solution in sodium-dried toluene. Subsequently, the toluene was removed by evacuation. The Schlenk tubes were purged three times with dry nitrogen and placed in an oil bath preheated to the polymerization temperature (120 °C). After a predetermined time the Schlenk tubes were removed from the oil bath and rapidly cooled in ice-cold water to quench the polymerization, and the polymer was dissolved in dichloromethane. Samples were taken for determination of the monomer conversion by \(^1\)H NMR spectroscopy. For purification, the obtained polymers were dissolved in chloroform, filtered through a sintered glass filter, and precipitated into an excess of ice-cold methanol. The precipitated polymers were collected, washed with fresh methanol, and dried at room temperature under reduced pressure.
General Procedure for Copolymerization. In a nitrogen atmosphere, a mixture of ITC and CL (100 mg scale) was charged into dried, freshly silanized 15 mL glass Schlenk tubes. The monomer mixture was gently warmed and vigorously shaken in order to obtain a homogeneous mixture of the monomers. To the monomer mixture $5 \times 10^{-3}$ mol of stannous octanoate (2% dry toluene solution, 1:200 catalyst:monomer ratio) per mole of total monomer was added as a solution in sodium-dried toluene. Subsequently, the toluene was removed by evacuation. The Schlenk tubes were purged three times with dry nitrogen and placed in an oil bath preheated to the polymerization temperature (120 °C). After a predetermined time the Schlenk tubes were quenched to room temperature, and the copolymer was dissolved in dichloromethane. Samples were taken for determination of the monomer conversion by $^1$H NMR spectroscopy. For purification, the obtained copolymers were dissolved in chloroform, filtered through a sintered glass filter, and precipitated into an excess of ice-cold methanol. The precipitated polymers were collected, washed with fresh methanol, and dried at room temperature under reduced pressure.

General Procedure for the Removal of Isopropylidene Protective Groups.\textsuperscript{15} Copolymer (100 mg) was dissolved in 1 mL of CH$_2$Cl$_2$. Then 1 mL of CF$_3$COOH (80%) was added into the CH$_2$Cl$_2$. After the reaction mixture was stirred at room temperature for a predetermined time, the resulting solution was poured into 10 mL of ice-cold methanol. The precipitated polymer was collected by vacuum filtration and dried at room temperature under reduced pressure.
3.9 References


CHAPTER 4
SPATIALLY DIRECTIONAL MULTIARM POLY(ε-CAPROLACTONE) BASED ON RESORCIN[4]ARENE CAVITAND CORE

4.1 Introduction

Linear aliphatic polyesters have attracted interest due to their biodegradability, biocompatibility, and permeability for many drugs delivery application.\textsuperscript{1} These class of polymers found it way in many biomedical applications such as surgical sutures, drug delivery systems, and internal bone fixation. Polycaprolactone in particular is an important biodegradable polymer and has been used as long range drug release delivery system due to its slow rate of degradation. Many attempts have been made to increase the degradation rate by copolymerization with different classes of compounds.\textsuperscript{1}

In the last two decades, branched polymers such as star-polymers,\textsuperscript{2} dendrimers,\textsuperscript{3} and hyperbrached polymers\textsuperscript{4} have attracted much attention for their unique architectures and wide range of potential applications such as micelles and encapsulation, self-assemblies and liquid crystals, layers, electroluminescent devices, sensors, conductive and ionic conductive polymers, photochemical molecular devices, catalysts, and biochemicals and pharmchemicals.

Multiarms-polymers have unusual bulk and solution properties, such as low melting point and low viscosities compare to their linear counterparts, which allow them
to be molded at lower temperature especially for polymers with low thermal stability such as polyesters.\textsuperscript{5} Essentially multiarms polymers have been synthesized by two main approaches, arms\textsuperscript{6} and core-first\textsuperscript{7} methods; the latter involve the used multifunctional core as initiator. Generally, the initiator core is used mainly to support the polymers arm with no further application for their presence. Multiarms polycaprolactone, polylactide, and poly(trimethylene carbonate) have been synthesized by using multifunctional alcohols.\textsuperscript{8(c-e)} However, effect of spatial orientation of polymer chains in multiarm polymers has never been investigated.

Attempt to utilize the functional core led to the use of multifunctional macrocyclic compounds as initiator cores, for instance cyclodextrins,\textsuperscript{8} calixarenes, and resorcinarenes.\textsuperscript{9-12} Calixarenes and resorcinarenes are macrocyclic phenolic compounds which have many potential applications as sensor materials for recognition of metal ions encapsulation, stabilization of guest molecules, and as catalyst platform. Due to their simple preparation, unique structure and applications, many star-shaped polymers have been synthesized based on calixerene and resorcinarenes as initiator core. Different polymerizations techniques were employed in their synthesis such as atom transfer radical polymerization (ATRP),\textsuperscript{9} reversible radical fragment transfer polymerization (RAFT),\textsuperscript{10} living cationic polymerization,\textsuperscript{11} and ring-opening polymerization (ROP).\textsuperscript{12} However, there are few reports in the literature of multiarm-polymers based on resorcinarenes core synthesized by ROP.\textsuperscript{13} For examples, resorcinarene-centered octa-arms star polycaprolactone, and polylactide have been reported.

