NEW APPROACHES FOR THE SYNTHESIS OF BIODEGRADABLE POLYMERS

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INVESTIGATIONS INTO THE CATALYTIC SYNTHESES OF BIODEGRADABLE POLYMERS

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The development of the field of polymer science and the rise of plastics as ubiquitous materials in almost every aspect of our daily lives is one of the defining scientific achievements of the 20th Century. Ironically, concerns with disposal of the ever-increasing amounts of plastics as well as uncertainty surrounding the future of petroleum-based chemical feedstocks have led 21st Century scientists to investigate alternatives to these very same materials. Biodegradable polymers represent a way to continue the use of plastics in many applications without concerns about long-term accumulation. Additionally, biodegradable polymers offer many properties not found in traditional polymers, most notably their compatibility with biological systems, allowing them to act as ideal materials for biomedical research. This work focuses on new and efficient syntheses of biodegradable polymers, particularly through the use of catalysis.

First, the synthesis of biodegradable cyclic polyketals was investigated in the hopes of generating high molecular weight materials. Polyacetals and polyketals are interesting alternatives to more established polyester-based biodegradable polymers in that they do not degrade to acidic species upon hydrolysis. Additionally, because polyketals are stable at neutral pH, but degrade quickly under mild acidic conditions, they are able to act as pH-sensitive materials. However, their syntheses are typically complicated and result in low molecular weight polymers, limiting their utility. Through the Lewis acid catalyzed intramolecular cyclization of epoxide-ketones, strained bicyclic ketals were generated that act as monomers for cationic

polymerization. This methodology allowed the synthesis of polyketals with exceptionally high molecular weights.

In addition to the study of ketal-based polymers, biodegradable polyesters were investigated. The synthesis of a new class of carboxylic acid-containing polyesters was developed via the self-condensation ring-opening polymerization of anhydride-alcohols. These anhydride-alcohol monomers may be produced from catalytic carbonylation of epoxides, allowing a number of backbone functionalities to be generated for the tuning of properties. Polyhydroxyalkanoates, a well known class of biodegradable polyesters, were investigated through both the creation of new carbonylation catalysts for efficient synthesis of their β-lactone monomers as well as the creation of new catalysts for controlled β-lactone ring-opening polymerizations.

Finally, unrelated to polymerization, the use of carbonylation for the catalytic synthesis of interesting materials.

BIOGRAPHICAL SKETCH

Bryan Thomas Whiting was born on December 9th, 1983 to Christopher and Ellen Whiting. For the first eighteen years of his life he had the distinct pleasure of living in the village of Doylestown, Ohio (no, not Pennsylvania). He had the opportunity to make friends in Hazel Harvey Elementary School and share the same classes until high school graduation. He participated in music and tennis, spent time with friends, and made a whole lot of Arby's sandwiches for little pay.

Bittersweet as it was, after graduation Bryan knew it was time to leave the nurturing nest of Doylestown and explore the world. He set out on a life-affirming voyage that would eventually land him at the College of Wooster, an almost unfathomable 20 miles away! After one semester, he was undecided whether he should major in chemistry or English, enjoying them both equally. Ultimately he made the decision based on which one had the higher probability of securing a job he would enjoy (not that serving coffee isn't rewarding in its own special ways). Luckily for him, the chemistry faculty at Wooster ensured that this was the right decision, and he went on to take every chemistry course offered in the catalog (while still earning a minor in English). After freshman year, he spent the summer working at Wooster on a consulting program for the Mathematic department (wait, math?). His second summer was spent in the Wooster Physics REU (it was at least a chemistry project this time), where he learned the joys of research, but there was something missing… His junior year he attended a seminar from Geoffrey Coates from Cornell University that blew him away. He asked Geoff after the talk if there was any chance of working for him during a summer program to which Geoff said, "Probably not, I don't think I'm going to be around… but go ahead and apply anyway, you never know."

After his junior year, he would spend the summer at an REU program in what would become the most influential 8 weeks of his life. First, the REU itself involved working in the laboratory of Geoffrey Coates at Cornell University investigating new syntheses of monomers for biodegradable polymers. Second, and more importantly, he was housed in the hot, overcrowded Clara Dickson Residence Hall, which happened to also be the summer residence of the beautiful (if somewhat intimidating) T. Theresa Hsu. After a long day of porphyrin synthesis, the dorm's lack of air conditioning was a blessing in disguise as it gave Bryan an excuse to ask Theresa to go on long walks around the fabulous Cornell campus. Their relationship officially began while stranded for six hours in a rest area off of the Pennsylvania freeway (but isn't that how all the great romances begin?) and decided that even the end of the REU program and Bryan's return to Ohio weren't enough reasons to give up such a good thing.

Bryan's senior year he drove to Ithaca to visit Theresa, finished his senior IS, played a whole lot of table tennis, and finally graduated from the College of Wooster *Summa Cum Laude*. He then made the decision to return to Ithaca, and officially joined the lab of Geoffrey Coates as a graduate student in the fall of 2006 along with Henry Kostalik and Peter Widger. He rejoined the carbonylation subgroup, moving back into S. T. Olin 572 on the fishbowl bench, where he would remain for his entire graduate career (best view in the lab!).

