DEVELOPMENT OF POLY(PHTHALALDEHYDES) AS CD, POLYMERS:
IMPARTING AMPLIFIED RESPONSES TO STIMULI-RESPONSIVE MATERIALS

A Dissertation in
Chemistry
by
Anthony M. DiLauro

© 2015 Anthony M. DiLauro

Submitted in Partial Fulfillment
of the Requirements
for the Degree of

Doctor of Philosophy

December 2015
The dissertation of Anthony M. DiLauro was reviewed and approved* by the following:

Scott T. Phillips  
Associate Professor of Chemistry  
Martarano Career Development Professorship  
Dissertation Advisor  
Chair of Committee

Alexander T. Radosevich  
Assistant Professor of Chemistry

Ayusman Sen  
Distinguished Professor of Chemistry

Kyle J. M. Bishop  
Assistant Professor of Chemical Engineering

Kenneth S. Feldman  
Chemistry Graduate Program Chair  
Professor of Chemistry

*Signatures are on file in the Graduate School
ABSTRACT

The emerging field of CD₉ polymers (polymers that are capable of continuous depolymerization mediated by a reaction based detection unit) represent a unique opportunity to develop materials that provide an highly selective amplified response to a specific stimulus. The design of CD₉ polymers feature a polymer capped with a stabilizing functionality chosen specifically to respond to a chemical or physical signal. When the signal of interest cleaves the bond between the polymer and this cap, the resulting polymer continuously and completely depolymerizes from head-to-tail. Poly(phthalaldehyde) (PPA) and its derivatives are a class of CD₉ polymers that depolymerize to monomer completely in seconds to minutes in environments that vary substantially in polarity. This dissertation describes efforts (i) to develop new methodology for synthesizing PPA, which enabled research into using PPA as stimuli-responsive microscale pumps and core-shell microcapsules, and (ii) to synthesize a novel poly(phthalaldehyde) derivative (poly(4,5-dichlorophthalaldehyde, PCl₂PA) with improved stability, which led to use of PCl₂PA as multi-responsive materials prepared using selective laser sintering.
TABLE OF CONTENTS

List of Figures and Schemes ............................................................................................................. viii

List of Tables ........................................................................................................................................ xii

Acknowledgements ........................................................................................................................... xiii

Chapter 1 Stimuli-Responsive Polymers that Respond through Depolymerization .................. 1

1.1 Introduction to Stimuli-Responsive Polymers .......................................................................... 1
1.2 Classes of Depolymerizable Polymers ....................................................................................... 3
  1.2.1 FD₈ Polymers .................................................................................................................. 4
  1.2.2 FD₆ Polymers .................................................................................................................. 6
  1.2.3 CD₈ Polymers ................................................................................................................ 8
  1.2.4 CD₆ Polymers ................................................................................................................ 10
1.3 Poly(benzyl carbamates) ........................................................................................................... 13
  1.3.1 Depolymerizable Poly(benzyl carbamates) as Diagnostic Reagents ............................ 14
  1.3.2 Poly(benzyl carbamate) Oligomers as Phase-Switching Reagents in Paper Microfluidic Devices ........................................................................................................ 15
1.4 Poly(benzyl ethers) ................................................................................................................... 17
1.5 CD₆ Polymers Based on Alternating Quinone Methide Elimination and Cyclization Reactions .................................................................................................................... 18
  1.5.1 Increasing the Rate of Depolymerization ........................................................................... 19
1.6 Polymers Based on Cyclization Reactions ................................................................................. 20
1.7 Poly(acetals) ............................................................................................................................. 21
  1.7.1 Polymer Ceiling Temperatures ........................................................................................ 21
  1.7.2 Poly(acetals) as CD₆ Polymers ........................................................................................ 22
  1.7.3 Poly(glyoxylates) as Depolymerizable Polymers ............................................................. 22
1.8 Conclusion .................................................................................................................................. 24
1.9 References .................................................................................................................................. 25

Chapter 2 Development of an Improved Synthesis of End-Cap-Functionalized Depolymerizable Poly(phthalaldehydes) ........................................................................................................... 33

2.1 Introduction to Poly(phthalaldehyde) ....................................................................................... 33
  2.1.1 Previous Methods for Synthesizing PPA ......................................................................... 38
2.2 Results and Discussion .............................................................................................................. 40
  2.2.1 General Procedure for Synthesizing End-Capped PPA ..................................................... 40
  2.2.2 Purification of 1,2-Benzenedicarboxaldehyde ................................................................ 42
  2.2.3 Controlling the Molecular Weight of PPA ..................................................................... 45
  2.2.4 Scope of Responsive and Functional Polymer End-Caps ............................................... 46
  2.2.5 Proof of End-Cap–Mediated Depolymerization ............................................................... 48
  2.2.6 Solid State Depolymerization of PPA .......................................................................... 51
5.3.2 Stability of PCl₃PA Compared to PPA at Ambient Temperatures .................. 119
5.3.3 Thermal Stability of PCl₃PA Compared to PPA .............................. 125
5.3.4 Selective Depolymerization of PCl₃PA ............................................. 125
5.3.5 Selective Laser Sintering of PCl₃PA .................................................. 131
5.3.6 Multi-Stimuli-Responsive Materials from PCl₃PA .............................. 138
5.3.7 Recovery of Products of Depolymerization from PCl₃PA ...................... 139

Chapter 6  General Experimental, Methods, Experimental Procedures, and Characterization ................................................................................................................. 146

6.1 General Experimental ...................................................................................... 146
6.2 Instrumentation ............................................................................................... 147
6.3 Chapter 2: Synthetic Procedures and Characterization .............................. 149
   6.3.1 General Procedure for Synthesizing Depolymerizable PPA .............. 149
   6.3.2 Developing a General Procedure for Purifying 1,2-
       Benzenedicarboxaldehyde ................................................................. 150
   6.3.3 Synthesis of End-Capping Reagents .............................................. 152
   6.3.4 Polymer Synthesis ......................................................................... 153
6.4 Chapter 2: Experimental Procedures and Characterization .................... 164
   6.4.1 Determining the Identity of Impurities in the Monomer ................. 164
   6.4.2 Response of Polymers 2-8 and 2-20 to Pd(0) in Solution .............. 165
   6.4.3 Solid-State Depolymerization of Polymers 2-6 and 2-21 ............... 165
6.5 Chapter 3: Synthetic Procedures and Characterization ............................ 166
   6.5.1 Polymer Synthesis ......................................................................... 166
6.6 Chapter 3: Experimental Procedures and Characterization .................... 175
   6.6.1 General Procedure for Preparing Polymer Films ......................... 175
   6.6.2 Response of the Films to β-D-glucuronidase .................................. 176
   6.6.3 Evaluating the Selectivity of the Pumps for Fluoride ..................... 177
   6.6.4 Effect of Polymer Molecular Weight on Pumping Speed .............. 177
   6.6.5 Effect of End-Cap Polarity on Pumping Speed .............................. 178
   6.6.6 XPS Analysis .................................................................................. 178
   6.6.7 Change in Film Thickness in Response to Fluoride ....................... 178
   6.6.8 SEM Imaging of the Polymer Films ............................................... 179
   6.6.9 Contact Angle Measurements ........................................................ 179
   6.6.10 Effect of Film Area and Thickness of Pumping Speed ................. 180
6.7 Chapter 4: Synthetic Procedures and Characterization ............................ 180
   6.7.1 Polymer Synthesis ......................................................................... 180
6.8 Chapter 4: Experimental Procedures and Characterization .................... 181
   6.8.1 Solution Phase Depolymerization of Polymer 2-19 (Mₚ = 54 kDa) ...... 181
   6.8.2 General Procedure for Fabricating Microcapsules from Polymer 2-19 .. 181
   6.8.3 Evaluating the Response of the Microcapsules to Fluoride ............... 183
   6.8.4 Control Experiments .................................................................... 184
   6.8.5 Fabricating and Testing Microcapsules with Different Shell Wall
       Thicknesses ....................................................................................... 184
   6.8.6 Effect of Polymer Molecular Weight on Rate of Release ............... 185
6.9 Chapter 5: Synthetic Procedures and Characterization ............................ 185
   6.9.1 Screening Oxidation Conditions ..................................................... 185
   6.9.2 Synthesis of 4,5-dichlorophthalaldehyde (5-13) ............................ 188
6.9.3 General Procedure 1 for Synthesizing Poly(4,5-dichlorophthalaldehyde)
(5-15, $M_n = 21$ kDa)........................................................................................................189

6.9.4 General Procedure 2 for Synthesizing Poly(4,5-dichlorophthalaldehyde)
(5-15, $M_n = 17$ kDa)........................................................................................................191

6.9.5 Polymer Synthesis........................................................................................................192

6.10 Chapter 5: Experimental Procedures and Characterization.......................................202

6.10.1 Solution Phase Stability Study..................................................................................202

6.10.2 Acid Stability Study.................................................................................................202

6.10.3 Solid Stability Study.................................................................................................203

6.10.4 Response of Polymers 5-14 and 5-15 to Pd(0) in Solution..................................203

6.10.4 Response of Polymers 5-16 and 5-17 to $F^-$ in Solution......................................204

6.10.5 Dose-Dependent Response of Polymer 5-14 to Pd(0)........................................204

6.10.6 Solid State Depolymerization of Polymers 5-18 and 5-15..................................205

6.10.7 Preparation of Polymers 5-14, 5-15, and 5-18 for Selective Laser Sintering.............205

6.10.8 Laser Sintered Rings of Polymers 5-14 and 5-18................................................206

6.10.9 Determining Line Width Error................................................................................207

6.10.10 Selective Laser Sintering of a Two Layer, Multi-Responsive Grating.....................208

6.10.11 Selective Laser Sintering of a Three Layer, Multi-Responsive Grating....................209

6.10.12 Recovering the Products of Depolymerization from Solid PCl$_2$PA....................210

6.11 References..................................................................................................................211

Appendix A Structural Characterization.............................................................................213

A. NMR Spectra..................................................................................................................213

B. GPC Chromatograms.....................................................................................................226

C. XPS Spectra....................................................................................................................286

D. DSC Curves......................................................................................................................288

Appendix B Data and Charts...............................................................................................289

A. Chapter 3: Data and Charts...........................................................................................289

B. Chapter 4: Data and Charts...........................................................................................290

C. Chapter 5: Data and Charts...........................................................................................295
LIST OF FIGURES AND SCHEMES

Figure 1-1. Graphical representations of the different classes of depolymerizable polymers, and the response of each class to a single reaction with a stimulus. ..........4

Figure 1-2. Representative example of an FD_b polymer and its application as a drug delivery vehicle. .................................................................6

Figure 1-3. Representative example of an FD_r polymer and its application as a diagnostic reagent. ..............................................................8

Figure 1-4. Representative example of a CD_b polymer and its application as a sensor. ..........10

Figure 1-5. Illustration of the general design of CD_r polymers. ........................................11

Figure 1-6. Representative examples of the five classes of CD_r polymers, and the depolymerization mechanism for each..........................................13

Figure 1-7. Depolymerizable poly(benzyl carbamate) 1-8 for use as a diagnostic reagent. ..15

Figure 1-8. Use of depolymerizable poly(benzyl carbamates) as phase-switching reagents for use in paper microfluidic devices......................................17

Figure 1-9. Examples of CD_r polymers based on alternating cyclization and elimination reactions. .................................................................................19

Figure 1-10. The propagation and depropagation steps of a chain polymerization reaction. .........................................................................................21

Figure 1-11. Depolymerization of NVOC end-capped poly(ethyl glyoxylate) (1-20) in response to 300-350 nm UV light. ......................................................23

Figure 2-1. Components of photoresist based on chemical amplification developed by Ito and Willson. ........................................................................35

Figure 2-2. Initial report of using synthesizing PPA end-capped with reaction-based detection units and using it as a CD_r polymer........................................36

Figure 2-3. Solid state depolymerization of PPA..................................................................37

Figure 2-4. Conditions developed by Hedrick and coworkers for the synthesis of PPA without responsive end-caps. .................................................................39

Figure 2-5. Complete and head-to-tail depolymerization of PPA initiated by end-cap cleavage at either end of the polymer ................................................40

Figure 2-6. Synthesis of end-capped PPA using a phosphazene catalyst to activate an alcohol initiator for anionic polymerization......................................41
Figure 2-7. $^1$H NMR spectra of the concentrated supernatant from one recrystallization of 1,2-benzenedicarboxaldehyde.................................................................44

Figure 2-8. Controlling the molecular weight of end-cap–functionalized PPA..................46

Figure 2-9. Synthesis of PPA with responsive and functional end-caps..........................47

Figure 2-10. $^1$H NMR spectra the provide evidence that PPA is end-capped as predicted....49

Figure 2-11. Selective, end-cap–mediated depolymerization of PPA...............................50

Figure 2-12. Solid-state depolymerization of films of polymers 2-21...............................51

Figure 3-1. Illustration of the need for the responsive end-caps of CD$_r$ polymers to be accessible for the polymer to respond rapidly in the solid state...............................57

Figure 3-2. The use of depolymerizable PPA as microscale pumps.................................58

Figure 3-3. Mechanism of the response of activity-based detection reagent 3-1 to β-D-glucuronidase...............................................................59

Figure 3-4. Using microscale pumps as a test system for evaluating the solid-state depolymerization of PPA.................................................................60

Figure 3-5. Silyl ether groups with varying polarities....................................................62

Figure 3-6. Syntheses of polymers 2-6, 2-19, and 3-3 with different molecular weights used as microscale pumps.................................................................64

Figure 3-7. Effect of the concentration of β-D-glucuronidase on the average speed of pumping provided by films of polymer 2-6 ($M_n = 8$ kDa)...............................65

Figure 3-8. The response of films made from polymer 2-6 ($M_n = 65$ kDa) to 0.1 M solutions of various sodium salts.................................................................66

Figure 3-9. Effect of polymer molecular weight on the average speed of pumping provided by films of polymer 2-6 in response to 9 μM β-D-glucuronidase.................67

Figure 3-10. Effect of end-cap polarity on the pumping speed of films of polymers 2-6, 2-19, and 3-3.................................................................68

Figure 3-11. SEM images of films of 2-6 ($M_n = 43$ kDa), 2-19 ($M_n = 42$ kDa), and 3-3 ($M_n = 42$ kDa) before and after being exposed to 0.1 M NaF for 30 min.................73

Figure 4-1. Illustration of a responsive capsule prepared from a CD$_r$ polymer.................82

Figure 4-2. Self-assembly of polymer 4-1 into micellar nanoparticles............................84

Figure 4-3. Light-responsive nanoparticles prepared from polymers 4-2 and 4-3.............85
Figure 4-4. Preparation of microcapsules from polymer 4-6 ........................................... 87

Figure 4-5. SEM images of microcapsules prepared from 4-6 end-capped with either the Boc or Fmoc protecting group. ................................................................. 88

Figure 4-6. Illustration of the general design of a microfluidic flow-focusing device. ........ 89

Figure 4-7. Selective depolymerization of polymer 2-19 ($M_n = 54$ kDa) in solution. ....... 91

Figure 4-8. Fabrication of core-shell microcapsules from polymer 2-19 using a microfluidic flow-focusing device. ................................................................. 92

Figure 4-9. SEM images of the freeze-dried microcapsules prepared from polymer 2-19 ($M_n = 47$ kDa). ................................................................. 93

Figure 4-10. SEM image showing a cross-section of a microcapsule prepared from polymer 2-19 ($M_n = 47$ kDa). ................................................................. 94

Figure 4-11. Confocal microscopy images obtained over 96 h of microcapsules prepared from polymer 2-19 ($M_n = 47$ kDa) that were exposed to 50 mM fluoride. .......... 95

Figure 4-12. % release of FITC-Dex over 96 h from microcapsules fabricated from polymer 2-19 ($M_n = 47$ kDa) with an average shell wall thickness of 1805 ± 79 nm. ....... 96

Figure 4-13. SEM images showing the changes in the morphology of the capsules over time when exposed to fluoride. ................................................................. 97

Figure 4-14. Effect of shell wall thickness of the rate of release from capsules prepared from polymer 2-19 ($M_n = 47$ kDa) in response to 50 mM fluoride. ............. 100

Figure 4-15. Effect of polymer molecular weight on the rate of release from capsules in response to 50 mM fluoride. ................................................................. 101

Figure 4-16. Tuning the rate of release from the microcapsules by varying the molecular weight of the polymers used to fabricate the capsules and by varying the thickness of the shell wall. ................................................................. 102

Figure 5-1. Non-specific degradation of polymer 2-14. .................................................... 108

Figure 5-2. Proposed pathways leading to depolymerization of poly(phthalaldehydes) ...... 110

Figure 5-3. Illustration of a multi-stimuli-responsive material that provides an amplified response prepared by selective laser sintering of PCl$_2$PA. ........................................... 114

Scheme 5-1. Synthesis of monomer 5-13 and PCl$_2$PA. .................................................... 117

Figure 5-4. Synthesis of PCl$_2$PA with different responsive end-caps. ............................. 119

Figure 5-5. Percent degradation of 7.0 mM solutions of polymers 2-14, 2-8, 2-20, 5-20, 5-14, and 5-15 after 6 days. ................................................................. 120
Figure 5-6. Percent degradation of 5.2 mM solutions of polymers 2-8, 2-20, 5-14, and 5-15 after 6 days in the presence of 100 equiv BzOH

Figure 5-7. Bench stability test for polymers 2-8 and 5-14.

Figure 5-8. Normalized TGA curves and thermal degradation temperatures for polymers 2-8, 2-20, 5-14, and 5-15.

Figure 5-9. Selective depolymerization of PCl2PA in response to Pd(0).

Figure 5-10. Selective depolymerization of PCl2PA in response to fluoride.

Figure 5-11. Dose-dependent depolymerization response of polymer 5-14 in response to Pd(0).

Figure 5-12. Solid state depolymerization of PCl2PA in response to fluoride.

Figure 5-13. GPC analysis of polymers 5-18 and 5-15 after exposure to fluoride in the solid state.

Figure 5-14. Sample optical microscopy image of the particles of PCl2PA formulated with plasticizer and ground using a mortar and pestle.

Figure 5-15. Our system for the selective laser sintering of PCl2PA.

Figure 5-16. Stability of polymers 5-14 and 5-18 to SLS.

Figure 5-17. Depolymerization of sintered rings in response to specific signals.

Figure 5-18. Control experiments for sintered disks made from polymers 5-14 and 5-18.

Figure 5-19. Multi-stimuli-responsive materials made from PCl2PA using SLS.

Scheme 5-2. Recovery of 5-12 from the depolymerization of a material fabricated from PCl2PA.
LIST OF TABLES

Table 2-1. Effect of monomer purification procedure on yield of polymer 2-6......................42

Table 3-1. Surface elemental composition and average pumping speeds for films of polymers 2-6 ($M_n = 33$ kDa), 2-19 ($M_n = 32$ and 47 kDa), and 3-3 ($M_n = 32$ kDa)............71

Table 3-2. Changes in the minimum and maximum thicknesses of films of polymers 2-6 ($M_n = 42$ kDa), 2-19 ($M_n = 43$ kDa), and 3-3 ($M_n = 43$ kDa) after exposure to 0.1 M NaF for 30 min.................................................................72

Table 3-3. Contact angles for films prepared from polymers 2-6 ($M_n = 43$ kDa), 2-19 ($M_n = 42$ kDa), and 3-3 ($M_n = 42$ kDa).................................................................74

Table 3-4. Average pumping speed provided by films of polymer 2-19 ($M_n = 43$ kDa) with different widths, lengths, and thicknesses in the presence of 9 μM β-D-glucuronidase .................................................................75

Table 4-1. Conditions for the fabrication of microcapsules from polymer 2-19 ($M_n = 47$ kDa) with different average shell wall thicknesses using microfluidic flow-focusing...99

Table 5-1. Substituent effects on the rate of acid-catalyzed hydrolysis of 1,3-dioxolanes....112

Table 5-2. Conditions and $^1$H NMR yields for the oxidation of 5-10 to 2-2..........................116
ACKNOWLEDGEMENTS

First, I would like to thank my advisor, Scott Phillips, for taking a chance on me when he let me join his lab five years ago. Scott has helped me immeasurably to grow as a scientist and to achieve what I have done so far. He has always pushed me to work towards bigger and better things, and for that I am truly grateful. I would also like to thank my current committee members, Alex Radosevich, Ayusman Sen, and Kyle Bishop, for their guidance, as well as Steven Weinreb, Ken Feldman, and Mike Hickner, who at different times have either served on my committee or stood in for other members. Alex has especially been a valuable source of guidance and information for me in my time as a graduate student.

The past and present members of the Phillips laboratory are the most eclectic, inspirational, brilliant, and supportive group of people I have ever met. I would not be half of the scientist or person I am today without them. A few people in particular have been instrumental in my grad school career. Thank you to Dr. Kyle Schmid for inviting me to join his trivia team and giving me an escape from lab on Tuesday and/or Wednesday nights. Thank you to Mike Olah for keeping me company on many a late night in lab. Thank you to Dr. Matt Baker for being a constant source of knowledge (despite his awful memory; yes, we do have ether in the SPS) and a great friend. Finally, thank you to Dr. Jesse Robbins, who was my host when I visited Penn State and my desk and bench neighbor for four of my five years here. Jesse has been equal parts a friend and mentor to me, and I am incredibly grateful that I got the chance to work (and sometimes dance) alongside her.

My family has always been there for me in my life, and has continued to be there through grad school as well. Thank you for always giving me a place to come home to, and for always being supportive and understanding, no matter what I have been going through.
Finally, and most of all, thanks to my long-suffering girlfriend Nicole Dunn, to whom this dissertation is dedicated. Nicole has been my best friend through the past five years, and has believed in me more than I have ever believed in myself. Thank you for helping me always to put things in perspective and for keeping me sane. Thank you for always understanding when I come home late or when I need to go into work on a Saturday. Finally, thank you for dragging me hiking and camping and biking and everywhere else and giving me an escape from the stresses of work. I would not have made it through the past five years without her.
Chapter 1

Stimuli-Responsive Polymers that Respond through Depolymerization

1.1 Introduction to Stimuli-Responsive Polymers

Stimuli-responsive, or “smart” polymers, are materials capable of changing their physical and/or chemical properties in response to an applied signal. Although the potential (and in some cases, realized) applications for stimuli-responsive polymers are varied, researchers have been particularly interested in using these polymers to develop artificial systems that mimic the ability of biological systems to respond to their environment. Examples of stimuli-responsive polymers range in terms of the chemical structures of the polymers and in terms of types of environmental stimuli to which the polymers respond (e.g., chemical, photo, biological, magnetic, electrical, thermal, mechanical). With regards to the physical or chemical responses of the polymers to a stimulus, common examples include: (i) coil-to-globule transitions (e.g., the thermal response of poly(N-isopropylacrylamide)); (ii) self-assembly and disassembly of polymeric structures; (iii) swelling and de-swelling of responsive hydrogels or of polymer brushes; (iv) sol-gel transitions, and (v) reversible restriction of movement in polymer chains by crystallization or vitrification (e.g., in shape memory polymers).

Comparatively, polymers that depolymerize in response to a stimulus are less common. However, several applications of such polymers have been shown in the literature, including: (i) as carriers and coatings for drug and gene delivery; (ii) as sensors; (iii) as lithographic resists; (iv) as pumps and motors for controlling movement on the nano- and microscale; (v) as recyclable materials, and (vi) as seals for controlling the flow of liquid. This chapter discusses the different types of depolymerizable polymers used as smart materials,
particularly CD, polymers, an emerging class of stimuli-responsive polymers that are capable of depolymerization in response to a specific signal through a continuous and head-to-tail mechanism.\textsuperscript{28-32}
1.2 Classes of Depolymerizable Polymers

The International Union of Pure and Applied Chemistry (IUPAC) defines depolymerization as “the process of converting a polymer into a monomer or a mixture of monomers.” The breadth of this definition means that many polymers (including polymers more traditionally referred to as degradable and biodegradable) can be described as depolymerizable. For example, between January 1, 2008 and January 15, 2014, there were 1723 scientific publications that focused on synthetic polymers that could be considered as being capable of depolymerization. To better delineate the different types of depolymerizable polymers, further classifications are used, as shown in Figure 1-1. These classifications are based on (i) the mechanism of depolymerization (fragmentation or continuous), and (ii) the specificity and selectivity of the depolymerization response. The following sections provide descriptions of each class of depolymerizable polymer, and present examples of each being used as stimuli-responsive materials.
1.2.1 FD\textsubscript{b} Polymers

FD\textsubscript{b} polymers\textsuperscript{34} (polymers that undergo fragmentation depolymerization from non-specific bond cleavage within the polymer backbone) represent the most common of the four classes of depolymerizable polymers: 95% of the 1723 publications (vide supra) fall into this category, compared with 3% for CD\textsubscript{b} polymers and 1% each for both FD\textsubscript{r} and CD\textsubscript{r} polymers.\textsuperscript{28} The majority of both degradable polymers used for biomedical applications\textsuperscript{35} and biodegradable plastics\textsuperscript{36} fall in this category, which is why FD\textsubscript{b} polymers are so ubiquitous and well-studied in comparison to the other three classes. For polymers capable of fragmentation depolymerization,
one reaction between the polymer and a stimulus results in two polymer fragments (Figure 1-1a). Therefore, complete depolymerization to the monomer would theoretically require \( n - 1 \) reactions (where \( n \) is the number of repeating units in the polymer) between the polymer and the stimulus. In addition, the depolymerization response of FD₈ polymers is non-specific. For example, the depolymerization of a representative example of this class of polymer, poly(L-lactic acid) (PLLA) (1-1) (Figure 1-2a), can occur through simple hydrolysis of the ester bonds connecting the polymer repeating units or in response to a number of other stimuli, including enzymes. As a stimuli-responsive material, PLLA has largely been used for medical applications due to its biocompatibility. In one example from the Wooley group, micelles and nanoparticles were prepared from block copolymers of PLLA and poly(N-(acryloxyoxy)succinimide-co-N-acryloylmorpholine) (1-2) (Figure 1-2b,c). The nanoparticles were shown to release Nile red, an encapsulated dye, either slowly through hydrolysis of the PLLA backbone (some release observed over 90 d) or more rapidly in the presence of the proteinase K enzyme (complete release observed after 2 d). The authors proposed that the carriers could be used to encapsulate and release more relevant therapeutics.
Figure 1-2. Representative example of an FD$_2$ polymer and its application as a drug delivery vehicle. (a) Bond cleavage in PLLA (1-1) in response to a stimulus. (b) Copolymer of PLLA and poly(N-acryloxyloxy)succinimide-co-N-acryloylmorpholine) (1-2).\textsuperscript{17} (c) Release from nanoparticles formulated from polymer 1-2 through depolymerization of the PLLA block. Adapted with permission from \textit{J. Am. Chem. Soc.}, \textbf{2012}, \textit{134}, 1234–1242. Copyright 2012 American Chemical Society.

1.2.2 FD$_2$ Polymers

FD$_2$ polymers (sometimes referred to in the literature as “chain-shattering” polymers)\textsuperscript{41-42} also depolymerize through a fragmentation mechanism. However, depolymerization is mediated by a reaction-based detection unit\textsuperscript{43} and not through random backbone cleavage. Reaction-based detection units are functionalities covalently linked to a polymer that are chosen to react with a specific chemical or physical stimulus and that act to stabilize the polymer.\textsuperscript{28-29} The chemistry of reaction-based detection units draws inspiration from protecting groups, which are usually
associated with small molecule organic synthesis. Upon reaction with the stimulus of interest, the reaction-based detection unit is (most commonly) cleaved from the polymer, removing the stabilizing effect and leading to fragmentation of the polymer into two lower-molecular-weight oligomers in the case of FD, polymers (Figure 1-1b). Importantly, a variety of reaction-based detection units can be used interchangeably, making it facile to alter the stimulus to which the polymer responds.

One example of an FD, polymer (1-3) reported by the Almutairi group is shown in Figure 1-3. The reaction-based detection unit in this example is an aryl boronate, which responds selectively to hydrogen peroxide. Oxidative cleavage of the aryl boronate results in a quinone methide elimination reaction from the benzyl linker, revealing a phenoxide in the backbone of the polymer (1-4). This phenoxide can undergo two quinone methide elimination reactions, cleaving two ester bonds. Thus, the reaction results in the cleavage of the polymer into two fragments as shown in the case of FD, polymers, albeit with a greater degree of selectivity. Recently, these polymers have been developed as stimuli-responsive carriers for the encapsulation of gadolinium oxide nanoparticles, which act as contrast agents for magnetic resonance imaging (MRI). The particles release the contrast agents in response to hydrogen peroxide, a reactive oxygen species that increases in concentration in response to inflammation and during the development of several diseases, including cancer, atherosclerosis, and ischemia. The hydrophobic structure of the carrier quenches the signal enhancement provided by the gadolinium nanoparticles. Thus, release of the nanoparticles in response to hydrogen peroxide increases the magnetic relaxation times, with values proportional to the concentration of hydrogen peroxide. The authors proposed that these carriers could be used as tools for biological studies or as improved diagnostic reagents. The Almutairi group has also demonstrated FD, polymers based off of the same design in which the aryl boronate functionality was replaced with reaction-based detection units that respond to ultraviolet and near infrared light.
1.2.3 CD₃ Polymers

Polymers classified as CD₃ undergo continuous depolymerization mediated by non-specific bond cleavage within the polymer backbone. Also referred to as polymer unzipping, continuous depolymerization is distinct from fragmentation depolymerization in that the cleavage of bonds by a stimulus propagates through the polymer backbone, breaking all bonds linking the
repeating units of the polymer from the site of the initial reaction. Thus, polymers capable of continuous depolymerization inherently provide an amplified response to a signal, in that a single reaction leads to many bonds being broken. In the case of CD$_b$ polymers, the depolymerization reaction occurs as a result of random chain scission in the polymer backbone and not through the specific interaction of a stimulus and a reaction-based detection unit.

Poly(olefin sulfones) are a set of polymers that typify CD$_b$ polymers. Prepared by the low temperature polymerization of sulfur dioxide and an alkene, these polymers are sensitive to basic conditions$^{23,26}$ and to high energy radiation (e.g., electron beams,$^{52}$ extreme ultraviolet light,$^{53}$ and gamma rays$^{54}$) (Figure 1-4a). Both base and radiation randomly cleave bonds in the polymer backbone, leading to reversion of the polymer to sulfur dioxide and the alkene.$^{22,26}$ Since this reactivity is inherent to the backbone of the polymer, changing the stimulus to which the polymers depolymerize would be difficult in comparison to polymers that respond through a reaction-based detection unit.

In 2010, Lobez and Swager utilized the known reactivity of poly(olefin sulfones) to develop a sensor for detecting high levels of radiation (Figure 1-4b).$^{22}$ The sensor consisted of a composite of a poly(olefin sulfone) and carbon nanotubes that connects two electrodes. The polymer acts as an insulator that is removed when exposed to radiation, thus restoring conductivity between the electrodes and providing a response that can be detected by an ammeter. The specific polymer used was poly(1-hexene sulfone) as a random co-polymer with repeating units containing azides, which were functionalized after polymerization using the 1,3-Huisgen cycloaddition with primary alkynes. The post-polymerization functionalization reaction was used to add a large aromatic hydrocarbon functionality (i.e., pyrene) and bismuth to the polymer. Pyrene was appended to improve the binding of the polymer to the carbon nanotubes, while the organobismuth moiety was added to increase the sensitivity of the composite to radiation. The sensor containing the polymer with pyrene and bismuth ($1$-$5$ in Figure 1-4c) showed a 5.12×
increase in conductivity in response to $5 \times 10^3$ rad of gamma radiation, which was significantly higher than devices containing the polymer functionalized only with pyrene (~0.15× increase in conductivity) or the poly(1-hexene sulfone) homopolymer (no increase in conductivity).\textsuperscript{22}

\textbf{Figure 1-4.} Representative example of a CD$_2$ polymer and its application as a sensor. (a) General conditions for polymerization and depolymerization reactions of poly(olefin sulfones). (b) Poly(olefin sulfone) derivative 1-5 used as a composite with carbon nanotubes for the development of devices for sensing radiation.\textsuperscript{22}

\subsection*{1.2.4 CD$_2$ Polymers}

CD$_2$ polymers are defined as polymers that undergo continuous depolymerization mediated by a reaction-based detection unit.\textsuperscript{28,32} In the literature, this class of polymers are also referred to as “self-immolative”\textsuperscript{55} (a term adopted from pro-drug chemistry)\textsuperscript{56} or “metastable”
polymers. CD$_r$ polymers are end-capped with reaction-based detection units that impart thermodynamic stability to the polymer (Figure 1-5).

![Diagram of CD$_r$ polymers]

**Figure 1-5.** Illustration of the general design of CD$_r$ polymers. Cleavage of the polymer end-cap results in a thermodynamically unstable species, which depolymerizes continuously and from head-to-tail to the monomer or other small molecule product.

When a specific stimulus cleaves the bond between the end-cap and the polymer, the resulting unstable polymeric species continuously depolymerizes head-to-tail to the constituent monomer or other small molecule product, ideally under ambient conditions. The design of CD$_r$ polymers therefore combines the inherent amplified response provided by CD$_b$ polymers with the selectivity shown in FD$_r$ polymers. As a result, CD$_r$ polymers have the potential to dramatically increase the rate, magnitude, and selectivity of response of a material to a stimulus in comparison to smart materials containing other types of depolymerizable polymers. Possible applications of such materials include: (i) plastics that are easily recycled; (ii) biomaterials; (iii) carriers that are capable of controlled release; and (iv) sensors for use as diagnostics.
Polymers capable of end-cap-mediated head-to-tail depolymerization were first suggested in a series of reports from the Physical Research Laboratories at Edgewood Arsenal in 1966.\textsuperscript{58-59} Although the reports focused primarily on the synthesis and characterization of poly(heptaldehyde), the author also proposed that end-capping the polymers with certain functionality could facilitate selective depolymerization, which could to be used to detect biological warfare agents. In 1978, DuPont patented the use of polyaldehydes end-capped with UV responsive groups as a component of a negative photoresist, where the aldehydes released through depolymerization could cross-link a polyamide or polyamine.\textsuperscript{60} In 1996, Hercules patented the use of ester end-capped polyaldehydes as components in disintegrable medical implants.\textsuperscript{61} However, the concept of polymers that continuously depolymerize through an end-cap-mediated mechanism did not appear in the scientific literature until 2008.\textsuperscript{55} For the purposes of this dissertation, the current examples of CD\textsubscript{r} polymers will be divided into five categories (as shown in Figure 1-6): (i) poly(benzyl carbamates);\textsuperscript{55,57,62-69} (ii) poly(benzyl ethers);\textsuperscript{70-71} (iii) polymers that depolymerize through alternating quinone methide elimination and cyclization reactions;\textsuperscript{72-76} (iv) polymers that depolymerize only through cyclization reactions;\textsuperscript{77} and (v) poly(acetals).\textsuperscript{78-85} The remainder of this chapter will discuss these different classes of CD\textsubscript{r} polymers.
Figure 1.6. Representative examples of the five classes of CD$_r$ polymers, and the depolymerization mechanism for each: (a) Poly(benzyl carbamates); (b) poly(benzyl ethers); (c) polymers that depolymerize through alternating cyclization and quinone methide elimination reactions; (d) polymers that depolymerize through cyclization reactions; and (e) poly(acetals).

1.3 Poly(benzyl carbamates)

The first type of CD$_r$ polymer detailed in the scientific literature were the poly(benzyl carbamates) reported by the Shabat group in 2008 (Figure 1-6a). Depolymerization of the polymer is triggered by cleavage of the reaction-based detection unit at the end of the polymer, revealing a carbamic acid. The carbamic acid rapidly undergoes decarboxylation to form an aniline. Successive 1,6-azaquinone methide elimination and decarboxylation reactions through the polymer backbone lead to the formation of carbon dioxide and an azaquinone methide intermediate as the initial products. The release of a gaseous product is the main driving force for the depolymerization reaction. The azaquinone methide species formed is a highly electrophilic Michael acceptor, and is rapidly intercepted by a nucleophile, such as water or an amine.
The primary advantage of poly(benzyl carbamates) is that the structure of the polymers is amenable to chemical changes that can alter, for example, the solubility of the polymer or the rate of depolymerization. However, the rate of depolymerization is highly dependent on environmental polarity due to the high activation energy of the azaquinone methide elimination reaction. Therefore, the time required for complete depolymerization is greater in low polarity solvents or in the solid state (due to the hydrophobicity of the polymer matrix). Even in polar environments, the time required for complete depolymerization of a poly(benzyl carbamate) ranges from 6 to 10 hours in a completely aqueous solution to 5 days in a 9:1 DMSO–water mixture (at 85 °C).

1.3.1 Depolymerizable Poly(benzyl carbamates) as Diagnostic Reagents

In the aforementioned 2008 report of depolymerizable poly(benzyl carbamates) by Shabat and coworkers, the polymers were designed to act as diagnostic reagents to detect enzymes. The monomer (1-6) was prepared in four steps from ethyl-4-aminobenzoate. The condensation polymerization reaction employed methodology previously developed for the synthesis of poly(urethanes), utilizing a Lewis acid, dibutyltin dilaurate (DBTL), as the catalyst and the phenyl carbamate functionality as a “blocked” isocyanate (Figure 1-7a). Since the initial report, DBTL has remained as the primary reagent employed for the polymerization of depolymerizable poly(benzyl carbamates), although the Boydston group has also reported the use of triethylamine as the catalyst. After a reaction time of 15 min, the poly(benzyl carbamate) was end-capped with 4-hydroxy-2-butanone. The resulting polymer (1-7) contained approximately 17 repeating units, as determined by 1H NMR. The tert-butyl ester group on each repeating unit was then deprotected using TFA to yield a water soluble polymer (1-8). Polymer
1-8 was evaluated for its response to the enzyme bovine serum albumin (BSA), which catalyzes the β-elimination of the 4-hydroxy-2-butanone end-cap. The depolymerization reaction was monitored by the increase in fluorescence emission observed with the release of the aniline monomer (1-9); complete depolymerization required approximately 10 h (Figure 1-7b). The authors proposed that the amplified, fluorescent response provided by the depolymerization of the polymer could be used to determine enzyme activity.