In this chapter, the synthesis of tetra-arms star-shaped polycaprolactone based on bowl shaped, conformationally locked and unlocked resorcinarenes cores via ROP
catalyzed by tin octanoate Sn(Oct)$_2$ is reported. Series of directional polymers with different arm lengths were synthesized. These polymers are of particular interest due to their robust cavity bearing framework upon which covalent modifications to either the upper or lower rims can be achieved without compromising the structural integrity of the inner cavity. The rigid bowl shape of resorcin[4]arene cavitands provide an ideal core platform for interrogation of the effect of spatial directionality in multiarm branched polymers. The polymers were characterized by NMR spectroscopy, and gel permeation chromatography (GPC). Thermal properties were examined using differential scanning calorimetry (DSC), and thermogravimetric (TGA). Wide-angle X-ray scattering (WAXS) and DSC were used to evaluated the crystallinity of the polymers.
4.2 Synthesis of Tetrol Resorcin[4]arenes Initiator Cores

Tetrahydroxy methyl resorcinarenes initiators 2c and 3c were synthesized in three steps (Scheme 4.1), as reported previously. Compound 1 was synthesized by acid catalyzed condensation of methylresorcinol and heptanal. The conformationally locked 2a was synthesized by reacting 1 with BrCH₂Cl; whereas the synthesis of the compound 2b was achieved by the reaction of octahydroxy resorcinarene 1 with methyl iodide. Upon bromination of the benzylic hydrogens with NBS yielded tetrabromo-methyl-resorcinarenes 2b and 3b were obtained. Tetrabromo compounds were converted to the tetrahydroxy cavitands, 2C and 3C by reaction with water/acetone mixture in presence of the base K₂CO₃.

Scheme 4.1 Synthesis of tetrahydroxy resorcinarenes initiator cores: (i) BrCH₂Cl, K₂CO₃, DMF, 70 °C. (ii) CH₃I, K₂CO₃, Acetone. (iii) NBS, AIBN, benzene. (iv) H₂O/Acetone, K₂CO₃.
The R groups in the lower rim of the resorcinarene derivatives highly influence the solubilities and conformations in solution. Shen *et al.*\textsuperscript{13} attempts at synthesis of star-polycaprolactone based on the octafunctional resorcinarenes with R-groups of methyl and phenyl failed due to their poor solubilities, however, when long alkyl chain such as the polymerization were successful.\textsuperscript{13} The \( \text{C}_6\text{H}_{13} \) hydrocarbon chain in the lower rim makes compounds 2c and 3c soluble in \( \varepsilon \)-caprolactone. The homogeneity of the reaction mixture facilitates the synthesis of the multiarms polycaprolactone.
4.3 Synthesis and Characterization of Tetra-Arm Poly(ε-caprolactone)s

Tetra-arms star-shaped polycaprolactone based on resorcinarene cores is synthesized via ROP catalyzed by tin octanoate Sn(Oct)$_2$ at 120 ºC in bulk for 24h.

(Scheme 4.2)

Scheme 4.2 Synthesis of directional polycaprolactone based on resorcin[4]arenes 2c and 3c.