After a year together, Theresa decided to begin her own graduate career at Stanford University in chemical engineering. Despite the odds being stacked against them, they knew they would make it work. After a year of alternating to visit each other and talking on the phone every night, Bryan proposed to Theresa in the Cascadilla gorge in April 2008 (luckily he didn't lose the ring down the falls). After

two years, three engagement photo sessions, a celebration in Taiwan, and a boatload of planning they married in Los Gatos California on September 5th, 2010.

In the lab, Bryan had the chance to work on some awesome projects, from catalysis to polymer synthesis to catalytic polymer synthesis! For the first time in his life, he had the chance to explore every crazy idea he came up with (and learned to make them a little less crazy over time). Additionally, while working as a teaching assistant and subsequently as a tutor for organic chemistry he learned that he really loved teaching. He accepted a one-year visiting assistant professor position at Trinity University in San Antonio, TX where he is excited to begin his teaching career in full (and even more excited at the chance of living in the same state as Theresa again!).

"New knowledge is the most valuable commodity on earth. The more truth we have to work with, the richer we become."

-Kurt Vonnegut

ACKNOWLEDGMENTS

Despite all of the work I have put in to earning my PhD, there is no doubt it would not have been possible without the love and support of some amazing people.

First, I want to thank my parents for everything they've taught me and in every way that they've supported and encouraged me for the last 28 years. My father taught me the importance working hard for what I want as well as to think for myself and to not take everything blindly at face value. My mother has taught me (as much as I may have resisted it) to take a step back and learn how to know myself as well as I can learn about any other subject. I know that they are always behind me and always there to help, listen, encourage, or give me a kick in the behind in the right direction.

There have been many people at Cornell who have been instrumental to my success. First and foremost is my research advisor, Professor Geoff Coates. Geoff is not only an amazing scientist, but a great person as well. He has served as a role model for me as a researcher (to constantly be searching for new ideas, even in places you wouldn't expect them) as well as outside of the lab (being a good researcher doesn't mean being a bad father or husband). As an advisor he has let me explore my own research interests while providing guidance when I needed it. It is obvious that he really cares about all of his students and working with him for the past five years has been a pleasure.

I am also grateful to Professors Peter Wolczanski and David Collum for taking the time to serve on my committee. Pete's inorganic and organometallic courses were the most memorable and difficult (and fun in hindsight) chemistry classes I've ever taken. Although I didn't get a chance to take a course from Dave, he is incredibly insightful (and brutally honest) and has offered me excellent advice when I needed it.

Graduate school is always challenging, but thanks to my labmates in the Coates group, it was also always a joy to come into work. I'd like to particularly thank the three with whom I've had the pleasure to live with at home in addition to lab: Peter Widger was our resident tech head and I know he'll do great as he starts his career at E-Ink. Michael "the franchise" Mulzer is best chemist I've ever had a chance to work with, an all-around great guy, and he can play a mean round of Goldeneye. Henry Kostalik aka "blue eyes" aka "drop ten" aka "devil's advocate" put up with me as a roommate for three years, was a groomsman in my wedding, and is one of the best guys I've ever known. He knows more about football than anyone probably should and more about alkaline anion exchange membranes than pretty much anyone on earth. I'm looking forward to attending he and Mandy's wedding next week.

In the 572 lab I've had the opportunity to work in close quarters with amazing folks as well. John Rowley didn't teach me everything I know about chemistry, but he put me on the right path. John Kramer and David Laitar made labwork my first year in grad school fun and served as two great role models. From my first summer as an undergraduate, Chris Byrne and Tamara Church showed me that you can be a chemist *and* a genuinely fun person at the same time. Joshua Fishman was an excellent undergraduate who learned faster than I could teach. I know he'll have a great career at Wisconsin and beyond. Erin Dunn and I were the only members of 572 for some time even if she can sometimes be a bad influence on me outside of lab. Chad Ellis may be the only one to never work on carbonylation, but I won't hold it against him, as he's one of the most thoughtful and intelligent people I've ever met. Finally, Kevin Noonan may have quit the carbonylation group, and I probably will hold it against him. Kidding aside, Kevin was one of the best things that happened to the Coates lab and I know he's going to be the best advisor Carnegie Mellon has ever seen.

Although I never had the chance to share a lab with them, Pasquale Iacono and Taz 'Syud' Ahmed became two of my best friends in the past 4 years and with Henry, Kevin, and whoever else came along for the ride we've had some of the best times I think it's possible to have in Ithaca. Taz is basically impossible to truly sum up any other way than 'awesome', so I'll leave it at that. Seriously, if you've never met him, I'm unable to do him proper justice. Pasquale has been, along with Henry, my closest friend during graduate school. He plays some mean football, makes a mean Cattleman's pizza, sings some mean RHCP, and polymerizes him some mean polyethylene. I'm going to miss stopping in to 570 every morning (but he better keep sending me videos from his google reader). Unlike Henry, I hope he and Heather stay in NYC forever so it will give Theresa and I an excuse to visit as often as possible.

I'd also like to thank Angie DiCiccio for both brightening up everyone's day, whether they like it or not and additionally, for helping each other through the joys of the MTA program. Finally I'd like to thank Brian Long, Rachna, 'C', Giang, Greg, Jeff, Amelia, Joe, Ryan, Jeung, Rafael, Giang, Dan, Renee, Nick, Hisashi and anyone else for great conversations and great memories.

Finally, and most importantly, I'd like to thank my wife Theresa for being the smartest, prettiest, and sweetest person I've ever known. It hasn't always been easy, but having her by my side (even in spirit) for the past five years has given me the strength to make it through every day. Even though we're already married, I can't wait to start the rest of our lives together.