Figure 1-7. Depolymerizable poly(benzyl carbamate) 1-8 for use as a diagnostic reagent. (a) Synthesis of polymer 1-8. (b) Depolymerization of polymer 1-8 in response to bovine serum albumin (BSA).

1.3.2 Poly(benzyl carbamate) Oligomers as Phase-Switching Reagents in Paper Microfluidic Devices

In 2012, Phillips and coworkers reported the development of paper microfluidic devices that contained a small molecule, hydrophobic reagent that converted to hydrophilic products in the presence of hydrogen peroxide. This “phase-switch” in the presence of an analyte changed the rate at which a sample flowed through the device. Since the rate of change depended on the concentration of hydrogen peroxide, the device allowed the user to determine the initial analyte concentration based on the time needed for the sample to completely flow through.
The chemistry of the small molecule reagent was similar to that of the poly(benzyl carbamates), in that a quinone methide-type elimination reaction triggered by cleavage of a reaction-based detection unit led to decarboxylation and cleavage of a carbamate functionality. This similarity led to a hypothesis that the sensitivity of a device based on flow through time could be improved by incorporating reagents that gave a greater magnitude of change in polarity in response to an analyte. To test this hypothesis, Phillips and coworkers used depolymerizable poly(benzyl carbamate) as phase-switching reagents in paper microfluidic devices (Figure 1-8a). The authors compared the sensitivity of devices incorporating aryl boronate–end-capped poly(benzyl carbamate) oligomers with 0, 1, 2, 5, and 8 repeating units (1-10–1-14) (Figure 1-8b). A 6× increase in sensitivity (measured by determining limit of detection of hydrogen peroxide) between 1-10 (n = 0) and 1-11 (n = 1) supported the initial hypothesis, although the increase in sensitivity when using the oligomers where n = 2, 5, and 8 was less pronounced. The authors proposed that this observation was the result of an increase in time required for complete depolymerization as the oligomers increased in length. For example, the depolymerization half-life for 1-11 (n = 1) in solution was about 12 min, while the depolymerization half-life for 1-14 (n = 8) was about 57 min. In subsequent work, the authors expanded on this strategy by using oligomer 1-14 (n = 8) as a phase-switching reagent in paper microfluidic devices that detected enzymes and heavy metals.
Figure 1-8. Use of depolymerizable poly(benzyl carbamates) as phase-switching reagents for use in paper microfluidic devices. (a) Design of paper microfluidic device using flow through time to determine the concentration of an analyte. (b) The poly(benzyl carbamate) oligomers used as phase-switching reagents to test the effect of molecule size on assay sensitivity. Adapted with permission from Macromolecules, 2013, 46, 5177–5183. Copyright 2013 American Chemical Society.

1.4 Poly(benzyl ethers)

Recently, poly(benzyl ethers) have emerged as a new class of CD$_2$ polymers. The work built off of previous research by the McGrath group, who developed depolymerizable benzyl ether dendrimers prepared by step-wise synthesis, and by the Itoh group, who developed conditions for preparing and polymerizing stabilized quinone methide monomers. The
depolymerization mechanism of poly(benzyl ethers) is similar to that of the poly(benzyl carbamates). Cleavage of the reaction-based detection unit by a stimulus reveals a phenol at the end of the polymer, which can be deprotonated to facilitate a series of quinone methide elimination reactions that proceed through the polymer backbone in a reverse of the anionic polymerization reaction typically used to prepare this class of polymer (Figure 1-6b). The driving force for the depolymerization reaction is the conjugation established with the aromatic species at the benzylic position of each repeating unit upon formation the quinone methide moiety.

Since the depolymerization is based on quinone methide elimination reactions, the rate of depolymerization is dependent on environmental polarity (e.g., the dielectric constant of the solvent). However, the rate of depolymerization for poly(benzyl ethers) is still fairly rapid, with complete conversion of the polymer to monomer observed in 30 minutes in DMF, although base is usually required. The benzyl ether linkages between the repeating units are stable, with no background degradation for polymers end-capped with non-responsive functionalities observed when they were exposed to acid, base, or elevated temperatures.

1.5 CD, Polymers Based on Alternating Quinone Methide Elimination and Cyclization Reactions

Polymer 1-15 (Figure 1-9) is the original CD, polymer based on alternating quinone methide elimination and cyclization reactions, which was reported by the Gillies group in 2009. The design drew inspiration from depolymerizable dendrimers that had previously been reported by the Shabat group. Each repeating unit of the polymer consisted of two key linker functionalities: (i) N,N'-dimethylethyleneamine, which is linked via a carbamate to (ii) 4-hydroxybenzyl alcohol. Cleavage of the reaction-based detection unit results in intramolecular
cyclization of the first linker to form a cyclic urea (1-18), followed by quinone methide elimination and decarboxylation to release the next repeating unit.

**Figure 1-9.** Examples of CD$_r$ polymers based on alternating cyclization and elimination reactions. Polymers 1-16 and 1-17 were developed to increase the rate of depolymerization of this class of polymer over the rate for the initial design (1-15).$^{72,73}$

### 1.5.1 Increasing the Rate of Depolymerization

Polymer 1-15 was fairly slow to depolymerize compared to other polymers with depolymerization mechanisms involving quinone methide-type elimination reactions (*i.e.*, poly(benzyl carbamates) and poly(benzyl ethers)). Even in a fairly polar 3:2 solution of buffered water and acetone, the polymer (with a degree of polymerization of 17) took 5 days to completely depolymerize after cleavage of the end-cap.$^{72}$ Small molecule studies on similar systems suggested that the cyclization step is the rate-limiting step in the depolymerization reaction.$^{94}$ Hypothesizing that the rate of cyclization (and therefore, the rate of depolymerization) could be improved by changing the nucleophile and electrophile involved in the cyclization step, Gillies and coworkers reported two new polymer designs, in which the $N,N'$-dimethylethyleneamine linker used in polymer 1-15 was replaced by 2-(methylamino)ethanol (1-16) and 2-mercaptoethanol (1-17) (Figure 1-9).$^{73}$ The polymers used for comparison were approximately the same length as polymer 1-15 was in previous test, and were tested under the same conditions.
Polymer 1-16, which changed the electrophile for the intramolecular cyclization reaction from a carbamate to a carbonate, completely depolymerized in 6 h. The effect was even more pronounced for polymer 1-17, in which the carbonate acted as the electrophile for the cyclization reaction and a thiol acted as the nucleophile. Polymer 1-17 depolymerized in 2 h, approximately 60× faster than 1-15.73

1.6 Polymers Based on Cyclization Reactions

CD, polymers that depolymerize solely through cyclization reactions are the least studied of the five classes, with only a single example reported by Gillies and coworkers in 2010.77 The polymer design (Figure 1-6d) consists of N,N′-dimethylethyleneamine linked to 2-mercaptoethanol, which cyclize upon cleavage of the reaction-based detection unit to form a urea and oxathiolan-2-one. Since the rate of cyclization is fairly slow compared to other reactions involved in depolymerization mechanisms, the depolymerization time for this polymer also was longer than other examples. After about 15 d, 80% of the polymer had depolymerized in a 3:2 mixture of buffered water and acetone. Even after 30 days, very little additional polymer had depolymerized. The authors proposed that the unreacted polymer had formed cyclic species, and therefore could not respond to the stimulus. Despite being slower to depolymerize than other examples, the polymer does offer the advantage of giving inert small molecule products from the depolymerization reaction, which may be more amenable to biological applications than polymers that give off highly reactive quinone methide-type species.77
1.7 Poly(acetals)

Poly(acetals), or poly(aldehydes), are a set of CD$_r$ polymers characterized by repeating carbon—oxygen bonds in the polymer backbone.\textsuperscript{95} The structure of these polymers results in a distinct mechanism of depolymerization, which is based on the phenomenon of polymer ceiling temperatures ($T_c$).\textsuperscript{78,80}

1.7.1 Polymer Ceiling Temperatures

Chain polymerization reactions consist of three main steps: (i) initiation, (ii) propagation, and (iii) termination.\textsuperscript{96} In the propagation step, the reactive species at the end of the polymer chain reacts with another monomer, increasing the degree of polymerization from $n$ to $n + 1$ (Figure 1-10).

\begin{equation}
\begin{array}{c}
\text{\textendash}\text{\textendash}\text{\textendash}\text{\textendash}\text{\textendash}\text{\textendash}M_n^* + M \xrightleftharpoons[k_{dp}]{k_p} \text{\textendash}\text{\textendash}\text{\textendash}\text{\textendash}\text{\textendash}\text{\textendash}M_{n+1}^*
\end{array}
\end{equation}

\textbf{Figure 1-10.} The propagation and depropagation steps of a chain polymerization reaction.\textsuperscript{96}

A rate constant $k_p$ exists for the propagation step, along with a rate constant $k_{dp}$ for the reverse reaction (the depolymerization or depropagation step). The ceiling temperature for a polymer is the temperature at which the propagation and depropagation rates are equal, which, through derivation, gives the mathematical definition $T_c = \frac{\Delta H_p}{\Delta S_p}$.\textsuperscript{96-97}

Even before the introduction of CD$_r$ polymers, poly(acetals) were known to have exceptionally low ceiling temperatures compared to other polymers.\textsuperscript{96} For example, while poly(ethylene) and poly(styrene) have $T_c$ values of 610 °C and 395 °C respectively,\textsuperscript{98} many
poly(acetals) have \( T_c \) values close to or below room temperature, such as poly(acetaldehyde) \( (T_c = -39 \, ^\circ C) \) and poly(propanal) \( (T_c = -31 \, ^\circ C) \).\(^{32,96}\) For these poly(acetals) and other polymer with low \( T_c \) values, the polymerization reaction must be run below the \( T_c \) and the reactive end of the polymer must be capped to remove the kinetic mechanism of depolymerization upon warming the reaction mixture to ambient temperature.

### 1.7.2 Poly(acetals) as CD\(_r\) Polymers

Recently, researchers have taken advantage of the low ceiling temperature of poly(acetals) in their use as CD\(_r\) polymers.\(^78\) If a poly(acetal) is end-capped with a reaction-based detection unit, then the reactive end of the polymer can be removed selectively to give a species that is close to or significantly above its \( T_c \) (Figure 1-6e). The thermodynamically unstable, hemi-acetal-terminated intermediate will then rapidly depolymerize to the aldehyde monomer in the reverse of an anionic polymerization reaction. Only two types of poly(acetals) have been demonstrated as CD\(_r\) polymers because of the low solubility of most poly(acetals):\(^{96}\) (i) poly(phthalaldehyde) (PPA) \( (T_c = -43 \, ^\circ C) \) (Figure 1-6e) and its derivatives,\(^{78,82,84-85}\) and (ii) poly(ethyl glyoxylate) \( (T_c = 35 \, ^\circ C) \) and its derivatives.\(^{32,83}\) The former class of poly(acetals) are the main focus of this dissertation, and will be discussed in more detail in Chapter 2.

### 1.7.3 Poly(glyoxylates) as Depolymerizable Polymers

The poly(glyoxylate) family was first reported in 1979 patent by Monsanto for use in biodegradable detergent formulations.\(^{99}\) More recently, poly(glyoxylates) have attracted interest
as biomaterials because of their hydrolytic instability and the low toxicity of the products, particularly poly(ethyl glyoxylate), where depolymerization of the polymer followed by hydrolysis of the monomer gives ethanol and glyoxylic acid hydrate as the main products.\textsuperscript{100-101}

The use of poly(glyoxylates) as CD\textsubscript{r} polymers was reported by Gillies and coworkers in 2014.\textsuperscript{83} They prepared poly(ethyl glyoxylate) through anionic polymerization of commercially available ethyl glyoxylate catalyzed by triethylamine at \(-20\) °C, followed by termination of the reaction by addition of 6-nitroveratryloxy carbonyl chloride (NVOC-Cl) to give poly(ethyl glyoxylate) end-capped with a reaction-based detection unit (polymer 1-20). Polymer 1-20 showed 70\% depolymerization after 80 min exposure to 300-350 nm UV light and incubation in 9:1 CD\textsubscript{3}CN–D\textsubscript{2}O for 24 h, with ethyl glyxolate hydrate (1-21) observed as the major small molecule product (Figure 1-11). The depolymerization reaction was likely incomplete due to the ceiling temperature of poly(ethyl glyoxylate) being slightly above room temperature, since complete removal of the end-cap was observed by \textsuperscript{1}H NMR. A control polymer end-capped with benzyl chloroformate showed no significant depolymerization under the same conditions. Polymer 1-20 also depolymerized in the solid state, as films of the polymer exposed to UV light for 17 h and incubated in buffered water showed complete mass loss after 17 d.\textsuperscript{83}
1.8 Conclusion

In this chapter, examples of stimuli-responsive materials containing FD<sub>b</sub>, FD<sub>r</sub>, and CD<sub>b</sub> polymers used as (i) drug carriers, (ii) diagnostic reagents, and (iii) sensors were presented. Furthermore, CD<sub>r</sub> polymers were shown as an emerging class of depolymerizable polymers with the potential to achieve many of the same goals as the other three classes, with added improvements in the selectivity of the depolymerization response, in the speed and magnitude of response to a signal, and in the number of signals to which the polymers can respond.

Although the exact desirable characteristics will depend on what application it is needed for, an “ideal” CD<sub>r</sub> polymer for use as a stimuli-responsive material arguably would meet the following general criteria: (i) facile syntheses for accessing monomer and polymer; (ii) capability to depolymerizable rapidly under ambient conditions, both in solution and in the solid state; (iii) ability to incorporate different reaction-based detection units to tune the stimulus to which the polymer responds; (iv) stability in the absence of the stimulus of interest (i.e., no background degradation); and (v) stability to various processing conditions to allow for the preparation of materials from the polymer. The examples of CD<sub>r</sub> polymers outlined in this chapter offer certain advantages towards achieving these standards, yet also feature limitations that suggest the need for new solutions to truly realize the potential of this class of polymer.

The focus of this dissertation is the development of poly(phthalaldehydes) as CD<sub>r</sub> polymers towards the objective of applying these poly(acetals) to stimuli-responsive materials. The approach to this problem has involved fundamental work (i) on developing an improved synthetic procedure for preparing depolymerizable PPA, and (ii) on increasing the stability of this class of polymer through the preparation of new PPA derivatives. These fundamental studies have in turn allowed for more applied research in using poly(phthalaldehydes) as microscale pumps, as responsive microcapsules, and as materials for additive manufacturing.
1.9 References


15. This class of polymer is distinct from examples of stimuli-responsive polymers that are also degradable.


40. Grayson, A. C. R.; Voskerician, G.; Lynn, A.; Anderson, J. M.; Cima, M. J.; Langer, R. Differential Degradation Rates *In Vivo* and *In Vitro* Of Biocompatible Poly(lactic acid) and


Chapter 2

Development of an Improved Synthesis of End-Cap-Functionalized Depolymerizable Poly(phthalaldehydes)

The author of this dissertation was responsible for developing the purification procedure for the monomer, validating the end-cap fidelity of the polymers, and testing the ability of the polymer to depolymerize in the solid state. The author and Dr. Jessica S. Robbins together developed the new methodology for synthesizing depolymerizable PPA. Dr. Jessica S. Robbins also synthesized several of the initiators used in Figure 2-9a.

2.1 Introduction to Poly(phthalaldehyde)

The first synthesis of poly(phthalaldehyde) (PPA) from 1,2-benzenedicarboxaldehyde was reported by Aso and Tagami in 1967. In their initial report, the authors noted that exposure of the polymer to 2,4-dinitrophenylhydrazine and sulfuric acid gave a 98% yield of the bis-2,4-dinitrophenylhydrazone of the monomer. However, the remarkable ability of the polymer to depolymerize rapidly under ambient conditions was not truly recognized until the early 1980s, when employees at IBM began to use the polymer in the development of new resists for photolithography.

Photolithography for the patterning of semiconductors involves a substrate (usually a silicon wafer) coated by a polymer layer known as a resist. The polymer film is exposed to radiation (e.g., UV light or X-rays) through a mask that defines the pattern needed. Exposure of the film to radiation causes a change in the solubility of the polymer; thus, when the surface is washed with a developing solvent, the exposed film either (a) is washed away (a “positive” resist) or (b) remains, while the unexposed polymer is washed away (a “negative” resist). The uncovered substrate surface is then etched, and the resist is removed to reveal the patterned substrate.
In the 1980s, commercial resists primarily used a UV responsive small molecule, diazonaphthoquinone (DNQ), to effect the desired change in solubility of the polymeric resist. However, DNQ has a quantum yield of 0.2–0.3, meaning that multiple photons were required for a single reaction. Thus, the sensitivity of the resist was highly limited. The strategy developed by Ito and Willson at IBM (in collaboration with Professor Fréchet) to overcome this limitation was chemical amplification, where each individual photoreaction triggers a number of subsequent chemical transformations.

Several chemical amplification systems were developed to achieve improved sensitivity, including resists formulated with PPA and onium salts, also referred to as photoacid generators (PAGs) (Figure 2-1). In this system, depolymerization of PPA causes a change in the solubility of the resist. PAGs such as triphenylsulfonium hexafluoroarsenate (2-1) form strong acids in response to light through the mechanism shown in Figure 2-1a. The acetal backbone of PPA is sensitive to acid, and depolymerizes to the monomer (2-2) (Figure 2-1b), regenerating the acid in the process. Thus, the chemical amplification is achieved through the depolymerization of PPA (in this case acting as a CD_b polymer) and through the catalytic activity of the acid. Ultimately, PPA was never used in resists for commercial applications because of the volatile nature of the monomer (2-2), which led to contamination of the sensitive instruments in the exposure tool upon polymer depolymerization.
Figure 2-1. Components of photoresist based on chemical amplification developed by Ito and Willson. (a) Mechanism for photoacid generation from triphenylsulfonium hexafluoroarsenate (2-1).3 (b) Mechanism of acid-catalyzed depolymerization of PPA.5

In 2010, PPA re-emerged as a new type of CD, polymer in a report by Seo and Phillips.8 Based on the low $T_c$ of the polymer, the removal of reaction-based detection units from the polymer was anticipated to give highly unstable species that would rapidly depolymerize (as shown in Figure 1-6e). The authors prepared the polymers via anionic polymerization using $n$-butyl lithium as the initiator at $-80^\circ$C for 10–13 days. The reactive polymer ends were then capped with electrophiles for an additional 3–4 days, namely tert-butyldimethylsilyl (TBS) chloride and allyl chloroformate to give fluoride (2-3) and palladium(0) (2-5) responsive polymers respectively (Figure 2-2). A control polymer (2-4) was prepared by end-capping with allyl triflate. In solution, polymer 2-3 depolymerized completely in 1 min when exposed to 0.5 equiv of tetrabutylammonium fluoride (TBAF), while 97% of polymer 2-4 remained after 25 min when exposed to the same conditions (Figure 2-2).8 Next, polymers 2-4 and 2-5 were exposed to tetrakis(triphenylphosphine)palladium(0), which deprotects allyl carbonates much more rapidly than allyl ethers.8-10 In response to 0.4 equiv of Pd(PPh$_3$)$_4$, polymer 2-5 depolymerized completely to monomer in 5 min, while 95% of polymer 2-4 remained after 320 min when exposed to 0.5 equiv of the catalyst (Figure 2-2).8 These results suggest that removal of the
reaction-based detection unit caused depolymerization of the polymer, rather than non-specific chain scission in the polymer backbone by either fluoride or palladium(0).

**Figure 2-2.** Initial report of using synthesizing PPA end-capped with reaction-based detection units and using it as a CD, polymer.8

To evaluate the selective solid-state depolymerization of PPA, a film consisting of polymer 2-4 surrounding a cylinder of polymer 2-3 was prepared (Figure 2-3). When a solution of TBAF was added to the film suspended in ethyl acetate (which dissolves the monomer and not the polymer), only the cylinder of 2-3 depolymerized, thus leaving a hole in the film after only 15 min of exposure.8
**Figure 2-3.** Solid state depolymerization of PPA. (a) Graphical representation of the patterned film prepared from polymers 2-3 and 2-4. (b) Photograph of the patterned film. The dotted circle indicates the approximate location of the cylinder of polymer 2-3. (c) Photograph of the film after exposure to fluoride for 15 min. Adapted with permission from *J. Am. Chem. Soc.*, 2010, 132, 9234–9235. Copyright 2010 American Chemical Society.

Compared to the other types of CD, polymers presented in Chapter 1, PPA offers several key advantages, including (i) rapid depolymerization times, on the order of seconds to minutes; (ii) commercial availability of the monomer, and (iii) ability to depolymerize in the solid state. However, the initial report on the polymer left several key areas for improvement, particularly in terms of polymer synthesis. First, the polymerization time (13–18 days in total) was prohibitively long. Second, initiation of the polymerization with *n*-butyl lithium limited the scope of functional end-caps that could be incorporated. Finally, variations in the yield of polymer were observed depending on the batch of monomer used. With these limitations in mind, we developed a new procedure for synthesizing depolymerizable PPA.
2.1.1 Previous Methods for Synthesizing PPA

Several different methodologies have previously been reported for the preparation of non-responsive PPA. Cationic polymerization has been shown with various Lewis acid catalysts, including BF$_3$·OEt$_2$, triethylxonium tetrafluoroborate, tin(IV) chloride, and triphenylcarbenium tetrafluoroborate. However, it has recently emerged that PPA prepared by cationic polymerization is cyclic, which prevents the incorporation of reaction-based detection units as end-caps. Less common methods for preparing PPA include polymerization with aluminum coordination catalysts and polymerization by γ-ray irradiation of a monomer solution. All of these examples give poor control of the composition of the polymer end-caps, which is key to the ability of CD$_r$ polymers to respond to a stimulus. Thus, we focused on developing anionic polymerization conditions instead.

In addition to n-butyl lithium, Grignard reagents, lithium and potassium tert-butoxide, sodium naphthalene, and sodium benzophenone have all been used as initiators for the anionic polymerization of PPA. However, we were most interested in the methodology reported by Hedrick and coworkers, in which they polymerized PPA without responsive end-caps using an alcohol initiator (1-pyrenemethanol) activated by 1-tert-butyl-2,2,4,4,4-pentakis(dimethylamino)-2λ$^5$,4λ$^5$-catenadi(phosphazene) (P$_2$-t-Bu base), a strong and non-ionic nitrogen base ($pK_a$(MeCN) = 33.5), and end-capping with trichloroacetyl isocyanate (TCAI) (Figure 2-4).
The polymerization reaction using \( \text{P}_{2-\text{t- Bu}} \) base had a duration of only 3 h, and the authors showed that polymer produced using this methodology had complete end-cap fidelity (i.e., the desired end-caps were completely incorporated into the polymers). This chapter describes our efforts (i) to expand upon the work of Hedrick and coworkers and develop new conditions for the preparation of stimuli-responsive, depolymerizable PPA that are scalable and reproducible and that allow for the incorporation of responsive groups on either end of the polymer; and (ii) to prove that the procedure yields polymers that are appropriately capped on both ends and that depolymerize both in solution and in the solid state (Figure 2-5).
2.2 Results and Discussion

2.2.1 General Procedure for Synthesizing End-Capped PPA

There were several key alterations that we made to the conditions reported by Hedrick et al. in the development of our own procedure. First, in our hands purifying the commercially available P$_2$-t-Bu base by drying over calcium hydride before use was not effective for obtaining polymer. We instead used the reagent as received. Second, increasing the time allowed for propagation of the polymer (i.e., between addition of the initiator and termination of the reaction)
from 1 h to 2 h gave improved yields. Third, because the majority of electrophiles that we used to end-cap the polymer had leaving groups that could form acidic byproducts, we also added pyridine when terminating the polymerization reaction. Fourth, in our hands the procedure given for purification of the monomer (2-2) did not reliably remove all impurities to ensure adequate polymer yields. We instead took a stepwise approach towards developing a procedure that would reproducibly purify the monomer for polymerization (Section 2.2.2). Finally, we qualitatively observed that if the reaction mixture for the polymerization did not become viscous after ~30 min or if a white precipitate formed, then little to no polymer was obtained after terminating the reaction and attempting to isolate the polymer. The first case was resolved through the addition of more P$_2$-t-Bu base. In the second case, the reaction mixture was warmed until it became homogenous again, followed by the addition of more P$_2$-t-Bu base. These alterations lead to the development of general conditions for synthesizing end-capped PPA shown in Figure 2-6 (see Chapter 6 for full experimental details). The yields of polymer obtained using this procedure range from 44 to 97%, depending on the identity of R$_1$–OH and R$_2$–X. Furthermore, this procedure allows for the reaction-based detection unit to be incorporated on either end of the polymer.

![Synthesis of end-capped PPA](image)

**Figure 2-6.** Synthesis of end-capped PPA using a phosphazene catalyst to activate an alcohol initiator for anionic polymerization. Both R$_1$ and R$_2$ can be responsive end-caps when using this procedure, as shown in Figure 2-5.\(^\text{17}\)
2.2.2 Purification of 1,2-Benzenedicarboxaldehyde

The anionic polymerization for preparing depolymerizable PPA is a sensitive reaction, particularly in the context of the purity of the monomer, 1,2-benzenedicarboxaldehyde (2-2). The presence of water in the monomer would lead to polymer capped by hemi-acetal functionality, which would depolymerize upon warming to room temperature as a result of the low $T_c$ of the species. Furthermore, other impurities could act as an initiating or terminating species in the polymerization reaction, which could prevent incorporation of the reaction-based detection units.

To determine the extent of purification necessary, we conducted a stepwise study on a batch of commercially available monomer and tested the effect of each step of that process on the yield of polymer 2-6 (Table 2-1).

**Table 2-1.** Effect of monomer purification procedure on yield of polymer 2-6. Adapted with permission from *Macromolecules*, 2013, 46, 2963–2968. Copyright 2013 American Chemical Society.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Purification Procedure</th>
<th>% Yield of 2-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>1 x Recrystallization(^a) + 12 h on High Vacuum(^b)</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>2 x Recrystallization(^a) + 12 h on High Vacuum(^b)</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>2 x Recrystallization(^a) + 36 h on High Vacuum(^b)</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>3 x Recrystallization(^a) + 12 h on High Vacuum(^b)</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>3 x Recrystallization(^a) + 36 h on High Vacuum(^b)</td>
<td>70 ± 7(^c)</td>
</tr>
</tbody>
</table>

\(^a\) Recrystallization from 5:2 methylene chloride—hexanes. \(^b\) Stored in vacuo at 1.1 mmHg. \(^c\) Average of three separate purification procedures and subsequent polymerization reactions.
These experiments showed that both removing impurities from the monomer through 3× recrystallization from 5:2 methylene chloride–hexanes and drying the monomer through 36 h in vacuo were necessary to obtain polymer with satisfactory yields. Next, we repeated the purification process two additional times on different batches of monomer to ensure its reproducibility (Entry 6 of Table 2-1). The average yield of these three experiments was 70 ± 7%.

The difference in % yields between Entries 4 and 6 suggest that water was not the only impurity removed using this procedure. To determine the identity of this impurity, the supernatant from the first recrystallization of the monomer was concentrated and analyzed by $^1$H NMR (Figure 2-7). Most of the peaks in the spectrum that did not correspond to the monomer matched the known spectrum of 2-carboxybenzaldehyde (2-7). The presence of 2-7 is likely caused by the oxidation of 2-2 in the presence of air, which is a well known reaction. As a result, freshly purified monomer was always stored in a glove box under an inert atmosphere for all subsequent polymerization reactions.
Figure 2-7. $^1$H NMR spectra of the concentrated supernatant from one recrystallization of 1,2-benzenedicarboxaldehyde. Peaks marked with an asterisk (*) correspond to the known chemical shifts for 2-carboxybenzaldehyde (2-7). Adapted with permission from *Macromolecules*, 2013, 46, 2963–2968. Copyright 2013 American Chemical Society.
2.2.3 Controlling the Molecular Weight of PPA

The molecular weight of a CD₇ polymer is an important consideration because the number of repeating units in a polymer chain controls the degree of amplification of a depolymerization reaction. The degree of amplification can have a significant effect when a CD₇ polymer is used as a stimuli-responsive material; for example, Phillips and coworkers have shown that using longer depolymerizable poly(benzyl carbamate) oligomers gave an increase in the sensitivity of an assay for hydrogen peroxide (Section 1.3.2). In their initial report, Hedrick and coworkers suggested that the polymerization initiated with an alcohol and catalyzed by P₂-t-Bu base was a living polymerization, since the relationship between the theoretical molecular weight and actual molecular weight of the polymers was linear. Thus, we reasoned that we could control polymer molecular weight by changing the stoichiometry of the initiator. In fact, a clear linear relationship was observed in a test of the effect of the equivalents of isopropanol (the initiating alcohol) on the number average molecular weight (Mₙ) of polymer 2-8 (Figure 2-8). The reaction initiated with 0.002 equiv of isopropanol was run using five grams of monomer and showed no decrease in yield, indicating the scalability of the procedure. Five grams was the highest monomer loading we attempted; we believe that larger scale reactions would also be possible.
Figure 2-8. Controlling the molecular weight of end-cap–functionalized PPA. The $M_n$ of polymer 2-8 was governed by the equivalents of isopropanol used to initiate the polymerization reaction. Adapted with permission from *Macromolecules*, 2013, 46, 2963–2968. Copyright 2013 American Chemical Society.

2.2.4 Scope of Responsive and Functional Polymer End-Caps

Based on the proposed mechanism for depolymerization, cleavage of a responsive group from either end of the polymer can cause depolymerization (Figure 2-5). The only other type of CD$_r$ polymer with this capability are the poly(glyoxylates).$^{22}$ However, the previous procedure for synthesizing depolymerizable PPA by initiating with $n$-butyl lithium allowed for the functionalization of one chain end.$^8$ In comparison, using P$_2$-t-Bu base with an alcohol initiator allows for the incorporation of reaction-based detection units or other functionalities at either end of the polymer.

Figure 2-9 shows examples of polymers that were initiated by different nucleophiles and that were terminated by different electrophiles.
Figure 2-9. Synthesis of PPA with responsive and functional end-caps. (a) Alcohol initiators used to initiate the polymerization of PPA. (b) Electrophiles used to terminate the polymerization of PPA. Adapted with permission from *Macromolecules*, 2013, 46, 2963–2968. Copyright 2013 American Chemical Society.

All thirteen polymers were prepared using the general procedure shown in Figure 2-6, although the synthesis of polymer 2-14 required a change in solvent as a result of the poor solubility of the end-capping reagent in THF. In terms of responsive polymers, there are examples with functionality that is responsive to (i) UV light (2-9, 2-10, 2-14),\(^{23-25}\) (ii) palladium(0) (2-8),\(^{26}\) and fluoride (2-6, 2-15, 2-19).\(^{27-28}\) Other examples include polymers initiated by multi-functional linkers (2-11, which was initiated from ethylene glycol) and polymers that incorporate functional handles for post-polymerization modification reactions (2-12, 2-13, and 2-18), all of which could be used to prepare more complex macromolecular architectures. Polymer 2-16 is terminated with
a dansyl group, a fluorescent moiety commonly used to determine environmental polarity. A variety of other nucleophiles and electrophiles could be incorporated into the polymer as well, although a decrease in polymer yield can be expected in certain cases, including when initiating with sterically bulky nucleophiles (e.g., 2-10) or terminating with alkyl and benzyl halides (e.g., 2-17 and 2-18).

2.2.5 Proof of End-Cap–Mediated Depolymerization

Since the chemistry of CD₃ polymers is mediated by a polymer end-cap, each polymer chain must incorporate the responsive end-cap in order to ensure a complete response to a stimulus. For PPA specifically, polymers that are not capped during the termination step of the polymerization reaction should depolymerize when the reaction mixture is warmed above the T_c. However, the presence of other species in the reaction (e.g., impurities in the monomer) may result in a portion of a polymer sample that does not depolymerize in response to the desired signal. Therefore, we used ¹H NMR to prove that our general purification and synthetic procedures (Figures 2-6 and 2-7) yields PPA with complete incorporation of the responsive end-caps. With this data in hand, we demonstrated that the polymer was capable of selective depolymerization in solution, and that this depolymerization reaction was mediated by cleavage of the reaction-based detection unit from the polymer.

The ratio of polymer end-caps to polymer repeating units make it difficult to see the protons of the end-caps by NMR for polymers with higher molecular weights. Therefore, we prepared two shorter polymers that had the same responsive moiety on opposite ends: polymer 2-6 (M_n = 7 kDa), which was initiated with tert-butyldimethylsilanol and terminated with acetic anhydride, and polymer 2-15 (M_n = 3 kDa), which was initiated with isopropanol and terminated
with tert-butyldimethylsilyl chloride. Analysis of the two polymers by $^1$H NMR shows the presence of peaks corresponding to both the responsive silyl groups and the non-responsive functionality at the other polymer chain end (Figure 2-10). Furthermore, the integrations of these peaks were close to the expected values. For example, for polymer 2-6, when the peak corresponding to the tert-butyl group from the silicon end-cap was set to 9, the acetate peak integrated to ~3.

Figure 2-10. $^1$H NMR spectra the provide evidence that PPA is end-capped as predicted. (a) Spectrum of low molecular weight polymer 2-6 ($M_n = 7$ kDa) showing the TBS and acetate end-caps. (b) Spectrum of low molecular weight polymer 2-15 ($M_n = 3$ kDa) showing the isopropyl and TBS end-caps. Adapted with permission from Macromolecules, 2013, 46, 2963–2968. Copyright 2013 American Chemical Society.

The primary method for analyzing solution phase depolymerization of CD, polymers is gel permeation chromatography (GPC), since the technique shows a clear change in the transition from polymer to monomer.8 Polymer 2-8 ($M_n = 34$ kDa) was dissolved in DCM and analyzed by GPC, both before and 30 min after being exposed to 10 equiv of Pd(PPh$_3$)$_4$ (Figure 2-11). The refractive index detector (RID) showed that complete depolymerization of 2-8 had occurred over these 30 min, as the main peak had shifted from an elution time of ~7 min (which corresponds to
a high molecular weight species) to an elution time of ~11.5 min (which corresponds to small molecules such as the monomer) (Figure 2-11b). In comparison, when a solution of control polymer 2-20 ($M_n = 50$ kDa) in DCM was also exposed to 10 equiv of Pd(PPh$_3)_4$, no significant change was observed in the elution time or in the area of the main peak (Figure 2-11c). Taken together, this $^1$H NMR and GPC data provide evidence that our general procedure does provide incorporation of reaction-based detection units as end-caps, and that these reaction-based detection units govern the selective depolymerization of PPA.

![Diagram](image1.png)

**Figure 2-11.** Selective, end-cap–mediated depolymerization of PPA. (a) Conditions for determining the response of polymers 2-8 ($M_n = 34$ kDa) and 2-20 ($M_n = 50$ kDa) to Pd(0). (b) Refractive index traces for 2-8 before (black) and 30 min after (blue) adding 2 equiv of Pd(0). (b) Refractive index traces for 2-20 before (black) and 30 min after (blue) adding 2 equiv of Pd(0).
2.2.6 Solid State Depolymerization of PPA

We chose to demonstrate solid-state depolymerization of PPA by utilizing the solubility change that occurs upon conversion of polymer to monomer, as shown in Figure 2-3.\textsuperscript{8} Polymer 2-21 was prepared by initiating with 4,5-dimethoxy-2-nitrobenzyl alcohol and terminating with the corresponding chloroformate. The 4,5-dimethoxy-2-nitrobenzyloxy carbonyl group, also referred to in the literature as the 6-nitroveratryloxy carbonyl (NVOC) group, is known to respond to UV light.\textsuperscript{23,25,30} Free-standing films of polymer 2-21 (\(M_n = 42\) kDa) and control polymer 2-6 (\(M_n = 54\) kDa) were formulated by solvent casting, and then were exposed to a broad spectrum UV floodlight (250 nm to 600 nm) (Figure 2-12).

![Diagram and images showing the depolymerization process](image)

**Figure 2-12.** Solid-state depolymerization of films of polymers 2-21. (a) and (d) Films of (a) 2-21 and (d) 2-6 before exposure to UV light. (b) and (e) Films of (b) 2-21 and (e) 2-6 after being exposed to UV light for 10 min. (c) and (f) Exposed films of (c) 2-21 and (f) 2-6 after being submerged in ethyl acetate for 1 min. The film has dissolved in (c) and is no longer visible. Adapted with permission from *Macromolecules*, 2013, 46, 2963–2968. Copyright 2013 American Chemical Society.
After 10 min, a clear physical change in polymer 2-21 was observed: the originally translucent film had turned yellow-orange and opaque (Figure 2-12b). The color change indicates both depolymerization to the monomer, which is yellow, and reaction of the NVOC group, which forms an orange byproduct after reaction with light.\textsuperscript{30} In comparison, no physical changes were observed for polymer 2-6 (Figure 2-12e). Both films were allowed to cool to room temperature and submerged in ethyl acetate, which dissolves the monomer but not the polymer. The film of polymer 2-21 complete dissolved within 1 min (Figure 2-12c), while there was no dissolution or obvious change in polymer 2-6 (Figure 2-12f), even when it was left submerged in the solution for an extended period. These results support the depolymerization of polymer 2-21 to monomer in the solid state through photolysis of the NVOC group. Although this example exists as a proof-of-concept demonstration, a polymer with these capabilities could find use as a photoresist in lithography or as a plastic that “vanishes” specifically if it is released into the environment.