Table 4.1 summarizes the results obtained for the polymerization of ε-caprolactone with 2c and 3c initiators. Four different arms length for two series based on
initiator 2c and 3c were synthesized. The polymers where obtained in high yield (91-95%), and GPC analysis shows unimodel distributions for all set of series (Figure 4.1, 4.2). The number-average molecular weight ($M_n$) for both sets of directional-polycaprolatone obtained for initiators 2c and 3c are comparable to each other and the polydispersities (PDI) ranged between 2.2-1.9.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Polymer</th>
<th>I/M $^a$</th>
<th>Yield $^b$</th>
<th>$M_n$ $^c$</th>
<th>$M_w/M_n$</th>
<th>$T_m$ $^d$</th>
<th>$\Delta H_m$ $^d$</th>
<th>$T_d$ $^e$</th>
<th>$X_c$ $^f$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2cSPL$_{40}$</td>
<td>40</td>
<td>95</td>
<td>7000</td>
<td>2.2</td>
<td>49.7</td>
<td>55.6</td>
<td>351</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>2cSPL$_{100}$</td>
<td>100</td>
<td>93</td>
<td>8800</td>
<td>2.1</td>
<td>53.6</td>
<td>69.9</td>
<td>359</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>2cSPL$_{160}$</td>
<td>160</td>
<td>92</td>
<td>12000</td>
<td>2.0</td>
<td>58.9</td>
<td>88.9</td>
<td>363</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>2cSPL$_{200}$</td>
<td>200</td>
<td>93</td>
<td>15000</td>
<td>2.0</td>
<td>60.6</td>
<td>91.2</td>
<td>368</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>3cSPL$_{40}$</td>
<td>40</td>
<td>94</td>
<td>6500</td>
<td>2.0</td>
<td>49.5</td>
<td>52.4</td>
<td>350</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>3cSPL$_{100}$</td>
<td>100</td>
<td>92</td>
<td>7900</td>
<td>2.0</td>
<td>52.7</td>
<td>66.2</td>
<td>357</td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>3cSPL$_{160}$</td>
<td>160</td>
<td>92</td>
<td>11500</td>
<td>1.9</td>
<td>54.3</td>
<td>70.2</td>
<td>361</td>
<td>51</td>
</tr>
<tr>
<td>8</td>
<td>3cSPL$_{200}$</td>
<td>200</td>
<td>91</td>
<td>14500</td>
<td>1.9</td>
<td>56.5</td>
<td>75.6</td>
<td>366</td>
<td>55</td>
</tr>
<tr>
<td>9</td>
<td>LPCL</td>
<td>200</td>
<td>95</td>
<td>15400</td>
<td>1.5</td>
<td>54.3</td>
<td>65.1</td>
<td>349</td>
<td>48</td>
</tr>
</tbody>
</table>

$^a$Polymerization condition; 120 °C for 24h in bulk. Initiator/catalyst (I/C) =200.
$^b$Monomer/initiator (M/I) = mole/mole.
$^c$Insoluble methanol portion.
$^d$Determined by GPC.
$^e$Measured by DSC.
$^f$Decomposition temperature measured by TGA at 10% decomposition.
$^g$Percent crystallinity ($X_c$) measured from DSC.
$^h$Linear polycaprolactone.
Figure 4.1 Representative GPC chromatograms for 2cSPL [Table 4.1, entry 1-4].

![Representative GPC chromatograms for 2cSPL](image1)

Figure 4.2 Representative GPC chromatograms for 3cSPL [Table 4.1, entry 5-8].

![Representative GPC chromatograms for 3cSPL](image2)

$^1$H-NMR spectra of 2cSPCL$_{40}$ and 3cSPCL$_{40}$ (Table 4.1, entry 1 and entry 5) are shown in Figure 4.3 and 4.6 respectively. The assignment is based on comparison
with $^1$H-NMR spectra of PCL and the initiators. In Figure 4.3 high intensity resonances are assigned to the PCL repeating units, and low intensities resonances are characteristic of the initiator core 2c. The peaks at 0.9 and 1.2 ppm are assigned to the methyl hydrogens ($-\text{CH}_3$), and methylene hydrogens Hf’s ($\text{CH}_2$) of the lower rim of the core. The methylene hydrogens He’s which shows around 2.2 ppm are buried under the PCL repeating units. A triplet around 3.6 is characteristic of the methylene hydroxy end groups of PCL chains. The brided methylene hydrogens (Hb) show at 4.75 and 5.75 ppm. Resonance at 4.25 ppm is for the hydrogen Hc and phenyl hydrogen show at 7.15. The peak around 5.0 ppm is assigned to the methylene hydrogens (Ha, $-\text{CH}_2$-O-CL) which indicate direct link between the PCL arms and the resorcinaerene initiator core 2c. Importantly, the resonance position of the methylenoxy hydrogen Ha is close to what has been reported previously in tetra-acetyl resorcinarene.\textsuperscript{17} The area under the peaks of the methylene hydroxy end-groups (8 x Ha) and the hydrogen of the bridged at 5.75 (4 x Hc) are within the ratio of 0.5 which suggest that all the hydroxy groups are linked the PCL [Figure 4.3].
In the $^{13}$C-NMR spectrum [Figure 4.4], five high intensity resonances are assigned to the PCL repeating units. Other high intensity resonances are assigned to the initiator core 2c upon comparison to the $^{13}$C NMR of initiator 2c.$^{17}$ Most importantly, the resonance for the methyleneoxy carbon (C-a) was deshielded to 70.1 ppm from 56.9 ppm (in tetraol cav tand 2c), which confirmed an ester link to the PCL chains (–CH$_2$–OCO–PCL). The DEPT-135 NMR spectrum (Figure 4-5) was used for unambiguous assignments. Also, the hydroxymethylene end group carbon (C-5') was observed at 62.7 ppm and the carbonyl (C-6') of the PCL–2c ester link was observed at 176.6 ppm.
Figure 4.4 $^{13}$C-NMR (500 MHz, CDCl$_3$) spectrum of directionalk-polycaprolactone based on initiator 2c [Table 4.1, entry 1] catalyzed by Sn(Oct)$_2$ at 120 °C.
**Figure 4.5** Dept135-NMR (500 MHz, CDCl$_3$) spectrum of directionalkpolycaprolactone based on initiator 2c [Table 4.1, entry 1] catalyzed by Sn(Oct)$_2$ at 120 $^\circ$C.