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CHAPTER ONE

Synthesis and Applications of Polyacetals and Polyketals: an Emerging Class of Biodegradable Polymers

1.1 Introduction:

Polyacetals and polyketals are polymers linked through the backbone with repeating acetal or ketal units (Figure 1.1). Nature takes advantage of these linkages in polymeric carbohydrates, which are the basis of a large variety of structural, functional, and energy-storing biomaterials. Because of the similarities to these naturally occurring polymers, synthetic polyacetals and polyketals are biodegradable and often biocompatible. A crucial advantage of polyacetals and polyketals compared to other biodegradable polymers such as polyesters is that their backbone linkages are relatively stable at neutral pH, but hydrolyze quickly under acidic conditions. Therefore these polymers can act as pH-sensitive materials. Their biodegradability makes polyacetals and polyketals interesting targets for two important applications: biomedical materials and non-accumulating commodity plastics.

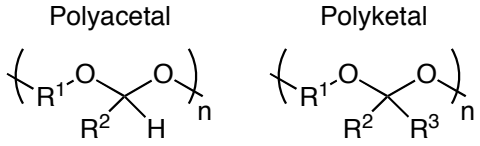


Figure 1.1 Generic structure of polyacetals and polyketals

Polyoxymethylene (POM) and related polyacetals based on the formaldehyde-acetal linkage are versatile materials with many applications.[1] However, because of their slow degradation and toxic formaldehyde release upon hydrolysis, they are not suitable materials for the applications covered within this review.

1.2 Biomaterials

The most important applications for polyacetals and polyketals are their use as biomedical materials. In the last thirty years the fields of controlled drug delivery and tissue engineering have moved to the forefront of biochemical and medical research.[2] Biodegradable polymers are essential proponents in the growth of both of these fields. Polymers can act as a matrix for the encapsulation of active pharmaceuticals, protecting them from the harsh conditions in the body, releasing them slowly at a controlled rate, or releasing them at the targeted site after an appropriate stimulus.[3,4] These properties can greatly enhance the efficacy of many therapies, and make new treatments viable when they had been previously impossible. Biodegradable polymers can also be used for tissue engineering, where the polymer first acts as a structural material but is eventually degraded and replaced by the body as it rebuilds its own systems.[5,6] This requires materials that are both mechanically sound as well as those that are biocompatible.

Although a number of polymers have been investigated for these applications, none have had as much success as the polyester poly(lactic acid) (PLA).[7] It is biorenewable, where it can be derived from corn, as well as biocompatible and biodegradable, where it is enzymatically hydrolyzed to lactic acid: a naturally occurring endogenous substance. Other polyesters have followed the success of PLA, and have also enjoyed significant investigation in these fields as well, including poly(glycolic acid), poly(3-hydroxybutyrate), poly(δ-valerolactone), poly(ε-caprolactone), poly(propylene succinate), and poly(propylene fumarate).[8]

Despite the utility of polyesters in a huge number of applications, they have drawbacks that have caused some researchers to investigate alternatives. Prime among the concerns with polyesters is their effect on local pH as they degrade into carboxylic acid species, particularly as this problem pertains to their use as biomaterials. *In vivo* studies have shown that polyester degradation can significantly lower local pH.[9] Although this build-up of acidic species is often not problematic, there are many sensitive targets, such as organ tissues, that are not able to tolerate this stress. Additionally, the acidic release has the potential to damage the pharmaceutical therapeutic agent that is being delivered. Polyacetals and polyketals on the other hand, do not release acidic products as they hydrolyze, instead generating only non-acidic diols and aldehydes/ketones (Figure 1.2).

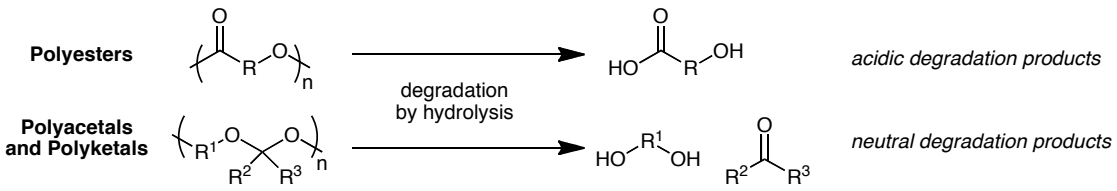


Figure 1.2 Degradation of polyesters and polyacetals/polyketals

1.2.1 Drug delivery

In addition to being biodegradable and their non-acidic degradation products, one of the most useful features of polyacetal and polyketal-based drug delivery systems are their quick degradation when exposed to acidic pH. This reactivity is advantageous because blood pH is 7.4, at which polyacetals and polyketals are relatively stable. However, many possible drug delivery targets such as cancerous

tissue or endogenous lysosomes have acidic environments, enabling targeted degradation and aiding release specificity.