2.3 Conclusion

In conclusion, we have demonstrated a reproducible and scalable general procedure for the synthesis of depolymerizable PPA that allows for the incorporation of various functionalities that respond to specific chemical or physical signals at either end of the polymer. This procedure allows for control over the molecular weight of the polymer and the composition of the polymer end-caps. Furthermore, we have demonstrated the rapid depolymerization of PPA both in solution and as a solid film. Most importantly, the improvements over the previous method of synthesizing depolymerizable PPA\textsuperscript{8} make the polymer far more accessible to chemists and more versatile for use as a stimuli-responsive material. Therefore, we anticipate that these efforts will
help both our group and others to expand the applications of PPA. In fact, since we initially reported these conditions, they have been used by other groups to prepare PPA copolymers that form supramolecular nanoparticles and networks, and PPA homopolymers used as mechanoresponsive materials. In my own research, the general procedure describe herein has enabled more applied research on PPA and its use in microscale pumps and in responsive microcapsules. These two areas are the focus of the next two chapters.

2.4 References


Chapter 3

Characterizing End-Cap Accessibility in Films of Depolymerizable Polymers Using Microscale Pumps

The author of this dissertation was responsible for synthesizing the end-capped PPA derivatives and for preparing samples for XPS analysis and analyzing the data obtained. Dr. Hua Zhang performed the pumping experiments and characterized the polymer films using profilometry. The author and Dr. Hua Zhang both analyzed the data from the pumping experiments. Dr. Matthew Baker ran the contact angle experiments. Flory Wong helped acquire the SEM images of the films. Dr. Vince Bojan and Dr. Jennifer Gray helped with XPS analysis.

3.1 Introduction

The ability of PPA to provide amplified responses to specific signals in the solid state suggests the potential for the development of new depolymerizable and stimuli-responsive materials with unique capabilities. PPA can facilitate rapid and substantial structural changes autonomously in the context of these materials based on the conversion of polymer to monomer in a cascade reaction, which is triggered by each individual reaction between the signal and the polymer end-cap (Figure 1-6e). Furthermore, the use of reaction-based detection units offers a level of selectivity to the responses of such materials that would otherwise be difficult to achieve.

When a CD, polymer such as PPA is used in a solid material, the rate of response will most often depend on the accessibility of the end-caps (Figure 3-1). Initially, the depolymerization reaction will only occur for polymer chains that have end-caps displayed at the interface between the material and its environment, with the exception of cases (i) when the material is submerged in a solvent that swells the polymer (e.g., a hydrogel in water), which would allow for better access to end-caps that are “buried”; and (ii) when the stimulus is physical and can penetrate into a material (e.g., the UV responsive film shown in Figure 2-12). In all
other cases, end-caps in the interior of the film will not respond until being uncovered by
depolymerization of the polymer chains between it and the interface or until the film reorders
itself to bring the end-caps to the surface.

**Figure 3-1.** Illustration of the need for the responsive end-caps of CD₇ polymers to be accessible
for the polymer to respond rapidly in the solid state. Reproduced with permission from

Because end-cap accessibility has such an effect on the rate of response of CD₇ polymers,
better understanding the effect is essential for the development of stimuli-responsive materials
from this class of polymers. However, since CD₇ polymers are an emerging field of research,
there has been limited work done on better understanding the effect of having exposed polymer
end-caps on the rate of response of solid materials. As a result, we sought to develop a test
system that would allow us to easily evaluate the depolymerization response of a solid state
material made from a CD₇ polymer. We believed that such a system would allow us to better
characterize end-cap accessibility and to develop new design strategies to improve end-cap
accessibility. The test system we chose were microscale pumps made from PPA.
3.1.1 Microscale Pumps

Microscale or microfluidic pumps\textsuperscript{2-6} are a class of stimuli-responsive materials that have attracted interest as part of a recent research thrust towards replicating biological materials and controlling movement on the micro and nano-scale.\textsuperscript{7-12} Although the mechanisms of pumping in these materials vary, microscale pumps in general are capable of autonomously performing a chemical reaction and creating a gradient (usually chemical), which causes directional motion in the fluid surrounding the pump.\textsuperscript{2-6} Compared to other types of smart materials, these pumps offer the unusual ability to not only change their properties in response to a stimulus, but also change their environment.\textsuperscript{13} As a result, microscale pumps have been explored for various applications, including use as drug and glucose delivery systems,\textsuperscript{3,14-15} as colloidal photodiodes,\textsuperscript{16} as tools for microanalytical devices,\textsuperscript{17-18} as systems for bone repair,\textsuperscript{19} and as diagnostics.\textsuperscript{20}

In 2012, PPA was first used as a microscale pump in a collaborative effort between the Sen and Phillips groups.\textsuperscript{20} When films of PPA end-capped with a TBS ether (2-3) were submerged in an aqueous solution and exposed to fluoride, depolymerization of the polymer led to the release of the monomer (2-2) into the surrounding solution (Figure 3-2).

![Figure 3-2](image)

**Figure 3-2.** The use of depolymerizable PPA as microscale pumps.\textsuperscript{20} (a) Depolymerization of TBS end-capped PPA (2-3) in response to fluoride. (b) Depolymerization of polymer 2-3 creates a concentration gradient of monomers, creating a convective flow in the surrounding solution.
The depolymerization reaction created a gradient of the monomers in the solution surrounding the film, which “turned on” the pump; i.e., a convective fluid flow was initiated. The pumping speed was determined by tracking the location of polystyrene tracer particles over time after the addition of fluoride. No pumping was observed in the absence of fluoride, while increasing the concentration of fluoride also increased average particle speed (i.e., the rate of pumping). The mechanism of the flow in this system has been postulated to be either diffusiophoretic or density-driven.\textsuperscript{15,20-28}

Due to the hydrophobic nature of PPA, enzymes likely would not interact with films made from polymers end-capped with enzymatically-responsive reaction-based detection units.\textsuperscript{29} However, the authors were able to show that pumping could be initiated by an enzyme through the use of an activity based detection reagent (3-1) (Figure 3-3).\textsuperscript{20} The enzyme β-D-glucuronidase (a biomarker for \textit{E. coli})\textsuperscript{30} catalyzes the hydrolysis of the glycosidic bond between the glucuronic acid functionality and the rest of the molecule,\textsuperscript{31} revealing a phenol that facilitates quinone methide formation and decarboxylation. The resulting aniline (3-2) eliminates two equivalents of fluoride,\textsuperscript{32} which initiates depolymerization of polymer 2-3 and turns on the pump.

![Figure 3-3](image_url)

\textbf{Figure 3-3.} Mechanism of the response of activity-based detection reagent 3-1 to β-D-glucuronidase. For each reaction with the enzyme, 3-1 releases 2 equivalents of fluoride.

This chapter focuses on the development of microscale pumps made from PPA as a test system for characterizing and improving end-cap accessibility in solid materials.\textsuperscript{21} Using the
pumping as a functional output allowed us to develop two strategies for increasing end-cap accessibility: (i) using polymers with lower molecular weights, and (ii) using polymers with more hydrophilic polymer end-caps. Finally, our observations with the microscale pumps were further supported by analytical characterization of the PPA films.

3.2 Experimental Design

3.2.1 Using Microscale Pumps to Define End-Cap Accessibility

Figure 3-4 illustrates the general concept of using microscale pumps made from depolymerizable PPA as a test system to determine end-cap accessibility.

Figure 3-4. Using microscale pumps as a test system for evaluating the solid-state depolymerization of PPA. (a) A film of PPA end-capped by a silyl ether does not respond until exposed to fluoride, which initiates the depolymerization of the polymer and (b) creates a gradient of monomer. This gradient of monomers initiates (c) a convective flow in the solution surrounding the film. (d) The location of the tracer particles can be tracked over time to determine the pumping speed of the system. Reproduced with permission from *Macromolecules*, 2013, 46, 7257–7265. Copyright 2013 American Chemical Society.

Depolymerizable PPA end-capped with silyl ethers (Figure 3-4a) was the ideal choice for these experiments because of the ability of the polymer to depolymerize as a solid material in the
presence of fluoride and initiate pumping.\textsuperscript{20,33} We also chose to continue with the strategy of using an activity-based detection reagent (3-1) to have the films respond to β-D-glucuronidase,\textsuperscript{20} since we hoped to eventually develop the pumps as diagnostic assays that use the pumping speed to determine the concentration of an analyte.\textsuperscript{34-35} For each pumping experiment, reagent 3-1 (9.3 mM in 75 mM phosphate buffer, pH 7.4, 1 wt% BSA) was incubated with the enzyme for 30 min at 23 °C to allow for fluoride production through the mechanism shown in Figure 3-3. Addition of the solution containing fluoride and the 6 µm tracer particles to a hybridization chamber that contained a film of PPA end-capped with silyl ethers (approximately 0.5 mm wide × 0.5 mm long × 25 µm thick) initiated the depolymerization of the polymer (Figure 3-4b). The magnitude of depolymerization will depend on the accessibility of the polymer end-caps to the stimulus, and the rate of pumping is controlled by the gradient of monomers (Figure 3-4c). Finally, the location of ~30 polystyrene tracer particles was determined every 2.5 s for 25 s total, which was used to calculate the average speed of the particles and the rate of pumping (Figure 3-4d). As a result, we could correlate the pumping speed to end-cap accessibility.

### 3.2.2 Modulating End-Cap Accessibility

We tested two variables for their effects on the response of the microscale pumps: (i) polymer molecular weight, and (ii) polarity of polymer end-caps. Based on the proposed mechanisms of depolymerization and pumping, we had two potential hypotheses in regards to the effect of polymer molecular weight. First, in solid materials made from polymers that are approximately the same size, shorter polymers will inherently have a greater concentration of end-caps on the surface of the object, since the ratio of repeating units to end-caps is lower for polymers with lower molecular weights. Therefore, one would expect the pumping speed to be greater in response to the same concentration of analyte. However, the amplification provided by
CD, polymers is increased by the length of the polymer. As a result, polymers with high molecular weights will release more monomers for each depolymerization reaction, which should give a greater pumping speed overall.

The second variable we tested was the polarity of the polymer end-caps. The TBS ether functionality that was used previously as the responsive unit on PPA for the microscale pumps (Figure 3-5a) is fairly hydrophobic. Therefore, the end-cap may associate better with the hydrophobic polymer film in these experiments than with the aqueous solution containing the analyte.

![Figure 3-5. Silyl ether groups with varying polarities.](image)

We theorized that replacing the tert-butyl group from TBS with a short poly(ethylene glycol) (PEG) chain (Figure 3-5b) would make the silyl ether end-cap much more hydrophilic and therefore increase the end-cap accessibility in aqueous solutions. However, the rate of silyl ether cleavage by fluoride and by hydrolysis is known to be affected by the steric environment around the silicon atom. Therefore, we also tested a silyl ether in which the tert-butyl group was replaced with an alkyl chain (Figure 3-5c), where the number of heavy atoms in the alkyl chain was close to the number of heavy atoms in the PEG chain of the second silyl ether. Testing the alkylated silyl end-cap would allow us to rule out a difference in reaction rate between fluoride...
and the end-cap for the TBS and PEGylated silyl ethers as the primary effect for any difference in pumping speed.

3.3 Results and Discussion

3.3.1 Synthesis of Silyl Ether End-Capped PPA

The methodology that we developed for preparing depolymerizable PPA (Chapter 2) allowed us to synthesize different molecular weight derivatives of PPA end-capped with different silyl ether groups (Figure 3-6). The abilities to control polymer molecular weight and to completely end-cap the polymer with the desired responsive group were essential to testing the effects of polymer length and polarity of polymer end-caps on the response of the microscale pumps.
Figure 3-6. Syntheses of polymers 2-6, 2-19, and 3-3 with different molecular weights used as microscale pumps. Adapted with permission from *Macromolecules*, 2013, 46, 7257–7265. Copyright 2013 American Chemical Society.

Synthesizing polymers 2-6 and 2-19 did not require any changes to the previously described procedure. For polymer 3-3, the poor solubility of end-capping reagent in most organic solvents made additional purification of the polymer necessary, namely dissolving the polymer in DCM and filtering.

3.3.2 Establishing Predictable Behavior for the Microscale Pumps

To establish that the microscale pumps were a reliable test system, we first tested the effect of analyte concentration (*i.e.*, [β-D-glucuronidase]) on the pumping speed with films made
from polymer **2-6** ($M_n = 8$ kDa) using the procedure described in Section 3.2.1 (Figure 3-7).

When exposed to enzyme concentrations between 1 and 9 µM, a dose-dependent, linear response was observed.

![Graph showing the effect of β-D-glucuronidase concentration on average speed of pumping.](image)

**Figure 3-7.** Effect of the concentration of β-D-glucuronidase on the average speed of pumping provided by films of polymer **2-6** ($M_n = 8$ kDa). The data points represent the average of 30 particles measured over 25 s. The error bars reflect the standard deviations from these averages. Adapted with permission from *Macromolecules, 2013, 46, 7257–7265*. Copyright 2013 American Chemical Society.

The microscale pumps also responded selectively to fluoride (Figure 3-8). When we exposed films of polymer **2-6** ($M_n = 65$ kDa) to 0.1 M solutions of the sodium salts of different anions, the pumping speed with sodium fluoride was 7.5× greater than with any of the other salts. This result suggested that any pumping observed in subsequent experiments was the result of fluoride produced in response to the enzyme and not due to non-specific reactions with the silyl ether end-caps or with the polymer backbone. Overall, these results helped validate that the microscale pumps were a well-behaved test system for further experiments.
Figure 3-8. The response of films made from polymer 2-6 \((M_n = 65 \text{ kDa})\) to 0.1 M solutions of various sodium salts. The data points represent the average of 30 particles measured over 25 s. The error bars reflect the standard deviations from these averages. Adapted with permission from *Macromolecules*, 2013, 46, 7257–7265. Copyright 2013 American Chemical Society.

3.3.3 Effect of Polymer Molecular Weight on Pumping Speed

Using the procedure described in Section 3.2.1, we tested the response of five derivatives of PPA end-capped with TBS ethers (2-6) with molecular weights of 8, 33, 45, 53, and 65 kDa (syntheses shown in Figure 3-6a) to 9 µM β-D-glucuronidase. The results, which are shown in Figure 3-9, suggested a clear inverse and linear relationship between polymer molecular weight and average pumping speed.
Figure 3-9. Effect of polymer molecular weight on the average speed of pumping provided by films of polymer 2-6 in response to 9 μM β-D-glucuronidase. The data points represent the average of 30 particles measured over 25 s. The error bars reflect the standard deviations from these averages. Reproduced with permission from Macromolecules, 2013, 46, 7257–7265. Copyright 2013 American Chemical Society.

The graph shows a 3× increase between the speed of pumping for the 8 kDa derivative of 2-6 and the 65 kDa derivativ. For comparison, the polymer end-cap composes 1.2% (in terms of heavy atom count) of an 8 kDa derivative of 2-6, as opposed to 0.1% of a 65 kDa derivative. These results support our first hypothesis on the effect of polymer molecular weight on pumping speed over our second hypothesis (Section 3.2.2). In other words, the greater end-cap density on the surface of a solid material made from a shorter CD₇ polymer is the dominant factor in the response of that material, rather than the greater amplified response provided by a longer polymer. Work by Gillies and coworkers has also suggested that longer CD₇ polymers (specifically polymers that depolymerized by alternating quinone methide elimination and cyclization reactions, which are shown in Section 1.5) take longer to depolymerize than shorter polymers.⁴⁹ Although this length effect may play a role in our system, we have never observed a difference in the time required for complete depolymerization of PPA derivatives with different
molecular weights, which is most likely the result of the rapid rate of depolymerization of PPA compared to other CD, polymers.

3.3.4 Effect of End-Cap Polarity on Pumping Speed

To test the second variable identified in Section 3.2.2 (end-cap polarity), we evaluated the pumping response of films made from five different lengths of PPA end-capped with the PEGylated silyl group (2-19) and five different lengths of PPA end-capped with the alkylated silyl group (3-3) with different lengths (syntheses shown in Figure 3-6b and c, respectively) to 9 μM β-D-glucuronidase. Figure 3-10 shows the results observed using these two polymers, along with the TBS end-capped PPA (2-6) data from Figure 3-9 for comparison (closed circles).

![Figure 3-10](image)

**Figure 3-10.** Effect of end-cap polarity on the pumping speed of films of polymers 2-6, 2-19, and 3-3. The closed circles and unbroken lines are for the response of the films to 9 μM β-D-glucuronidase. The open circles and dotted lines are for the response of the films to no enzyme. The data points represent the average of 30 particles measured over 25 s. The error bars reflect the standard deviations from these averages. Adapted with permission from *Macromolecules*, 2013, 46, 7257–7265. Copyright 2013 American Chemical Society.
First, we observed that the trend of an inverse and linear relationship between polymer molecular weight and average pumping speed shown with polymer 2-6 in Figure 3-9 held true with polymers 2-19 and 3-3 as well. Second, we noticed that the results appeared to support our theory that more hydrophilic end-caps would give greater pumping responses, at least for the lower molecular weight polymers. For example, polymer 2-19 with a molecular weight of 32 kDa responded with pumping speed 2.4× greater than polymer 2-6 with a molecular weight of 33 kDa and 4.4× greater than polymer 3-3 with a molecular weight of 32 kDa. In addition, polymer 2-19 with a molecular weight of 47 kDa responded with an average pumping speed that, within in the error of the experiment, was equivalent to polymer 2-6 with molecular weight of 8 kDa. However, at higher molecular weights (i.e., $M_n \approx 60$ kDa) the pumping response to the analyte was approximately equal for all three polymer end-caps. When using films prepared from polymers of this length, it is likely that the end-cap density is so low that the effect of improved accessibility based on end-cap polarity is minimized. Finally, polymers capped with the very hydrophobic alkylated silicon group (polymer 3-3) gave a much lower response than for PPA with either the hydrophobic TBS silyl ether (2-6) or the hydrophilic PEGylated silyl ether (2-19). As a result, the difference in average pumping speeds between polymers 2-6 and 2-19 was most likely not the result of the difference in steric environment around the two silicon end-caps.

Figure 3-10 also shows the results of the average pumping speeds for the five derivatives of each polymer in the presence of no enzyme (open circles). Since the speeds of the tracer particles (which are likely the result of random Brownian motion) are approximately equivalent in all cases, the differences in average pumping speeds in the presence of enzyme are not the result of differences in background hydrolysis rates between the silyl end-caps.
3.3.5 Summary of the Results from Using Microscale Pumps as a Test System

Overall, the results obtained from testing the effects of polymer molecular weight and end-cap hydrophilicity on the pumping speed provided by films of PPA suggest the importance of end-cap accessibility to the response of solid objects made from CD, polymers. Our results also support several design strategies that could be utilized to improve the response of CD, polymers in the solid state. However, there are also other explanations that could explain the differences in rates of pumping. For example, Holmes-Farley and Whitesides have shown that the wettability of polymer films can affect the rate of reaction between reactants in a solution surrounding the film and functional groups at the interface between the solution and the solid.\textsuperscript{40} In examples from Daglen and Tyler and from Meyer and coworkers, polymer morphology affected the rate of polymer degradation.\textsuperscript{41,42} Consequently, we further characterized and evaluated films made from the polymers with different silicon end-caps using (i) X-ray photoelectron spectroscopy (XPS), (ii) profilometry, (iii) scanning electron microscopy (SEM), and (iv) goniometry to verify the role of end-cap accessibility in the results shown in 3-10. Finally, we tested the effects of size and thickness of the polymer films on pumping speed.

3.3.6 Characterizing the Polymer Films

3.3.6.1 Elemental Composition of Film Surface

XPS is a surface characterization technique that can determine the elemental composition of the top 10 nm of a surface.\textsuperscript{43} XPS was ideal for verifying that the effects of end-cap polarity and polymer length were the result of differences in end-cap accessibility because of the spatial control of the technique and because we could easily distinguish the silicon in the polymer end-
caps from the carbon and oxygen in the polymer backbone. The results from XPS analysis of the films prepared from polymers 2-6 \((M_n = 33 \text{ kDa})\), 2-19 \((M_n = 32\) and 47 kDa), and 3-3 \((M_n = 32 \text{ kDa})\), along with the corresponding average pumping speeds in response to 9 µM β-D-glucuronidase, are shown in Table 3-1.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Polymer (M_n) (kDa)</th>
<th>% Carbon</th>
<th>% Oxygen</th>
<th>% Silicon</th>
<th>Pumping Speed (µm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-6</td>
<td>33</td>
<td>74.3 ± 0.16</td>
<td>21.4 ± 0.14</td>
<td>4.22 ± 0.10</td>
<td>1.08 ± 0.25</td>
</tr>
<tr>
<td>2-19</td>
<td>32</td>
<td>69.7 ± 0.17</td>
<td>22.0 ± 0.14</td>
<td>8.30 ± 0.11</td>
<td>2.55 ± 0.35</td>
</tr>
<tr>
<td>3-3</td>
<td>32</td>
<td>73.1 ± 0.16</td>
<td>21.8 ± 0.18</td>
<td>5.12 ± 0.12</td>
<td>0.58 ± 0.17</td>
</tr>
<tr>
<td>2-19</td>
<td>47</td>
<td>75.6 ± 0.20</td>
<td>20.7 ± 0.14</td>
<td>3.65 ± 0.12</td>
<td>1.24 ± 0.28</td>
</tr>
</tbody>
</table>

The polymers with different silicon end-caps and with molecular weights of 32 kDa and 33 kDa were analyzed to determine the effect of end-cap polarity on the concentration of silicon in the top 10 nm of the polymer films. The polymers end-capped with the TBS \((2-6, M_n = 33 \text{ kDa})\) and alkylated silyl ether functionalities \((3-3, M_n = 32 \text{ kDa})\) had 4.22 ± 0.10% and 5.10 ± 0.12% silicon respectively. On the other hand, polymer 2-19 \((M_n = 33 \text{ kDa})\) had 8.30 ± 0.11% silicon, which indicated that polymers capped by more hydrophilic silicon groups had 1.6× more end-caps at the surface of the polymer than polymers capped by more hydrophobic groups. Comparatively, the average pumping speed for polymer 2-19 with a molecular weight of 33 kDa was 2.4× greater than the pumping speeds observed for either polymer 2-6 or polymer 3-3 with comparable molecular weights. It is also worth noting that the % silicon values are significantly higher than the % silicon as determined by heavy atom count per polymer (for example, polymer 2-6 with a molecular weight of 33 kDa had 4.22% silicon by XPS vs. 0.04% silicon by heavy atom count). This result was expected because of the established end-cap enrichment effect for solid materials made from polymers.44

By analyzing the elemental composition of polymer films with different numbers of repeating units and the same end-caps, we also confirmed the effect of polymer length on end-cap
accessibility. Specifically, polymer 2-19 with a molecular weight of 47 kDa had 3.65 ± 0.11% silicon, 2.3× less than the same polymer with a molecular weight of 33 kDa. This value correlates well with the 2.1× reduction in average pumping speed from the longer polymer to the shorter polymer.

3.3.6.2 Changes in Film Thickness through Depolymerization

Films of polymers 2-6, 2-19, and 3-3 did not change in thickness by profilometry during the 25 s duration of the pumping experiments. Therefore, the effect of differences in the rates of erosion of the films was minimized. However, when films of the three polymers were exposed to 0.1 M solutions of sodium fluoride for 30 min (72× longer than the duration of the experiments described in Section 3.2.1), polymer 2-19 showed a significantly greater change in film thickness (33% in 30 min) than polymers 2-6 and 3-3 (7–9% in 30 min) (Table 3-2). This result further supported our theory that more hydrophilic end-caps would give faster rates of response than more hydrophobic end-caps.

Table 3-2. Changes in the minimum and maximum thicknesses of films of polymers 2-6 (\(M_n = 42\) kDa), 2-19 (\(M_n = 43\) kDa), and 3-3 (\(M_n = 43\) kDa) after exposure to 0.1 M NaF for 30 min. Adapted with permission from *Macromolecules, 2013, 46, 7257–7265*. Copyright 2013 American Chemical Society.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Polymer (M_n) (kDa)</th>
<th>Minimum Height Before Exposure (µm)</th>
<th>Maximum Height Before Exposure (µm)</th>
<th>Minimum Height After Exposure (µm)</th>
<th>Maximum Height After Exposure (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-6</td>
<td>42</td>
<td>7.2</td>
<td>22</td>
<td>6.2</td>
<td>20</td>
</tr>
<tr>
<td>2-19</td>
<td>43</td>
<td>3.0</td>
<td>12</td>
<td>1.2</td>
<td>8</td>
</tr>
<tr>
<td>3-3</td>
<td>43</td>
<td>20</td>
<td>28</td>
<td>19</td>
<td>26</td>
</tr>
</tbody>
</table>

The difference in responses to fluoride between the polymers used for these experiments and the patterned films that contained TBS end-capped PPA (Figure 2-3) were most likely caused by the different solvent systems used. Aqueous solutions and mixed aqueous-organic
solutions are known to slow reactions between fluoride and silyl ether groups because of the hydrogen bonding ability of the fluoride anion.\textsuperscript{45-47}

3.3.6.3 Morphology of the Polymer Films

When films cast from polymers 2-6 ($M_n = 42$ kDa), 2-19 ($M_n = 43$ kDa), and 3-3 ($M_n = 42$ kDa) were analyzed by SEM, all three showed similar, uniform surfaces, suggesting that there were no significant differences in the visible morphology of the three samples (Figure 3-11a,b,c). However, after 30 min of exposure to 0.1 M NaF, the films had all responded differently. Very little change was observed for polymer 3-3 (Figure 3-11f), which also gave the slowest pumping speeds in Figure 3-10. On the other hand, polymer 2-6 showed some response to fluoride (Figure 3-11b), although the response was not as significant as the cracking and dimpling in the film made from polymer 2-19 (Figure 3-11d), which also gave the fastest pumping speed.

![Figure 3-11](image.png)

**Figure 3-11.** SEM images of films of 2-6 ($M_n = 43$ kDa), 2-19 ($M_n = 42$ kDa), and 3-3 ($M_n = 42$ kDa) before and after being exposed to 0.1 M NaF for 30 min. Adapted with permission from *Macromolecules*, 2013, 46, 7257–7265. Copyright 2013 American Chemical Society.
3.3.6.4 Effect of End-Cap on Polymer Wettability

We evaluated films cast from 2-6 ($M_n = 42$ kDa), 2-19 ($M_n = 43$ kDa), and 3-3 ($M_n = 42$ kDa) using goniometry (Table 3-3). The contact angles for the three films (83.27 ± 2.38°, 82.97 ± 1.02°, and 83.31 ± 1.12° respectively) were effectively equivalent, suggesting that the differences in end-cap concentration on the surface of the polymer films determined by XPS analysis were not significant enough to change the wettability of the films.

Table 3-3. Contact angles for films prepared from polymers 2-6 ($M_n = 43$ kDa), 2-19 ($M_n = 42$ kDa), and 3-3 ($M_n = 42$ kDa). Adapted with permission from Macromolecules, 2013, 46, 7257–7265. Copyright 2013 American Chemical Society.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
<th>Average</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-6</td>
<td>80.57</td>
<td>85.04</td>
<td>84.21</td>
<td>83.27</td>
<td>2.38</td>
</tr>
<tr>
<td>2-19</td>
<td>81.82</td>
<td>82.80</td>
<td>84.30</td>
<td>82.97</td>
<td>1.02</td>
</tr>
<tr>
<td>3-3</td>
<td>84.58</td>
<td>82.48</td>
<td>82.87</td>
<td>83.31</td>
<td>1.12</td>
</tr>
</tbody>
</table>

3.3.6.5 Effect of Film Surface Area and Volume on Pumping Speed

The film thicknesses determined by profilometry (Table 3-2) showed the inherent variability in the technique used to prepare the films, which theoretically could change the pumping response of the films. Similarly, any differences in the length and width of the films would change the surface area of the film, which also could affect pumping speed. However, when we prepared from polymer 2-19 ($M_n = 43$ kDa) that were (i) 2× and 3× larger (in terms of area) and (ii) 2× and 3× thicker, and then exposed those films to 9 µM β-D-glucuronidase (as described in Section 3.2.1), very little variation was observed in the average pumping speeds compared to a film with the usual dimensions (Table 3-4). At most, the pumping speeds for the larger and thicker films deviated from the values obtained from 0.5 mm wide × 0.5 mm long × 25
µm thick film by 11%, which was similar to the typical error in the experiments shown in Figure 3-10.

Table 3-4. Average pumping speed provided by films of polymer 2-19 (\(M_n = 43\) kDa) with different widths, lengths, and thicknesses in the presence of 9 µM β-D-glucuronidase. Adapted with permission from *Macromolecules, 2013, 46, 7257–7265*. Copyright 2013 American Chemical Society.

<table>
<thead>
<tr>
<th>Film Width (mm)</th>
<th>Film Length (mm)</th>
<th>Film Thickness (µm)</th>
<th>Average Speed (µm/s)</th>
<th>Standard Deviation (µm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.5</td>
<td>25</td>
<td>1.34</td>
<td>0.20</td>
</tr>
<tr>
<td>0.7</td>
<td>0.7</td>
<td>25</td>
<td>1.49</td>
<td>0.19</td>
</tr>
<tr>
<td>0.9</td>
<td>0.9</td>
<td>25</td>
<td>1.28</td>
<td>0.12</td>
</tr>
<tr>
<td>0.5</td>
<td>0.5</td>
<td>50</td>
<td>1.42</td>
<td>0.27</td>
</tr>
<tr>
<td>0.5</td>
<td>0.5</td>
<td>75</td>
<td>1.36</td>
<td>0.18</td>
</tr>
</tbody>
</table>

3.3.6.6 Summary of Characterizing the Polymer Films

The results described in Sections 3.3.6.2, 3.3.6.3, and 3.3.6.4 suggest that the differences in pumping speed between the films with different silicon end-caps are not due to differences in (i) the rate of erosion of the polymer films, (ii) the morphology of the films, or (iii) the wettability of the films. In addition, we believe that any variability in the surface area or volume of the films used in the pumping experiments would have a minimal effect on the results. Finally, XPS analysis of the films, along with the observations made by SEM and profilometry for the films that were exposed to fluoride for 30 min, support our theory that variations in the pumping speed are caused by the concentration of end-caps on the surface of the film, which can be modulated by changing the molecular weight of the polymers or the polarity of the end-caps.
3.4 Conclusion

In conclusion, we have developed and validated microscale pumps as a test system for evaluating the response of films prepared from PPA. The microscale pumps have allowed us to better understand the effect of end-cap accessibility on the response of solid objects prepared from CD$_r$ polymers, and to develop two principles for increasing end-cap concentration at the interface between an aqueous solution and a polymeric material: (i) decreasing the molecular weight of the polymer, and (ii) increasing the hydrophilicity of the polymer end-cap. We believe that this system could be used to develop other new design strategies for improving end-cap accessibility, such as using amphiphilic diblock copolymers. Furthermore, these findings are not limited to developing microscale pumps from depolymerizable PPA. We expect that both the results described in this chapter specifically and the focus on end-cap accessibility more generally will help guide the design of stimuli-responsive materials comprised of CD$_r$ polymers, such as core-shell microcapsules (the focus on the next chapter), responsive nanoparticles and polymersomes, shape-changing and vanishing plastics, organic-inorganic hybrid films, and phase-switching reagents used for diagnostics. In fact, a recent report has expanded upon our initial design strategies for improving end-cap accessibility for CD$_r$ polymers. Using the poly(benzyl ether) backbone (Section 1.4), Phillips and coworkers have developed polymers that incorporate reaction-based detection units into each repeating unit along the polymer backbone. Although these poly(benzyl ethers) do not respond as quickly in the solid state as PPA and its derivatives, these cumulative advances may lead to CD$_r$ polymers that achieve nearly instantaneous responses.
3.5 References


40. Holmes-Farley, S. R.; Whitesides, G. M. Reactivity of Carboxylic Acid and Ester Groups in the Functionalized Interfacial Region of "Polyethylene Carboxylic Acid" (PE-CO₂H) and Its


52. de Gracia Lux, C.; McFearin, C. L.; Joshi-Barr, S.; Sankaranarayanan, J.; Fomina, N.; Almutairi, A. A Single UV or Near IR Triggering Event Leads to Polymer Degradation into Small Molecules. ACS Macro Lett. 2012, 1, 922–926.
Chapter 4

Use of Microfluidic Flow Focusing Devices to Fabricate Responsive Core-Shell Microcapsules from Depolymerizable PPA

The author of the dissertation was responsible for synthesizing the end-capped PPA derivatives and for characterizing the selective response of the polymers in solution. Dr. Alireza Abbaspourrad was responsible for developing the procedure for fabricating the microcapsules, for evaluating the response of the microcapsule to fluoride, and for characterizing the microcapsules. The author and Dr. Alireza Abbaspourrad both analyzed the data from the release studies.

4.1 Introduction

Based on the results obtained from the microscale pump test system described in Chapter 3, we concluded that the response of solid materials prepared from depolymerizable PPA could be enhanced by changing the molecular weight of the polymers and by increasing the hydrophilicity of the reaction-based detection unit end-caps. Subsequently, we sought to expand upon these principles and to use them to guide the design of other types of smart materials as well. We were particularly interested in developing polymeric carriers from PPA that were capable of controlled release of their encapsulated contents (Figure 4-1) because of their potential applications in biomedicine, agriculture, cosmetics, gastronomics, and electronics.

![Figure 4-1. Illustration of a responsive capsule prepared from a CD, polymer. End-caps on the surface of the capsule are cleaved in response to a specific signal, resulting in depolymerization of the polymers within the shell wall. The depolymerization response of the capsules leads to the opening of pores in the shell wall and release of the encapsulated cargo.](image-url)
Responsive nano- and microcapsules function by undergoing a physical or chemical change in response to a stimulus, triggering release of any encapsulated cargo. However, despite the promise of these smart materials, there have been limited examples of polymer capsules capable of providing highly selective responses with a magnitude greater than that of the applied stimulus. The use of CD₃ polymers as the membranes in responsive capsules represents a potential strategy to meet this need. In comparison to more traditional mechanisms for release from polymer carriers that cause small structural changes for each reaction with a stimulus, the depolymerization mechanism of CD₃ polymers can result in a massive and rapid physical and structural change in a capsule shell wall, even in response to low concentrations of an analyte, because of the amplified chemical change that occurs upon conversion of polymer to monomer. Furthermore, the end-cap–mediated mechanism of depolymerization renders the triggered release highly selective.

An illustration of the basic design of a core-shell microcapsule with a CD₃ polymer membrane is shown in Figure 4-1. The microcapsule is stable in the absence of the applied signal, retaining the encapsulated cargo. The addition of a specific stimulus leads to the cleavage of the polymer end-caps on the surface of the capsule, which initiates the depolymerization of the polymers in the shell wall. Depolymerization to monomer results in a solubility switch and disintegration of parts of the shell wall, which leads to the opening of pores that allow for release of the encapsulated payload. In this chapter, we describe the fabrication of core-shell microcapsules with PPA membranes.
4.1.1 CD, Polymers as Responsive Carriers

Of the classes of CD, polymers shown in Figure 1-6, only polymers that depolymerize through alternating elimination and cyclization reactions\textsuperscript{15,17} and poly(benzyl car bamates)\textsuperscript{16,18} have been used for encapsulation.

4.1.1.1 Nanoparticles

In 2009, Gillies and coworkers reported nanoparticles prepared from block copolymer 4-1 (Figure 4-2).\textsuperscript{15}

![Image of polymer 4-1 self-assembly into micellar nanoparticles](image)

**Figure 4-2.** Self-assembly of polymer 4-1 into micellar nanoparticles. Adapted with permission from *J. Am. Chem. Soc.*, 2009, *131*, 18327–18334. Copyright 2009 American Chemical Society.

Polymer 4-1 consists of a hydrophobic CD, polymer block end-capped with a hydrophilic PEG chain, which renders the polymer amphiphilic. This amphiphilic nature facilitated the self-assembly of the polymer into micellar nanoparticles when sonicated in water, allowing for encapsulation of the fluorescent dye Nile Red in the aqueous core of the structures. The diameters of the particles formed varied from less than 100 nm to several hundred nanometers.
These micelles did not respond to a specific stimulus; instead, the ester linkage between the two blocks in 4-1 hydrolyzed under nearly physiological conditions (i.e., 37 °C, pH 7.4). An 85% decrease in the fluorescence within the nanostructures was observed over 14 days as a result of the release of encapsulated dye.

More recently, Almutairi reported the fabrication of nanoparticles from polymers with the same backbone as those shown by Gillies, but end-capped with the NVOC group (4-2) and the 6-bromo-7-hydroxycoumarin group (4-3) (Figure 4-3a).

**Figure 4-3.** Light-responsive nanoparticles prepared from polymers 4-2 and 4-3. (a) Polymers that depolymerize through alternating cyclization and elimination reactions and that are end-capped by the NVOC (4-2) and the 6-bromo-7-hydroxycoumarin (4-3) groups. (b) SEM image of the nanoparticles formed from polymer 4-2. Adapted with permission from *ACS Macro Lett.*, 2012, 1, 922–926. Copyright 2012 American Chemical Society.
Both of these photolabile groups respond to UV light and near IR light (through two photon excitation).\textsuperscript{17,20-22} The nanoparticles were prepared by first adding a solution of the polymer and Nile Red in DCM to an aqueous solution. Evaporation of the DCM lead to the formation of nanoparticles with average diameters of 150 nm for polymer 4-2 (Figure 4-3b) and 230 nm for polymer 4-3. When particles composed of polymer 4-2 were exposed to 350 nm UV light for 1 min and incubated at 37 °C, a 65% decrease in fluorescence within the carriers (presumably through release of the encapsulated dye) was observed nearly immediately. With longer irradiation times, up to 80% of fluorescence was lost. The particles formed polymer 4-3 lost 40% fluorescence upon exposure to 350 nm light for 5 min, but showed no additional release with prolonged exposure. The slower response of polymer 4-3 is most likely the result of an ion pair formed during photocleavage of the coumarin-based end-cap, which must be separated by the solvent to prevent recombination.\textsuperscript{23-24}

4.1.1.2 Microcapsules

In 2010, Moore and coworkers reported microcapsules prepared from poly(benzyl carbamates).\textsuperscript{16} Copolymer 4-6 was prepared via a DBTL-catalyzed condensation polymerization of monomers 4-4 and 4-5 (Figure 4-4a). The polymerization reaction was terminated by addition of either tert-butanol or 9-fluorenylmethanol to append Boc\textsuperscript{25} or Fmoc\textsuperscript{26} groups at the terminus of the polymer. To prepare capsules from polymer 4-6, the TBS ethers in the polymer side chains were deprotected by fluoride (Figure 4-4b). The unmasked alcohols were then reacted with a multifunctional isocyanate. Interfacial polymerization of the unreacted isocyanates with 1,4-butandiol in the presence of gum arabic (an emulsifier) led to the formation of highly cross-linked microcapsules with organic cores and diameters between 5 and 40 µm.\textsuperscript{16}
When microcapsules prepared from polymer 4-6 end-capped with the Fmoc protecting group were exposed to 5% piperidine in THF, complete release of the cargo was observed in 24 h. Microcapsules prepared from polymer 4-6 end-capped with the Boc protecting group released their contents more slowly, requiring 48 h for complete release after exposure to 4 M HCl in 9:1 water–EtOH. The difference in response times may be the result of the aniline intermediates formed in the depolymerization reaction of poly(benzyl carbamates) (Figure 1-6a) becoming protonated under acidic conditions. SEM images were taken of both sets of capsules after they had completely released their encapsulated cargo in response to the corresponding stimulus (Figure 4-5). In both cases, the shell walls had become shriveled and cracked. When the reaction conditions were interchanged, very little cargo release was observed and the morphology of the capsules also did not change significantly (Figure 4-5).
Figure 4-5. SEM images of microcapsules prepared from 4-6 end-capped with either the Boc or Fmoc protecting group. The images were taken before and after exposure to 4 M HCl in 9:1 water–EtOH or 5% piperidine in THF for 48 h. Adapted with permission from *J. Am. Chem. Soc.*, 2010, 132, 10266–10268. Copyright 2010 American Chemical Society.