**Figure 4.6** shows $^1$H NMR spectrum of 3cSPCL$_{40}$ [Table 4.1, entry 5]. Along with the high intensity resonances for PCL repeating units, low intensity resonances are visible in the $^1$HNMR spectrum corresponding to the resorcinarene initiator 3c. The lower rim hydrogens are clearly visible in the spectrum; the methyl hydrogens (Hg’s), methylene hydrogens (Hf’s), methylene hydrogens (He’s) next the prochiral center show at 0.77, 1.19, and 1.79 ppm respectively. The methoxy hydrogens (Hb’s) of the upper rim appear at 3.7 which are in the same region of the methylene hydroxy hydrogens end-groups 3.66 ppm. The signals overlap of the methoxy hydrogens and the methylene end group unable us to calculated ratio of resorcinarene 3c to end-groups of PCL. However, the resonance around 5 ppm corresponds to the benzyl hydrogens (8 x Ha), which indicated the direct link between the PCL arms and the initiator core 3c. The ratio of the
integration of the peak at 5 ppm with phenyl hydrogens (4 x Hc) at 6.70 ppm is 0.5 which is direct evidence that all the hydroxyl benzyl groups are linked to the PCL arms of the initiator 3c.

Figure 4.6 $^1$H-NMR (500 MHz, CDCl$_3$) spectrum of 3cSPL$_{40}$ [Table 4.1, entry 5] catalyzed by Sn(Oct)$_2$ at 120 °C.
4.4 Thermal Properties

The thermal properties were evaluated using DSC and TGA. The synthesized polymers were compared to the linear polycaprolactone (LPCL) prepared using Sn(Oct)$_2$ as initiator with number-average molecular weight ($M_n$) of 15400 g/mol, and PDI of 1.5 [Table 4.1, entry 9]. Generally increasing the PCL chain length resulted in increase in the $T_m$, however there are differences in the $T_m$ depending on the structure of the initiator core. Initially the $T_m$ values of smaller PCL arms are comparable to each other. For example, 2cSPL40 has $T_m = 49.7$ and 3cSPL40 $T_m$ is 49.5. Increasing the feed ratio to 100 resulted in smaller difference of 1 degree, further increase in the PCL arms length resulted in 4 °C in the $T_m$ value. The difference in the $T_m$ could be attributed to the nature of structure of the resorcinarencence initiators. The presence of a bridge in the upper rim of the initiator 2c enhances the spatial interaction between the PCL arms resulting in increase in $T_m$ values, relative to the more flexible 3c due to the absence of the bridge in the upper rim. Interestingly both synthesized multiarms-PCL based on initiators 2c and 3c have higher $T_m$ than LPCL (Figure 4.7).
Figure 4.7. DSC thermograms: (a) LPCL [Table 4.1, entry 9]. (b) 3cSPL200 [Table 4.1, entry 8]. (c) 2cSPL200 [Table 4.1, entry 4].

TGA analyses were carried out for the synthesized directional polymers and compared to LPCL. The thermal decomposition temperatures ($T_d$) at 10 % weight loss were measured from the TGA thermograms. $T_d$ for multiarms-PCL for the both initiator cores with same feed ratios are similar to each other and increase with increasing the feed. Although the polymers based on 2c show slightly higher $T_d$ values (Table 4.1). Figure 4.8 show thermograms of multiarms-PCL based on initiator 2c and 3c along with LPCL. Both multiarms-polymers showed higher $T_d$ when compared to LPCL. Similar to the DSC data, polymers based on initiator 2c have higher $T_d$ than those based on initiator 3c.
The data obtained for the TGA support that the presence of resorcinarene core directed the spatial interaction of the PCL arms.

**Figure 4.8.** TGA thermograms: (a) LPCL [Table 4.1, entry 9]. (b) 3cSPL\_200 [Table 4.1, entry 8]. (c) 2cSPL\_200 [Table 4.1, entry 4].
4.5 Crystallization Behaviors