1.2.1.1 Rigid cyclic diol-dimethyl ketal polymers: PPADK/PCADK

Exemplifying the advantages of polyacetals and polyketals for drug delivery applications are the polyketal systems developed by the Murthy group, poly(1,4-phenyleneacetone dimethylene ketal) (PPADK)[10] and poly(cyclohexane-1,4-diyl acetone dimethylene ketal) (PCADK).[11] PPADK and PCADK are synthesized by step-growth condensation of their parent diol and 2,2-dimethoxypropane (Figure 1.3). This facile method allows for the fast synthesis of polymers. Due to the nature of step-growth condensations,[12] they are somewhat limited in molecular weight, with PPADK having a maximum reported M_w = 11000 g/mol and PCADK having maximum M_w = 6000 g/mol. They are solids, which allows them to be processed into appropriate particles by emulsion-evaporation techniques. Both polyketals degrade into non-acidic diols and acetone. PPADK microparticles were demonstrated to be capable of encapsulating a model pharmaceutical, however, worries about potential toxicity of the benzenedimethanol degradation products limited its studies. However, PCADK is particularly interesting because its two products are known to be benign: acetone is an endogenous metabolite and 1,4-cyclohexanedimethanol is a Food and Drug Administration (FDA) approved indirect food additive (Figure 1.4).

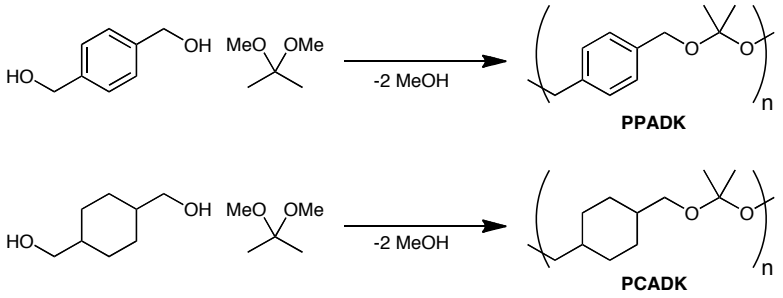


Figure 1.3 Synthesis of PPADK and PCADK by polycondensation

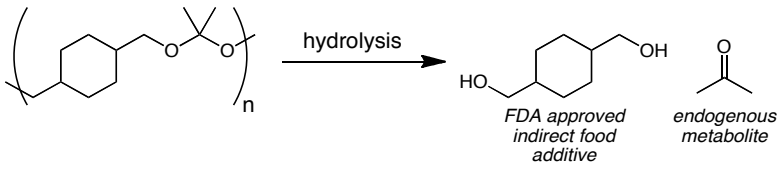


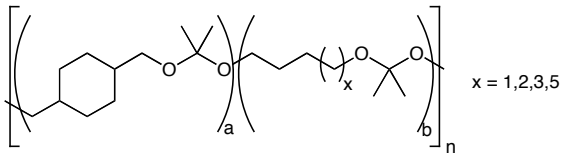
Figure 1.4 PCADK degrades into benign small molecules acetone and 1,4-cyclohexanedimethanol upon hydrolysis

Because of its non-toxic and non-acidic degradation products, PCADK was investigated as a drug delivery vehicle for a p38 inhibitor to control inflammatory response and reactive oxygen species in heart tissue damaged from myocardial infarction.[13] In double blind studies with rat models, the PCADK-(p38 inhibitor) complex was able to produce p38 inhibition for up to seven days. As a result, superoxide levels (a test of reactive oxygen species) were reduced, whereas injection of the free inhibitor or only polyketal showed no effects. The study demonstrated the ability of PCADK to effect significantly improved cardiac function as a result of the drug-PCADK conjugate therapy compared to controls.

To increase the scope of PCADK particles, they Murthy group synthesized a series of copolymers with aliphatic diols.[14] Although PCADK had already been successful for sensitive drug delivery applications, its hydrolytic degradation was too

slow for use in the treatment of acute inflammatory diseases. However, by forming copolymers with aliphatic diols it was possible to make a series of polyketals with tunable degradation rates (Table 1.1).

Table 1.1 Tunable degradation of polyketals by aliphatic diol incorporation



Polymer composition				*Polymer properties*			
entry	a	b	x	M_n (g/mol)	M_w/M_n	$t_{1/2}$ at pH 4.5	$t_{1/2}$ at pH 7.4 (estimated)
1	0.9675	0.0325	1	2637	1.55	1.0 day	54 days
2	0.8670	0.1330	2	2596	1.43	1.8 days	39 days
3	0.8532	0.1468	3	2122	1.54	4.4 days	53 days
4	0.8731	0.1269	5	2181	1.79	18.6 days	360 days

In another study, the PCADK-pentanediol copolymer was investigated to induce $CD8^+$ cytotoxic T-cell response through the dual delivery of protein-based vaccines with toll-like receptor agonists.[15] Microparticles were loaded with protein ovalbumin as the model protein vaccine and poly(inosidic acid)-poly(cytidylic acid), a synthetic dsRNA analog as an immunostimulant. The polyketal system was chosen because of the acid sensitivity of the nucleobases in poly(inosidic acid)-poly(cytidylic acid) as well as the fast selective polymer degradation upon encapsulation by lysosomes. The dual-loaded particles successfully induced a T-cell response at very low doses.