4.1.2 Methods for Preparing Core-Shell Polymeric Capsules

Various methods have been developed for the fabrication of core-shell capsules from polymers, including (i) emulsification or interfacial polymerization, which was used to prepare microcapsules reported by Moore and coworkers (Figure 4-4b), (ii) layer-by-layer (LbL) assembly, (iii) coacervation, (iv) internal phase separation, which was used to prepare the nanoparticles reported by Almutairi and coworkers (Figure 4-3b), (v) spray drying, (vi) extrusion, and (vii) nanoprint lithography. However, many of these techniques involve relatively harsh conditions (e.g., acid, base, high temperatures) that may be incompatible with
Comparatively, the formation of microcapsules using microfluidic flow-focusing devices requires relatively mild conditions. Flow-focusing devices, which were first developed by the Weitz group, forms double emulsion droplets through the injection of three phases. The devices consist of two smaller cylindrical capillaries inserted into opposite ends of a larger square capillary (Figure 4-6).

![Illustration of the general design of a microfluidic flow-focusing device. Adapted with permission from Adv. Mater., 2014, 26, 2205–2218. Copyright 2014 John Wiley and Sons.](image)

The aqueous inner phase is injected into the left cylindrical capillary and comprises the liquid core of the capsules. The middle phase, usually an organic solvent that is immiscible with water, contains the material used to form the shell wall. This phase is injected into the space between the square capillary and the left cylindrical capillary. The outer phase, which is injected from the right, completes the formation of the double emulsion droplets, which enter the collection capillary. The formation of the capsule shell wall is completed by either evaporation of the solvent from the middle phase, consolidation of the membrane by post-fabrication cross-linking, or solidification of liquefied polymer. In addition to the mild conditions used, flow focusing devices offer further advantages over other techniques, including (i) formation of highly monodisperse (i.e., uniform in size) structures, (ii) high encapsulation efficiencies, (iii) control over the thickness of the shell wall, and (iv) encapsulation of aqueous cores. In collaboration with Dr. Alireza Abbaspourrad from the Weitz group, we used a microfluidic flow focusing device to fabricate core-shell microcapsules with depolymerizable PPA membranes. These microcapsules were capable of releasing their cargo selectively
through the depolymerization of the polymers in the shell wall triggered by a specific chemical signal (as illustrated in Figure 4-1). Finally, we found that the rate of release from the capsules could be modulated by changing either the thickness of the shell wall or the molecular weight of the polymers used.

4.2 Results and Discussion

4.2.1 Synthesis of Polymer 2-19

Polymer 2-19, which was initiated by isopropanol and terminated by 2-methoxypoly(ethylenoxy)$_6$dimethylchlorosilane, was used for the fabrication of the microcapsules because it exhibited a more rapid response as a solid material (in the context of the microscale pumps) than the polymers with more hydrophobic end-caps (i.e., 2-6 and 3-3). The five specific polymers employed ($2-19, M_n = 32, 37, 47, 54, \text{ and } 61 \text{ kDa}$) were the same as those used in the experiments described in Chapter 3. The syntheses of these polymers are shown in Figure 3-10b.

4.2.2 Solution Phase Depolymerization of 2-19

Before fabricating microcapsules from 2-19, we tested the ability of the polymer to respond selectively in solution. When polymer 2-19 ($M_n = 54 \text{ kDa}$) was exposed to 10 equiv of tetrabutylammonium fluoride (TBAF), complete depolymerization was observed in 6 h by GPC (Figure 4-7). On the other hand, no depolymerization was observed in 5 h when 2-19 was
exposed to 10 equiv of tetrabutylammonium chloride (TBACl). This result verified that the polymer was capable of complete and selective depolymerization in response to fluoride.

**Figure 4-7.** Selective depolymerization of polymer 2-19 ($M_n = 54$ kDa) in solution. The refractive index traces show the polymer before exposure to a stimulus (black) and 6 h after being exposed to 10 equiv of either TBAF (blue) or TBACl (orange).

### 4.2.3 Fabrication of Microcapsules from Depolymerizable PPA

The design of the microfluidic flow focusing device was used to fabricate microcapsules from polymer 2-19 ($M_n = 47$ kDa) is shown in Figure 4-8a.
The inner phase was an aqueous solution with 5 wt% poly(vinyl alcohol) (PVA) and 0.1 mM fluorescein isothiocyanate-labeled dextran (FITC-Dex) ($M_n = 4 \text{ kDa}$), which was used to test the ability of the microcapsules to respond to fluoride. The middle phase contained a 10 wt% solution of 2-19 ($M_n = 47 \text{ kDa}$) in chloroform for our initial experiments. Finally, the outer phase was another aqueous solution with 10 wt% PVA. PVA was used in both the inner and outer phases to balance the osmotic pressure between the two aqueous solutions during the fabrication of the capsules and to promote the formation of the double emulsion droplets, which are shown in Figure 4-8b. The ratio between the three flow rates for our initial experiments was 600:700:8000 μL/h (inner–middle–outer). After collecting the droplets, they were kept at room temperature for 3 h, which allowed for evaporation of the chloroform from the middle phase and formation of the shell walls. Figure 4-8c shows the monodisperse capsules formed using this technique. We further characterized the size and morphology of these capsules by freeze-drying and performing
SEM imaging, which showed smooth and homogenous shell walls with an average diameter of ~140 µm (Figure 4-9a,b).

![SEM images of freeze-dried microcapsules prepared from polymer 2-19 (M_n = 47 kDa). Reproduced with permission from Macromolecules, 2013, 46, 3309–3313. Copyright 2013 American Chemical Society.](image)

**Figure 4-9.** SEM images of the freeze-dried microcapsules prepared from polymer 2-19 (M_n = 47 kDa). Reproduced with permission from Macromolecules, 2013, 46, 3309–3313. Copyright 2013 American Chemical Society.

### 4.2.4 Determining Average Shell Wall Thickness

To determine the thickness of the shell walls produced using the flow-focusing device, freeze-dried capsules were broken open using a razor blade. SEM images of the resulting samples showed cross-sections of the shell walls of 14 capsules; a representative image is shown in Figure 4-10. Using this method, we found that the capsules formed using the procedure described in Section 4.2.3 (i.e., flow rates with a ratio of 600:700:8000 µL/h and a 10 wt% solution of polymer in the middle phase) had an average shell wall thickness of 1805 ± 79 nm.
Figure 4-10. SEM image showing a cross-section of a microcapsule prepared from polymer 2-19 ($M_n = 47$ kDa). The microcapsule was cut open using a razor blade, and the thickness of the shell wall was determined. Reproduced with permission from *Macromolecules*, 2013, 46, 3309–3313. Copyright 2013 American Chemical Society.

4.2.5 Response of the Microcapsules to Fluoride

Confocal microscopy was used to visualize the response of the microcapsules to fluoride. When capsules fabricated from polymer 2-19 with a molecular weight of 47 kDa were exposed to a 50 mM solution of fluoride in phosphate buffered water (pH 7.1, with 17% THF and 2.5% EtOAc), the fluorescence within the capsules decreased over a period of 96 h (Figure 4-11). This decrease in fluorescence is similar to that observed in the nanoparticles reported by Gillies and Almutairi (Section 4.1.1.1), and is characteristic of a dye like FITC-Dex being released from a high concentration environment inside the capsules to a low concentration environment outside of the capsules.
Figure 4-11. Confocal microscopy images obtained over 96 h of microcapsules prepared from polymer 2-19 ($M_n = 47$ kDa) that were exposed to 50 mM fluoride. Adapted with permission from *Macromolecules* 2013, 46, 3309–3313. Copyright 2013 American Chemical Society.

To quantify the rate of cargo release from the imaged capsules shown in Figure 4-11, we made a calibration curve for fluorescence intensity as a function of FITC-Dex concentration in bulk solutions (Figure 6-1). This calibration curve allowed us to determine the kinetics of the release of FITC-Dex by calculating the concentration of the dye in the capsules at various time points and determining the percent that had been released based on an initial dye concentration of 0.1 mM. Specifically, we found that the capsules fabricated from polymer 2-19 ($M_n = 47$ kDa) shown in Figure 4-11 exhibited complete release of FITC-Dex in 84 h (Figure 4-12). The kinetics of release appeared to be sigmoidal in shape; in contrast, Gillies and Moore observed hyperbolic release profiles with their systems (Sections 4.1.1.1 and 4.1.1.2).
Figure 4-12. % release of FITC-Dex over 96 h from microcapsules fabricated from polymer 2-19 ($M_n = 47$ kDa) with an average shell wall thickness of 1805 ± 79 nm. The capsules were stored in aqueous solutions with 17% THF and 2.5% EtOAc and were exposed to 50 mM TBAF (black), 50 mM TBACl (red), 50 mM NaCl (blue), or were simply stored in the mixed aqueous-organic solvent system (orange). The % release was determined by comparing the fluorescence intensity in the capsules to a calibration curve (Figure 6-1) generated from premade solutions of FITC-Dex. The data points represent the average of 100 measurements and the error bars reflect the standard deviations from these averages. Adapted with permission from *Macromolecules*, 2013, 46, 3309–3313. Copyright 2013 American Chemical Society.

Three control experiments were performed to verify the selective response of the capsules to fluoride. In the first two experiments, the capsules fabricated from polymer 2-19 ($M_n = 47$ kDa) were exposed to 50 mM TBACl (red in Figure 4-12) and 50 mM NaCl (blue in Figure 4-12) under the same solvent conditions. While exposure to fluoride led to complete cargo release after 84 h, the capsules exposed to the chloride salts TBACl nd NaCl showed 8 ± 2% and 4 ± 2% release of FITC-Dex after 96 h, respectively. This observation suggested that the release of the dye-labeled polymer was caused by the selective depolymerization mediated by the response of the silyl ether end-cap. In the third control experiment, no additional salt was added to the mixed aqueous–organic solvent system (orange in Figure 4-12). Only 2 ± 1% release of FITC-Dex was observed after 96 h under these conditions, which led us to conclude that the release of the
encapsulated cargo was not caused by osmotic pressure differences between the solutions inside and outside of the capsules.

4.2.6 Characterizing the Mechanism of Release by SEM

Imaging of the microcapsules exposed to fluoride by SEM at different time points along the release profile shown in Figure 4-12 provided further insight into the mechanism of release from the capsules. Specifically, we analyzed the capsules composed of 2-19 ($M_n = 47$ kDa) (i) before exposure to fluoride (Figure 4-13a,b), (ii) after 48 h of exposure to fluoride (Figure 4-13c,d), and (iii) after 96 h of exposure to fluoride (Figure 4-13e,f). Finally, we analyzed the capsules after 96 h of exposure to chloride to provide further evidence of the selective response provided by the polymers within the shell walls (Figure 4-13g,h).

**Figure 4-13.** SEM images showing the changes in the morphology of the capsules over time when exposed to fluoride. The images were obtained from freeze-dried samples after being exposed to 50 mM fluoride for (a) and (b) 0 h, (c) and (d) 48 h, and (e) and (f) 96 h. (g) and (h) Images that were obtained after exposing the capsules to 50 mM chloride for 96 h. The capsules were fabricated from polymer 2-19 with a molecular weight of 47 kDa and had an average shell

From this analysis, we observed that the homogenous shell wall at 0 h shown in Figure 4-13a and b appeared to have not changed significantly when viewed at lower magnification after 48 h of exposure to fluoride (Figure 4-13c). However, a closer view of the surface of the capsules revealed that the shell wall was covered with pores that presumably formed upon depolymerization of the polymers in the capsule membrane, which allowed for the 31 ± 2% release of FITC-Dex after 48 h shown in Figure 4-11e and Figure 4-12. After 96 h of exposure to fluoride, the change in the morphology of the capsules was much more significant (Figure 4-13e,f). The capsules had deteriorated, and the surface was covered with pores and other cavities. At the same point, confocal microscopy showed complete release of FITC-Dex (Figure 4-11j and Figure 4-12). The transformation of the morphology of the membrane containing polymer 2-19 after being exposed to fluoride was similar to the change we had observed in the case of a film prepared from the same polymer and exposed to 0.1 M NaF (Figure 3-11c,d).

In contrast, capsules that had been exposed to chloride for 96 h (Figure 4-13g,h) were largely unchanged from the initial SEM images shown in Figure 4-13a and b. This result suggests that polymer 2-19 responds selectively to fluoride both in solution (Figure 4-7) and in the solid state.

The SEM images in Figure 4-13 also helped to explain why the release profile in Figure 4-12 appears to be sigmoidal. When the capsules are first exposed to fluoride, only the polymers at the surface of the shell wall will start to depolymerize, making the initial rate of response slow. Furthermore, there will be a period when the pores that begin to form in the shell wall (shown in Figure 4-13d) connect the solution inside and outside the capsules, but the pores are too small to allow the encapsulated dye-labeled polymer to be released. These effects result in an initial lag period. However, as more polymers in the shell wall depolymerize, the capsule wall begins to deteriorate and the pores become larger (as shown in Figure 4-13e and f), making more of the
silyl ether end-caps accessible to fluoride and increasing the overall rate of response to the stimulus. Therefore, the rate of release of the cargo increases, as is observed at ~40 h in Figure 4-12.

4.2.7 Effect of Shell Wall Thickness of the Release Profile of the Microcapsules

By changing the flow rate of the middle phase and the concentration of polymer in the middle phase in the flow-focusing device, we were able to change the average shell wall thickness of the capsules produced from polymer 2-19 ($M_n = 47$ kDa) (Table 4-1). The average shell wall thickness values were determined from the average thickness of six capsules using the procedure described in Section 4.2.4.

Table 4-1. Conditions for the fabrication of microcapsules from polymer 2-19 ($M_n = 47$ kDa) with different average shell wall thicknesses using microfluidic flow-focusing. Adapted with permission from *Macromolecules*, 2013, 46, 3309–3313. Copyright 2013 American Chemical Society.

<table>
<thead>
<tr>
<th>[Polymer] (wt%)</th>
<th>Inner phase flow (µL/h)</th>
<th>Middle phase flow (µL/h)</th>
<th>Outer phase flow (µL/h)</th>
<th>Average Shell Wall Thickness (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>600</td>
<td>100</td>
<td>8000</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>600</td>
<td>450</td>
<td>8000</td>
<td>650</td>
</tr>
<tr>
<td>6</td>
<td>600</td>
<td>700</td>
<td>8000</td>
<td>1000</td>
</tr>
<tr>
<td>10</td>
<td>600</td>
<td>700</td>
<td>8000</td>
<td>1800</td>
</tr>
</tbody>
</table>

The capsules with shell wall thicknesses of 100, 650, 1000, and 1800 nm were evaluated for their response to fluoride (Figure 4-14). As expected, the capsules with thinner shell was released the encapsulated FITC-Dex more quickly than the capsules with thicker shell walls, and showed less of an initial induction period in the release profile. However, the microcapsules with
thinner shell walls would also be generally less stable and more likely to rupture under an applied mechanical force than the microcapsules with thicker shell walls.

**Figure 4-14.** Effect of shell wall thickness of the rate of release from capsules prepared from polymer 2-19 ($M_n = 47$ kDa) in response to 50 mM fluoride. The % release was determined by comparing the fluorescence intensity in the capsules to a calibration curve (Figure 6-1) generated from premade solutions of FITC-Dex. The data points represent the average of 100 measurements and the error bars reflect the standard deviations from these averages. Reproduced with permission from *Macromolecules, 2013, 46, 3309–3313*. Copyright 2013 American Chemical Society.

### 4.2.8 Effect of Polymer Molecular Weight on the Release Profile of the Microcapsules

The four other molecular weights of polymer 2-19 ($M_n = 32, 37, 54,$ and 61 kDa) were used to prepare microcapsules using the same procedure described in Section 4.2.3 for fabricating capsules from polymer 2-19 with a molecular weight of 47 kDa, which allowed us to maintain a uniform shell wall thickness. The capsules prepared from each polymer were exposed to 50 mM fluoride and the release of FITC-Dex was monitored for 96 h (Figure 4-15). As shown with the capsules of different shell wall thicknesses (Figure 4-14), the microcapsules prepared from
polymers with different molecular weight displayed sigmoidal release profiles, while the rate of release was clearly faster for shorter polymers. This result further supported our conclusions from the experiments using the microscale pumps; i.e., solid materials prepared from CD$_r$ polymers such as PPA with lower molecular weights allow for faster rates of response to a stimulus as a result of a higher end-cap density.

**Figure 4-15.** Effect of polymer molecular weight on the rate of release from capsules in response to 50 mM fluoride. The % release was determined by comparing the fluorescence intensity in the capsules to a calibration curve (Figure 6-1) generated from premade solutions of FITC-Dex. The data points represent the average of 100 measurements and the error bars reflect the standard deviations from these averages. Reproduced with permission from *Macromolecules, 2013, 46, 3309–3313. Copyright 2013 American Chemical Society.*

Figure 4-16 summarizes the results from our studies on the effects of polymer length and capsule shell wall thickness on the rate of FITC-Dex release from microcapsules in response to fluoride. Specifically, the graph shows linear relationships between the time required for 90% release of FITC-Dex and both (i) the molecular weight of polymer 2-19 used in capsule fabrication (blue), and (ii) the average shell wall thickness of the capsules (orange). Since the molecular weight of PPA (Figure 2-8)$^{40}$ and the thickness of the shell wall in microcapsules prepared using a flow-focusing device (Table 4-1) can easily be controlled, we believe that both
of these variables can be harnessed to modulate the response of core-shell microcapsules with PPA membranes.

![Graph showing relationship between polymer $M_n$ (kDa) and average shell wall thickness (nm)]

**Figure 4-16.** Tuning the rate of release from the microcapsules by varying the molecular weight of the polymers used to fabricate the capsules and by varying the thickness of the shell wall. Time to 90% release (of FITC-Dex) was calculated from the graphs in Figures 4-14 and 4-15. The data points represent the average of 100 measurements. The horizontal error bars for average shell wall thickness represent the standard deviation in shell wall thickness of six representative capsules. The vertical error bars represent the standard deviation values determined from the best-fit line generated from samples sets (10 values) taken from each time point in Figures 4-14 and 4-15; they are smaller than most of the data points. Adapted with permission from *Macromolecules, 2013, 46*, 3309–3313. Copyright 2013 American Chemical Society.

### 4.3 Conclusion

In conclusion, we have fabricated core-shell microcapsules from PPA using a microfluidic flow-focusing device. These responsive microcapsules release their encapsulated cargo in response to a specific stimulus through depolymerization of the polymers within the shell wall. The rate of release from the capsules can be tuned by changing (i) the molecular weight of...
the polymer used to formulate the capsules and (ii) the thickness of the shell walls, which can easily be controlled using the flow-focusing device.

In the future, we anticipate that microfluidic flow-focusing devices will be used to rapidly prepare capsules from CD₉ polymers with different polymer backbones and that respond to various stimuli. As a result, the envisaged advantages of using CD₉ polymers in the context of responsive microcapsules and other polymeric carriers, namely (i) the selectivity of the response of the polymers to specific stimuli through the use of reaction-based detection units, and (ii) the inherent amplification of the depolymerization reaction, will become even more apparent.

### 4.4 References


Chapter 5

Improving the Stability of Poly(phthalaldehydes): Application Towards the Fabrication of Multi-Responsive Materials Using Additive Manufacturing

The author of this dissertation was responsible for synthesizing PCl$_2$PA, testing the stability of the polymer, evaluating the depolymerization of the polymer in solution and in the solid state, testing the size of the particles used for selective laser sintering, and developing the procedure for recovering the products of depolymerization. Dr. Gregory G. Lewis was responsible for formulating the polymer for selective laser sintering and for developing the SLS procedure for the preparation of depolymerizable objects.

5.1 Introduction

Chapters 2 through 4 have shown the potential of PPA end-capped with responsive functionalities to act as a stimuli-responsive material capable of providing specific and amplified responses in signals in the context of shape-changing$^1$ and “vanishing” plastics$^2$, responsive microcapsules$^3$, and microscale pumps.$^4$-$^5$ However, the re-emergence of PPA as a responsive material is not limited to examples in which the polymer depolymerizes through an end-cap-mediated mechanism. Other applications have been explored in recent years with PPA end-capped with non-responsive groups that take advantage of the rapid depolymerization of the polymer caused by the inherent reactivity of the polymer backbone with certain stimuli (e.g., acid and heat)$^6$. These examples include the use of PPA as a resist for thermal probe lithography,$^7$-$^{11}$ as a thermally responsive block in an amphiphilic copolymer$^{12}$, as a material that self-assembles into nanoparticles and networks$^{13}$, as a mechanoresponsive material$^{14}$-$^{15}$, as a nanochannel template$^{16}$, and as a cyclic polymer$^{17}$, which has been applied as a reconfigurable polymer$^{18}$ and as a substrate for transient electronic devices$^{19}$-$^{20}$ and for graphene transfer$^{21}$. 
The widespread interest in PPA belies its limitations, namely that the polymer exhibits background degradation under relatively benign conditions. We have observed non-specific degradation of PPA end-capped with responsive functional groups not only when exposed to mild acid or to elevated temperatures but also when stored in solution or as a solid at room temperature. For example, Figure 5-1 shows the degradation of polymer 2-14 ($M_n = 14$ kDa) when stored in a solution of $d_8$-THF for 6 d.

![Diagram](image)

**Figure 5-1.** Non-specific degradation of polymer 2-14. (a) Reaction sequence for the experiment. (b) $^1$H NMR spectra for polymer 2-14 ($M_n = 14$ kDa) over a period of six day protected from light. Percent degradation was calculated from $^1$H NMR integration values for the aldehyde peak of the monomer relative to an internal standard with a known concentration, and is equal to (moles of monomer)/(total possible moles of monomer at 100% degradation) × 100. Adapted with permission from *Polym. Chem.*, 2015, 6, 3252–3258. Copyright 2015 Royal Society of Chemistry.

The solution of the polymer was stored protected from light, so that any formation of monomer (2-2) is non-specific (i.e., not caused by cleavage of the UV responsive polymer end-cap). The percent degradation was calculated to be 19% after 6 d by comparing the integration for the
aldehyde peak from the monomer to a peak for an internal standard (1,3,5-trimethoxybenzene) with a known concentration.

As a result of the instability of PPA under ambient conditions, special care must be taken when storing and handling PPA, which limits the development of the polymer as a stimuli-responsive material. Furthermore, the thermal instability of PPA prevents the use of many processing techniques for fabricating plastics out of the polymer, since these procedures require heating. One solution to these limitations was proposed by Moore and coworkers, who have reported that cyclic PPA shows greater stability than linear PPA under ambient conditions and when heated (the average onset temperature for thermal depolymerization of cyclic PPA was 14 °C higher than that of linear PPA). While this strategy is promising, the current methodology for preparing cyclic PPA does not allow for the incorporation of reaction-based detection units, limiting the stimuli to which the polymer can respond.
Figure 5-2. Proposed pathways leading to depolymerization of poly(phthalaldehydes). (a) Desired mechanism of depolymerization through cleavage of the polymer end-cap by a specific stimulus. (b) and (c) Proposed mechanisms for the non-specific degradation of poly(phthalaldehydes). Adapted with permission from *Polym. Chem.*, 2015, 6, 3252–3258. Copyright 2015 Royal Society of Chemistry.

The proposed mechanism of depolymerization for poly(phthalaldehydes) (when acting as a CD, polymer) is the cleavage of the polymer end-cap in response to a specific signal, revealing a hemi-acetal terminated species (5-1), which is thermodynamically unstable and will therefore rapidly depolymerize to the 1,2-aromatic dialdehyde monomer (Figure 5-2a). Based on this mechanism and the acid-catalyzed degradation mechanism of PPA (Figure 2-1b), we theorized that the non-specific degradation of the polymer shown in Figure 5-1 was caused by heterolytic bond cleavage, either at the end of the polymer (Figure 5-2b) or at a random site in the polymer backbone (Figure 5-2c). Both pathways involve the formation of thermodynamically unstable...
species (5-3, 5-5), which should act in a similar manner to the putative intermediate in the desired mechanism of depolymerization (5-1).

The two proposed mechanisms in Figure 5-2b and c helped guide our development of a polymer design that retained the rapid and selective depolymerization capability of linear PPA while also minimizing background degradation, particularly when kept under ambient conditions and when exposed to elevated temperatures. To achieve this aim, we prepared a novel PPA derivative with electron withdrawing groups appended to the polymer backbone. This chapter details those efforts, as well as the characterization of the stability and reactivity of the new polymer. Finally, an operationally simple adaptation of selective laser sintering (an additive manufacturing technique) was employed to fabricate multi-stimuli-responsive plastics from the polymer.

5.2 Experimental Design

5.2.1 Design of Poly(4,5-dichlorophthalaldehyde)

The proposed mechanisms for non-specific degradation of poly(phthalaldehydes) shown in Figure 5-2b and c involve heterolytic bond cleavage effected by formation of an oxocarbenium ion intermediate (5-2 and 5-4). These mechanisms allowed us to draw upon the physical organic chemistry literature for substituent effects on the reactivity of acetics in order to develop design principles that would increase the stability of a PPA derivative. Specifically, a report by Fife and Jao in 1965 suggested that the activation energy for formation of an oxocarbenium ion in the hydrolysis of cyclic, benzylic acetics is increased by adding electron withdrawing groups to the pendant aromatic ring. The five substituted 1,3-dioxolanes that the authors tested and the
corresponding Hammett *para* substituent constants and rates of hydrolysis in 1:1 water and dioxanes are shown in Table 5-1. The rates of hydrolysis for 2-(4-chlorophenyl)-1,3-dioxolane (5-9) and 2-(4-nitrophenyl)-1,3-dioxolane (5-10) were 4x and 469x slower respectively than the rate of hydrolysis for 4-phenyl-1,3-dioxolane (5-8). In contrast, adding electron donating groups *para* to the benzylic acetal increased the rate of hydrolysis as much as 32x for acetal 5-6. Thus, we hypothesized that we could increase the overall stability of the acetal functionality in the polymer backbone by appending electron withdrawing groups.

**Table 5-1.** Substituent effects on the rate of acid-catalyzed hydrolysis of 1,3-dioxolanes.\(^{28,29}\)

<table>
<thead>
<tr>
<th>acetal</th>
<th>R</th>
<th>(\sigma_{para})</th>
<th>(k_H) (1/mol*min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-5</td>
<td>-OCH(_3)</td>
<td>-0.268</td>
<td>824.1</td>
</tr>
<tr>
<td>5-6</td>
<td>-CH(_3)</td>
<td>-0.170</td>
<td>119.2</td>
</tr>
<tr>
<td>5-7</td>
<td>-H</td>
<td>0</td>
<td>25.4</td>
</tr>
<tr>
<td>5-8</td>
<td>-Cl</td>
<td>+0.227</td>
<td>6.19</td>
</tr>
<tr>
<td>5-9</td>
<td>-NO(_2)</td>
<td>+0.778</td>
<td>0.0541</td>
</tr>
</tbody>
</table>

The specific monomer that we chose to pursue based on our hypothesis was 4,5-dichlorophthalaldehyde. Poly(4,5-dichlorophthalaldehyde) (PCl\(_2\)PA) would have electron withdrawing groups *para* to both acetal carbons, thus offering a greater stabilizing effect than a monosubstituted derivative. In addition, a polymer prepared from phthalaldehyde derivatives with substituents *ortho* to acetal carbons may be destabilized due to steric interactions with the polymer backbone, and the monomer would likely be more difficult to synthesize.\(^{30}\) A monomer
with chlorine substituents were chosen over a derivative with more electron withdrawing groups (e.g., nitro) for three main reasons. First, preparing a monomer with such an electron poor aromatic ring could pose a safety hazard. Second, electron withdrawing groups would lower the $pK_a$ of the benzylic hydrogen atoms on the polymer, which could render the polymer much more unstable to base. For example, the $pK_a$ of toluene in DMSO is between 43 and 45, while the $pK_a$ of 4-nitrotoluene in DMSO is 20.4. Finally, formation of the hydrate of the dialdehyde would be more favorable with electron withdrawing groups, which could complicate the purification of the monomer.

5.2.2 Additive Manufacturing with PCl$_2$PA

In addition to solving the problem of the instability of PPA in solution (as shown in Figure 5-1), we expected that the design of PCl$_2$PA would improve upon the instability of the unsubstituted polymer to temperatures above 150 °C. This thermal instability ruled out most common techniques for polymer processing, which often involve elevated temperatures. We were particularly interested in exploring the use of PCl$_2$PA in additive manufacturing, a collection of technologies defined by the controlled deposition of layers of materials to construct a three dimensional object based on a computer-aided design. In comparison to more traditional polymer processing techniques such as injection molding (“subtractive” manufacturing), additive manufacturing offers the ability to rapidly prototype and manufacture complex objects, and to quickly change the design of the object.

Various types of additive manufacturing have been developed that utilize polymers, including stereolithography/photopolymerization, extrusion-based 3D printing, powder bed fusion, and beam deposition. However, there has been comparatively limited work in
developing new materials for additive manufacturing. In particular, the additive manufacturing of stimuli-responsive polymers is a largely unexplored area of research. Our interest in the additive manufacturing of PCl₂PA was motivated by the idea of fabricating macroscopic plastics that provide different amplified responses to different stimuli through depolymerization, as shown in Figure 5-3. Because of the mechanism of depolymerization for poly(phthalaldehydes) (Figure 5-2a), the products from the response of the plastic could be collected, re-polymerized, and re-processed. Such a system would enable materials with sustainable life cycles that could change in shape and function in response to specific environmental signals, therefore allowing them to mimic the capabilities of biological materials such as the leaves of rhododendrons.⁴⁰-⁴¹

![Diagram](image-url)

**Figure 5-3.** Illustration of a multi-stimuli-responsive material that provides an amplified response prepared by selective laser sintering of PCl₂PA. The material is composed of patterned polymer, but the blue and red layers have different detection units. Thus, the blue layer depolymerizes in response to one stimulus, and the red layer depolymerizes in response to a second stimulus. Recovery of the products from the depolymerization reaction allows for a sustainable life cycle for the material. Reproduced with permission from *Angew. Chem. Int. Ed.*, 2015, 127, 6298–6303. Copyright 2015 John Wiley and Sons.
5.3 Results and Discussion

5.3.1 Synthesis of PCl$_2$PA

We planned on synthesizing the monomer of PCl$_2$PA, 4,5-dichlorophthalaldehyde, by oxidizing 4,5-dichloro-1,2-benzenedimethanol, which could be obtained by reducing commercially available compounds (4,5-dichlorophthalic acid or 4,5-dichlorophthalic anhydride). However, a limited number of examples for preparing 1,2-aromatic dialdehydes by oxidation of the corresponding diol have been reported.$^{30,42-46}$ Thus, we used the oxidation of 1,2-benzenedimethanol ($\text{5-10}$) to 1,2-benzenedicarboxaldehyde ($\text{2-2}$) as a test reaction to screen common conditions for preparing aldehydes from primary alcohols (Table 5-2). We chose this test system because of the commercial availability of diol $\text{5-10}$.
Table 5-2. Conditions and $^1$H NMR yields for the oxidation of 5-10 to 2-2. Adapted with permission from *Polym. Chem.*, 2015, 6, 3252–3258. Copyright 2015 Royal Society of Chemistry.

![Diagram showing the conversion of 5-10 to 2-2 through the addition of conditions]  

<table>
<thead>
<tr>
<th>entry</th>
<th>reagents</th>
<th>temp ($^\circ$C)</th>
<th>$^1$H NMR yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(COCl)$_2$, DMSO, then Et$_3$N</td>
<td>-78</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>IBX</td>
<td>80</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>BaMnO$_4$</td>
<td>23</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>PDC</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>MnO$_2$</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>NaOCl, TEMPO, NaHCO$_3$, KBr</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

The yield of each oxidation reaction was determined by $^1$H NMR. The Swern oxidation reaction$^{47}$ (Entry 1) gave a nearly quantitative yield of 2-2, while oxidation with IBX (Entry 2) also showed high conversion to the desired product. The NMR spectra for entries 3, 4, and 5 all showed that the main product of the reaction was the lactone (i.e., phthalide), which was presumably formed via oxidation of a lactol intermediate. Finally, entry 6 gave very low conversion of 5-10 to 2-2, instead yielding a mixture of products that were difficult to differentiate by NMR.

With these conditions, 4,5-dichlorophthalaldehyde (5-13) was synthesized as shown in Scheme 5-1.
Reduction of 4,5-dichlorophthalic acid (5-11) to 4,5-dichloro-1,2-benzenedimethanol (5-12) was effected by borane in THF.\(^{46}\) The use of lithium aluminum hydride instead of borane gave lower yields and made purification of the product more difficult as a result of byproduct formation from nucleophilic aromatic substitution of one of the chlorine substituents. The Swern oxidation of 5-12 to 5-13 was repeated 9 times to ensure the reproducibility of the procedure, giving an average yield of 50 ± 10%.

The yield of 5-13 obtained using the Swern procedure was lower than the yield of 2-2 shown in Table 5-2 because of mass lost while purifying the monomer for anionic polymerization (see Table 2-1 for the effect of purity on the yield of PPA). Several techniques were tested to determine the optimal purification procedure. In our hands, purification of 5-13 by column chromatography was not reproducible. At times, it was effective for removing impurities, while in other instances we observed significant degradation of the dialdehyde. We have seen similar degradation (in conjunction with the blackening of the silica gel used in the procedure) in other, unpublished work on the synthesis of 1,2-aromatic dialdehydes. Instead, we were able to obtain 5-13 with high purity through a combination of selective dissolution, sublimation, and recrystallization. First, the crude solid from the Swern oxidation was dissolved in THF and
filtered, which removed the triethylammonium salt byproducts. Second, the resulting solid was sublimated at 110 °C under vacuum, which separated the monomer from colored byproducts that could not be removed by recrystallization alone. Finally, we obtained 5-13 by recrystallizing twice from chloroform.

4,5-Dichlorophthalaldehyde (5-13) could be polymerized using either P₂-t-Bu or P₁-t-Bu base (tert-butylimino-tri(pyrrolidino)phosphorane) (Scheme 5-1). The procedure for the reaction was inspired by our previously reported methodology for synthesizing depolymerizable PPA (Chapter 2),² with two important alterations based on observations from a recent report from Coulembier and coworkers.¹¹ Specifically, the authors found that PPA with lower polydispersities could be obtained (i) by mixing the phosphazene base and the alcohol initiator before adding it to the monomer solution, and (ii) by using a less basic phosphazene species (pKₐ (MeCN) of P₁-t-Bu = 27; pKₐ (MeCN) of P₂-t-Bu = 33.5).¹¹ The other observation that we made in regards to synthesizing PCl₂PA was that decreased yields were observed when terminating the polymerization with weaker electrophiles. For example, using acetic anhydride to end-cap the polymer gave yields around 30%, compared to 70–80% yields when end-capping with acetyl chloride. Using our modified procedure, PCl₂PA with various end-caps can be obtained with yields around 70% and with PDI values around 1.4. Figure 5-4 shows that PCl₂PA can be synthesized with end-caps responsive to fluoride (5-16 and 5-18),⁴⁸ palladium (5-14),⁴⁹ 254 nm light (5-19),⁵⁰-⁵¹ and 365 nm light (5-20),⁵⁰-⁵¹ as well as control polymers with non-responsive end-caps (5-15 and 5-17).
5.3.2 Stability of PCl$_2$PA Compared to PPA at Ambient Temperatures

To compare the stability of PCl$_2$PA in neutral solutions to that of PPA, we performed the experiment shown in Figure 5-1 (i.e., polymers stored in $d_8$-THF at room temperature and protected from light) with six polymers with different end-caps (Figure 5-5). After six days, the degradation of each polymer was determined by calculating the concentration of the monomer.