Both DSC and TGA indicated that the resorcinarene initiators 2e and 3e induces the spatial interactions between the PCL arms. Therefore, the crystallization behaviors for both multiarms-polycaprolactone were evaluated by DSC and WAXS along with linear polycaprolactone. The calculation of the percent crystallinity ($X_c$) based on the enthalpy of melting of 100% crystalline PCL (see equation 1 below). Increasing the PCL arms length increased the percent crystallinity of the polymers as longer chain tend to pack efficiently and the effect of the fixed end chain of the polymers becomes less significant. However, the cavitand resorcinarenes 2e show higher crystallization than the relatively more flexible structure of 3e initiator in all feed ratios due to the absence of the methylene bridge which lock the conformation and direct the polymer chain in same direction resulting in increase in crystallinity. The influence of the core becomes more obvious with increasing the length of the PCL arms. For instance, smaller PCL chains of 2eSPL40 and 3eSPL40 have $\%X_c$ of 39 and 36.5 %, and increasing the feed ratio to 200, the different in percent $X_c$ increased to 10 % in favor of the multiarms-polymer based on the bridged resorcinarene 2e. The data suggests that the structure of the core is influencing the spatial directionality of the PCL arms. Both synthesized multiarms polymers show higher crystallinity than the LPCL with similar molecular weight. The percent crystallinity of LPCL is in agreement with the literature value of 42% determined by small-angle X-ray scattering (SAXS) and NMR.\(^{18}\)

$$X_c = \frac{\Delta H_m}{\Delta H_{100}} \times 100$$  \hspace{1cm} (1)
Further investigation of the crystallinity of the polymers were carried using wide-angle X-ray scattering (WAXS). WAXS diffractograms of 2cSPL\textsubscript{200}, 3cSPL\textsubscript{200}, and LPCL are shown in Figure 4.9. WAXS pattern shows the same profile of the main peaks with different intensities at 21.4° (390), 22.1° (95), and 23.8° (190) for 2cSPL\textsubscript{200}, and at 21.4° (360), 22.1° (80), and 23.8° (120) for 3cSPL\textsubscript{200}. The intensities of the peaks are higher for 2cSPL\textsubscript{200} which indicate higher crystallinity than 3cSPL\textsubscript{200}. LPCL showed same main reflections at 21.4° (90) 22.1° (20), and 23.8° (40) but with much lower intensities. DSC and WAXS data indicate that the crystallinity of the multiarms-PCL based on initiator 2c and 3c was significantly higher than the LPCL with similar molecular weight. The spatial directionality of the polymer chains, a result of the rigid bowl shaped resorcinarene cavitand core, results in enhanced interaction among the PCL arms resulting in higher thermal stability and crystallinity.
Figure 4.9 WAXS diffractograms overly of LPCL, 2cSPL$_{200}$ and 3cSPL$_{200}$.
4.6 Conclusions

Tetra-arms spatially directional polycaprolactones based on resorcinarenes cavitand core were synthesized. The presence of four arms PCL chains was confirmed by the analysis of \( ^1 \text{H-NMR} \) spectra. The thermal properties of the multiarms-polymers were investigated using DSC and TGA. DSC and WAXS were used to evaluate the crystallinity of the polymers. For the spatially directional polycaprolactones, \( T_d \) calculated at 10% weight loss in the TGA thermograms was higher than that of linear PCL of comparable \( M_n \). DSC and WAXS analysis show increased crystallinity of the polymers based on both initiator cores. The higher rigidity of the initiator 2c resulted in higher thermal stability and crystallinity compare to relatively more flexible initiator 3c. The data implies that the spatial directionality of the polymer chains, a result of the rigid bowl shaped resorcinarene cavitand core, results in enhanced interaction among the PCL arms resulting in higher thermal stability and crystallinity.
4.7 Experiment

**Materials.** All reagents were used without further purification unless otherwise are specified. Stannous 2-ethyl-hexanoate (stannous octanoate, 95%) was purchased from the Aldrich Chemical Company. \(\varepsilon\)-Caprolactone was dried over CaH\(_2\) and distilled under reduced pressure and stored under nitrogen atmosphere. Azobisisobutylonitrile (AIBN) was crystallized from hot ethanol. N-bromosuccinimide (NBS) was crystallized from boiling water before use.

**Measurements.** Molecular weights were measured by gel permeation chromatography (GPC) using a Shimadzu HPLC system equipped with a model LC-10ADvp pump, model SIL-10A auto injector, model RID-10A refractive index detector (RI), model SPD-10AV UV-Vis detector, and waters HR 4E styrigel column. CHCl\(_3\) (HPLC grade) was used as an eluent at a flow rate of 1.0 mL/min. The sample concentration and injection volumes were 0.5 % (w/v) and 100 \(\mu\)L, respectively. EzChrome Elite (Scientific Software Inc.) was used to calculate molecular weights based on a calibration curve generated by narrow molecular weight distribution polystyrene standards (5.00 \(\times\) \(10^2\), 8.00 \(\times\) \(10^2\), 2.10 \(\times\) \(10^3\), 4.00 \(\times\) \(10^3\), 9.00 \(\times\) \(10^3\), 1.90 \(\times\) \(10^4\), 5.00 \(\times\) \(10^4\), 9.26 \(\times\) \(10^4\), 2.33 \(\times\) \(10^5\), and 3.00 \(\times\) \(10^5\) g/mol, Perkin-Elmer).