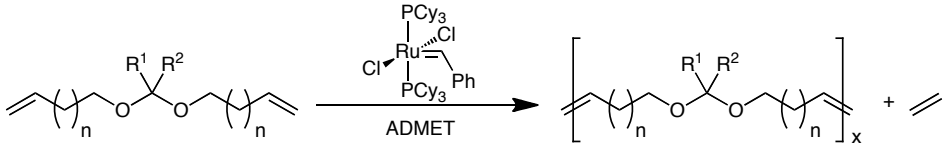
1.2.1.2 Polyketals from ADMET for protein delivery

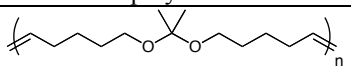
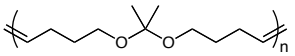
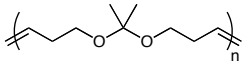
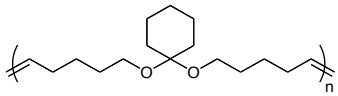
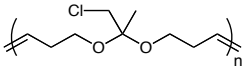
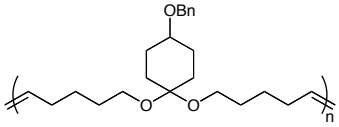
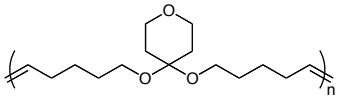
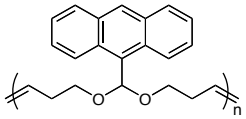
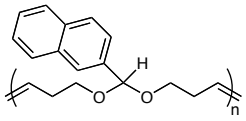
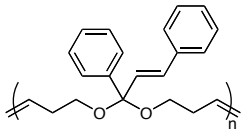
Although polycondensations and alcohol addition to vinyl ethers allows fast access to polyketals, they each have drawbacks. Both have limited functional group tolerance, allowing a limited number of linkers or side-chains possible to be incorporated into the polymers. In the case of polycondensations, high molecular weight polymer is often difficult to achieve because it is necessary to drive the reaction to very high conversions, which in turn requires the removal of the small molecule byproducts.[12]

A novel approach to moving away from these limited synthetic methods is through pre-formation of the ketal or acetal linkage in a monomer, which may then be polymerized by more efficient means. One polymerization methodology that projects favorably in this regard is acyclic diene metathesis polymerization (ADMET) because of its tolerance for a wide range of functional groups. The synthesis of a polyacetal by ADMET was first reported in 1998,[16] but it was not investigated again until recently.

Expanding their research beyond PCADK and PPADK, the Murthy group synthesized a library of polyketals and polyacetals synthesized by the ADMET of acetal- and ketal-functionalized dienes (Table 1.2).[17] The majority of the new polymers were liquids at room temperature, however, an anthracene-based polyacetal (entry 9) was a solid, and was further investigated as a drug-delivery vehicle for protein catalase.

Table 1.2 Polyketals and polyacetals synthesized by ADMET of ketal- and acetal-functionalized dienes



entry	polymer	M_n (g/mol)	M_w/M_n	physical state
1		8275	1.13	liquid
2		8434	2.23	liquid
3		9755	2.04	liquid
4		11298	1.15	liquid
5		6490	2.14	liquid
6		12530	1.18	liquid
7		4875	2.16	liquid
8		4880	1.40	solid
9		7660	2.12	liquid
10		6780	1.45	solid

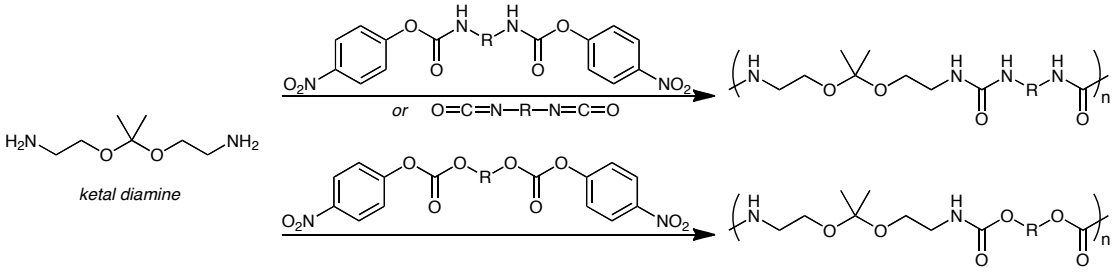
Using emulsion techniques, a polyacetal microparticle was loaded with protein catalase, an enzyme that is able to detoxify hydrogen peroxide and has shown great promise in treating inflammatory disease by targeting macrophages.[17] The polyacetal-catalase conjugates showed significant reduction of H_2O_2 production in macrophages

versus the free catalase or controls. Further tests showed that the polyacetals had low toxicity at the concentrations used in the study.

1.2.1.3 Alternating polyketal-ureas and polyketal-urethanes

Continuing efforts to develop more efficient methods of polyketal synthesis, the Fréchet group investigated new classes of biodegradable polymers based on the polymerization of ketal-functionalized diamines with carbonates, carbamates, or isocyanates to afford either alternating polyketal-ureas or polyketal-urethanes.[18] The formation of ureas or urethanes is significantly more facile than that of acyclic ketals, greatly facilitating the polymerization and enabling the synthesis of relatively high molecular weight polymers. Using this protocol, they synthesized a library of ketal-functionalized polymers with varying hydrophobicities (Table 1.3) in the hopes of tuning degradation rate.