<table>
<thead>
<tr>
<th>polymer</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$M_n$ (kDa)</th>
<th>PDI</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-14</td>
<td>$i$Pr</td>
<td></td>
<td>13</td>
<td>1.8</td>
<td>84</td>
</tr>
<tr>
<td>5-15</td>
<td>$i$Pr</td>
<td>Ac</td>
<td>17</td>
<td>1.4</td>
<td>84</td>
</tr>
<tr>
<td>5-16</td>
<td>$i$Pr</td>
<td>TBS</td>
<td>24</td>
<td>1.7</td>
<td>74</td>
</tr>
<tr>
<td>5-17</td>
<td>$i$Pr</td>
<td>Cl$_3$C</td>
<td>23</td>
<td>1.4</td>
<td>50</td>
</tr>
<tr>
<td>5-18</td>
<td>TBS</td>
<td>TBS</td>
<td>18</td>
<td>1.9</td>
<td>99</td>
</tr>
<tr>
<td>5-19</td>
<td>$i$Pr</td>
<td></td>
<td>15</td>
<td>1.8</td>
<td>70</td>
</tr>
<tr>
<td>5-20</td>
<td>$i$Pr</td>
<td></td>
<td>25</td>
<td>1.7</td>
<td>84</td>
</tr>
</tbody>
</table>
Figure 5-5. Percent degradation of 7.0 mM solutions of polymers 2-14, 2-8, 2-20, 5-20, 5-14, and 5-15 after 6 days. The solutions were protected from light. (a) Conditions for the experiment. (b) Percent degradation for each polymer. Percent degradation was calculated as described in Figure 5-1. The data for polymer 2-14 is the average and standard deviation of 3 experiments. Adapted with permission from Polym. Chem., 2015, 6, 3252–3258. Copyright 2015 Royal Society of Chemistry.
For the polymer end-capped with carbonates, a clear increase in stability is observed for PCl₂PA. Polymers 2-14 and 2-8 degrade by 0.8-3.2% per day, while polymers 5-20 and 5-14 show 1% degradation or less over six days. The difference in stability between the carbonate end-caps is most likely the result of the difference in pKₐ between allyl alcohol (pKₐ (water) = 15.5) and 4,5-dimethoxy-2-nitrobenzyl alcohol (pKₐ (water) = ~13.6). The lower pKₐ for 4,5-dimethoxy-2-nitrobenzyl alcohol makes the functionality a better leaving group, increasing the rate of degradation by the mechanism shown in Figure 5-2b.

The polymers end-capped by esters, 2-20 and 5-15) both show negligible degradation over six days. Again, the pKₐ values for the carboxylic acid leaving groups (estimated to be ~3 based on a pKₐ of 2.92 for carbonic acid methyl ester in water) and the carboxylic acid leaving groups (pKₐ (water) = 4.76 for acetic acid) can be used to explain the difference in stability based on end-cap composition. Although this result suggests that end-capping PPA with esters can be used to overcome the polymer instability in neutral solutions, most responsive units that we and others have demonstrated are linked to the polymer as carbonates. Therefore, the stabilizing effect of the electron withdrawing groups in PCl₂PA allows for a more general solution to the issue of background degradation in poly(phthalaldehydes) with reaction-based detection units.

The stabilizing effect of the electron withdrawing chlorine substituents extends beyond storage in neutral solutions. Although the acetal backbone of poly(phthalaldehydes) is usually considered to be sensitive to acid, PCl₂PA shows a remarkable stability compared to PPA in acidic solution (Figure 5-6).
Figure 5-6. Percent degradation of 5.2 mM solutions of polymers 2-8, 2-20, 5-14, and 5-15 after 6 days in the presence of 100 equiv BzOH. The solutions were protected from light. (a) Conditions for the experiment. (b) Percent degradation for each polymer. Percent degradation was calculated as described in Figure 5-1. The data for polymer 2-8 is the average and standard deviation of 3 experiments. Adapted with permission from Polym. Chem., 2015, 6, 3252–3258. Copyright 2015 Royal Society of Chemistry.

For this experiment, two PPA derivatives (2-8 and 2-20) and two PCl2PA derivatives (5-14 and 5-15) were stored in $d_8$-THF solutions that also contained 100 equiv of benzoic acid ($pK_a$(THF) = 25.11). After six days, over 30% of polymers 2-8 and 2-20 had degraded, while polymers 5-14 and 5-15 degraded by 1% and 2% respectively. Under these conditions, the ester
end-capped polymers and the carbonate end-capped polymers with both substituents showed no significant difference in terms of degradation, suggesting that our strategy is able to stabilize poly(phthalaldehydes) against both possible mechanisms of degradation shown in Figure 5-2b and c.

Both our group and other groups have observed that solid, linear PPA is also not stable if kept at room temperature for a significant amount of time. For example, when storing polymer 2-8 (\(M_n = 34 \text{ kDa}\)) in a laboratory hood for 130 days, 95% of the polymer degraded (Figure 5-7a). Visually, the sample had turned from a white powder to a yellow crystalline solid. As a result, we have always stored PPA at low temperatures and under an inert atmosphere. PCl\(_2\)PA, however, is bench stable and does not require any special handling; when storing polymer 5-14 (\(M_n = 31 \text{ kDa}\)) in a laboratory hood for 130 days, no significant degradation was observed by \(^1\)H NMR (Figure 5-7b).
Figure 5-7. Bench stability test for polymers 2-8 and 5-14. (a) $^1$H NMR of polymer 2-8 ($M_n = 34$ kDa) after being stored under ambient conditions in the solid state for 130 days. (b) $^1$H NMR of polymer 5-14 ($M_n = 31$ kDa) after being stored under ambient conditions in the solid state for 130 days. Adapted with permission from Angew. Chem. Int. Ed., 2015, 127, 6298–6303. Copyright 2015 John Wiley and Sons.
5.3.3 Thermal Stability of PCl₂PA Compared to PPA

Polymers 2-8, 2-20, 5-14, and 5-15 were tested by thermal gravimetric analysis (TGA) to evaluate the temperature at which they began to degrade thermally (Figure 5-8). When comparing polymers with the same end-caps, a difference in onset temperature of about 40 °C was observed between PPA and PCl₂PA. There was also an increase in thermal stability (~10 °C difference in onset temperature between 2-8 and 2-20 and between 5-14 and 5-15) for ester end-capped polymers in comparison to carbonate end-capped polymers.

![Normalized TGA curves and thermal degradation temperatures for polymers 2-8 (black), 2-20 (orange), 5-14 (blue), and 5-15 (pink). Adapted with permission from Polym. Chem., 2015, 6, 3252–3258. Copyright 2015 Royal Society of Chemistry.](image)

<table>
<thead>
<tr>
<th>Polymer</th>
<th>$M_n$ (kDa)</th>
<th>Onset Temp (°C)</th>
<th>Endset Temp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-8</td>
<td>34</td>
<td>160</td>
<td>189</td>
</tr>
<tr>
<td>2-20</td>
<td>38</td>
<td>174</td>
<td>202</td>
</tr>
<tr>
<td>5-14</td>
<td>30</td>
<td>205 ± 2</td>
<td>230 ± 5</td>
</tr>
<tr>
<td>5-15</td>
<td>17</td>
<td>213</td>
<td>236</td>
</tr>
</tbody>
</table>

Figure 5-8. Normalized TGA curves and thermal degradation temperatures for polymers 2-8 (black), 2-20 (orange), 5-14 (blue), and 5-15 (pink). Adapted with permission from Polym. Chem., 2015, 6, 3252–3258. Copyright 2015 Royal Society of Chemistry.

5.3.4 Selective Depolymerization of PCl₂PA

The incorporation of electron withdrawing groups into the poly(phthalaldehyde) backbone does not prevent PCl₂PA from acting as a CDₐ polymer and depolymerizing rapidly and selectively to monomer in solution and in the solid state. When a solution of polymer 5-14 ($M_n =$
17 kDa) was exposed to 2 equiv of Pd(PPh₃)₄, the refractive index detector showed complete conversion from polymer to monomer after 30 minutes (Figure 5-9a,b). No depolymerization was observed by GPC when a solution polymer 5-15 (Mₙ = 24 kDa) was exposed to the same conditions (Figure 5-9c), suggesting that PCl₂PA also depolymerizes through an end-cap–mediated mechanism.

![Diagram](image)

**Figure 5-9.** Selective depolymerization of PCl₂PA in response to Pd(0). (a) Conditions for measuring the extent of depolymerization of polymers 5-14 (Mₙ = 17 kDa) and 5-15 (Mₙ = 24 kDa). (b) Refractive index traces for 5-14 before (black) and 30 minutes after (blue) adding 2 equiv of Pd(0). (c) Refractive index traces for 5-15 under identical conditions to those described in (b). Adapted with permission from *Angew. Chem. Int. Ed.*, 2015, 127, 6298–6303. Copyright 2015 John Wiley and Sons.
To show that the depolymerization response was not limited to palladium, we evaluated the response of polymers 5-16 ($M_n = 24$ kDa) and 5-17 ($M_n = 23$ kDa) to TBAF (Figure 5-10a). The polymers were dissolved in THF, and a solution of TBAF in 2:1 phosphate buffer (0.1 M, pH 7.1) and THF was added. Again, the polymer end-capped by the responsive unit (5-16) was observed by GPC to have depolymerized completely in 30 minutes (Figure 5-10b), while the control polymer (5-17) did not respond (Figure 5-10c).

**Figure 5-10.** Selective depolymerization of PCl$_2$PA in response to fluoride. (a) Conditions for measuring the extent of depolymerization of polymers 5-16 ($M_n = 24$ kDa) and 5-17 ($M_n = 23$ kDa). (b) Refractive index traces for 5-16 before (black) and 30 minutes after (blue) adding 1.6 equiv of fluoride. (c) Refractive index traces for 5-17 under identical conditions to those described in (b). Adapted with permission from *Angew. Chem. Int. Ed.*, 2015, 127, 6298–6303. Copyright 2015 John Wiley and Sons.
The extent of depolymerization of PCl₂PA depends on the concentration of the analyte present. When solutions of polymer 5-14 \((M_n = 30 \text{ kDa})\) were exposed to varying concentrations (0 mM to 1.6 mM) of Pd(PPh₃)₄ and analyzed by \(^1\)H NMR after 30 minutes, we observed a clear dose-dependent depolymerization response (Figure 5-11).

Figure 5-11. Dose-dependent depolymerization response of polymer 5-14 in response to Pd(0). (a) Conditions for evaluating the response of polymers 5-14 \((M_n = 30 \text{ kDa})\) and 5-15 \((M_n = 21 \text{ kDa})\) to different concentrations of Pd(PPh₃)₄. (b) Percent depolymerization of polymers 5-14 and 5-15 in response to different concentrations of Pd(0). Percent depolymerization was calculated using \(^1\)H NMR integration values for the aldehydes peak of the monomer relative to an internal standard with a known concentration. Percent depolymerization is equal to \((\text{moles of monomer})/(\text{total possible moles of monomer at 100\% depolymerization}) \times 100\). The lines are provided as visual aids. Adapted with permission from Polym. Chem., 2015, 6, 3252–3258. Copyright 2015 Royal Society of Chemistry.

The hyperbolic response curve begins to plateau around 1.2 mM of Pd(0), where approximately 100\% of the polymer has depolymerized. Furthermore, the \(^1\)H NMR spectra after 30 minutes of exposure to the higher concentrations of palladium show that the only product of
depolymerization was 4,5-dichlorophthalaldehyde (5-13). In comparison, polymer 5-15 ($M_n = 20$ kDa) shows only 3% depolymerization or less by NMR under the same conditions. We believe that the ability of PCl$_2$PA to provide a selective and dose-dependent response could be used to develop an assay in which the extent of depolymerization is used to determine the concentration of an analyte. The stability of the polymer is particularly important when used in this context, since any non-specific degradation of PCl$_2$PA would result in a decrease in the sensitivity of the assay.

To evaluate the solid-state depolymerization of PCl$_2$PA, we again chose to test the system by observing the solubility change that occurs when polymers convert to monomer. We prepared 3.5 mm × 1.8 mm cylinders of polymers 5-18 ($M_n = 15$ kDa) and 5-15 ($M_n = 33$ kDa) by solvent casting 200 mg/mL solutions of the polymers with 20 wt% plasticizer (dimethyl phthalate) into a silicon mold. We first evaluated the cylinders by submerging them in a 12 mM solution of TBAF in 160:1 acetonitrile–phosphate buffer (0.1 M, pH 7.1), which dissolves the monomer but not the polymer (Figure 5-12). The depolymerization of the cylinder made from polymer 5-18 in response to fluoride caused it to disappear in 5 h, while the cylinder made from polymer 5-15 showed no change in size, even when exposed in the solution of fluoride for 10 h.
Figure 5-12. Solid state depolymerization of PCl$_2$PA in response to fluoride. The disk prepared from polymer 5-18 ($M_n = 15$ kDa) disappeared within 5 hours. The disk prepared from polymer 5-15 ($M_n = 33$ kDa) did not significantly change in size under the same conditions. Adapted with permission from Angew. Chem. Int. Ed., 2015, 127, 6298–6303. Copyright 2015 John Wiley and Sons.

We verified that the disappearance of the cylinder of polymer 5-18 was caused by depolymerization by repeating the same experiment and then concentrating the solutions containing the polymer cylinders after 5 h. The resulting residues were re-dissolved in THF and analyzed by GPC. Figure 5-13a shows this GPC data and that of a cylinder prepared from polymer 5-18 that had not been exposed to fluoride. The difference between the two RI traces reveals that polymer 5-18 has completely converted to small molecules in response to fluoride. Therefore, the disappearance of the cylinder shown in Figure 5 was not caused by a change in solubility resulting from cleavage of the TBS end-caps. On the other hand, polymer 5-15 has not significantly responded to or reacted with the fluoride (Figure 5-13b), since the GPC traces before and after exposure both show the presence of polymer with the same retention time. Based on these results, we concluded that PCl$_2$PA was also capable of selective, end-cap–mediated depolymerization in the solid state.
5.3.5 Selective Laser Sintering of PCl₂PA

PCl₂PA exhibited significantly improved stability at both ambient and elevated temperatures compared to PPA, while retaining the ability to depolymerize in a continuous and selective manner in solution and in the solid state. Based on these results, we believed that the polymer was a good candidate for developing multi-stimuli-responsive materials, as shown in Figure 5-3. We first attempted to extrude the polymer into a filament, which could in turn could be 3D printed. However, the polymer appeared to degrade during the extrusion process. We
believe that this degradation was the result of (i) the instability of poly(phthalaldehydes) towards mechanical force,\textsuperscript{14} and/or (ii) the lack of a glass transition ($T_g$) or melting temperature ($T_m$) for PCl$_2$PA, as determined by differential scanning calorimetry (DSC) (Figure 6-90). The $T_g$ and $T_m$ are most likely above the thermal degradation temperature of the polymer, which has also been observed with PPA.\textsuperscript{55}

Next, we turned to selective laser sintering (SLS), a type of powder bed fusion in which particles of a material are fused together into a pattern using a laser.\textsuperscript{25-27} The sintering process does not involve the melting of the material; instead, the particles fuse together based on the heating induced by the laser.\textsuperscript{26} After one layer is fused, more powder is added, and the next layer of the object is sintered to grow the object in three dimensions.

To prepare the polymer for SLS, we first formulated PCl$_2$PA with 30 wt% plasticizer (dibutyl phthalate). We also could add dyes at this point to add color to the polymer. The resulting solid was cooled using liquid nitrogen, then ground into fine particles using a mortar and pestle. Cooling with liquid nitrogen minimized any chain scission in the polymer caused by the application of mechanical force and made the solids easier to grind. Analysis of the resulting powder under an optical microscope showed irregularly shaped particles that had average lengths of 26 ± 16 µm (average of 39 particles; lengths were calculated using ImageJ) (Figure 5-14).
After the formulation process, the polymer powder was transferred to silicon mold, leveled, and sintered using a CO\textsubscript{2} laser into a pattern transferred from a digital design (the design was made in Adobe Illustrator) (Figure 5-15).

Each individual layer was defined by “printing” three times with the laser. After one layer of the object was fused together, additional polymer powder was added, and the next layer was sintered together. Once the object was completed, it was removed from the silicon mold and rinsed 3× with methanol. In terms of the fidelity of the dimensions of the object obtained compared to the
digital dimensions, Dr. Gregory Lewis determined that this process gives an increase in line width of $0.50 \pm 0.06$ mm.

We verified that PCl$_2$PA was stable to this SLS procedure by using GPC to characterize polymers $5\text{-}14$ ($M_n = 13$ kDa) and $5\text{-}18$ ($M_n = 18$ kDa) (i) after formulation with plasticizer and being ground into a fine powder by mortar and pestle, and (ii) after being sintered (Figure 5-16).

![Figure 5-16. Stability of polymers 5-14 and 5-18 to SLS. (a) Refractive index traces of polymer 5-14 ($M_n = 13$ kDa) before and after sintering. (b) Refractive index traces of polymer 5-18 ($M_n = 18$ kDa) before and after sintering. Adapted with permission from Angew. Chem. Int. Ed., 2015, 127, 6298–6303. Copyright 2015 John Wiley and Sons.](image)

The RI traces clearly show the presence of polymer with the same retention time for both polymers, as well as the lack of any additional small molecules appearing during the sintering process. The large peak with a retention time near 20 minutes corresponds to the plasticizer.
Despite the heat generated by the CO\textsubscript{2} laser during sintering, the degradation of PCl\textsubscript{2}PA was negligible.

As an initial demonstration of the SLS process, we prepared sintered rings with a diameter of 7.5 mm from polymers 5-14 (\(M_n = 13 \text{ kDa}\)) and 5-18 (\(M_n = 18 \text{ kDa}\)) (Figure 5-17a). Both rings were exposed to the corresponding stimuli: a solution of 2.7 mM Pd(PPh\textsubscript{3})\textsubscript{4} and 143 mM benzenesulfinic acid sodium salt (an allyl scavenger)\textsuperscript{36} in 7.5:7.5:1 benzene–MeOH–DCM for polymer 5-14, and a solution of 111 mM TBAF in 17:1 MeCN–phosphate buffer (0.1 M, pH 7.1) for polymer 5-18. Figure 5-17b and c show that the ring made from polymer 5-14 completely disappeared within 30 minutes. Similarly, the ring made from 5-18 disappeared within 60 minutes in response to fluoride (Figures 5-17a–c).
Figure 5-17. Depolymerization of sintered rings in response to specific signals. (a) The rings made from polymer 5-14 (red) and polymer 5-18 (blue). The red ring was exposed to 2.7 mM Pd(PPh\(_3\))\(_4\) and 143 mM benzenesulfonic acid in a 7.5:7.5:1 solution of benzene–MeOH–DCM. The blue ring was exposed 111 mM TBAF in 17:1 MeCN–buffer. Time lapse photographs at (b) 0 minutes, (c) 30 minutes, and (d) 60 minutes show the disappearance of both rings in less than an hour. Reproduced with permission from *Angew. Chem. Int. Ed.*, 2015, 127, 6298–6303. Copyright 2015 John Wiley and Sons.

To ensure that the depolymerization of the rings shown in Figure 5-17 was still caused by selective depolymerization, two control experiments were performed. First, a sintered ring made from polymer 5-14 (\(M_n = 13\) kDa) was exposed to a solution of 143 mM benzenesulfonic acid sodium salt in 7.5:7.5:1 benzene–MeOH–DCM (i.e., the same conditions as in Figure 5-17...
without palladium) (Figure 5-18a–c). Second, a sintered ring made from 5-18 ($M_n = 18$ kDa) was exposed to a solution of 111 mM tetrabutylammonium chloride (TBACl) in 17:1 MeCN–phosphate buffer (0.1 M, pH 7.1) (Figure 5-18d–f). Even after over 3.5 hours, neither ring had significantly changed in size. The selective response of both polymers as solids suggests that the chemical composition of PCl$_2$PA does not change after sintering the polymer, despite the physical changes.

![Figure 5-18](image.png)

**Figure 5-18.** Control experiments for sintered disks made from polymers 5-14 and 5-18. (a)–(c) Time lapse photographs of the disk made from polymer 5-14 when exposed to 143 mM benzenesulfinic acid in a 7.5:7.5:1 solution of benzene–MeOH–DCM. (d)–(f) Time lapse photographs of the disk made from polymer 5-18 when exposed to 111 mM TBACl in 17:1 MeCN–buffer. Reproduced with permission from *Angew. Chem. Int. Ed.*, 2015, 127, 6298–6303. Copyright 2015 John Wiley and Sons.
5.3.6 Multi-Stimuli-Responsive Materials from PCl₂PA

Once we had established (i) that PCl₂PA is stable to SLS process, and (ii) that the polymer retains the ability to selectively depolymerize in the solid state after being sintered, we sought to use SLS to develop multi-stimuli-responsive materials from PCl₂PA, as shown in Figure 5-3. As an initial demonstration, we fabricated a two layer 3D grating from polymers 5-14 ($M_n = 13$ kDa) and 5-18 ($M_n = 18$ kDa). The top layer consisted of three parallel cylinders sintered from polymer 5-18 formulated with blue dye, while the bottom layer consisted of polymer 5-14 formulated with red dye and sintered into the pattern of three cylinders perpendicular to the three in the top layer (Figure 5-19a). When exposed to 111 mM fluoride in 17:1 MeCN–phosphate buffer (0.1 M, pH 7.1), the blue, top layer (5-18) depolymerized and dissolved in 30 minutes, while the red, bottom layer (5-14) showed no significant change. The complete depolymerization of the grating was achieved after exposing the remaining layer to a solution of 2.7 mM Pd(PPh₃)₄ and 143 mM benzenesulfinic acid sodium salt in 7.5:7.5:1 benzene–MeOH–DCM for 30 minutes.

Figure 5-19. Multi-stimuli-responsive materials made from PCl₂PA using SLS. (a) Two layer grating made from polymers 5-18 (blue) and 5-14 (red). The top layer depolymerized and disappeared in response to fluoride, while the bottom layer was stable until the addition of Pd(0), which converted the sintered object into soluble products. (b) Three layer grating made from polymers 5-14 (red, triangles), 5-18 (blue, circles), and 5-15 (orange, squares). Reproduced with

In an additional demonstration, we used SLS to prepare a three layer grating from polymers 5-14 \((M_n = 13 \text{ kDa})\), 5-18 \((M_n = 18 \text{ kDa})\), and 5-15 \((M_n = 22 \text{ kDa})\) (Figure 5-19b). The layers in the grating are: (i) the top, red layer of triangles made from polymer 5-14; (ii) the middle, blue layer of circles made from polymer 5-18, and (iii) the bottom, orange layer of squares made from polymer 5-15. The top and middle layers were removed selectively in response to Pd(0) and fluoride respectively, leaving only the bottom layer, which does not respond to either signal (Figure 5-19c). In the process of removing the layers of the object, the size of the pores of the grating changes, effectively changing the function of the material depending on which chemical signal is present.

### 5.3.7 Recovery of Products of Depolymerization from PCl\(_2\)PA

Recovering the products of the depolymerization reaction of PCl\(_2\)PA would allow for the regeneration of the polymer without having to consume more raw materials. First, we tried to recover the monomer (5-13) directly from the solid state depolymerization of a material made from polymer 5-18. Since 5-13 degrades in the presence of silica gel (Section 5.3.1), we attempted to purify the monomer by sublimation and recrystallization. However, neither procedure was adequate for recovering 5-18, most likely due to the presence of plasticizer and the stimulus (TBAF and other tetrabutylammonium byproducts) after the depolymerization reaction. Instead, we were able to reduce the monomer directly after the depolymerization reaction and obtain 4,5-dichloro-1,2-benzenedimethanol (5-12) with a 65% recovery based on the initial mass of the polymeric material (Scheme 5-2). This process then intersects with the synthesis of the
monomer (Scheme 5-1), which could allow for the development of a sustainable life cycle for stimuli-responsive materials based on PCl₂PA.

![Scheme 5-2](image)

**Scheme 5-2.** Recovery of 5-12 from the depolymerization of a material fabricated from PCl₂PA.

### 5.4 Conclusion

In conclusion, we have reported the synthesis of a novel poly(phthalaldehyde) derivative: poly(4,5-dichlorophthalaldehyde). PCl₂PA shows substantially improved stability compared to PPA in both neutral and acidic solutions as well as a solid under ambient conditions. Furthermore, the improved thermal stability of PCl₂PA allowed us to use selective laser sintering to prepare stimuli-responsive materials from the polymer that could provide different, selective responses to different chemical signals.

An ideal CDₐ polymer should possess the seemingly contradictory characteristics of possessing the ability to rapidly depolymerize both in solution and in the solid state in response to a specific signal, while remaining completely stable in the absence of that signal. In this thesis, I have described the development of poly(phthalaldehyde) and poly(4,5-dichlorophthalaldehyde) as CDₐ polymers. The principles developed from this work should help guide not only the future use of these two polymers as stimuli-responsive materials, but also further advancements in the field with new types of polymers and new classes of smart materials.

### 5.5 References


Chapter 6

General Experimental, Methods, Experimental Procedures, and Characterization

6.1 General Experimental

All reactions were performed in flame-dried glassware under a positive pressure of argon unless otherwise noted. For polymerization reactions, glassware was flame-dried and stored in a glove box overnight, and argon was passed through an Agilent oxygen trap BOT-4. Air-and moisture-sensitive liquids were transferred by syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation (25–40 mmHg) at ambient temperature, unless noted otherwise. All reagents used were purchased commercially and were used as received unless noted otherwise. 1-tert-Butyl-2,2,4,4,4-pentakis(dimethylamino)-2λ5,4λ5-catenadi(phosphazene) (P$_2$-t-Bu base) in THF (2.0 M) and tert-butylimino-tri(pyrrolidino)phosphorane (P$_1$-t-Bu base) were purchased commercially and stored in a glove box under an inert atmosphere before use. 1,2-Benzenedicarboxaldehyde was purified by recrystallizing 3× from 5:2 dichloromethane–hexanes, drying under vacuum for 2 d, and storing in a glove box under inert atmosphere as described below. 1-[[((Chlorocarbonyl)oxy)methyl]-4,5-dimethoxy-2-nitrobenzene was synthesized as described by Katritzky et al.$^1$ 4-vinylbenzyl chloride was purified as described by Armarego and Chai.$^2$ 2-nitrobenzyl carbonochloridate was synthesized as described by Hu et al.$^3$ (2S,3S,4S,5R,6S)-6-(4-((4-(Difluoromethyl)phenylcarboxamidoxyloxy)methyl)phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid (3-1) was synthesized as described by Zhang et al.$^4$ 2-Iodoxybenzoic acid (IBX) was synthesized as described by Frigerio et al.$^5$ Dry isopropanol was distilled over CaH$_2$ at
760 mmHg and stored over 3Å molecular sieves. Dry pyridine was distilled over CaH₂ at 760 mmHg. Dry ethylene glycol was distilled over Ca₃SO₄ at 760 mmHg and stored over 3Å molecular sieves. Tetrahydrofuran, dichloromethane, and dimethylsulfoxide were purified by the method developed by Pangborn et al. Flash-column chromatography was performed as described by Still et al., employing silica gel (60-Å pore size, 32–63 μm, standard grade, Dynamic Adsorbents). Thin layer chromatography was carried out on Dynamic Adsorbents silica gel TLC (20 × 20 cm w/h, F-254, 250 μm).

6.2 Instrumentation

Proton nuclear magnetic resonance spectra were recorded using either a Bruker DPX-300 (300 MHz), a Bruker AMX-360 (360 MHz), or a Bruker DRX-400 (400 MHz) at 23 °C unless noted otherwise. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to tetramethylsilane ((CH₃)₄Si, 0.00 ppm) or to residual protium in the solvent (d₈-THF, 3.58 ppm and 1.73 ppm, or C₆D₆, 7.16 ppm, or CD₂Cl₂, 5.32 ppm, or d₆-DMSO, 2.50 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad peak), integration, and coupling constant (J) in hertz. Carbon nuclear magnetic resonance spectra were recorded using either a Bruker DPX-300 (75 MHz) or a Bruker DRX-400 (100 MHz) at 25 °C. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent (CDCl₃, 77.16 ppm, or CD₂Cl₂, 53.84 ppm, or d₆-DMSO, 39.52 ppm).

Gel permeation chromatography (GPC) analyses were performed using an Agilent Technologies 1200 GPC equipped with a refractive index detector, a Malvern Viscotek model
270 Dual Detector with right and low-angle light scattering, and either a Viscotek T-column (300 mm × 7.8 mm, CLM3012) and Agilent Resipore column (300 mm × 7.5 mm) in series, two Agilent Resipore (300 mm × 7.5 mm) columns in series, or a single Agilent Resipore column (300 mm × 7.5 mm) using THF as the mobile phase (flow rate: 1 mL/min, 25 °C). The GPC was calibrated using monodisperse polystyrene standards from Malvern.

The optical microscopy images in Chapters 3 and 5 were obtained using a Zeiss Axiovert 200 microscope. The optical and confocal microscopy images in Chapter 4 were obtained using a Leica TCS SP5 confocal microscope.

SEM images of the polymer films in Chapter 3 were acquired using a FEI Nova NanoSEM 630 using secondary electron detection at 1 kV. SEM images of the microcapsules in Chapter 4 was acquired using a Zeiss FESEM SupraVP using secondary electron detection at 1 kV.

XPS spectra were acquired using a Kratos Axis Ultra XPS with a monochromatic Al Kα X-ray source operated at 14 kV, 20 mA in hybrid slot mode. The survey scans are accomplished using a pass energy of 80 eV, with a 0.5 eV step size and 150 ms dwell time.

Thermal gravimetric analysis (TGA) was accomplished using a TA Instruments 2050 TGA. Scans were collected in the range of 25 °C to 300 °C with a ramping rate of 10 °C/min under a dry N₂ atmosphere. Differential scanning calorimetry was accomplished using a TA Instruments DSC Q2000. Tzero aluminum pans with lids were used as sample test containers and nitrogen was used as the same purge gas. DSC measurements included 2 cyclic scans, where a cyclic scan includes both heating and cooling processes. Temperature range for scans varied between –20 and 170 °C.

Selective laser sintering (SLS) was accomplished using an Epilog Mini 24 Laser system (raster mode; 35% speed; 9% power; auto-focus toggled off). Object layouts were created in Adobe Illustrator, and then sent to the laser system.
6.3 Chapter 2: Synthetic Procedures and Characterization

6.3.1 General Procedure for Synthesizing Depolymerizable PPA

Purified 1,2-benzenedicarboxaldehyde (see Section 6.3.2) (1.0 equiv, 2-2) was sealed in a round-bottom flask charged with a NdFeB magnetic stir bar in a glove box under a N₂ atmosphere. Outside of the glove box, anhydrous THF was added to the round-bottom flask to create a 0.6 M solution of the monomer; the resulting solution was degassed via three freeze-pump-thaw cycles and subsequently backfilled with oxygen-free argon. The desired initiator (0.002 equiv) was added, and the reaction mixture was cooled to −78 °C. After 2 min, a solution of 1-tert-butyl-2,2,4,4,4-pentakis(dimethylamino)-2λ₅,4λ₅-catenadi(phosphazene) (P₂-t-Bu base) in THF (2.0 M, 0.004 equiv) was added in one portion to the solution containing the monomer and initiating alcohol. The reaction mixture was stirred vigorously (~350 rpm) at −78 °C and monitored carefully. If a white precipitate formed, the reaction mixture was warmed until the solution became homogeneous again, then additional quantities of the P₂-t-Bu base solution in THF (0.0013 equiv) were added. If the solution did not become visibly viscous after 30 min, then additional quantities of the P₂-t-Bu base solution (0.0013 equiv) were added. Two hours after the final catalyst loading step, the polymer was end-capped via sequential addition of pyridine (0.5 equiv) and an electrophile (0.1 equiv) to the −78 °C solution. The solution containing the end-capped polymer was allowed to warm to rt over 2 h. The polymer was precipitated by adding the reaction mixture to a solution of cold methanol (4 × the volume of THF in the reaction mixture).

The resulting suspension was filtered, and the precipitate was washed using a solid phase washing vessel by adding solvent, bubbling N₂ through the solution at a vigorous rate for 15 min,
then draining the solvent. The washing steps included the following solvents in the indicated order: MeOH, EtOAc, MeOH, EtOAc, hexanes, EtOAc, and 2× hexanes. The resulting polymer was dried under reduced pressure (4.5 mmHg) overnight.

### 6.3.2 Developing a General Procedure for Purifying 1,2-Benzenedicarboxaldehyde

The following purification steps were performed on commercially available 1,2-benzenedicarboxaldehyde (2-2). The procedures in the following list correspond to the entries presented in Table 2-1. After each step, a polymerization reaction using the general procedure (Section 6.3.1) on a 2 g scale was performed. tert-Butyldimethylsilanol (4.3 µL, 0.03 mmol, 0.002 equiv) was used as the initiator. The polymerization reaction was quenched by sequential addition of pyridine (0.6 mL, 7.46 mmol, 0.5 equiv) and acetic anhydride (0.14 mL, 1.5 mmol, 0.1 equiv). The yields of polymer 2-6 were obtained after washing and drying the polymer.

**Entry 1.** Monomer was used as received. Polymer 2-6 obtained from the reaction with this monomer was a white solid (0.18 g, 9%).

**Entry 2.** 1,2-Benzenedicarboxaldehyde (80 g, 596 mmol) was dissolved in boiling dichloromethane (250 mL) and the solution was filtered and concentrated. The resulting solid was recrystallized from 5:2 dichloromethane—hexanes, and the crystals were dried under reduced pressure for 12 h in a Schlenk flask (1.1 mmHg), and then transferred to a glove box without opening the flask to air. Polymer 2-6 obtained from the reaction using this monomer was a white solid (0.49 g, 25%).
**Entry 3.** 1,2-Benzenedicarboxaldehyde (80 g, 596 mmol) was dissolved in boiling dichloromethane (250 mL) and the solution was filtered and concentrated. The resulting solid was recrystallized twice from 5:2 dichloromethane—hexanes, and the crystals were dried under reduced pressure for 12 h in a Schlenk flask (1.1 mmHg), and then transferred to a glovebox without opening the flask to air. Polymer 2-6 obtained from the reaction using this monomer was a white solid (0.47 g, 24%).

**Entry 4.** 1,2-Benzenedicarboxaldehyde (80 g, 596 mmol) was dissolved in boiling dichloromethane (250 mL) and the solution was filtered and concentrated. The resulting solid was recrystallized twice from 5:2 dichloromethane—hexanes, and the crystals were dried under reduced pressure for 36 h in a Schlenk flask (1.1 mmHg), and then transferred to a glovebox without opening the flask to air. Polymer 2-6 obtained from the reaction using this monomer was a white solid (0.22 g, 11%).

**Entry 5.** 1,2-Benzenedicarboxaldehyde (80 g, 596 mmol) was dissolved in boiling dichloromethane (250 mL) and the solution was filtered and concentrated. The resulting solid was recrystallized 3× from 5:2 dichloromethane—hexanes, and the crystals were dried under reduced pressure for 12 h in a Schlenk flask (1.1 mmHg), and then transferred to a glovebox without opening the flask to air. Polymer 2-6 obtained from the reaction using this monomer was a white solid (0.58 g, 29%).

**Entry 6.** 1,2-Benzenedicarboxaldehyde (80 g, 596 mmol) was dissolved in boiling dichloromethane (250 mL) and the solution was filtered and concentrated. The resulting solid was recrystallized 3× from 5:2 dichloromethane—hexanes, and the crystals were dried under reduced pressure for 36 h in a Schlenk flask (1.1 mmHg), and then transferred to a glovebox
without opening the flask to air. Polymer 2-6 obtained from the reaction using this monomer was a white solid (1.26 g, 63%). \( M_n = 41 \text{ kDa} \) and \( M_w = 101 \text{ kDa} \). \( ^1\text{H} \text{NMR (CD}_2\text{Cl}_2): \delta 7.48 \text{ (br s, 4 H)}, 7.11-6.63 \text{ (br m, 2 H)}; ^{13}\text{C NMR (CD}_2\text{Cl}_2): \delta 139.2, 130.2, 123.5, 104.2 \text{ (m)}. \)

Once a purification procedure had been determined that gave a satisfactory yield of the polymer, it was repeated two additional times and the monomer was used to prepare polymers as described above. These experiments gave 1.4 g (70%, \( M_n = 48 \text{ kDa}, M_w = 141 \text{ kDa} \)) and 1.51 g (76%, \( M_n = 50 \text{ kDa}, M_w = 117 \text{ kDa} \)) of polymer 2-6.

6.3.3 Synthesis of End-Capping Reagents

Compounds 2-22 and 2-23 were synthesized by Dr. Jessica Robbins.

**Synthesis of 2-(tert-butyldiphenylsilyloxy)ethanol (2-22)**

*tert*-Butyldiphenylsilyl chloride (0.9 mL, 3.6 mmol, 1 equiv) and imidazole (0.4 g, 5.4 mmol, 1.5 equiv) were added to a solution of ethylene glycol (0.2 mL, 3.6 mmol, 1.0 equiv) in tetrahydrofuran (12 mL) at 23 °C. The reaction mixture was stirred for 30 min at 23 °C and then poured into saturated aqueous ammonium chloride (10 mL). Ethyl acetate (10 mL) was added and the organic layer was extracted with saturated aqueous ammonium chloride (10 mL) and was dried over sodium sulfate. The sodium sulfate was removed by filtration, the solvent was removed by rotary evaporation, and the residue was purified by silica gel flash column chromatography (100% hexanes, increasing to 30% ethyl acetate in hexanes) to provide 2-(*tert*-butyldiphenylsilyloxy)ethanol (2-22) as a white, amorphous solid (0.69 g, 2.3 mmol, 64%), which was identified by spectral comparison with literature data.\(^9\)

**Synthesis of 6-azidohexan-1-ol (2-23)**
A suspension of 6-bromoheaxanol (0.5 mL, 3.8 mmol, 1 equiv) and sodium azide (0.4 g, 5.7 mmol, 1.5 equiv) in acetonitrile (1.5 mL) was stirred at 60 °C for 4 h. The reaction mixture was cooled to 23 °C and diluted with ethyl acetate (5 mL). The organic layer was washed with water (2 × 10 mL) and was dried over sodium sulfate. The sodium sulfate was removed by filtration, the solvent was removed by rotary evaporation, and the residue was purified by silica gel flash column chromatography (10% ethyl acetate in hexanes, increasing to 30% ethyl acetate in hexanes) to provide 6-azidohexan-1-ol (2-23) as a yellow oil (0.4 g, 2.8 mmol, 73%), which was identified by spectral comparison with literature data.\textsuperscript{10}

6.3.4 Polymer Synthesis

The following procedures are arranged based on the order in which the polymers appear in the chapter.