**NMR analysis.** \(^1\)H and \(^{13}\)C-NMR spectra were recorded on a Bruker DPX-250, and Varian Inova 500 spectrometers. Sample concentrations were about 10% (w/v) in CDCl\(_3\) containing 1% TMS as an internal reference.
**Thermal analysis.** Thermal analyses were performed on a DuPont DSC 2920 TA instrument attached to a Thermal Analyst 2000 TA instrument computer. Indium was used as the standard for the temperature calibration and the analyses were made under constant stream of nitrogen with a heating rate 10 °C/min and cooling rate of 40 °C/min. The relative crystallinity of samples was calculated according to equation:

\[ X_c = \frac{\Delta H_m}{\Delta H_m^o} \times 100 \]

Where \( X_c \) is the percent crystallinity, \( \Delta H_m \) is the enthalpy of melting of the sample, and \( \Delta H_m^o \) is the heat of melting of 100% crystalline PCL. The value of \( \Delta H_m^o \) used in the calculation is 136.4 J/g.\(^{14}\)

Thermogravimetric analysis (TGA) measurements were performed with a PerkinElmer STA 6000 Simultaneous Thermal Analyzer (purge gas nitrogen and scan rate of 10°C/Min). The decomposition temperatures (\( T_d \)) of the polymers were measured at 10% weight lost.

**Wide-angle X-ray scattering (WAXS).** WAXS spectra were collected with a Bruker AXS D8 Advance powder diffractometer with CuK \( \alpha \) radiation (\( \lambda = 1.54058 \) Å). Samples were analyzed from 3° to 40° 2\( \theta \) using a step size of 0.05° 2\( \theta \) with a collection time of 0.5 per step at 25 °C.

**Synthesis of Octol-resorcin[4]arene (1)\(^{15}\).** Methyl resorcinol (10g, 0.081mol) was dissolved in ethanol (62.7mL, 775mL/mol) and 37% aqueous HCl (15.1mL, 185mL/mol). The solution was cooled in ice bath and heptaldehyde (11.3mL, 0.081mol) was added slowly over a period of 30 min. The reaction mixture was allowed to warm to
room temperature and refluxed for 12 h. The yellow colored precipitate was filtered and washed several times with distilled water until it turns neutral to pH paper. Yield 10.7 g (88%). MP: >220 °C (decomposed). $^1$H NMR (250 MHz, DMSO-d6) δ: 0.84 (t, 12H, J = 6.25Hz), 1.23(m, 32H), 1.93(s, 12H), 2.21(s, 8H), 4.18 (t, 4H J = 7.75Hz)), 7.21 (s, 4H), 8.69(bs, 8H). $^{13}$C NMR (100 MHz, DMSO-d6) δ: 10.7, 14.2, 22.9, 28.9, 29.8, 32.1, 35.4, 38.4, 73.0, 113.6, 122.0, 124.6, 154.0.

**Synthesis of bridged resorcin[4]arene (2a)** Compound 1 (5g, 5.5 mmol) was dissolved in 55 mL DMF in 125 mL in surek-sealed tube. Potassium carbonate (12 g, 88 mmol) was added and stirred for 0.5 h. Then bromochloromethane (7.7 mL, 88 mmol) was added at room temperature. The reaction mixture was sealed and immersed in preheated oil bath 80 °C for 24h. The reaction mixture was poured into cold ice water and the white solid was collected by section filtration. Yield 4.9 g (94%). $^1$H NMR (250 MHz, CDCl$_3$) δ: 0.82 (t, 12H, J = 6.25Hz), 1.23(m, 32H), 1.90 (s, 12H), 2.11(s, 8H), 4.17 (d, 4H J = 7.0), 4.69 (t, 4H J = 8.0 Hz), 5.79 (d, 4H J = 7.0), 6.90 (s, 4H). $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ: 10.3, 14.1, 22.7, 27.9, 29.2, 30.1, 31.8, 37.0, 98.5, 117.6, 123.6, 137.9 153.2.

**Synthesis of octamethoxy resorcin[arene (3a)** Compound 1 (5g, 5.6 mol) was dissolved in 50 mL acetone in 125 mL sure-sealed tube. Potassium carbonate (12.1 g, 88 mmol) was added and stirred for 0.5 h. Then methyl iodide (5.5 mL, 88 mmol) was added at room temperature. After addition, the reaction mixture was sealed and immersed in preheated oil bath 80 °C for 24h. The tube was cold down in ice water and the solid
was filtered off. The compound was crystallized in acetone/methanol mixture. White crystals were obtained. Yield 4.4g (80%). MP = 109 °C. 

\[^1\]H NMR (250 MHz, CDCl\(_3\)) \(\delta:\) 0.76 (t, 12H, J = 6.25Hz), 1.11 (m, 32H), 1.77 (m, 8H), 2.16(s, 12H), 3.43 (s, 24H), 4.37 (t, 4H J = 7.25 Hz), 6.45 (s, 4H).

\[^{13}\]C NMR (62.9 MHz, CDCl\(_3\)) \(\delta:\) 10.2, 14.1, 22.8, 28.6, 29.6, 31.9, 35.6, 37.5, 59.9, 98.5, 123.4, 124.2, 133.1 155.5.