Table 1.3 Reaction of ketal-diamines to form polyurethanes and polyureas



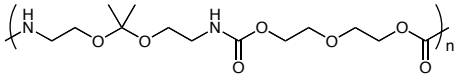
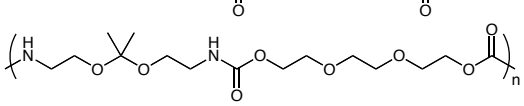
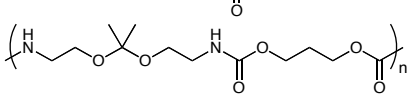
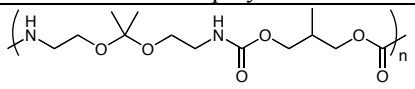
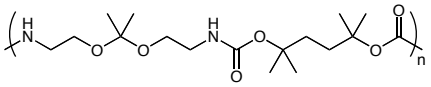
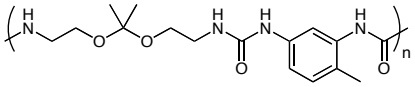
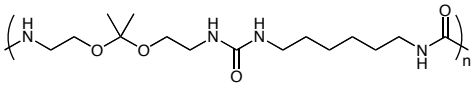
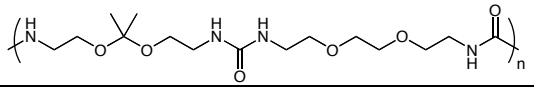
entry	polymer	M_n (g/mol)	M_n/M_w
1		22000	1.8
2		20000	1.4
3		15000	1.6

Table 1.3 Reaction of ketal-diamines to form polyurethanes and polyureas (cont.)

entry	polymer	M_n (g/mol)	M_n/M_w
4		33000	1.3
5		11000	1.7
6		42000	2.0
7		not soluble	-
8		17000	2.4

Certain polyketal-urethanes (entries 3-5) were successfully formed into particles, and their degradation rates were tested. Consistent with Murthy's findings with the PCADK copolymers, ketal degradation was directly related to the hydrophobicity of the chain, where the most hydrophobic ketals have the slowest degradation rates. The particles were tested for cytotoxicity and were found to have low toxicity up to 1 mg/mL concentration. Unfortunately, they were unable to form microparticles from the polyureas (entries 6-8), which were too insoluble in dichloromethane, as well as the PEG-functionalized polyurethanes (entries 1 and 2), which produced unstable emulsions.

Using the polyketal-urethanes, the Fréchet group investigated their use as delivery agents for protein-based vaccine delivery systems.[19] With ovalbumin as a model protein vaccine, they loaded microparticles of the fastest degrading and slowest degrading polyketal-urethanes (Figure 1.5) and tested for immune response. The fast-degrading particle-protein conjugate led to a 28-fold increase in T-cell activation versus free ovalbumin during *in vitro* incubation with macrophages. Further studies *in*

vivo also showed an increase in immune response from the fast-degrading particle, but no difference in response from the more hydrophobic polyketal versus free ovalbumin. This demonstrates that the ability to tune degradation kinetics is essential for delivery efficacy. Finally, toxicity studies showed these particles and their degradation products were benign, having toxicities on the same order of magnitude as PLA microparticles.

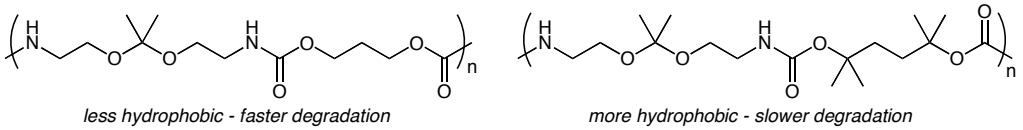


Figure 1.5 Polyketal-urethanes tested for protein-based vaccine delivery

1.2.1.4 Acetals or ketals as acid-sensitive linkers for polycation gene delivery oligomers

In a recent study acetals have been investigated to enhance the efficacy of gene delivery. One of the challenges in gene delivery therapies has been the lack of suitable delivery agents. High molecular weight polycations have high transfer capabilities, but also high toxicity[20,21]. Oligomeric ethyleneimine polycations are less toxic, but are also less efficient vectors. The Wagner group utilized the fast degradation of acetals or ketals to link oligoethyleneimine to increase their transfer efficiency while allowing them to degrade under acidic conditions to less harmful species.[22] The polymers were synthesized amine conjugate addition to α,β-unsaturated esters or imides (Figure 1.6). With the same methodology they synthesized the non-degradable equivalents as controls. The polyacetals and polyketals-linked oligomers showed significantly

decreased toxicity in comparison to their non-degradable counterparts while maintaining high efficiency for gene transfer.

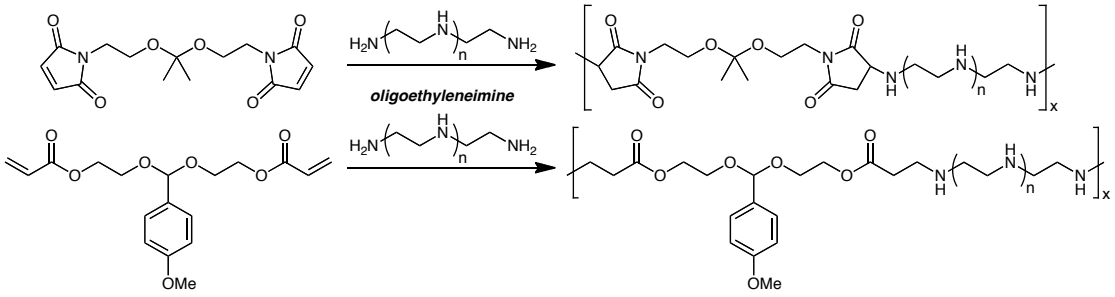


Figure 1.6 Synthesis of acetal or ketal-linked oligoethyleneimine for gene delivery