**Synthesis of Polymer 2-8 (\(M_n = 34\text{ kDa}\))**

\[
\text{Polymer 2-8} \quad (\text{2-8})
\]

\(M_n = 34\text{ kDa}\)

Polymer 2-8 was synthesized on a 5.0 g (37 mmol) scale using the general procedure described in section 6.3.1. Dry isopropanol (5.7 µL, 0.075 mmol, 0.002 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (1.5 mL, 19 mmol, 0.5 equiv) and allyl chloroformate (0.4 mL, 3.7 mmol, 0.1 equiv). After purification, polymer 2-8 was obtained as a white solid (4.1 g, 82%). \(M_n = 34\text{ kDa}\) and \(M_w = 71\text{ kDa}\).
Polymers 2-8

**Synthesis of Polymer 2-8** ($M_n = 46 \text{ kDa}$)

Polymer 2-8 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in Section 6.3.1. Dry isopropanol (2.0 µL, 0.026 mmol, 0.0018 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and allyl chloroformate (0.16 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-8 was obtained as a white solid (1.88 g, 94%). $M_n = 46 \text{ kDa}$ and $M_w = 105 \text{ kDa}$.

**Synthesis of Polymer 2-8** ($M_n = 52 \text{ kDa}$)

Polymer 2-8 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in Section 6.3.1. Dry isopropanol (1.6 µL, 0.020 mmol, 0.0014 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and allyl chloroformate (0.16 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-8 was obtained as a white solid (1.86 g, 93%). $M_n = 52 \text{ kDa}$ and $M_w = 125 \text{ kDa}$. 
**Synthesis of Polymer 2-8 (Mₙ = 63 kDa)**

![Polymer 2-8](image)

Polymer 2-8 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in Section 6.3.1. Dry isopropanol (1.2 µL, 0.015 mmol, 0.001 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and allyl chloroformate (0.16 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-8 was obtained as a white solid (1.95 g, 97%). Mₙ = 63 kDa and Mₚ = 89 kDa.

**Synthesis of Polymer 2-8 (Mₙ = 71 kDa)**

![Polymer 2-8](image)

Polymer 2-8 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in Section 6.3.1. Dry isopropanol (1.0 µL, 0.013 mmol, 0.00088 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and allyl chloroformate (0.16 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-8 was obtained as a white solid (1.71 g, 85%). Mₙ = 71 kDa and Mₚ = 179 kDa.
Synthesis of Polymer 2-9 ($M_n = 50$ kDa)

Polymer 2-9 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in Section 6.3.1. 4,5-dimethoxy-2-nitrobenzyl alcohol (6.4 mg, 0.03 mmol, 0.002 equiv) was dissolved in anhydrous THF (0.3 mL) and added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and acetic anhydride (0.14 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-9 was obtained as a white solid (1.56 g, 78%). $M_n = 50$ kDa and $M_w = 118$ kDa.

Synthesis of Polymer 2-10 ($M_n = 42$ kDa)

Polymer 2-10 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described Section 6.3.1. Triphenylmethanol (7.8 mg, 0.03 mmol, 0.002 equiv) was dissolved in anhydrous THF (0.2 mL) and added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and acetic anhydride (0.14
mL, 1.5 mmol, 0.1 equiv). After purification, polymer **2-10** was obtained as a white solid (0.88 g, 44%). $M_n = 42$ kDa and $M_w = 73$ kDa.

**Synthesis of Polymer 2-6 ($M_n = 54$ kDa)**

![ Polymer 2-6 structure ](attachment:polymer_2-6_structure.png)

Polymer **2-6** was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in Section 6.3.1. *tert*-Butyldimethylsilanol (4.7 µL, 0.03 mmol, 0.002 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and acetic anhydride (0.14 mL, 1.5 mmol, 0.1 equiv). After purification, polymer **2-6** was obtained as a white solid (1.54 g, 77%). $M_n = 53$ kDa and $M_w = 107$ kDa.

**Synthesis of Polymer 2-11 ($M_n = 92$ kDa)**

![ Polymer 2-11 structure ](attachment:polymer_2-11_structure.png)

Polymer **2-11** was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in Section 6.3.1. Dry ethylene glycol (0.8 µL, 0.015 mmol, 0.001 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine
158 mL, 7.5 mmol, 0.5 equiv) and acetic anhydride (0.14 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-11 was obtained as a white solid (1.5 g, 75%). $M_n = 92$ kDa and $M_w = 188$ kDa.

**Synthesis of Polymer 2-12 ($M_n = 39$ kDa)**

![Polymer 2-12](image)

Polymer 2-12 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in Section 6.3.1. 2-(tert-butyldiphenylsilyloxy)ethanol (2-22) (9 mg, 0.03 mmol, 0.002 equiv) was dissolved in anhydrous THF (0.1 ml) and added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and acetic anhydride (0.14 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-12 was obtained as a white solid (1.43 g, 72%). $M_n = 39$ kDa and $M_w = 70$ kDa.

**Synthesis of Polymer 2-13 ($M_n = 48$ kDa)**

![Polymer 2-13](image)

Polymer 2-13 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in Section 6.3.1. 6-azidohexan-1-ol (2-23) (4.3 mg, 0.03 mmol, 0.002 equiv) was dissolved in anhydrous THF (0.1 ml) and added as the initiator. The polymerization reaction was
quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and acetic anhydride (0.14 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-13 was obtained as a white solid (1.06 g, 53%). $M_n = 48$ kDa and $M_w = 87$ kDa.

Synthesis of Polymer 2-14 ($M_n = 39$ kDa)

![2-14](image)

Polymer 2-14 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in Section 6.3.1, with the exception that anhydrous methylene chloride was used in place of anhydrous THF. Dry isopropanol (2.3 µL, 0.03 mmol, 0.002 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and a solution of 1-[[chlorocarbonyl]oxy]methyl]-4,5-dimethoxy-2-nitrobenzene (0.4 g, 1.5 mmol, 0.1 equiv) in anhydrous methylene chloride (3 mL). After purification, polymer 2-14 was obtained as a light yellow solid (1.76 g, 88%). $M_n = 39$ kDa and $M_w = 57$ kDa.

Synthesis of Polymer 2-15 ($M_n = 37$ kDa)

![2-15](image)
Polymer 2-15 was synthesized on a 1.0 g (7.5 mmol) scale using the general procedure described in Section 6.3.1. Dry isopropanol (1.1 µL, 0.03 mmol, 0.002 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and a solution of tert-butyldimethylchlorosilane (0.2 g, 1.5 mmol, 0.1 equiv) in anhydrous tetrahydrofuran (1 mL). After purification, polymer 2-15 was obtained as a white solid (1.81 g, 91%). \(M_n = 37\) kDa and \(M_w = 100\) kDa.

**Synthesis of Polymer 2-16 (\(M_n = 25\) kDa)**

Polymer 2-16 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in Section 6.3.1. Dry isopropanol (0.9 µL, 0.015 mmol, 0.002 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and a solution of dansyl chloride (0.2 g, 0.8 mmol, 0.1 equiv) in anhydrous tetrahydrofuran (5 mL). After purification, polymer 2-16 was obtained as a white solid (0.87 g, 87%). \(M_n = 25\) kDa and \(M_w = 57\) kDa.

**Synthesis of Polymer 2-17 (\(M_n = 26\) kDa)**
Polymer 2-17 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in Section 6.3.1. Dry isopropanol (2.3 µL, 0.03 mmol, 0.002 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and methyl iodide (0.09 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-17 was obtained as a white solid (1.0 g, 50%). $M_n = 26$ kDa and $M_w = 61$ kDa.

**Synthesis of Polymer 2-18 ($M_n = 37$ kDa)**

Polymer 2-18 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in Section 6.3.1. Dry isopropanol (2.3 µL, 0.03 mmol, 0.002 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and 4-vinylbenzyl chloride (0.21 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-18 was obtained as a white solid (1.1 g, 54%). $M_n = 37$ kDa and $M_w = 88$ kDa.

**Synthesis of Polymer 2-19 ($M_n = 47$ kDa)**
Polymer 2-19 was synthesized on a 3.0 g (22 mmol) scale using the general procedure described in Section 6.3.1. Dry isopropanol (3.4 µL, 0.044 mmol, 0.002 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and 2-methoxypoly(ethylenoxy)propyl)dimethylchlorosilane (1.1 mL, 2.2 mmol, 0.1 equiv). After purification, polymer 2-19 was obtained as a white solid (1.9 g, 63%). $M_n = 47$ kDa and $M_w = 74$ kDa.

**Synthesis of Polymer 2-6 ($M_n = 7$ kDa)**

Polymer 2-6 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in Section 6.3.1. tert-Butyldimethylsilanol (0.088 mL, 0.6 mmol, 0.038 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and acetic anhydride (0.16 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-6 was obtained as a white solid (0.55 g, 28%). $M_n = 7$ kDa and $M_w = 12$ kDa. $^1$H NMR (CD$_2$Cl$_2$): $\delta$ 7.95-6.72 (br m, 435 H), 2.26 (br s, 3 H), 1.10 (br s, 9 H), 0.40 (br m, 6 H).

**Synthesis of Polymer 2-15 ($M_n = 3$ kDa)**
Polymer 2-15 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in Section 6.3.1. Dry isopropanol (0.043 mL, 0.6 mmol, 0.038 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and a solution of tert-butyldimethylchlorosilane (0.2 g, 1.5 mmol, 0.1 equiv) in anhydrous tetrahydrofuran (1 mL). After purification, polymer 2-15 was obtained as a white solid (0.62 g, 31%). $M_n = 3$ kDa and $M_w = 10$ kDa. $^1$H NMR (CD$_2$Cl$_2$): δ 7.95-6.72 (br m, 517 H), 4.33 (br m, 1 H), 1.42 (br s, 8 H), 1.13 (br s, 9 H), 0.40 (br m, 6 H).

**Synthesis of Polymer 2-20 ($M_n = 50$ kDa)**

Polymer 2-20 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in Section 6.3.1. Dry isopropanol (3.4 µL, 0.045 mmol, 0.003 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and acetic anhydride (0.14 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-20 was obtained as a white solid (1.43 g, 72%). $M_n = 50$ kDa and $M_w = 97$ kDa.
Synthesis of Polymer 2-21 ($M_n = 42$ kDa)

Polymer 2-21 was synthesized on a 3.0 g (22 mmol) scale using the general procedure described in Section 6.3.1, with the exception that anhydrous methylene chloride was used in place of anhydrous THF. 4,5-dimethoxy-2-nitrobenzyl alcohol (9.6 mg, 0.044 mmol, 0.002 equiv) was dissolved in anhydrous THF (0.4 mL) and added to act as the initiator. The polymerization reaction was quenched with sequential addition of dry pyridine (0.9 mL, 11 mmol, 0.5 equiv) and a solution of 1-[[chlorocarbonyl]oxy]methyl]-4,5-dimethoxy-2-nitrobenzene (0.6 g, 2.2 mmol, 0.1 equiv) in anhydrous methylene chloride (5 mL). After purification, polymer 2-21 was obtained as a light yellow solid (2.75 g, 92%). $M_n = 42$ kDa and $M_w = 76$ kDa.

6.4 Chapter 2: Experimental Procedures and Characterization

6.4.1 Determining the Identity of Impurities in the Monomer

The supernatant obtained after one recrystallization of 1,2-benzenedicarboxaldehyde (Entry 2 in Section 6.3.2) was concentrated and the resulting solid dissolved in DMSO-d$_6$ and
analyzed by $^1$H NMR. Most of the peaks present that did not correspond with the monomer matched the known proton shifts of 2-carboxybenzaldehyde (2-7) (Figure 2-7).\textsuperscript{11}

### 6.4.2 Response of Polymers 2-8 and 2-20 to Pd(0) in Solution

Polymer 2-8 ($M_n = 34$ kDa) (30 mg, 0.0009 mmol) was dissolved in methylene chloride (0.5 mL). An 18 mM solution of Pd(PPh$_3$)$_4$ in methylene chloride (0.5 mL, 0.009 mmol, 10 equiv) was added in one portion to the polymer solution. The resulting solution was agitated by vortexing for 10 s. After standing for 30 min, an aliquot of the solution (0.05 mL) was withdrawn and was diluted with THF (0.95 mL); this sample was used directly for GPC analysis (Figure 2-11b).

Polymer 2-20 ($M_n = 50$ kDa) (44 mg, 0.0009 mmol) was dissolved in methylene chloride (0.5 mL). An 18 mM solution of Pd(PPh$_3$)$_4$ in methylene chloride (0.5 mL, 0.009 mmol, 10 equiv) was added in one portion to the polymer solution. The resulting solution was agitated by vortexing for 10 s. After standing for 30 min, an aliquot of the solution (0.05 mL) was withdrawn and was diluted with THF (0.95 mL); this sample was used directly for GPC analysis (Figure 2-11c).

### 6.4.3 Solid-State Depolymerization of Polymers 2-6 and 2-21

Polymer 2-21 (0.4 g, $M_n = 42$ kDa) was dissolved in THF (1 mL). Polymer 2-6 (0.40 g, $M_n = 54$ kDa) was dissolved in THF (1.5 mL). The solutions were deposited on separate glass
slides using a syringe. After drying for 24 h at 23 °C under an atmosphere of air, the film was removed from the slide using a razor blade.

The film fabricated from polymer 2-21 (Figure 2-12a) was exposed to UV light using an Intelli-Ray 600 UV floodlight (600 watt/140 V lamp) at 100% intensity for 10 min. The film was allowed to cool to room temperature (the temperature within the floodlight reached ~78 ° when in operation for 10 min), whereupon it formed an opaque yellow/orange film (Figure 2-12b). This film was submerged in ethyl acetate. Complete dissolution of the film was observed in less than 1 min (Figure 2-12c).

The film fabricated from polymer 2-6 (Figure 2-12d) was exposed to UV light using an Intelli-Ray 600 UV floodlight (600 watt/140 V lamp) at 100% intensity for 10 min (Figure 2-12e). The film was allowed to cool to room temperature, and then was submerged in ethyl acetate. No physical change was observed in the film (Figure 2-12e and f).

6.5 Chapter 3: Synthetic Procedures and Characterization

6.5.1 Polymer Synthesis

Synthesis of Polymer 2-6 ($M_n = 8$ kDa)

Polymer 2-6 was synthesized on a 3.0 g (22 mmol) scale using the general procedure described in section 6.3.1. Tert-butyldimethylsilanol (32 µL, 0.2 mmol, 0.009 equiv) was added
as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.9 mL, 11 mmol, 0.5 equiv) and acetic anhydride (0.21 mL, 2.2 mmol, 0.1 equiv). After purification, polymer 2-6 was obtained as a white solid (0.35 g, 12%). $M_n = 8$ kDa and $M_w = 14$ kDa.

**Synthesis of Polymer 2-6 ($M_n = 33$ kDa)**

![Image of 2-6 polymer structure]

Polymer 2-6 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in section 6.3.1. Tert-butyldimethylsilanol (10 µL, 0.06 mmol, 0.0042 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and acetic anhydride (0.14 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-6 was obtained as a white solid (0.8 g, 40%). $M_n = 33$ kDa and $M_w = 55$ kDa.

**Synthesis of Polymer 2-6 ($M_n = 42$ kDa)**

![Image of 2-6 polymer structure]

Polymer 2-6 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in section 6.3.1. Tert-butyldimethylsilanol (7 µL, 0.05 mmol, 0.003 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine
(0.6 mL, 7.5 mmol, 0.5 equiv) and acetic anhydride (0.14 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-6 was obtained as a white solid (1.52 g, 76%). $M_n = 42$ kDa and $M_w = 68$ kDa.

**Synthesis of Polymer 2-6 ($M_n = 45$ kDa)**

![Chemical structure of polymer 2-6](image)

Polymer 2-6 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in section 6.3.1. *Tert*-butyldimethylsilanol (6 µL, 0.04 mmol, 0.0026 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and acetic anhydride (0.14 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-6 was obtained as a white solid (0.3 g, 15%). $M_n = 45$ kDa and $M_w = 85$ kDa.

**Synthesis of Polymer 2-6 ($M_n = 53$ kDa)**

![Chemical structure of polymer 2-6](image)

Polymer 2-6 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in section 6.3.1. *Tert*-butyldimethylsilanol (7 µL, 0.04 mmol, 0.003 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and acetic anhydride (0.14 mL, 1.5 mmol, 0.1 equiv). After
purification, polymer 2-6 was obtained as a white solid (0.6 g, 30%). $M_n = 53$ kDa and $M_w = 93$ kDa.

**Synthesis of Polymer 2-6 ($M_n = 65$ kDa)**

![Diagram of polymer 2-6]

Polymer 2-6 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in section 6.3.1. *Tert*-butyldimethylsilanol (4.7 µL, 0.03 mmol, 0.002 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and acetic anhydride (0.14 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-6 was obtained as a white solid (1.95 g, 82%). $M_n = 65$ kDa and $M_w = 103$ kDa.

**Synthesis of Polymer 2-19 ($M_n = 32$ kDa)**

![Diagram of polymer 2-19]

Polymer 2-19 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in section 6.3.1. Dry isopropanol (3.4 µL, 0.05 mmol, 0.003 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and 2-(methoxyoxypoly(ethyleneoxy)$_{6-9}$propyl)dimethylchlorosilane...
(0.7 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-19 was obtained as a white solid (0.98 g, 49%). $M_n = 32$ kDa and $M_w = 50$ kDa.

**Synthesis of Polymer 2-19 ($M_n = 37$ kDa)**

Polymer 2-19 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in section 6.3.1. Dry isopropanol (2.6 µL, 0.03 mmol, 0.0023 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and 2-(methoxyoxypoly(ethylenoxy)₆₋₉propyl)dimethylchlorosilane (0.7 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-19 was obtained as a white solid (0.95 g, 43%). $M_n = 37$ kDa and $M_w = 55$ kDa.

**Synthesis of Polymer 2-19 ($M_n = 43$ kDa)**

Polymer 2-19 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in section 6.3.1. Dry isopropanol (3.4 µL, 0.05 mmol, 0.003 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and 2-(methoxyoxypoly(ethylenoxy)₆₋₉propyl)dimethylchlorosilane
(0.7 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-19 was obtained as a white solid (1.1 g, 53%). $M_n = 43$ kDa and $M_w = 68$ kDa.

**Synthesis of Polymer 2-19 ($M_n = 47$ kDa)**

Described in Section 6.3.4.

**Synthesis of Polymer 2-19 ($M_n = 54$ kDa)**

![Chemical structure](image)

Polymer 2-19 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in section 6.3.1. Dry isopropanol (1.6 µL, 0.02 mmol, 0.0014 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and 2-(methoxyoxypoly(ethylenoxy)$_{6-9}$propyl)dimethylchlorosilane (0.7 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-19 was obtained as a white solid (1.8 g, 90%). $M_n = 54$ kDa and $M_w = 88$ kDa.

**Synthesis of Polymer 2-19 ($M_n = 61$ kDa)**

![Chemical structure](image)

$M_n = 61$ kDa
Polymer 2-19 was synthesized on a 2.0 g (15 mmol) scale using the general procedure described in section 6.3.1. Dry isopropanol (1.1 µL, 0.02 mmol, 0.001 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.6 mL, 7.5 mmol, 0.5 equiv) and 2-(methoxyoxypoly(ethylenoxy)₆-propyl)dimethylchlorosilane (0.7 mL, 1.5 mmol, 0.1 equiv). After purification, polymer 2-19 was obtained as a white solid (1.42 g, 49%). $M_n = 61$ kDa and $M_w = 96$ kDa.

**Synthesis of Polymer 3-3 ($M_n = 20$ kDa)**

Polymer 3-3 was synthesized on a 1.0 g (7.5 mmol) scale using the general procedure described in section 6.3.1, with the exception that after washing the polymer, it was redissolved in dichloromethane (10 mL), then filtered through a syringe filter into cold MeOH. The precipitate was washed again with MeOH. Dry isopropanol (4.3 µL, 0.06 mmol, 0.0075 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.3 mL, 3.7 mmol, 0.5 equiv) and a solution of triacontylchlorodimethylsilane (0.4 g, 0.75 mmol, 0.1 equiv) in THF (4 mL). After purification, polymer 3-3 was obtained as a white solid (0.59 g, 59%). $M_n = 20$ kDa and $M_w = 35$ kDa.
Synthesis of Polymer 3-3 ($M_n = 32$ kDa)

Polymer 3-3 was synthesized on a 1.0 g (7.5 mmol) scale using the general procedure described in section 6.3.1, with the exception that after washing the polymer, it was redissolved in dichloromethane (10 mL), then filtered through a syringe filter into cold MeOH. The precipitate was washed again with MeOH. Dry isopropanol (1.7 µL, 0.022 mmol, 0.003 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.3 mL, 3.7 mmol, 0.5 equiv) and a solution of triacontylchlorodimethylsilane (0.4 g, 0.75 mmol, 0.1 equiv) in THF (4 mL). After purification, polymer 3-3 was obtained as a white solid (0.87 g, 87%). $M_n = 32$ kDa and $M_w = 55$ kDa.

Synthesis of Polymer 3-3 ($M_n = 43$ kDa)

Polymer 3-3 was synthesized on a 1.0 g (7.5 mmol) scale using the general procedure described in section 6.3.1, with the exception that after washing the polymer, it was redissolved in dichloromethane (10 mL), then filtered through a syringe filter into cold MeOH. The precipitate was washed again with MeOH. Dry isopropanol (1.3 µL, 0.02 mmol, 0.0023 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine
(0.3 mL, 3.7 mmol, 0.5 equiv) and a solution of triacontylchlorodimethylsilane (0.4 g, 0.75 mmol, 0.1 equiv) in THF (4 mL). After purification, polymer 3-3 was obtained as a white solid (0.82 g, 82%). $M_n = 43$ kDa and $M_w = 90$ kDa.

**Synthesis of Polymer 3-3 ($M_n = 49$ kDa)**

Polymer 3-3 was synthesized on a 1.0 g (7.5 mmol) scale using the general procedure described in section 6.3.1, with the exception that after washing the polymer, it was redissolved in dichloromethane (10 mL), then filtered through a syringe filter into cold MeOH. The precipitate was washed again with MeOH. Dry isopropanol (1.1 µL, 0.02 mmol, 0.002 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.3 mL, 3.7 mmol, 0.5 equiv) and a solution of triacontylchlorodimethylsilane (0.4 g, 0.75 mmol, 0.1 equiv) in THF (4 mL). After purification, polymer 3-3 was obtained as a white solid (0.7 g, 70%). $M_n = 49$ kDa and $M_w = 90$ kDa.

**Synthesis of Polymer 3-3 ($M_n = 54$ kDa)**
Polymer 3-3 was synthesized on a 1.0 g (7.5 mmol) scale using the general procedure described in section 6.3.1, with the exception that after washing the polymer, it was redissolved in dichloromethane (10 mL), then filtered through a syringe filter into cold MeOH. The precipitate was washed again with MeOH. Dry isopropanol (0.5 µL, 0.007 mmol, 0.001 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.3 mL, 3.7 mmol, 0.5 equiv) and a solution of triacontylchlorodimethylsilane (0.4 g, 0.75 mmol, 0.1 equiv) in THF (4 mL). After purification, polymer 3-3 was obtained as a white solid (0.78 g, 78%). \( M_n = 54 \text{ kDa and } M_w = 116 \text{ kDa.} \)

6.6 Chapter 3: Experimental Procedures and Characterization

6.6.1 General Procedure for Preparing Polymer Films

A solution of polymer 2-6 (\( M_n = 8 \text{ kDa} \)) (5 µL) in dichloromethane (50 mg/mL) was deposited on a glass microscope slide. The film was dried under vacuum for 12 h, and, using a razor blade, was cut into a square with approximate dimensions of 0.5 mm × 0.5 mm (the thickness of the film was approximately 25 µm); the excess polymer was scraped off of the slide. The slide was placed into the hybridization chamber (purchased from Grace Bio-labs, Cat. No. SA20-0.5).
6.6.2 Response of the Films to β-D-glucuronidase

Stock solutions were prepared of β-D-glucuronidase (0.94 mg, 0.014 µmol) in 500 µL of phosphate buffer (75 mM, pH 7.4, 1 wt% BSA), substrate 3-1 (11 mg, 0.023 mmol) in 1 ml of phosphate buffer (75 mM, pH 7.4, 1 wt% BSA), and 6 µm-sized polystyrene tracer particles (purchased from Polyscience Inc., Cat. No. 07312) in phosphate buffer (75 mM, pH 7.4, 1 wt% BSA). To vary the enzyme concentration, these solutions were mixed, along with phosphate buffer solutions containing no enzyme or substrate to give solutions with final volumes of 500 µL, as shown in Table 6-1.

<table>
<thead>
<tr>
<th>[β-D-glucuronidase] (µM)</th>
<th>Enzyme solution (µL)</th>
<th>Solution of 3-1 (µL)</th>
<th>Tracer particle solution (µL)</th>
<th>Phosphate buffer solution (µL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>166</td>
<td>200</td>
<td>20</td>
<td>114</td>
</tr>
<tr>
<td>8</td>
<td>148</td>
<td>200</td>
<td>20</td>
<td>132</td>
</tr>
<tr>
<td>6</td>
<td>111</td>
<td>200</td>
<td>20</td>
<td>169</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>200</td>
<td>20</td>
<td>196</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>200</td>
<td>20</td>
<td>233</td>
</tr>
<tr>
<td>1</td>
<td>17</td>
<td>200</td>
<td>20</td>
<td>253</td>
</tr>
</tbody>
</table>

The solutions containing the enzyme and substrate 3-1 were incubated for 30 min at 23 °C before being added to the hybridization chamber containing the film of polymer 2-6 ($M_n = 8$ kDa). While filling the chamber, care was taken to avoid forming air bubbles in the chamber. The chamber was sealed with adhesive tape to prevent evaporation. Immediately after adding the solution containing the enzyme and substrate, the movement of the tracer particles was captured using a Zeiss Axiovert 200 microscope (in reflectance/transmission mode) at 20× magnification. The video was processed at 5x or 20x speed before tracking the coordinates of the tracer particles using Physvis. For each experiment, 30 particles from three sides of the polymer films were selected. Their coordinates were acquired using Physvis every 2.5 s over a period of 25 s. These coordinates were converted into speed (Figure 3-7 and Table 6-3 in Appendix B).
6.6.3 Evaluating the Selectivity of the Pumps for Fluoride

To hybridization chambers containing films of polymer 2-6 (M_n = 65 kDa), 0.1 M solutions of various sodium salts (thiocyanate, sulfate, iodide, bromide, chloride, nitrate, phosphate, and fluoride) were added. The solutions were added carefully to avoid forming air bubbles in the chamber. Immediately after adding the salt solution, the movement of the tracer particles was captured using a Zeiss Axiovert 200 microscope and then processed and analyzed as described in Section 6.6.2; the resulting data is shown in Figure 3-8 and Table 6-4 in Appendix B.

6.6.4 Effect of Polymer Molecular Weight on Pumping Speed

Films of the variants of polymer 2-6 with different molecular weights (i.e., M_n = 8 kDa, 33 kDa, 45 kDa, 53 kDa, and 65 kDa) were prepared as described in Section 6.6.1 and added to hybridization chambers. To each chamber was added a 9 µM enzyme solution that had been incubated for 30 min with substrate 3-1 (see Table 6-1). Immediately after adding the solution containing the enzyme and substrate, the movement of the tracer particles was captured using a Zeiss Axiovert 200 microscope and then processed and analyzed as described in Section 6.6.2; the resulting data is shown in Figure 3-9 and Table 6-5 in Appendix B.
6.6.5 Effect of End-Cap Polarity on Pumping Speed

Films of polymer 2-10 ($M_n = 32$ kDa, 37 kDa, 47 kDa, 54 kDa, and 61 kDa) and polymer 4 ($M_n = 20$ kDa, 32 kDa, 43 kDa, 49 kDa, and 54 kDa) were prepared as described in Section 6.6.1 and added to hybridization chambers. To each chamber was added a 9 µM enzyme solution that had been incubated for 30 min with substrate 3-1. Immediately after adding the solution containing the substrate and enzyme, the movement of the tracer particles was captured using a Zeiss Axiovert 200 microscope and then processed and analyzed as described in Section 6.6.2; the resulting data is shown in Figure 3-10 and Tables 6-6 and 6-7 in Appendix B.

6.6.6 XPS Analysis

Glass slides (1 mm thick) with dimensions of 1 cm × 1 cm were cut using an Epilog Mini 24 CO₂ laser cutter. Solutions of polymer 2 ($M_n = 33$ kDa), 3 ($M_n = 32$ kDa and 47 kDa), and 4 ($M_n = 32$ kDa) in dichloromethane (50 mg/ml) were deposited on separate slides so that the resulting films completely covered the surfaces of the slides. The films were dried under vacuum for 12 h and then analyzed for elemental composition by XPS (Figures 6-86–6-89 in Appendix A). The resulting spectra were analyzed using CasaXPS (Table 3-1).

6.6.7 Change in Film Thickness in Response to Fluoride

Film of polymers 2-6 ($M_n = 42$ kDa), 2-19 ($M_n = 43$ kDa), and 2-6 ($M_n = 33$ kDa) was evaluated by profilometry using a Tencor Alpha-Step 500. The films were then placed in separate hybridization chambers. To each hybridization chamber was added a 0.1 M solution of
sodium fluoride. Thirty minutes after adding the fluoride solution, the film was removed and dried under vacuum. The films were then evaluated again by profilometry. The data for all three polymers is shown in Table 3-2.

6.6.8 SEM Imaging of the Polymer Films

Films of polymers 2-6 ($M_n = 42$ kDa), 2-19 ($M_n = 43$ kDa), and 2-6 ($M_n = 33$ kDa) were prepared on silicon wafers and imaged by SEM (Figure 3-11a,c,e). The films were then placed in separate hybridization chambers. To each hybridization chamber was added a 0.1 M solution of sodium fluoride. Thirty minutes after adding the fluoride solution, the films were removed and dried under vacuum. The films were then imaged again by SEM (Figure 3-11b,d,f).

6.6.9 Contact Angle Measurements

On a smooth celluloid plastic surface, films of polymers 2-6 ($M_n = 42$ kDa), 2-19 ($M_n = 43$ kDa), and 2-6 ($M_n = 33$ kDa) were formed by depositing solutions of the polymers and drying under reduced pressure for 3 h. The surface contact angle of each film was measured in triplicate using a Ramé-Hart Model 590 Advanced Automated Goniometer (Table 3-3).
6.6.10 Effect of Film Area and Thickness of Pumping Speed

*Films with 2× and 3× area:* Three films of polymer 2-19 ($M_n = 43$ kDa) were prepared as described in Section 6.6.1, with the exception that one film was cut to give a film with dimensions of 0.7 mm wide × 0.7 mm long and another was cut to give a film with dimensions of 0.9 mm wide × 0.9 mm long. These two films, along with a film with the standard area and thickness (0.5 mm wide × 0.5 mm long × 25 µm) were evaluated for their response to 9 µM β-D-glucuronidase as described in Section 6.6.2 (Table 3-4).

*Films with 2× and 3× thickness:* Two films of polymer 2-19 ($M_n = 43$ kDa) were prepared as described in Section 6.6.1, with the exception that after the initial deposition of polymer solution both films were allowed to dry before another drop of polymer solution was deposited, thus giving films 2× as thick as the standard size film. For one of these films, this process was repeated again to give a film 3× as thick as the standard size film. These two films were evaluated for their response to 9 µM β-D-glucuronidase as described in Section 6.6.2 (Table 3-3).

6.7 Chapter 4: Synthetic Procedures and Characterization

6.7.1 Polymer Synthesis

*Synthesis of Polymer 2-19 ($M_n = 33, 37, 47, 54,$ and 61 kDa)*

The syntheses of the polymers used to fabricate responsive microcapsules are described in Section 6.3.4 ($M_n = 47$ kDa) and Section 6.5.1 ($M_n = 33, 37, 54,$ and 61 kDa).
6.8 Chapter 4: Experimental Procedures and Characterization

6.8.1 Solution Phase Depolymerization of Polymer 2-19 ($M_n = 54$ kDa)

Polymer 2-19 ($M_n = 54$ kDa) (0.02 g, 0.0004 mmol) was dissolved in THF (250 µL). A 0.67 M solution of tetrabutylammonium fluoride in 2:1 aqueous phosphate buffer–THF (6 µL, 0.004 mmol, 10 equiv) was added at 23 °C. The reaction mixture was vortexed for 5 s. After 6 h, an aliquot (0.025 mL) was taken from the reaction mixture, diluted with THF (1 mL), and analyzed by GPC (Figure 4-7).

Response to chloride: Polymer 2-19 ($M_n = 54$ kDa) (0.02 g, 0.0004 mmol) was dissolved in THF (250 µL). A 0.67 M solution of tetrabutylammonium chloride in 2:1 aqueous phosphate buffer–THF (6 µL, 0.004 mmol, 10 equiv) was added at 23 °C. The reaction mixture was vortexed for 5 s. After 6 h, an aliquot (0.025 mL) was taken from the reaction mixture, diluted with THF (1 mL), and analyzed by GPC (Figure 4-7).

6.8.2 General Procedure for Fabricating Microcapsules from Polymer 2-19

The responsive microcapsules with PPA membranes were fabricated using a glass capillary microfluidic device, which was used to prepare monodisperse water/oil/water (W/O/W) double emulsion drops as templates. The device was constructed by inserting two tapered cylindrical capillaries (purchased from World Precision Instruments, Inc., No. 1B100-6) into the opposite ends of a square capillary (AIT glass); the inner dimension of the square capillary were slightly larger than the outer diameter of the cylindrical capillaries, which enabled precise alignment of both cylindrical capillaries within the square capillary. The left cylindrical capillary was used to inject the innermost fluid: a 5 wt. % aqueous solution of polyvinyl alcohol (PVA)
(M<sub>W</sub> 13000-23000 Da, 87% hydrolyzed), containing fluorescein isothiocyanate-labeled dextran (FITC-Dex) (M<sub>n</sub> = 4 kDa) with a concentration of 0.1 mM. This injection capillary was treated with n-octadecyltrimethoxysilane to make it hydrophobic, preventing the wetting of the aqueous phase on the capillary wall. The right cylindrical glass capillary was used as a collection tube and was treated with 2-(methoxy(polyethyleneoxy)propyl)trimethoxysilane to make the capillary wall hydrophilic, preventing the wetting of the oil phase on the wall of the collection tube. To fabricate solid microcapsules, a middle oil phase consisting of a 10 wt% solution of polymer 2-19 (M<sub>n</sub> = 47 kDa) was injected from the left, which flows in the same direction as the inner aqueous phase through the interstices between the left injection cylindrical capillary and the square capillary. A 10 wt% aqueous solution of PVA was injected through the interstices of the square and collection capillaries to emulsify the co-flowing fluids into double emulsion drops. This technique enables the inner (core) and middle (shell) phases to hydrodynamically focus and break up at the orifice of the collection cylindrical capillary, resulting in formation of monodisperse W/O/W double emulsions, as shown in Figure 4-8b. The ratio of the flow rates of the inner–middle–outer phases was 600:700:8000 µL/h. After the double emulsion droplets were collected, the solvent in the middle oil phase diffuses into the continuous phase as the droplets are stored for 3 hours under ambient conditions; this results in precipitation of the polymer and subsequent consolidation of middle phase to form a uniform solid polymeric membrane, as evidenced by Figure 4-8c. The monodisperse microcapsules (Figure 4-9) were washed with DI water and incubated in phosphate buffer (pH = 7.1) for further studies.

To determine the average shell wall thickness, several microcapsules were freeze-dried and then broken manually using a razor blade. The resulting sample was imaged by SEM, and the thickness of the cross-section of fourteen capsules was acquired (Figure 4-10 and Table 6-8 in Appendix B).
6.8.3 Evaluating the Response of the Microcapsules to Fluoride

The capsules fabricated from polymer 2-19 ($M_n = 47$ kDa) with an average shell wall thickness of 1805 ± 79 nm were dispersed in an aqueous solution (100 mL) that contained 5 g of ethyl acetate. This suspension (1 mL) was added to a glass cell, followed by 1 mL of a 0.1 M solution of tetrabutylammonium fluoride in 2:1 aqueous phosphate buffer (0.1 M, pH 7.1)–THF to give a final concentration of 50 mM fluoride. The cell was sealed with epoxy to prevent evaporation of the solvents.

The intensity of the fluorescence within the polymer microcapsules was monitored by confocal microscopy (Figure 4-11). Using a calibration curve of fluorescence intensity vs. concentration of FITC-DEX (Figure 6-1), we calculated the concentration of FITC-DEX remaining in the capsules from the fluorescence intensity values obtained from the microscopy images (Figure 4-12 and Table 6-9 in Appendix B).

![Normalized TGA curves and thermal degradation temperatures for polymers 2-8 (black), 2-20 (orange), 5-14 (blue), and 5-15 (pink). Adapted with permission from Polym. Chem, 2015, 6, 3252–3258. Copyright 2015 Royal Society of Chemistry.](image-url)

**Figure 6-1.** Normalized TGA curves and thermal degradation temperatures for polymers 2-8 (black), 2-20 (orange), 5-14 (blue), and 5-15 (pink). Adapted with permission from *Polym. Chem,* 2015, 6, 3252–3258. Copyright 2015 Royal Society of Chemistry.
6.8.4 Control Experiments

For the control experiments, the capsules made from polymer 2-19 \((M_n = 47 \text{ kDa})\) were evaluated as described in Section 6.8.3, with the exception that the 2:1 aqueous phosphate buffer (0.1 M, pH 7.1)−THF solution added to the suspensions of the capsules contained 0.1 M of either tetrabutylammonium chloride or sodium chloride (final concentration of chloride was 50 mM), or no salt in place of tetrabutylammonium fluoride (Figure 4-12 and Table 6-9 in Appendix B).