**Synthesis of tetrabromide cavitand (2b)** Compound 2a (4g, 4.3 mmol) and AIBN (100, 0.6 mmol) dissolved in 50 mL degassed benzene. Then NBS (5.4g, 30 mmol) was added and the reaction mixture was reflux overnight. After completion the solid precipitate (succinimide) was filtered off and benzene was evaporated. The residue was dissolved in acetone and crystallized by the addition of ethanol. White precipitate was collected. Yield 4.4g (83%). MP: >104 °C (sublime). 

\[^1\]H NMR (250 MHz, CDCl\(_3\)) \(\delta:\) 0.82 (t, 12H, J = 6.25Hz)), 1.22(m, 32H), 2.12 (m, 8H), 4.34 (s, 8H), 4.46 (d, 4H J = 7.0), 4.71 (t, 4H J = 7.75 Hz), 5.94 (d, 4H J = 7.75), 7.06 (s, 4H). 

\[^{13}\]C NMR (62.9 MHz, CDCl\(_3\)) \(\delta:\) 14.1, 22.6, 23.0, 27.3, 29.5, 30.1, 36.8, 99.1, 121.0, 124.5, 138.1, 153.5.

**Synthesis of tetrabromo-octamethoxy resorcinarene (3b)** Compound 2a (4g, 4 mmol) and AIBN (80, 0.5 mmol) dissolved in 50 mL degassed benzene. Then NBS (5.4g, 30 mmol) was added and the reaction mixture was reflux overnight. After completion the solid precipitate (succinimide) was filtered off and benzene was evaporated. The residue was dissolved in boiling ethanol and let to cool at room temperature. White precipitate was collected. Yield 4.5g (88%). MP: >162 °C. 

\[^1\]H NMR (250 MHz, CDCl\(_3\)) \(\delta:\) 0.87 (t, 12H, J = 6.25Hz), 1.26 (m, 32H), 1.89 (m, 8H), 3.77 (s,
24H), 4.55 (t, 4H J = 7.25 Hz), 4.64 (s, 8H), 6.45 (s, 4H). $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ: 14.1, 22.7, 23.9, 26.4, 29.5, 31.8, 36.0, 37.1, 61.6, 125.9, 127.8, 133.6, 156.1

Synthesis of Tetrol cavitand (2c) Compound 2b (1g, 0.8 mmol) was dissolved in 40 acetone/water (9:1) in sure-sealed tube. Then K$_2$CO$_3$ (0.3g, 2.2 mmol) was added, and the reaction mixture was immersed in preheated oil bath at 80 °C for 24h. After completion the acetone was evaporated and residue was dissolved in ethyl acetate and extracted with brine solution. The white solid was obtained as white solid after purification by plug silica gel eluting 20 % ethyl acetate/hexane. Yield 720 mg (90 %). $^1$H NMR (250 MHz, CDCl$_3$) δ: 0.81(t, 12H, CH$_3$), 1.21 (m, 32H), 2.23 (m, 8H), 4.44 (m, 16H), 4.84 (t, 4H, J=7.32 Hz), 5.78 (d, 4H). $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ: 14.1, 22.6, 26.5, 27.8, 29.4, 30.1, 31.8, 36.8, 56.9, 100.2, 120.6, 137.9, 153.6.

Synthesis of tetrahydroxy-octamethoxy resorcinarene (3c) Compound 3b (1g, 0.76 mmol) was dissolved in 40 acetone/water (9:1) in sure-sealed tube. Then K$_2$CO$_3$ (0.3g, 2.2 mmol) was added, and the reaction mixture was immersed in preheated oil bath at 80 °C for 24h. After completion the acetone was evaporated and residue was dissolved in ethyl acetate and extracted with brine solution. The compound was further purified by plug silica gel eluting 20 % ethyl acetate/hexane. The compound was obtained as white solid. Yield 740 mg (92%), MP = 154 °C. $^1$H NMR (250 MHz, CDCl$_3$) δ: 0.80 (t, 12H, J = 6.25Hz)), 1.30 (m, 32H), 1.90 (m, 8H), 3.70 (s, 24H), 3.90 (s, 8H), 4.50 (t, 4H J = 7.25 Hz), 6.70 (s, 4H). $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ: 14.1, 22.8, 28.5, 29.6, 31.9, 35.5, 37.2, 56.5, 61.8, 127.2, 129.8, 136.6, 155.6.
General procedure of synthesis of directional poly(ε-caprolactone)s. Dry resorcin[4]arene initiators (2c and 3c) were added into a 15 mL tube and dry under vacuum at 50°C. Then the tube was cap by rubber ring under nitrogen atmosphere and ε-caprolactone was injected into the tube and warmed until the initiator dissolved. The tube was immersed in preheated oil bath at 120°C and the catalyst (dry toluene solution, 1:200 catalyst/initiator ratios) was injected into reaction mixture immediately. The reaction was reacted for 24 hours to 48 hours and the product was dissolve in dichloromethane and precipitated in ice-cold methanol.
4.8 References