1.2.1.5 PHF - Fleximer

The Papisov group recently investigated a novel approach to high molecular weight polyacetals with pendant alcohol functionality. Starting with polydextran, the pyranose ring structure was exhaustively cleaved with sodium periodate, followed by aldehyde reduction with sodium borohydride, resulting in the synthesis of poly(hydroxymethylethylene hydroxymethylformal) (PHF) (Figure 1.7).[23]

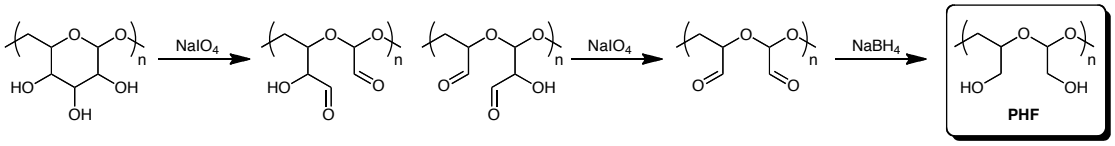


Figure 1.7 Synthesis of PHF from polydextran

PHF is a linear polyacetal with pendant alcohol functionality able to use its functional similarity to carbohydrates to act as a 'stealth' polymer. It is possible to retain much of the molecular weight of the starting polydextran and PHF was isolated with molecular weights as high as 500 kg/mol. Additionally, PHF was shown to be

very non-toxic and have fast clearance from blood via renal filtration. In the same report Papisov *et al.* also demonstrated the ability of PHF to form crosslinked gels and graft copolymers. PHF has also been successfully used as a drug-delivery vehicle for the anti-tumor agent camptothecin.[24]

1.2.1.6 Polyacetals for thermogels

Thermogels are polymer compositions that are soluble in water at room temperature, but form a firm gel at body temperature. These qualities make them attractive targets for therapeutics for both the ease of administration by injection as well as for the localization of the polymer post-administration.[25] Because of their degradability and low toxicity of degradation products, two different polyacetal-based thermogels were recently investigated. The Heller group investigated polyacetals with grafted PEG strands for their thermogelling behavior and release profiles and compared them to traditional polyether thermogels as well as poly(ortho ester) analogs.[26] More recently the Jo group investigated the use of acetal linkers for PEG-poly(propylene glycol)-PEG triblock copolymers, which also showed gellation at body temperature and expected degradation under acidic conditions.[27]

1.2.1.7 Chemically-embedded pharmaceuticals

In addition to forming polymer microparticles that may be loaded with pharmaceutical agents, the fast degradation of polyketals and polyacetals in acidic conditions facilitate another drug-delivery technique: covalently bound pharmaceuticals in the polymer chain. This methodology prevents leaching of active

compound by simple diffusion, as it cannot be released until the polymer backbone degrades.

The Vicent group has investigated this variation by copolymerizing a diol drug, diethylstilboestrol, with divinyl ether as well as the terpolymerization with vinyl ether as well as a PEG diol (Figure 1.8).[28] The copolymer had a lower molecular weight (M_w = 6900 g/mol) and contained 41% diethylstilboestrol by weight, but had limited solubility in water. The PEG-based polymers had M_w = 19000 and 48000 g/mol and between 4 and 5% diethylstilboestrol content and were very water-soluble. As expected, the degradation was significantly higher at more acidic pH, leading to complete release of diethylstilboestrol in 120 hours at pH 5.5 from the PEG-terpolymer. Although some isomerization to the unwanted *cis*-isomer occurred under acidic conditions, it was limited to 20% of total diethylstilboestrol produced.

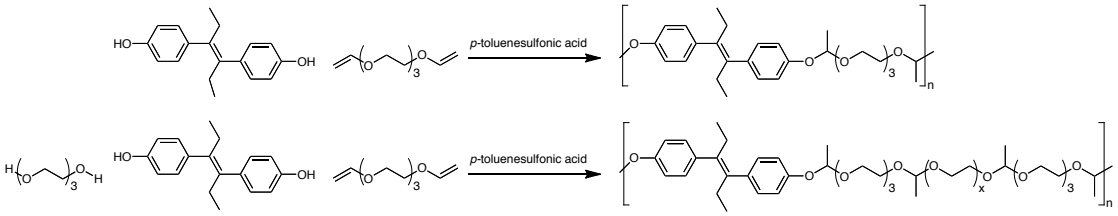


Figure 1.8 Synthesis of diethylstilboestrol-polyacetals

1.2.1.7 Polyketals with amine functionality for enhanced acidic degradation

The Almutairi group recently reported a new polyketal system with improved sensitivity to pH through dual pH-responsive moieties. Using conjugate addition to diacrylate-functionalized ketals, they synthesized polyketals with amino functionality (Figure 1.9).[29] Because of the inherent basicity of the incorporated amines, the polymer is protonated significantly at pH below 6, leading to increased hydrophilicity

and subsequently fast hydrolysis of the ketal linkage. The Almutairi group showed that the polymers degraded significantly faster than previously synthesized ketals of similar hydrophobicity at pH = 5, but were very stable at pH = 7.4.