6.8.5 Fabricating and Testing Microcapsules with Different Shell Wall Thicknesses

To fabricate microcapsules of polymer 2-19 \((M_n = 47 \text{ kDa})\) with different shell wall thicknesses, the general procedure for the fabrication of microcapsules described above was used, with the exception that the wt% of the polymer solution in the middle phase and the flow rate of the middle phase were varied as shown in Table 4-1.

To determine the average shell wall thickness, a sample of each batch of the microcapsules was tested as described in Section 6.8.2. The resulting samples were imaged by SEM, and the thickness of the cross-section of six capsules was determined for each batch (Tables 6-10–6-13 in Appendix B).

To determine the effect of shell wall thickness on the rate of release from the microcapsules, the capsules with average shell thicknesses of 100, 650, 1000, and 1800 nm were evaluated for their response to fluoride as described in Section 6.8.3 (Figure 4-14 and Table 6-14 in Appendix B).
6.8.6 Effect of Polymer Molecular Weight on Rate of Release

To determine the effect of polymer molecular weight on the rate of release from the microcapsules, capsules were fabricated from polymer 2-19 with molecular weights of 33, 37, 54, and 61 kDa as described in Section 6.8.2 (i.e., using 10 wt. % solutions of each polymer and a ratio of flow rates of 600:700:800 µl/min.) These capsules were evaluated for their response to fluoride as described in Section 6.8.3 (Figure 4-15 and Table 6-15 in Appendix B).

6.9 Chapter 5: Synthetic Procedures and Characterization

6.9.1 Screening Oxidation Conditions

Entry 1 – Swern Oxidation

To a round bottom flask charged with a magnetic stir bar was added oxalyl chloride (0.34 mL, 4 mmol, 2.2 equiv) and dichloromethane (4.5 mL). The reaction mixture was cooled to −78 °C and a solution of dimethylsulfoxide (0.57 mL, 8 mmol, 4.4 equiv) in dichloromethane (1.1 mL) was added dropwise via syringe. After 10 min, a solution of 1,2-benzenedimethanol (5-10) (250 mg, 1.8 mmol, 1 equiv) and the internal standard (1,3,5-triisopropylbenzene; 42 mg, 0.21 mmol) in 1:1 DCM–DMSO (0.5 mL) was added dropwise. After 30 min, triethylamine (4.5 mL, 32 mmol, 18 equiv) was added slowly to the reaction mixture, which was subsequently warmed to room temperature over 1 h, then took an aliquot from the reaction mixture, concentrated, and analyzed by 1H NMR (Figure 6-9 in Appendix A). The yield of 2-2 as determined using the internal standard was 95%.
Entry 2 – IBX Oxidation

To a round bottom flask charged with a magnetic stir bar and a reflux condenser was added 2-iodoxybenzoic acid (1.5 g, 5.4 mmol, 3 equiv) and ethyl acetate (75 mL). A solution of 1,2-benzenedimethanol (5-10) (250 mg, 1.8 mmol, 1 equiv) and the internal standard (1,3,5-trimethoxybenzene; 100 mg, 0.6 mmol) in acetone (5 mL) was added, and the reaction was heated to 80 °C. After 6 h, the reaction was cooled to room temperature, and an aliquot was taken, concentrated and analyzed by $^1$H NMR (Figure 6-10 in Appendix A). The yield of 2-2 as determined using the internal standard was 72%.

Entry 3 – Barium Manganate Oxidation

To a round bottom flask charged with a magnetic stir bar was added 1,2-benzenedimethanol (5-10) (250 mg, 1.8 mmol, 1 equiv) and dichloromethane (25 mL). Barium manganate (3.8 g, 15 mmol, 8 equiv) was added, and the reaction was stirred at room temperature. After 16 h, the reaction was diluted with dichloromethane (25 mL), then filtered through Celite. The solid filter cake was washed with dichloromethane (2 × 25 mL). The resulting filtrate was concentrated to give 220 mg of solid. Analysis of the solid by $^1$H NMR (Figure 6-11 in Appendix A) showed a ratio of 2-2 to phthalide of 2:5, which corresponded to a yield of 28%.

Entry 4 – PDC Oxidation

To a round bottom flask charged with a magnetic stir bar was added potassium dichromate (2.7 g, 7.2 mmol, 4 equiv) and dichloromethane (57 mL). A solution of 1,2-benzenedimethanol (5-10) (250 mg, 1.8 mmol, 1 equiv) and the internal standard (1,3,5-trimethoxybenzene; 100 mg, 0.6 mmol) in dichloromethane (11 mL) was added, and the reaction was stirred at room temperature. After 6.5 h, an aliquot was taken from the reaction mixture,
concentrated, and analyzed by $^1$H NMR (Figure 6-12 in Appendix A). The yield of 2-2 as determined using the internal standard was 19%.

**Entry 5 – Manganese Dioxide Oxidation**

To a round bottom flask charged with a magnetic stir bar was added 1,2-benzenedimethanol (5-10) (250 mg, 1.8 mmol, 1 equiv) and dichloromethane (25 mL). Manganese dioxide (1.75 g, 20 mmol, 11 equiv) was added, and the reaction was stirred at room temperature. After 72 h, the reaction was filtered through Celite. The solid filter cake was washed with dichloromethane (2 × 25 mL). The resulting filtrate was concentrated. The standard (1,3,5-trimethoxybenzene; 100 mg, 0.6 mmol) was added, and the mixture was analyzed by $^1$H NMR (Figure 6-13 in Appendix A). The yield of 2-2 as determined using the internal standard was 5%.

**Entry 6 – Oxoammonium Oxidation**

To a round bottom flask charged with a magnetic stir bar was added 1,2-benzenedimethanol (5-10) (250 mg, 1.8 mmol, 1 equiv), the internal standard (1,3,5-trimethoxybenzene; 100 mg, 0.6 mmol), TEMPO (3 mg, 0.018 mmol, 0.01 equiv), potassium bromide (22 mg, 0.18 mmol, 0.1 equiv) and dichloromethane (6 mL). The reaction mixture was cooled to 10 °C. A solution of 0.87 M aqueous sodium hypochlorite (5 mL, 4.4 mmol, 2.4 equiv) was buffered by adding sodium bicarbonate (85 mg, 1.0 mmol), then added to the reaction mixture dropwise via syringe filter. After 15 min, the organic layer of the reaction was separated, dried over sodium sulfate, then concentrated and analyzed by $^1$H NMR (Figure 6-14 in Appendix A). The yield of 2-2 as determined using the internal standard was 1%.
6.9.2 Synthesis of 4,5-dichlorophthalaldehyde (5-13)

To a round-bottom flask charged with a magnetic stir bar and an addition funnel was added 4,5-dichlorophthalic acid (5-11) (11 g, 47 mmol, 1 equiv) and tetrahydrofuran (64 mL). The contents of the flask were placed under a N₂ atmosphere, and the reaction mixture was cooled to 0 °C. A solution of borane in THF (1 M, 122 mL, 122 mmol, 2.6 equiv) was added dropwise via the addition funnel, after which the reaction mixture was warmed to room temperature. After 18 h, the reaction mixture was cooled to 0 °C and diluted by dropwise addition of a 2:1 solution of water–THF (100 mL). Solid potassium carbonate was added until the solution became biphasic. The aqueous layer was separated and washed with THF (2 × 65 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated. The crude product was purified using silica gel flash chromatography with 15% THF in hexanes as the eluent, increasing to 75% THF in hexanes. 4,5-Dichloro-1,2-benzenedimethanol (5-12) was obtained as a white solid (9.1 g, 44.0 mmol, 95%). IR (cm⁻¹) 3260; ¹H NMR (d₆-DMSO) δ 7.56 (s, 2H), 5.38 (q, 2H, J = 5), 4.48 (t, 4H, J = 5); ¹³C NMR (d₆-DMSO) δ 140.4, 128.8, 127.9, 59.0; MS (Q MS APCI−, m/z): 204.9 (M − H⁻); HRMS (TOF MS CI+, m/z) Calculated for C₈H₆O₂Cl₂ (M + H)⁺: 206.9977; Found: 206.9980.

To a round-bottom flask charged with a magnetic stir bar and an addition funnel was added oxalyl chloride (8.3 mL, 97 mmol, 2.2 equiv) and dichloromethane (100 mL). The reaction mixture was cooled to −78 °C and a solution of dimethylsulfoxide (14 mL, 193 mmol, 4.4 equiv)
in dichloromethane (28 mL) was added dropwise via the addition funnel. After 20 min, a solution of 4,5-dichloro-1,2-benzenedimethanol (5-12) (9.1 g, 44.1 mmol, 1 equiv) in 1:1 DCM–DMSO (66 mL) was added dropwise. After 1 h, triethylamine (109 mL, 780 mmol, 18 equiv) was added slowly to the reaction mixture, which was subsequently warmed to room temperature over 1 h. The reaction mixture was diluted by addition of cold water (320 mL). The aqueous layer was separated and extracted with DCM (2 × 160 mL). The organic layers were combined, washed with saturated aqueous bicarbonate (160 mL) and brine (320 mL), dried over MgSO₄, filtered and concentrated. The resulting residue was dissolved in THF (150 mL) and filtered to remove remaining ammonium salts. The product was purified by sublimation at 110 °C under vacuum, followed by recrystallizing twice from chloroform and drying overnight under vacuum. 4,5-Dichlorophthalaldehyde (5-13) was obtained as a light yellow solid (6.0 g, 30 mmol, 67%). Repeated nine times, this procedure gave an average yield of 50 ± 10%. The resulting solid was stored in a glovebox under inert atmosphere before use. IR (cm⁻¹) 1680; ¹H NMR (d₆-DMSO) δ 10.41 (s, 2H), 8.19 (s, 2H); ¹³C NMR (d₆-DMSO) δ 191.0, 136.8, 135.8, 131.7; MS (TOF MS EI⁺, m/z): 201.9 (M)⁺; HRMS (TOF MS EI⁺, m/z) Calculated for C₈H₄O₂Cl₂ (M)⁺: 201.9585; Found: 201.9588.

6.9.3 General Procedure 1 for Synthesizing Poly(4,5-dichlorophthalaldehyde) (5-15, Mₛ = 21 kDa)
4,5-Dichlorophthalaldehyde (5-13) (1 g, 4.9 mmol, 1 equiv) was sealed in a round-bottom flask charged with a NdFeB magnetic stir bar in a glovebox under a N₂ atmosphere. Outside of the glovebox, anhydrous THF (16 mL) was added to the round-bottom flask to create a 0.3 M solution of the monomer. The resulting solution was degassed via three freeze-pump-thaw cycles and subsequently backfilled with argon. Dry isopropanol (0.8 µL, 0.01 mmol, 0.002 equiv) was added. The reaction mixture was cooled to −78 °C, and a solution of 1-tert-butyl-2,2,4,4,4-pentakis(dimethylamino)-2λ⁵,4λ⁵^-catenadi(phosphazene) (P₂-t-Bu base) in THF (2.0 M, 7 µL, 0.014 mmol, 0.0028 equiv) was added in one portion to the solution. The reaction mixture was stirred vigorously (~350 rpm) at −78 °C. After 4 h, the polymer was end-capped via sequential addition of pyridine (0.2 ml, 2.5 mmol, 0.5 equiv) and acetyl chloride (36 µL, 0.5 mmol, 0.1 equiv) to the −78 °C solution. The solution was allowed to warm to rt over 2 h, after which it was concentrated. The residue was redissolved in THF (5 mL) and was poured into a solution of cold methanol (100 mL). The solvent was drained using a polymer washer. MeOH (50 mL) was added to the solid material and N₂ was bubbled through this solution for 10 min, after which the solvent was drained. This process (starting from redissolution) was repeated three times. After the third iteration, the resulting solid was washed with EtOAc (50 mL) then MeOH (50 mL). The resulting polymer was dried under vacuum for 6 h to yield polymer 5-15 as a white solid (0.7 g, 70%). \( M_n = 21 \text{ kDa} \) and \( M_w = 26 \text{ kDa} \); \(^1\text{H NMR} \ (\text{CDCl}_3) \delta 7.90–7.11 \text{ (br s, 2H), 7.02–6.09 \text{ (br m, 2H)}}\); \(^{13}\text{C NMR} \ (\text{CDCl}_3) \delta 138.1, 134.7, 125.3, 102.4 \text{ (m)}.\)
6.9.4 General Procedure 2 for Synthesizing Poly(4,5-dichlorophthalaldehyde) (5-15, \(M_n = 17\) kDa)

4,5-Dichlorophthalaldehyde (5-13) (0.5 g, 2.5 mmol, 1 equiv) was sealed in a round-bottom flask charged with a NdFeB magnetic stir bar in a glovebox under a N₂ atmosphere. Outside of the glovebox, anhydrous THF (8 mL) was added to the round-bottom flask to create a 0.3 M solution. The reaction mixture was cooled to −78 °C, and a solution of dry isopropanol (0.14 µL, 0.003 mmol, 0.001 equiv) and tert-butylimino-tri(pyrrolidino)phosphorane (P₁-t-Bu base) (1.5 µL, 0.005 mmol, 0.002 equiv) in THF (0.1 mL) was added in one portion to the solution. The reaction mixture was stirred vigorously (~350 rpm) at −78 °C. After 2 h, the polymer was end-capped via sequential addition of pyridine (0.1 mL, 1.2 mmol, 0.5 equiv) and acetyl chloride (18 µL, 0.2 mmol, 0.1 equiv) to the −78 °C solution. The solution was allowed to warm to rt over 2 h, after which it was concentrated. The residue was redissolved in THF (2.5 mL) and was poured into a solution of cold methanol (50 mL). The solvent was drained using a polymer washer. MeOH (50 mL) was added to the solid material and N₂ was bubbled through this solution for 10 min, after which the solvent was drained. This process (starting from redissolution) was repeated three times. After the third iteration, the resulting solid was washed with EtOAc (50 mL) then MeOH (50 mL). The resulting polymer was dried under vacuum for 6 h to yield polymer 5-15 as a white solid (0.42 g, 84%). \(M_n = 17\) kDa and \(M_w = 24\) kDa.
6.9.5 Polymer Synthesis

The following procedures are arranged based on the order in which the polymers appear in the chapter.

**Synthesis of Polymer 5-14 ($M_n = 13$ kDa)**

Polymer 5-14 was synthesized on a 1 g (4.9 mmol) scale using general procedure 2 from Section 6.9.4, with the exceptions that the initial equivalents of isopropanol and $P_1-t$-Bu base were 0.005 and 0.009 respectively and that the polymer was end-capped by sequential addition of dry pyridine (0.2 mL, 2.7 mmol, 0.5 equiv) and allyl chloroformate (0.05 mL, 0.5 mmol, 0.1 equiv). After purification, polymer 5-14 was obtained as a white solid (0.84 g, 84%). $M_n = 13$ kDa and $M_w = 24$ kDa.

**Synthesis of Polymer 5-16 ($M_n = 24$ kDa)**

Polymer 5-16 was synthesized on a 0.5 g (2.5 mmol) scale using general procedure 2 from Section 6.9.4, with the exceptions that the initial equivalents of isopropanol and $P_1-t$-Bu base were 0.005 and 0.009 respectively and that the polymer was end-capped by sequential
addition of dry pyridine (0.1 mL, 1.2 mmol, 0.5 equiv) and a solution of tert-butyldimethylsilyl chloride (38 mg, 0.25 mmol, 0.1 equiv) in anhydrous THF (0.1 mL). After purification, polymer 5-16 was obtained as a white solid (0.37 g, 74%). $M_n = 24$ kDa and $M_w = 40$ kDa.

**Synthesis of Polymer 5-17 ($M_n = 23$ kDa)**

![Diagram of 5-17]

Polymer 7 was synthesized on a 0.5 g (2.5 mmol) scale using general procedure 2 from Section 6.9.4, with the exceptions that the initial equivalents of isopropanol and $P_1$-$t$-Bu base were 0.005 and 0.009 respectively and that the reaction was quenched by addition of trichloroacetyl isocyanate (0.03 mL, 0.25 mmol, 0.1 equiv). After purification, polymer 5-17 was obtained as a white solid (0.3 g, 50%). $M_n = 23$ kDa and $M_w = 33$ kDa.

**Synthesis of Polymer 5-18 ($M_n = 18$ kDa)**

![Diagram of 5-18]

Polymer 5-18 was synthesized on a 1.0 g (4.9 mmol) scale using general procedure 2 from Section 6.9.4, with the exceptions that the alcohol initiator was tert-butyldimethylsilanol (4 μL, 0.03 mmol, 0.005 equiv), the initial equivalents of $P_1$-$t$-Bu base were 0.009, and the reaction
was quenched by sequential addition of dry pyridine (0.2 mL, 2.5 mmol, 0.5 equiv) and a solution of tert-butyldimethylsilyl chloride (79 mg, 0.5 mmol, 0.1 equiv) in anhydrous tetrahydrofuran (0.1 mL). After purification, polymer 5-18 obtained as a white solid (0.99 g, 99%). $M_n = 18$ kDa and $M_w = 35$ kDa.

**Synthesis of Polymer 5-19 ($M_n = 15$ kDa)**

![5-19](image)

Polymer 5-19 was synthesized on a 0.4 g (2.0 mmol) scale using general procedure 2 from Section 6.9.4, with the exceptions that the initial equivalents of isopropanol and P$_t$-Bu base were 0.005 and 0.009 respectively and that the reaction was quenched by sequential addition of dry pyridine (0.08 mL, 1.0 mmol, 0.5 equiv) and a solution of 2-nitrobenzyl carbonochloridate (42 mg, 0.2 mmol, 0.1 equiv) in anhydrous tetrahydrofuran (0.2 mL). After purification, polymer 5-19 was obtained as a white solid (0.28 g, 70%). $M_n = 15$ kDa and $M_w = 26$ kDa.
Synthesis of Polymer 5-20 ($M_n = 25$ kDa)

Polymer 5-20 was synthesized on a 0.75 g (3.7 mmol) scale using general procedure 2 from Section 6.9.4, with the exceptions that the initial equivalents of isopropanol and $P_{1-t}$-Bu base were 0.005 and 0.009 respectively and that the reaction was quenched by sequential addition of dry pyridine (0.15 mL, 1.9 mmol, 0.5 equiv) and a solution of 1-[[chlorocarbonyl]oxy]methyl]-4,5-dimethoxy-2-nitrobenzene (0.1 g, 0.4 mmol, 0.1 equiv) in anhydrous dichloromethane (0.5 mL). After purification, polymer 5-20 was obtained as a white solid (0.63 g, 84%). $M_n = 25$ kDa and $M_w = 41$ kDa.

Synthesis of Polymer 2-14 ($M_n = 14$ kDa)

Polymer 2-14 was synthesized on a 1.0 g (7.5 mmol) scale using the general procedure described in Section 6.3.1. Dry isopropanol (2.3 µL, 0.03 mmol, 0.004 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.3
mL, 3.7 mmol, 0.5 equiv) and a solution of 1-[(chlorocarbonyl)oxy]methyl]-4,5-dimethoxy-2-nitrobenzene (0.2 g, 0.75 mmol, 0.1 equiv) in anhydrous methylene chloride (3 mL). After purification, polymer 2-14 was obtained as a light yellow solid (0.75 g, 75%). $M_n = 14$ kDa and $M_w = 32$ kDa.

**Synthesis of Polymer 2-8 ($M_n = 34$ kDa)**

Polymer 2-8 was synthesized on a 1.0 g (7.5 mmol) scale using the general procedure described in Section 6.3.1. Dry isopropanol (1.7 µL, 0.022 mmol, 0.003 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.3 mL, 3.7 mmol, 0.5 equiv) and allyl chloroformate (0.08 mL, 0.75 mmol, 0.1 equiv). After purification, polymer 2-8 was obtained as a white solid (0.76 g, 76%). $M_n = 34$ kDa and $M_w = 57$ kDa.

**Synthesis of Polymer 2-20 ($M_n = 16$ kDa)**

Polymer 2-20 was synthesized on a 1.0 g (7.5 mmol) scale using the general procedure described in Section 6.3.1. Dry isopropanol (4.6 µL, 0.06 mmol, 0.008 equiv) was added as the
The polymerization reaction was quenched by sequential addition of dry pyridine (0.3 mL, 3.7 mmol, 0.5 equiv) and acetic anhydride (0.07 mL, 0.75 mmol, 0.1 equiv). After purification, polymer 2-20 was obtained as a white solid (0.21 g, 21%). $M_n = 16$ kDa and $M_w = 34$ kDa.

**Synthesis of Polymer 5-20 ($M_n = 14$ kDa)**

Polymer 5-20 was synthesized on a 1.5 g (7.4 mmol) scale using general procedure 1 from Section 6.9.3, with the exceptions that the initial concentration of monomer in THF was 0.2 M, the duration of the polymerization reaction was 6 h from the initial addition of the phosphazene base to the termination step, and that the reaction was quenched by sequential addition of dry pyridine (0.3 mL, 3.7 mmol, 0.5 equiv) and a solution of 1-[[[(chlorocarbonyl)oxy]methyl]-4,5-dimethoxy-2-nitrobenzene (0.2 g, 0.4 mmol, 0.1 equiv) in anhydrous dichloromethane (0.5 mL). After purification, polymer 5-20 was obtained as a white solid (0.63 g, 84%). $M_n = 14$ kDa and $M_w = 30$ kDa.
Synthesis of Polymer 5-14 ($M_n = 30$ kDa)

![Structure of Polymer 5-14]

$M_n = 30$ kDa

Polymer 5-14 was synthesized on a 2.0 g (10 mmol) scale using general procedure 1 from Section 6.9.3, with the exceptions that the initial concentration of monomer in THF was 0.2 M and that the polymer was end-capped by sequential addition of dry pyridine (0.4 mL, 5 mmol, 0.5 equiv) and allyl chloroformate (0.1 mL, 1 mmol, 0.1 equiv). After purification, polymer 5-14 was obtained as a white solid (0.84 g, 84%). $M_n = 30$ kDa and $M_w = 42$ kDa.

Synthesis of Polymer 5-15 ($M_n = 24$ kDa)

![Structure of Polymer 5-15]

$M_n = 24$ kDa

Polymer 5-15 was synthesized on a 1.5 g (7.5 mmol) scale using general procedure 1 from Section 6.9.3, with the exceptions that the initial concentration of monomer in THF was 0.2 M, the duration of the polymerization reaction was 6 h after the initial addition of the phosphazene base to the termination step, and that the polymer was end-capped by sequential addition of dry pyridine (0.3 mL, 3.7 mmol, 0.5 equiv) and acetic anhydride (0.07 mL, 0.75 mmol, 0.1 equiv). After purification, polymer 5-15 was obtained as a white solid (0.45 g, 30%). $M_n = 24$ kDa and $M_w = 38$ kDa.
Synthesis of Polymer 2-20 ($M_n = 39$ kDa)

Polymer 2-20 was synthesized on a 1.0 g (7.5 mmol) scale using the general procedure described in Section 6.3.1. Dry isopropanol (3.4 µL, 0.045 mmol, 0.006 equiv) was added as the initiator. The polymerization reaction was quenched by sequential addition of dry pyridine (0.3 mL, 3.7 mmol, 0.5 equiv) and acetic anhydride (0.07 mL, 0.75 mmol, 0.1 equiv). After purification, polymer 2-20 was obtained as a white solid (0.81 g, 81%). $M_n = 21$ kDa and $M_w = 26$ kDa.

Synthesis of Polymer 5-14 ($M_n = 31$ kDa)

Polymer 5-14 was synthesized on a 1.0 g (5 mmol) scale using general procedure 2 from Section 6.9.4, with the exception that the polymer was end-capped by sequential addition of dry pyridine (0.2 mL, 2.5 mmol, 0.5 equiv) and allyl chloroformate (0.2 mL, 2.5 mmol, 0.1 equiv). After purification, polymer 5-14 was obtained as a white solid (0.74 g, 74%). $M_n = 31$ kDa and $M_w = 41$ kDa.
Synthesis of Polymer 5-14 ($M_n = 17$ kDa)

Polymer 5-14 was synthesized on a 1.1 g (5.4 mmol) scale using general procedure 1 from Section 6.9.3, with the exceptions that the initial concentration of monomer in THF was 0.2 M, the duration of the polymerization reaction was 6 h from the initial addition of the phosphazene base to the termination step, and that the reaction was quenched by sequential addition of dry pyridine (0.2 mL, 2.7 mmol, 0.5 equiv) and allyl chloroformate (0.06 mL, 0.5 mmol, 0.1 equiv). After purification, polymer 5-14 was obtained as a white solid (0.74 g, 67%). $M_n = 17$ kDa and $M_w = 28$ kDa.

Synthesis of Polymer 5-18 ($M_n = 15$ kDa)

Polymer 5-18 was synthesized on a 0.5 g (2.5 mmol) scale using general procedure 2 from Section 6.9.4, with the exceptions that the alcohol initiator was tert-butyldimethylsilanol (2 μL, 0.01 mmol, 0.005 equiv), the initial equivalents of $P_{1-t}$-Bu base were 0.009, and the reaction was quenched by sequential addition of dry pyridine (0.1 mL, 1.2 mmol, 0.5 equiv) and a solution of tert-butyldimethylsilylchloride (38 mg, 0.25 mmol, 0.1 equiv) in anhydrous tetrahydrofuran
(0.1 mL). After purification, polymer 5-18 was obtained as a white solid (0.31 g, 62%). $M_n = 15$ kDa and $M_w = 25$ kDa.

**Synthesis of Polymer 5-15 ($M_n = 33$ kDa)**

![Diagram of polymer 5-15](attachment:image)

Polymer 5-15 was synthesized on a 0.6 g (3.0 mmol) scale using general procedure 2 from Section 6.9.4, with the exception that the initial equivalents of isopropanol and P$_{1-t}$-Bu base were 0.005 and 0.009 respectively. After purification, polymer 5-15 was obtained as a white solid (0.31 g, 62%). $M_n = 33$ kDa and $M_w = 46$ kDa.

**Synthesis of Polymer 5-15 ($M_n = 22$ kDa)**

![Diagram of polymer 5-15](attachment:image)

Polymer 5-15 was synthesized on a 0.6 g (3.0 mmol) scale using general procedure 2 from Section 6.9.4, with the exception that the initial equivalents of isopropanol and P$_{1-t}$-Bu base were 0.005 and 0.009 respectively. After purification, polymer 5-15 was obtained as a white solid (0.84 g, 84%). $M_n = 22$ kDa and $M_w = 28$ kDa.
6.10 Chapter 5: Experimental Procedures and Characterization

6.10.1 Solution Phase Stability Study

Solutions of polymers 2-14 ($M_n = 14$ kDa), 2-8 ($M_n = 34$ kDa), 2-20 ($M_n = 16$ kDa), 5-20 ($M_n = 14$ kDa), 5-14 ($M_n = 30$ kDa) and 11 ($M_n = 24$ kDa) (0.0035 mmol) with concentrations of 7.0 mM were prepared in $d_8$-THF (0.5 mL) that contained a known concentration of an internal standard (1,3,5-trimethoxybenzene). The polymer solutions were stored protected from light at 23 °C. After 6 d, the quantity of monomer in each solution was measured using $^1$H NMR by comparing the integration values of the aldehyde peak of the monomer to the aromatic peak of the internal standard (Figure 5-5 and Table 6-18 in Appendix B). The experiment with polymer 2-14 was repeated three times.

6.10.2 Acid Stability Study

Polymers 2-8 ($M_n = 34$ kDa), 2-20 ($M_n = 39$ kDa), 5-14 ($M_n = 30$ kDa) and 5-15 ($M_n = 21$ kDa) (0.0026 mmol) were dissolved in $d_8$-THF (0.5 mL) that contained a known concentration of an internal standard (1,3,5-trimethoxybenzene) and 0.52 M benzoic acid (0.26 mmol, 100 equiv) to give 5.2 mM solutions of polymer. The polymer solutions were stored protected from light at 23 °C. After 6 d, the quantity of monomer in each solution was measured using $^1$H NMR by comparing the integration values of the aldehyde peak of the monomer to the aromatic peak of the internal standard (Figure 5-6 and Table 6-19 in Appendix B). The experiment with polymer 2-8 was repeated three times.
6.10.3 Solid Stability Study

Polymers 2-18 ($M_n = 31$ kDa) and 5-14 ($M_n = 34$ kDa) were stored under air at 23 °C. After 130 d, samples of the polymer were dissolved in solutions of $d_8$-THF that contained known concentrations of an internal standard (1,3,5-trimethoxybenzene) (Figure 5-7). The quantity of monomer in each solution was measured using $^1$H NMR by comparing the integration values of the aldehyde peak of the monomer to the aromatic peak of the internal standard.

6.10.4 Response of Polymers 5-14 and 5-15 to Pd(0) in Solution

Polymer 5-14 ($M_n = 17$ kDa) (15 mg, 0.0009 mmol) was dissolved in THF (0.5 mL). A 3.5 mM solution of Pd(PPh$_3$)$_4$ in THF (0.5 mL, 0.00018 mmol, 2 equiv) was added in one portion to the solution of polymer. The resulting solution was agitated by vortexing for 5 s. After standing for 30 min, an aliquot of the solution (0.1 mL) was withdrawn and was diluted in THF (0.9 mL). This sample was used for GPC analysis (Figure 5-9b).

Polymer 5-15 ($M_n = 24$ kDa) (22 mg, 0.0009 mmol) was dissolved in THF (0.5 mL). A 3.5 mM solution of Pd(PPh$_3$)$_4$ in THF (0.5 mL, 0.00018 mmol, 2 equiv) was added in one portion to the solution of polymer. The resulting solution was agitated by vortexing for 5 s. After standing for 30 min, an aliquot of the solution (0.1 mL) was withdrawn and was diluted in THF (0.9 mL). This sample was used for GPC analysis (Figure 5-9c).
6.10.4 Response of Polymers 5-16 and 5-17 to F⁻ in Solution

A 0.33 M stock solution of fluoride was prepared by dissolving tetrabutylammonium fluoride trihydrate (TBAF·3H₂O) (28 mg, 0.09 mmol) in 0.09 mL THF and 0.18 mL of 0.1 M phosphate buffer (pH 7.1).

Polymer 5-16 (Mₙ = 24 kDa) (10 mg, 0.00042 mmol) was dissolved in THF (1 mL). The 0.33 M solution of TBAF·3H₂O in 2:1 buffered water–THF (2 μL, 0.00067 mmol, 1.6 equiv) was added in one portion to the solution of polymer. The resulting solution was agitated by vortexing for 5 s. After standing for 30 min, the solution was analyzed by GPC (Figure 5-10b).

Polymer 5-17 (Mₙ = 23 kDa) (9.8 mg, 0.00042 mmol) was dissolved in THF (1 mL). The 0.33 M solution of TBAF·3H₂O in 2:1 buffered water–THF (2 μL, 0.00067 mmol, 1.6 equiv) was added in one portion to the solution of polymer. The resulting solution was agitated by vortexing for 5 s. After standing for 30 min, the solution was analyzed by GPC (Figure 5-10c).

6.10.5 Dose-Dependent Response of Polymer 5-14 to Pd(0)

Solutions (0.5 mL) containing varying concentrations of tetrakis(triphenylphosphine)palladium(0) (0 mM, 0.16 mM, 0.41 mM, 0.82 mM, 1.2 mM, or 1.6 mM) in THF were added to 1.8 mM solutions of polymers 5-14 (Mₙ = 30 kDa) and 5-15 (Mₙ = 20 kDa) in THF (0.5 mL solutions, 0.89 μmol polymer). The resulting solutions were agitated by vortexing for 5 s and then left undisturbed for 30 min. Aliquots (0.25 mL) from the solutions were added to 0.25 mL of d₅-THF that contained a known concentration of an internal standard (1,3,5-trimethoxybenzene). The extent of depolymerization was measured using peak integration values in ¹H NMR spectra (Figure 5-11 and Tables 6-20 and 6-21 in Appendix B).
6.10.6 Solid State Depolymerization of Polymers 5-18 and 5-15

Cylinders of polymers 5-18 ($M_n = 15$ kDa) and 5-15 ($M_n = 33$ kDa) were prepared by depositing 200 mg/mL solution of the polymers in chlorobenzene (with 20 wt% dimethyl phthalate as a plasticizer) in a silicon mold and allowing the disks to dry under air overnight. The disks were removed from the mold and dried under vacuum for 6 h.

To evaluate the response of the polymers to fluoride, the disks were submerged in acetonitrile (8 mL). A 1 M solution of TBAF·3H$_2$O in 1:1 MeCN–0.1 M phosphate buffered water (pH 7.1) (0.1 mL, 0.1 mmol fluoride) was added (final concentration of fluoride was 12 mM), and the disks were monitored by camera (Figure 5-12). The solutions were concentrated, then redissolved in tetrahydrofuran and analyzed by GPC (Figure 5-13).

6.10.7 Preparation of Polymers 5-14, 5-15, and 5-18 for Selective Laser Sintering

Particles of polymers 5-14 ($M_n = 13$ kDa), 5-15 ($M_n = 22$ kDa), and 5-18 ($M_n = 18$ kDa) were prepared by dissolving 500 mg of polymer in 10 mL of tetrahydrofuran (with 30 wt% dibutyl phthalate as plasticizer). To color the polymer, concentrated food coloring (McCormick® Assorted Food Color and Egg Dye) was added (polymer 5-14 = 2 drops red; polymer 5-15 = 1 drop red, 1 drop yellow; polymer 5=18 = 2 drops blue). The polymer solution was concentrated by rotary evaporation under reduced pressure, and then dried under vacuum for 6 h. The dried polymer was then transferred to a mortar and cooled using liquid nitrogen. The cooled, brittle, polymer was then ground using a pestle for 3 minutes, with further cooling using liquid nitrogen.
each minute. The polymer powder was then transferred to a vial to dry under vacuum for 1 h. To determine the size of the polymer particles, the polymer was suspended in MeOH. The suspension was added to a glass slide, and the solvent was allowed to dry under air. The resulting particles were analyzed using a Zeiss Axiovert 200 microscope at 20× magnification in transmission/reflectance mode (Figure 5-14), and the sizes of the particles were determined using ImageJ.

6.10.8 Laser Sintered Rings of Polymers 5-14 and 5-18

A small quantity of the powder of polymers 5-14 ($M_n = 13$ kDa) or 5-18 ($M_n = 18$ kDa) was transferred to a silicon mold, to completely cover the bottom surface of the mold. A 7.5 mm diameter ring was sintered (see Section 6.2 for the settings used) into the initial layer of polymer powder three times. Additional polymer was added to completely cover the sintered regions of the powder bed, and then leveled. The powder bed was sintered further with the same design two times. Further cycles of powder addition and sintering were repeated to yield a ring ~1.5 mm thick. The sintered ring was then removed from the powder bed and rinsed 3× with methanol.

Powders of 5-14 ($M_n = 13$ kDa) and 5-18 ($M_n = 18$ kDa) formulated with plasticizer as described in Section 6.10.7 and sintered rings prepared from the same polymers were dissolved in tetrahydrofuran and analyzed by GPC (Figure 5-16).

Two rings prepared from SLS of 5-14 ($M_n = 13$ kDa) were submerged separately in benzene (3 mL each). A 0.3 M solution of benzenesulfinic acid sodium salt (PhSO$_2$Na) in MeOH was added to both solution (3 mL each, 0.9 mmol PhSO$_2$Na). A 0.04 M solution of Pd(PPh$_3$)$_4$ in DCM (0.4 mL, 0.02 mmol Pd(0)) was added to the first (final concentration of Pd(0) was 2.7 mM). DCM (0.4 mL) was added to the second. The two rings were monitored by camera
(Figures 5-17 and 5-18a–c). After 60 min, the ring exposed to Pd(0) had disappeared (Figure 5-17d), while the control ring had not changed in size, even after staying submerged for an extended period (Figure 5-18b and c).

Two rings prepared from SLS of 5-18 ($M_n = 18$ kDa) were submerged separately in MeCN (8 mL each). A 1 M solution of TBAF·$\text{H}_2\text{O}$ in 1:1 MeCN–0.1 M phosphate buffered water (pH 7.1) (1 mL, 1 mmol fluoride) was added to the first (final concentration of fluoride was 111 mM). A 1 M solution of tetrabutylammonium chloride hydrate (TBACl·$\text{H}_2\text{O}$) in 1:1 MeCN–0.1 M phosphate buffered water (pH 7.1) (1 mL, 1 mmol chloride) was added to the second. The two rings were monitored by camera (Figures 5-17 and 5-18d–f). After 60 min, the ring exposed to fluoride had disappeared (Figure 5-17d), while the disk exposed to chloride had not changed in size, even after staying submerged for an extended period (Figure 5-18e and f).

### 6.10.9 Determining Line Width Error

Polymer 5-18 ($M_n = 18$ kDa) was transferred to a silicon mold. Five 1.06 mm wide lines were sintered into the initial layer of polymer powder three times. Additional polymer was added to completely cover the sintered regions of the powder bed, and then leveled. The powder bed was sintered further with the same design two times. Further cycles of powder addition and sintering were repeated to yield lines ~1.5 mm thick. The width of the lines was then measured (Table 6-2).

**Table 6-2.** Determining line width error of selective laser sintering with PCl$_2$PA.

<table>
<thead>
<tr>
<th>Line</th>
<th>Electronic Width (mm)</th>
<th>Measured Width (mm)</th>
<th>Difference (mm)</th>
<th>Line Width Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.06</td>
<td>1.52</td>
<td>0.46</td>
<td>143</td>
</tr>
<tr>
<td>2</td>
<td>1.06</td>
<td>1.62</td>
<td>0.56</td>
<td>153</td>
</tr>
<tr>
<td>3</td>
<td>1.06</td>
<td>1.58</td>
<td>0.52</td>
<td>149</td>
</tr>
<tr>
<td>4</td>
<td>1.06</td>
<td>1.61</td>
<td>0.55</td>
<td>152</td>
</tr>
</tbody>
</table>
6.10.10 Selective Laser Sintering of a Two Layer, Multi-Responsive Grating

A small quantity of the powder of polymer 5-14 ($M_n = 13$ kDa) was transferred to a silicon mold until the bottom surface of the mold was completely covered. Three 1.2 cm length lines were sintered into the initial layer of polymer powder three times. Additional polymer was added to completely cover the sintered regions of the powder bed, and then leveled. The powder bed was sintered further with the same design two times. Further cycles of powder addition and sintering were repeated to yield lines ~1.5 mm thick.