Polymers from renewable resources, which are biodegradable and biocompatible, have been an attractive area of research. The utility of the biocompatible polymers is also highlighted in biomedicine for degradable scaffoldings and drug delivery applications. L-tartaric acid, a widely available and relatively inexpensive natural resource from a large variety of fruits, because of its natural abundance and functional diversity stand out as highly convenient raw material for the synthesis of polycarbonate. In here we describe the synthesis and polymerization of (5S,6S)-Dimethyl 5,6-O-isopropylidene-1,3-dioxepin-2-one (ITC, 3) by lipase and its one-shot block block copolymerization with ε-caprolactone. The spatial effect of directional multiarm poly(ε-caprolactone) based on resorcin[4]arene cavitand core is also investigated.

A new seven-membered cyclic carbonate monomer (ITC) derived from L-tartaric acid is synthesized in three simple steps. Four commercially available lipases were screened for the polymerization of monomer (ITC) in bulk at 80 °C. Immobilized Candida antarctica lipase -B (Novozym-435) was found to be the most efficient catalyst to carry out the ROP of ITC. The relationship between reaction time, monomer conversion, molecular weight, and weight distribution were investigated for Novozyme-435 catalyse the polymerization. NMR examination of the polymers revealed hydroxy end groups.
We also synthesized the copolymer using ITC and ϵ-CL. From three catalysts, namely stannous octanoate [Sn(Oct)$_2$], triisopropoxide aluminum [Al(OiPr)$_3$], and diethylzinc monohydrate (ZnEt$_2$-H$_2$O) screened for the homopolymerization of the monomer ITC, Sn(Oct)$_2$ was found to be the most efficient catalyst. The homopolymerization of ITC catalyzed by Sn(Oct)$_2$ followed a first-order rate law. The results are in agreement with the general mechanism of the ROP of a nonterminating chain polymerization. Optically active copolymers with various feed ratios were synthesized by the ringopening copolymerization of ITC with ϵ-CL catalyzed by Sn(Oct)$_2$ at 120 °C for 12 h, in bulk. Detailed investigation of the copolymers revealed them to be AB block copolymers. It is the first report of “one-shot feeding” block copolymer synthesis of ϵ-caprolactone by ring-opening polymerization with a cyclic carbonate monomer. The deprotection of the ketal groups using trifluoroacetic acid offered poly[ITC-block-CL] with pendant hydroxy groups with minimal degradation in the polymer chain. Physical, chemical, and biodegradation evaluations are currently underway in our laboratories.

Tetra-arms spatially directional polycaprolactones based on resorcinarenes cavitand core were synthesized. The presence of four arms PCL chains was confirmed by the analysis of $^1$H-NMR spectra. The thermal properties of the multiarms-polymers were investigated using DSC and TGA. DSC and WAXS were used to evaluate the crystallinity of the polymers. For the spatially directional polycaprolactones, $T_d$ calculated at 10% weight loss in the TGA thermograms was higher than that of linear PCL of comparable $M_n$. DSC and WAXS analysis show increased crystallinity of the polymers based on both initiator cores. The higher rigidity of the initiator 2c resulted in
higher thermal stability and crystallinity compared to relatively more flexible initiator 3c. The data implies that the spatial directionality of the polymer chains, a result of the rigid bowl shaped resorcinarene cavitand core, results in enhanced interaction among the PCL arms resulting in higher thermal stability and crystallinity.
ABOUT THE AUTHOR

Ruizhi Wu was born in Foshan, Guangdong, China. In 2002 he received B.S. degree in polymer material chemistry from Zhongshan University in China. In 2003, he came to USA and pursued a doctorate degree in synthetic polymer chemistry under Dr Kirpal S. Bisht’s instruction in the University of South Florida. His work has resulted in 2 national ACS meeting poster presentations and 4 publications ranging from Tetrahedron, Biomacromolecules, Macromolecules and Chemical Communications. Ruizhi has accepted a position as research associate at Louisiana State University, Heath Science Center, where he will continue his research.