Polymer 5-18 ($M_n = 18$ kDa) was added to completely cover the sintered regions of the powder bed, and then leveled. Three 1.2 cm length lines, perpendicular to the initial three, were sintered into the top layer of polymer three times. Additional polymer was added to completely cover the sintered regions of the powder bed, and then leveled. The powder bed was sintered further with the same design two times. Further cycles of powder addition and sintering were repeated to yield a grating ~3 mm thick. The grating was then removed from the powder bed and washed 3x with methanol.

The two layer grating (Figure 5-19a) was submerged in MeCN (8 mL). A 1 M solution of TBAF·3H2O in 1:1 MeCN–0.1 M phosphate buffered water (pH 7.1) (1 mL, 1 mmol fluoride) was added (final concentration of fluoride was 111 mM). The object was monitored by camera. After 30 min, the top layer had disappeared, leaving only the bottom layer. The solution was removed by pipette, and benzene (3 mL) was added. A 0.3 M solution of benzenesulfinic acid sodium salt in MeOH was added (3 mL, 0.9 mmol of benzenesulfinic acid sodium salt). A 0.04 M solution of Pd(PPh3)4 in DCM (0.4 mL, 0.02 mmol Pd(0)) was added (final concentration of

<table>
<thead>
<tr>
<th>5</th>
<th>1.06</th>
<th>1.47</th>
<th>0.41</th>
<th>139</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>1.06</td>
<td>1.56</td>
<td>0.5</td>
<td>147</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0</td>
<td>0.06</td>
<td>0.06</td>
<td>6</td>
</tr>
</tbody>
</table>
Pd(0) was 2.7 mM). After 30 min, the grating had disappeared completely as a result of analyte-induced depolymerization.

6.10.11 Selective Laser Sintering of a Three Layer, Multi-Responsive Grating

A small quantity of the powder of polymer 5-15 ($M_n = 22$ kDa) was transferred to a silicon mold, until the bottom surface of the mold was completely covered. A $3 \times 3$ grid consisting of 1.3 cm length was sintered into the initial layer of polymer powder three times. Additional polymer was added to completely cover the sintered regions of the powder bed, and then leveled. The powder bed was sintered further with the same design two times. Further cycles of powder addition and sintering were repeated to yield a grid ~1.5 mm thick.

Polymer 5-18 ($M_n = 18$ kDa) was added to completely cover the sintered regions of the powder bed, and then leveled. Four 0.5 cm diameter rings, in a grid, were sintered into the top layer of polymer three times. Additional polymer was added to completely cover the sintered regions of the powder bed, and then leveled. The powder bed was sintered further with the same design two times. Further cycles of powder addition and sintering were repeated to yield an object ~3 mm thick.

Polymer 5-14 ($M_n = 13$ kDa) was added to completely cover the sintered regions of the powder bed, and then leveled. Four 0.5 cm equilateral triangles, in a grid, were sintered into the top layer of polymer three times. Additional polymer was added to completely cover the sintered regions of the powder bed, and then leveled. The powder bed was sintered further with the same design two times. Further cycles of powder addition and sintering were repeated to yield an object ~4.5 mm thick. The object was removed from the powder bed and then rinsed 3× with methanol.
The three layered grating, consisting of polymers 5-14 ($M_n = 13$ kDa, top layer, red, triangles), 5-18 ($M_n = 18$ kDa, middle layer, blue, circles), and 5-15 ($M_n = 22$ kDa, bottom layer, orange, squares) was submerged in a 0.3 M solution of benzenesulfinic acid sodium salt in MeOH (3 mL, 0.9 mmol PhSO$_2$Na). A 6 mM solution of Pd(PPh$_3$)$_4$ in benzene (3 mL, 0.02 mmol Pd(0)) was added (final concentration of Pd(0) was 2.9 mM). The object was monitored by camera (Figure 5-19c). After 60 min, the top layer had disappeared, leaving the middle and bottom layer. The solution was removed by pipette, and MeCN (8 mL) was added. A 1 M solution of TBAF·3H$_2$O in 1:1 MeCN–0.1 M phosphate buffered water (pH 7.1) (1 mL, 1 mmol fluoride) was added (final concentration of fluoride was 111 mM). After 120 min, the middle layer of the grating disappeared, leaving only the bottom layer.

6.10.12 Recovering the Products of Depolymerization from Solid PCl$_2$PA

A cylinders (37 mg with 20 wt% plasticizer, ~30 mg of polymer) was prepared from polymer 5-18 ($M_n = 18$ kDa) as described in Section 6.10.6. The disks were submerged in MeCN (8 mL). A 1 M solution of TBAF·3H$_2$O in 1:1 MeCN–0.1 M phosphate buffered water (pH 7.1) (0.1 mL, 0.1 mmol fluoride) was added. After 5 h, the solution was concentrated. The resulting residue was dissolved in DCM (1.5 mL) and MeOH (1.5 mL). The reaction mixture was cooled to 0 °C, and sodium borohydride (17 mg, 0.46 mmol, 3 equiv based on 0.15 mmol of dialdehyde) was added. After 1 h, the reaction mixture was concentrated. The resulting residue was dissolved in saturated aqueous ammonium chloride (10 mL). The aqueous layer was washed with EtOAc (3 × 10 mL) and THF (1 × 10 mL). The organic layers were combined, dried over sodium sulfate, filtered, and then concentrated. The crude product was purified using silica gel flash chromatography with 20% THF in hexanes as the eluent, increasing to 70% THF in
hexanes. 4,5-Dichloro-1,2-benzenedimethanol (2) was obtained as a white solid (20 mg, 0.1 mmol, 65% recovery).

6.11 References


12. Lower polymer yields were observed from polymerization reactions terminated with weaker electrophiles such as acetic anhydride compared to reactions with more electrophilic species (e.g., acetyl chloride).

13. The $d_8$-THF in each experiment was used from directly from freshly opened ampoules. We estimated that the water content of the solvent was 91 ± 4 ppm based on the certificates of analysis for the ampoules that were provided by the supplier.
Appendix A

Structural Characterization

A. NMR Spectra

Figure 6-2. $^1$H NMR spectrum for polymer 2-6 ($M_n = 41$ kDa). This polymer was synthesized as part of developing the procedure for purifying the monomer (Table 2-1).
Figure 6-3. $^{13}$C NMR spectrum for polymer 2-6 ($M_n = 41$ kDa).

Figure 6-4. $^1$H NMR spectrum for polymer 2-6 ($M_n = 7$ kDa). The polymer was used to characterize the polymer end-caps by NMR (Figure 2-10).
Figure 6-5. $^1$H NMR spectrum for polymer 2-8 ($M_n = 34$ kDa). This polymer was used in Chapter 5 for the solution, acid, and solid stability studies and for the TGA measurements (Figures 5-5–5-8).

Figure 6-6. $^1$H NMR spectrum for polymer 2-14 ($M_n = 14$ kDa). This polymer was used for the solution stability study (Figure 5-5).
Figure 6-7. $^1$H NMR spectrum for polymer 2-15 ($M_n = 3$ kDa). The polymer was used to characterize the polymer end-caps by NMR (Figure 2-10).

Figure 6-8. $^1$H NMR spectrum for polymer 2-20 ($M_n = 16$ kDa). This polymer was used in Chapter 5 for the solution stability study.
Figure 6-9. $^1$H NMR spectrum for the oxidation of 5-10 to 2-2 using Swern oxidation conditions (Table 5-2).

Figure 6-10. $^1$H NMR spectrum for the oxidation of 5-10 to 2-2 using IBX (Table 5-2).
Figure 6-11. $^1$H NMR spectrum for the oxidation of 5-10 to 2-2 using BaMnO$_4$ (Table 5-2).

Figure 6-12. $^1$H NMR spectrum for the oxidation of 5-10 to 2-2 using PDC (Table 5-2).
Figure 6-13. $^1$H NMR spectrum for the oxidation of 5-10 to 2-2 using MnO$_2$ (Table 5-2).

Figure 6-14. $^1$H NMR spectrum for the oxidation of 5-10 to 2-2 using oxoammonium oxidation conditions (Table 5-2).
Figure 6-15. $^1$H NMR spectrum for 5-12.

Figure 6-16. $^{13}$C NMR spectrum for 5-12.
Figure 6-17. $^1$H NMR spectrum for 5-13.

Figure 6-18. $^{13}$C NMR spectrum for 5-13.
Figure 6-19. $^1$H NMR spectrum for polymer 5-14 ($M_n = 30$ kDa). This polymer was used for the solution and acid stability studies (Figure 5-5 and 5-6), for TGA measurements (Figure 5-8), and for characterizing the dose-dependent response of the polymer to Pd(0) (Figure 5-11).

Figure 6-20. $^1$H NMR spectrum for polymer 5-15 ($M_n = 21$ kDa). The synthesis of this polymer is described in General Procedure 1 in Section 6.9.3. In addition, the polymer was used for the acid stability studies (Figure 5-6) and for characterizing the dose-dependent response of the polymer to Pd(0) (Figure 5-11).
Figure 6-21. $^{13}$C NMR spectrum for polymer 5-15 ($M_n = 21$ kDa).

Figure 6-22. $^1$H NMR spectrum for polymer 5-16 ($M_n = 24$ kDa). This polymer was used to test the ability of PCl$_2$PA to depolymerize in solution (Figure 5-9).
Figure 6-23. $^1$H NMR spectrum of polymer 5-17 ($M_n = 23$ kDa). This polymer was used to test the ability of PCl$_2$PA to depolymerize in solution (Figure 5-10).

Figure 6-24. $^1$H NMR spectrum for polymer 5-18 ($M_n = 15$ kDa). This polymer was used to prepare the polymer cylinders for testing solid state depolymerization (Figure 5-12).
Figure 6-25. $^1$H NMR spectrum for polymer 5-20 ($M_n = 14$ kDa). This polymer was used for the solution stability study (Figure 5-5).
B. GPC Chromatograms

Figure 6-26. GPC chromatogram for polymer 2-6 ($M_n = 41 \text{ kDa}$). This polymer was synthesized as part of developing the procedure for purifying the monomer (Table 2-1).
Figure 6-27. GPC chromatogram for polymer 2-6 ($M_n = 48$ kDa). This polymer was synthesized as part of developing the procedure for purifying the monomer (Table 2-1).
Figure 6-28. GPC chromatogram for polymer 2-6 ($M_n = 50$ kDa). This polymer was synthesized as part of developing the procedure for purifying the monomer (Table 2-1).
Figure 6-29. GPC chromatogram for polymer 2-6 ($M_n = 7$ kDa). The polymer was used to characterize the polymer end-caps by NMR (Figure 2-10).
Figure 6-30. GPC chromatogram for polymer 2-6 ($M_n = 52$ kDa). This polymer was used for the solid state depolymerization study (Figure 2-12).
**Figure 6.31.** GPC chromatogram for polymer 2-6 ($M_n = 8$ kDa). This polymer was used for the microscale pump experiments in Chapter 3.
Figure 6-32. GPC chromatogram for polymer 2-6 ($M_n = 33$ kDa). This polymer was used for the microscale pump experiments in Chapter 3.
Figure 6-33. GPC chromatogram for polymer 2-6 ($M_n = 45$ kDa). This polymer was used for the microscale pump experiments in Chapter 3.
Figure 6-34. GPC chromatogram for polymer 2-6 ($M_n = 53$ kDa). This polymer was used for the microscale pump experiments in Chapter 3.
Figure 6-35. GPC chromatogram for polymer 2-6 ($M_n = 65$ kDa). This polymer was used for the microscale pump experiments in Chapter 3.
Figure 6-36. GPC chromatogram for polymer 2-6 ($M_n = 42$ kDa). This polymer was used for characterizing the polymer films in Section 3.3.6.
**Figure 6-37.** GPC chromatogram for polymer 2-8 ($M_n = 34$ kDa). This polymer was synthesized as part of the experiment for controlling polymer molecular weight (Figure 2-8) and was used for the solution phase depolymerization experiment (Figure 2-11).
Figure 6-38. GPC chromatogram for polymer 2-8 ($M_n = 46$ kDa). This polymer was synthesized as part of the experiment for controlling polymer molecular weight (Figure 2-8).
**Figure 6-39.** GPC chromatogram for polymer 2-8 ($M_n = 52$ kDa). This polymer was synthesized as part of the experiment for controlling polymer molecular weight (Figure 2-8).
Figure 6-40. GPC chromatogram for polymer 2-8 ($M_n = 63$ kDa). This polymer was synthesized as part of the experiment for controlling polymer molecular weight (Figure 2-8).
Figure 6-41. GPC chromatogram for polymer 2-8 ($M_n = 71$ kDa). This polymer was synthesized as part of the experiment for controlling polymer molecular weight (Figure 2-8).
Figure 6-42. GPC chromatogram for polymer 2-8 ($M_n = 34$ kDa). This polymer was used in Chapter 5 for the solution, acid, and solid stability studies and for the TGA measurements (Figures 5-5–5-8).
Figure 6.43. GPC chromatogram for polymer 2-9 ($M_n = 50$ kDa).
Figure 6-44. GPC chromatogram for polymer 2-10 ($M_n = 42$ kDa).
Figure 6-45. GPC chromatogram for polymer 2-11 ($M_n = 92$ kDa).
Figure 6-46. GPC chromatogram for polymer 2-12 ($M_n = 39$ kDa).
Figure 6-47. GPC chromatogram for polymer 2-13 \( (M_n = 48 \text{ kDa}) \).
Figure 6-48. GPC chromatogram for polymer 2-14 ($M_n = 39$ kDa). This polymer was synthesized as part of determining the scope of possible polymer end-caps (Figure 2-9).
Figure 6-49. GPC chromatogram for polymer 2-14 ($M_n = 14$ kDa). This polymer was used for the solution stability studies (Figure 5-5).
Figure 6-50. GPC chromatogram for polymer 2-15 ($M_n = 37$ kDa). This polymer was synthesized as part of determining the scope of possible polymer end-caps (Figure 2-9).
Figure 6-51. GPC chromatogram for polymer 2-15 ($M_n = 3$ kDa). The polymer was used to characterize the polymer end-caps by NMR (Figure 2-10).
Figure 6.52. GPC chromatogram for polymer 2-16 ($M_n = 25$ kDa).
Figure 6.53. GPC chromatogram for polymer 2-17 ($M_n = 26$ kDa).
Figure 6-54. GPC chromatogram for polymer 2-18 ($M_n = 37$ kDa).
Figure 6-55. GPC chromatogram for polymer 2-19 ($M_n = 47$ kDa). This polymer was used for the microscale pump experiments in Chapter 3.
Figure 6-56. GPC chromatogram for polymer 2-19 ($M_n = 32$ kDa). This polymer was used for the microscale pump experiments in Chapter 3.
Figure 6-57. GPC chromatogram for polymer 2-19 ($M_n = 37$ kDa). This polymer was used for the microscale pump experiments in Chapter 3.
Figure 6-58. GPC chromatogram for polymer 2-19 ($M_n = 54$ kDa). This polymer was used for the microscale pump experiments in Chapter 3.
Figure 6-59. GPC chromatogram for polymer 2-19 ($M_n = 61$ kDa). This polymer was used for the microscale pump experiments in Chapter 3.
Figure 6-60. GPC chromatogram for polymer 2-19 ($M_n = 43$ kDa). This polymer was used for characterizing the polymer films in Section 3.3.6.
Figure 6-61. GPC chromatogram for polymer 2-20 ($M_n = 50$ kDa). This polymer was used for the solution phase depolymerization study (Figure 2-11).
Figure 6-62. GPC chromatogram for polymer 2-20 ($M_n = 16$ kDa). This polymer was used for the solution stability study (Figure 5-5).
Figure 6-63. GPC chromatogram for polymer 2-20 ($M_n = 39$ kDa). This polymer was used for the acid stability stability study (Figure 5-6) and for TGA measurements (Figure 5-8).
Figure 6-64. GPC chromatogram for polymer 2-21 ($M_n = 42$ kDa).
Figure 6-65. GPC chromatogram for polymer 3-3 ($M_r = 20$ kDa). This polymer was used in the microscale pump experiments in Chapter 3.
Figure 6-66. GPC chromatogram for polymer 3-3 ($M_n = 32$ kDa). This polymer was used in the microscale pump experiments in Chapter 3.
Figure 6-67. GPC chromatogram for polymer 3-3 ($M_n = 43$ kDa). This polymer was used in the microscale pump experiments in Chapter 3.
Figure 6-68. GPC chromatogram for polymer 3-3 (Mₙ = 49 kDa). This polymer was used in the microscale pump experiments in Chapter 3.
**Figure 6-69.** GPC chromatogram for polymer 3-3 ($M_n = 54$ kDa). This polymer was used in the microscale pump experiments in Chapter 3.
Figure 6-70. GPC chromatogram for polymer 5-14 ($M_n = 13$ kDa). This polymer was used for selective laser sintering in Chapter 5.
Figure 6-71. GPC chromatogram for polymer 5-14 ($M_n = 30$ kDa). This polymer was used in the solution and acid stability studies (Figures 5-5 and 5-6), for TGA measurements (Figure 5-8), and for evaluating the dose-dependent response of PCl$_2$PA to Pd(0) (Figure 5-11).
Figure 6-72. GPC chromatogram for polymer 5-14 ($M_n = 31$ kDa). This polymer was used for the solid stability study (Figure 5-7).
Figure 6-73. GPC chromatogram for polymer 5-14 \( (M_n = 17 \text{kDa}) \). This polymer was used for the solution depolymerization study (Figure 5-9).
Figure 6-74. GPC chromatogram for polymer 5-15 ($M_n = 17$ kDa). This synthesis of this polymer was described in General Procedure 1 (Section 6.9.3). It was also used for TGA measurements (Figure 5-8).
Figure 6-75. GPC chromatogram for polymer 5-15 ($M_n = 21$ kDa). This synthesis of this polymer was described in General Procedure 2 (Section 6.9.4). It was also used for the acid stability study (Figure 5-6) and for evaluating the dose-dependent response of $\text{PCI}_2\text{PA}$ to Pd(0) (Figure 5-11).
Figure 6-76. GPC chromatogram for polymer 5-15 ($M_n = 24$ kDa). This polymer was used for the solution and solid stability studies (Figure 5-5 and 5-7).
Figure 6-77. GPC chromatogram for polymer 5-15 ($M_n = 33$ kDa). This polymer was used for the solid depolymerization study (Figures 5-12 and 5-13).
Figure 6.78. GPC chromatogram for polymer 5-15 ($M_n = 22$ kDa). This polymer was used for selective laser sintering in Chapter 5.
Figure 6-79. GPC chromatogram for polymer 5-16 ($M_n = 24$ kDa). This polymer was used to test the ability of PCl$_2$PA to depolymerize in solution (Figure 5-9).
**Figure 6-80.** GPC chromatogram for polymer 5-16 ($M_n = 23$ kDa). This polymer was used to test the ability of PCl$_2$PA to depolymerize in solution (Figure 5-10).
Figure 6-81. GPC chromatogram for polymer 5-18 ($M_n = 18$ kDa). This polymer was used for selective laser sintering in Chapter 5.
Figure 6-82. GPC chromatogram for polymer 5-18 ($M_n = 15$ kDa). This polymer was used for the solid depolymerization experiment (Figures 5-12 and 5-13).
Figure 6.83. GPC chromatogram for polymer 5-19 ($M_n = 24$ kDa).
Figure 6-84. GPC chromatogram for polymer 5-20 ($M_n = 25$ kDa). This polymer was synthesized as part of the experiment to show the scope of possible end-caps (Figure 5-4).
Figure 6-85. GPC chromatogram for polymer 5-16 ($M_n = 24$ kDa). This polymer was used for the solution stability study (Figure 5-5).
C. XPS Spectra

Figure 6-86. XPS spectrum for polymer 2-6 \((M_n = 33 \text{ kDa})\).

Figure 6-87. XPS spectrum for polymer 2-19 \((M_n = 32 \text{ kDa})\).
Figure 6-88. XPS spectrum for polymer 3-3 \((M_n = 32 \text{ kDa})\).

Figure 6-89. XPS spectrum for polymer 2-19 \((M_n = 47 \text{ kDa})\).
D. DSC Curves

Figure 6-90. DSC curve for polymer 5-14 ($M_n = 31$ kDa). No $T_g$ or $T_m$ was observed.
Appendix B

Data and Charts

A. Chapter 3: Data and Charts

Table 6-3. Average speed of the tracer particles pumped by a fim of polymer 2-6 ($M_n = 8$ kDa) at different concentrations of β-D-glucuronidase (Figure 3-7).

<table>
<thead>
<tr>
<th>β-D-glucuronidase (µM)</th>
<th>Average Speed (µm/s)</th>
<th>Standard Deviation (µm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>1.71</td>
<td>0.13</td>
</tr>
<tr>
<td>8</td>
<td>1.52</td>
<td>0.16</td>
</tr>
<tr>
<td>6</td>
<td>1.02</td>
<td>0.21</td>
</tr>
<tr>
<td>4</td>
<td>1.12</td>
<td>0.22</td>
</tr>
<tr>
<td>2</td>
<td>0.88</td>
<td>0.13</td>
</tr>
<tr>
<td>1</td>
<td>0.78</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Table 6-4. Average speed of the tracer particles pumped by a fim of polymer 2-6 ($M_n = 65$ kDa) in the presence of 0.1 M solutions of different sodium salts of the anions (Figure 3-8).

<table>
<thead>
<tr>
<th>Anion</th>
<th>Average Speed (µm/s)</th>
<th>Standard Deviation (µm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN⁻</td>
<td>0.044</td>
<td>0.011</td>
</tr>
<tr>
<td>SO₄²⁻</td>
<td>0.041</td>
<td>0.011</td>
</tr>
<tr>
<td>I⁻</td>
<td>0.047</td>
<td>0.008</td>
</tr>
<tr>
<td>Br⁻</td>
<td>0.040</td>
<td>0.005</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>0.077</td>
<td>0.018</td>
</tr>
<tr>
<td>NO₃⁻</td>
<td>0.039</td>
<td>0.006</td>
</tr>
<tr>
<td>PO₄³⁻</td>
<td>0.040</td>
<td>0.010</td>
</tr>
<tr>
<td>F⁻</td>
<td>0.58</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Table 6-5. Average speed of the tracer particles pumped by a fim of polymer 2-6 with different molecular weights in the presence of 9 µM β-D-glucuronidase (Figure 3-9)

<table>
<thead>
<tr>
<th>Polymer $M_n$ (kDa)</th>
<th>Average Speed (µm/s)</th>
<th>Standard Deviation (µm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>1.71</td>
<td>0.13</td>
</tr>
<tr>
<td>33</td>
<td>1.08</td>
<td>0.25</td>
</tr>
<tr>
<td>45</td>
<td>0.99</td>
<td>0.09</td>
</tr>
<tr>
<td>53</td>
<td>0.69</td>
<td>0.18</td>
</tr>
<tr>
<td>65</td>
<td>0.58</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Table 6-6. Average speed of the tracer particles pumped by a fim of polymer 2-19 with different molecular weights in the presence of 9 µM β-D-glucuronidase (Figure 3-9)

<table>
<thead>
<tr>
<th>Polymer $M_n$ (kDa)</th>
<th>Average Speed (µm/s)</th>
<th>Standard Deviation (µm/s)</th>
</tr>
</thead>
</table>


Table 6-7. Average speed of the tracer particles pumped by a fim of polymer 3-3 with different molecular weights in the presence of 9 µM β-D-glucuronidase (Figure 3-9)

<table>
<thead>
<tr>
<th>Polymer Mₐ (kDa)</th>
<th>Average Speed (µm/s)</th>
<th>Standard Deviation (µm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1.14</td>
<td>0.09</td>
</tr>
<tr>
<td>32</td>
<td>0.58</td>
<td>0.17</td>
</tr>
<tr>
<td>43</td>
<td>0.79</td>
<td>0.16</td>
</tr>
<tr>
<td>49</td>
<td>0.50</td>
<td>0.10</td>
</tr>
<tr>
<td>53</td>
<td>0.53</td>
<td>0.07</td>
</tr>
</tbody>
</table>

B. Chapter 4: Data and Charts

Table 6-8. Shell wall thicknesses for microcapsules fabricated using a microfluidic flow focusing device with flow rates of 600:700:8000 µL/h and a 10 wt% of polymer 2-19 (Mₐ = 47 kDa).

<table>
<thead>
<tr>
<th>Capsule</th>
<th>Shell Wall Thickness (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1650</td>
</tr>
<tr>
<td>2</td>
<td>1730</td>
</tr>
<tr>
<td>3</td>
<td>1735</td>
</tr>
<tr>
<td>4</td>
<td>1755</td>
</tr>
<tr>
<td>5</td>
<td>1770</td>
</tr>
<tr>
<td>6</td>
<td>1785</td>
</tr>
<tr>
<td>7</td>
<td>1790</td>
</tr>
<tr>
<td>8</td>
<td>1800</td>
</tr>
<tr>
<td>9</td>
<td>1805</td>
</tr>
<tr>
<td>10</td>
<td>1830</td>
</tr>
<tr>
<td>11</td>
<td>1865</td>
</tr>
<tr>
<td>12</td>
<td>1905</td>
</tr>
<tr>
<td>13</td>
<td>1915</td>
</tr>
</tbody>
</table>
Table 6-9. % FITC-Dex released over 96 h from microcapsules fabricated from polymer 2-19 ($M_n = 47 \text{kDa}$) with an average shell wall thickness of 1805 ± 79 nm (Figure 4-12). The data at each time point represent the average of 100 measurements.

<table>
<thead>
<tr>
<th>conditions</th>
<th>50 mm TBAF</th>
<th>50 mm TBACl</th>
<th>50 mm NaCl</th>
<th>control</th>
</tr>
</thead>
<tbody>
<tr>
<td>time (h)</td>
<td>% release</td>
<td>standard deviation</td>
<td>% release</td>
<td>standard deviation</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>30</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>36</td>
<td>16</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>42</td>
<td>22</td>
<td>6</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>48</td>
<td>31</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>54</td>
<td>35</td>
<td>5</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>60</td>
<td>51</td>
<td>6</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>66</td>
<td>73</td>
<td>4</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>72</td>
<td>82</td>
<td>0</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>78</td>
<td>93</td>
<td>0</td>
<td>7.5</td>
<td>2</td>
</tr>
<tr>
<td>84</td>
<td>100</td>
<td>0</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>90</td>
<td>100</td>
<td>0</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>96</td>
<td>100</td>
<td>0</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 6-10. Shell wall thicknesses for microcapsules fabricated using a microfluidic flow focusing device with flow rates of 600:100:8000 μL/h and a 3 wt% of polymer 2-19 ($M_n = 47 \text{kDa}$).

<table>
<thead>
<tr>
<th>Capsule</th>
<th>Shell Wall Thickness (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>110</td>
</tr>
</tbody>
</table>
Table 6-11. Shell wall thicknesses for microcapsules fabricated using a microfluidic flow focusing device with flow rates of 600:450:8000 µL/h and a 6 wt% of polymer 2-19 ($M_n = 47$ kDa).

<table>
<thead>
<tr>
<th>Capsule</th>
<th>Shell Wall Thickness (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>590</td>
</tr>
<tr>
<td>2</td>
<td>610</td>
</tr>
<tr>
<td>3</td>
<td>645</td>
</tr>
<tr>
<td>4</td>
<td>665</td>
</tr>
<tr>
<td>5</td>
<td>690</td>
</tr>
<tr>
<td>6</td>
<td>700</td>
</tr>
<tr>
<td>Average</td>
<td>650</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>44</td>
</tr>
</tbody>
</table>

Table 6-12. Shell wall thicknesses for microcapsules fabricated using a microfluidic flow focusing device with flow rates of 600:700:8000 µL/h and a 6 wt% of polymer 2-19 ($M_n = 47$ kDa).

<table>
<thead>
<tr>
<th>Capsule</th>
<th>Shell Wall Thickness (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>890</td>
</tr>
<tr>
<td>2</td>
<td>900</td>
</tr>
<tr>
<td>3</td>
<td>930</td>
</tr>
<tr>
<td>4</td>
<td>1060</td>
</tr>
<tr>
<td>5</td>
<td>1100</td>
</tr>
<tr>
<td>6</td>
<td>1120</td>
</tr>
<tr>
<td>Average</td>
<td>1000</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>105</td>
</tr>
</tbody>
</table>
Table 6-13. Shell wall thicknesses for microcapsules fabricated using a microfluidic flow focusing device with flow rates of 600:700:8000 µL/h and a 10 wt% of polymer 2-19 (Mₙ = 47 kDa).

<table>
<thead>
<tr>
<th>Capsule</th>
<th>Shell Wall Thickness (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1550</td>
</tr>
<tr>
<td>2</td>
<td>1680</td>
</tr>
<tr>
<td>3</td>
<td>1800</td>
</tr>
<tr>
<td>4</td>
<td>1840</td>
</tr>
<tr>
<td>5</td>
<td>1930</td>
</tr>
<tr>
<td>6</td>
<td>2000</td>
</tr>
<tr>
<td>Average</td>
<td>1000</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>165</td>
</tr>
</tbody>
</table>

Table 6-14. Effect of shell wall thickness of the rate of release from capsules prepared from polymer 2-19 (Mₙ = 47 kDa) in response to 50 mM fluoride (Figure 4-14). The data at each time point represent the average of 100 measurements.

<table>
<thead>
<tr>
<th>shell wall thickness (nm)</th>
<th>100 ± 19</th>
<th>650 ± 44</th>
<th>1000 ± 105</th>
<th>1800 ± 165</th>
</tr>
</thead>
<tbody>
<tr>
<td>time (h)</td>
<td>% release</td>
<td>standard deviation</td>
<td>% release</td>
<td>standard deviation</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>29</td>
<td>2</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>18</td>
<td>48</td>
<td>5</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>24</td>
<td>76</td>
<td>4</td>
<td>36</td>
<td>8</td>
</tr>
<tr>
<td>30</td>
<td>87</td>
<td>6</td>
<td>49</td>
<td>2</td>
</tr>
<tr>
<td>36</td>
<td>98</td>
<td>5</td>
<td>58</td>
<td>9</td>
</tr>
<tr>
<td>42</td>
<td>99</td>
<td>6</td>
<td>69</td>
<td>5</td>
</tr>
<tr>
<td>48</td>
<td>99</td>
<td>4</td>
<td>82</td>
<td>4</td>
</tr>
<tr>
<td>54</td>
<td>100</td>
<td>0</td>
<td>88</td>
<td>2</td>
</tr>
<tr>
<td>60</td>
<td>100</td>
<td>0</td>
<td>98</td>
<td>2</td>
</tr>
<tr>
<td>66</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 6-15. Effect of polymer molecular weight on the rate of release from capsules in response to 50 mM fluoride (Figure 4-15). The data at each time point represent the average of 100 measurements.

<table>
<thead>
<tr>
<th>polymer Mₙ (kDa)</th>
<th>32</th>
<th>37</th>
<th>54</th>
<th>61</th>
</tr>
</thead>
<tbody>
<tr>
<td>time (h)</td>
<td>% release</td>
<td>standard deviation</td>
<td>% release</td>
<td>standard deviation</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>2</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>18</td>
<td>12</td>
<td>4</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>24</td>
<td>27</td>
<td>4</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>30</td>
<td>39</td>
<td>3</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>36</td>
<td>48</td>
<td>6</td>
<td>42</td>
<td>3</td>
</tr>
<tr>
<td>42</td>
<td>65</td>
<td>2</td>
<td>53</td>
<td>2</td>
</tr>
<tr>
<td>48</td>
<td>77</td>
<td>2</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>54</td>
<td>86</td>
<td>5</td>
<td>75</td>
<td>8</td>
</tr>
<tr>
<td>60</td>
<td>93</td>
<td>3</td>
<td>83</td>
<td>5</td>
</tr>
<tr>
<td>66</td>
<td>98</td>
<td>2</td>
<td>91</td>
<td>4</td>
</tr>
<tr>
<td>72</td>
<td>100</td>
<td>0</td>
<td>95</td>
<td>4</td>
</tr>
<tr>
<td>78</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>84</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>90</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>96</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 6-16. Effect of shell wall thickness on the time to 90% release from capsules prepared from polymer 2-19 ($M_n = 47$ kDa) in response to 50 mM fluoride (Figure 4-16). The standard deviation represent values determined from the line of best fit generated from samples sets (10 values) taken from each time point in Table 6-14.

<table>
<thead>
<tr>
<th>Shell Wall Thickness (nm)</th>
<th>Time to 90% release (h)</th>
<th>Standard deviation (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 ± 19</td>
<td>30</td>
<td>1.0</td>
</tr>
<tr>
<td>650 ± 44</td>
<td>48</td>
<td>1.6</td>
</tr>
<tr>
<td>1000 ± 105</td>
<td>57</td>
<td>2.6</td>
</tr>
<tr>
<td>1800 ± 165</td>
<td>75</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Table 6-17. Effect of polymer molecular weight on the time to 90% release from capsules in response to 50 mM fluoride (Figure 4-16). The standard deviation represent values determined from the line of best fit generated from samples sets (10 values) taken from each time point in Tables 6-9 and 6-15.

<table>
<thead>
<tr>
<th>Polymer $M_n$ (kDa)</th>
<th>Time to 90% release (h)</th>
<th>Standard deviation (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>56</td>
<td>1.3</td>
</tr>
<tr>
<td>37</td>
<td>64</td>
<td>1.7</td>
</tr>
<tr>
<td>47</td>
<td>78</td>
<td>0.8</td>
</tr>
<tr>
<td>54</td>
<td>80</td>
<td>0.8</td>
</tr>
<tr>
<td>61</td>
<td>88</td>
<td>2.0</td>
</tr>
</tbody>
</table>

C. Chapter 5: Data and Charts

Table 6-18. Percent degradation of 7.0 mM solutions of polymers 2-8, 2-20, 5-14, and 5-15 after 6 days (Figure 5-6). The solutions were protected from light.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Integration of Monomer</th>
<th>Integration of Standard</th>
<th>% Degradation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-14</td>
<td>2</td>
<td>2.3</td>
<td>18</td>
</tr>
<tr>
<td>5-14</td>
<td>2</td>
<td>54.46</td>
<td>1</td>
</tr>
<tr>
<td>5-14</td>
<td>2</td>
<td>403.1</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 6-19. Percent degradation of 5.2 mM solutions of polymers 2-8, 2-20, 5-20, 5-14, and 5-15 in the presence of 100 equiv of benzoic acid after 6 days (Figure 5-6). The solutions were protected from light.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Integration of Monomer</th>
<th>Integration of Standard</th>
<th>% Degradation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-8</td>
<td>2</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>2-8</td>
<td>2</td>
<td>0.65</td>
<td>35</td>
</tr>
<tr>
<td>2-8</td>
<td>2</td>
<td>0.73</td>
<td>31</td>
</tr>
<tr>
<td>2-20</td>
<td>2</td>
<td>0.6</td>
<td>31</td>
</tr>
<tr>
<td>5-14</td>
<td>2</td>
<td>23.66</td>
<td>1</td>
</tr>
<tr>
<td>5-15</td>
<td>2</td>
<td>37.14</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 6-20. Depolymerization of polymer 5-14 ($M_n = 30$ kDa) in response to increasing concentrations of Pd(0) (Figure 5-11).

<table>
<thead>
<tr>
<th>[Pd(0)] (mM)</th>
<th>Integration of Monomer</th>
<th>Integration of Standard</th>
<th>% Depolymerization</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>581.43</td>
<td>1</td>
</tr>
<tr>
<td>0.16</td>
<td>2</td>
<td>6.62</td>
<td>45</td>
</tr>
<tr>
<td>0.41</td>
<td>2</td>
<td>4.00</td>
<td>75</td>
</tr>
<tr>
<td>0.82</td>
<td>2</td>
<td>3.33</td>
<td>90</td>
</tr>
<tr>
<td>1.2</td>
<td>2</td>
<td>3.18</td>
<td>94</td>
</tr>
<tr>
<td>1.6</td>
<td>2</td>
<td>3.21</td>
<td>93</td>
</tr>
</tbody>
</table>

Table 6-21. Depolymerization of polymer 5-15 ($M_n = 20$ kDa) in response to increasing concentrations of Pd(0) (Figure 5-11).

<table>
<thead>
<tr>
<th>[Pd(0)] (mM)</th>
<th>Integration of Monomer</th>
<th>Integration of Standard</th>
<th>% Depolymerization</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>0.16</td>
<td>2</td>
<td>470.63</td>
<td>1</td>
</tr>
<tr>
<td>0.41</td>
<td>2</td>
<td>161.91</td>
<td>3</td>
</tr>
<tr>
<td>0.82</td>
<td>2</td>
<td>277.62</td>
<td>2</td>
</tr>
<tr>
<td>1.2</td>
<td>2</td>
<td>409.59</td>
<td>1</td>
</tr>
<tr>
<td>1.6</td>
<td>2</td>
<td>148.4</td>
<td>3</td>
</tr>
</tbody>
</table>
Anthony Michael DiLauro was born in 1988 in Warwick, RI. He graduated from Warwick Veterans Memorial High School in 2006. He earned his B.A. with distinction in Chemistry with a Mathematics minor from Boston University in 2010. After graduation, he pursued his Ph.D. in Chemistry at The Pennsylvania State University, joining the laboratory of Professor Scott Phillips. His research during his time at Penn State has focused on the design and synthesis of depolymerizable polymers. During his graduate career, he received the Materials Research Society Silver Graduate Student Award, the Rustum and Della Roy Award for Innovation in Materials Research, and the Braucher Award for Excellence in Graduate Research. He also was chosen to present at the ACS Division of Organic Chemistry Graduate Research Symposium and the ACS Excellence in Graduate Polymer Research Symposium. In July 2015, he will begin a postdoctoral research position in the laboratory of Professor Stephen Craig at Duke University.