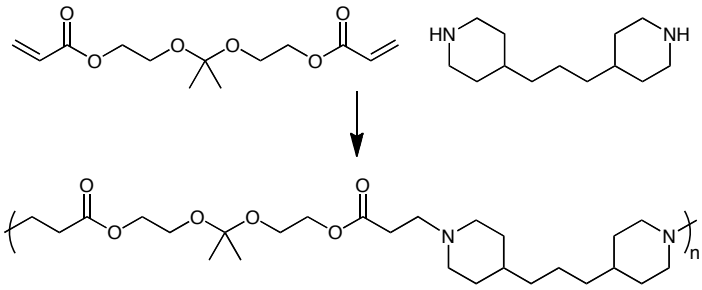


Figure 1.9 Amine-functionalized polyketals for enhanced pH responsiveness

1.2.1.9 Nonlinear architectures for interesting applications

Liquid filled microcapsules are valuable because they can encapsulate large volume per thin polymer wall, and they release their payload rapidly upon rupture (burst degradation). Reacting their diamine-functionalized ketal monomers described in section 1.2.1.3 with trifunctional acid chlorides, the Fréchet group formed a network of branched polyactetal-polyamides (Figure 1.10).[30] The acyl substitution of amines to acid chlorides is extremely fast, which they utilized to form microcapsules via an emulsion-reaction technique. They imaged the synthesized capsules by TEM and SEM and determined that they were hollow inside of a thin polymer shell. Additionally, the release profiles of a fluorescent dye showed that the capsules release via burst degradation at and acidic pH of 5, but only slowly leached material at pH 7.5.

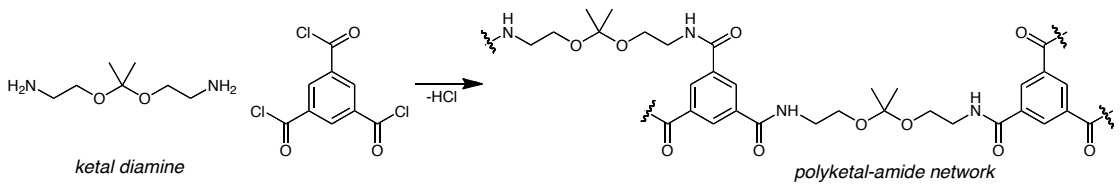


Figure 1.10 Synthesis of polyketal-amide polymers for degradable liquid-filled microcapsules

The Ramakrishnan group investigated a dendritic polyacetal to create a material with tunable degradation rates. They synthesized a dentritic material by the self-condensation-transacetalization of 4-hydroxymethylbenzaldehyde as either the dimethyl, dibutyl, or dihexyl acetal (Figure 1.11).[31] Dendrimers with M_w up to 50 kg/mol were synthesized by this method and it was found that degradation was strongly dependant on monomer. Despite the similarity of the core structure, the degradation kinetics were strongly influenced by the peripheral alkyl chains. As observed with other polyacetal systems, increased hydrophobicity led to increased stability to acidic hydrolysis.

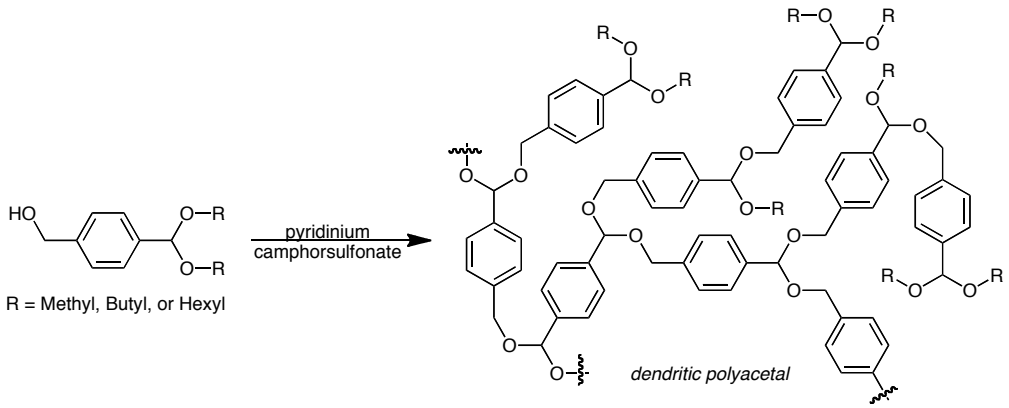


Figure 1.11 Dendritic polyacetals with tunable degradation

1.2.2 Polymeric therapeutics: non-natural carbohydrates

The ring-opening polyerization of bicyclic anhydrosugars for the synthesis of carbohydrates and carbohydrate derivatives is a mature and much-researched field. Although a number of carbohydrates are still inaccessible by synthetic chemistry, many important targets have been synthesized by this method and numerous reviews exist on the subject.[32,33,34] For the purposes of the current review, however, there are some recent studies that have investigated interesting biomedical applications of non-natural carbohydrate-like polyacetals.

Unlike the polyacetals previously discussed, these carbohydrate mimics have not found use in drug delivery. However, the polymers themselves often have interesting physiological behaviors due to their structural similarity to carbohydrate biomaterials. Sulfated carbohydrates are known to have activity as both blood anticoagulants and anti-HIV agents, where they are thought to inhibit the binding of the HIV virus to CD4 positive cells by electrostatic interactions.[35] Although naturally occurring sugars typically exist in their 6-membered pyranose form, it is possible to access the structural isomer 5-membered furanose form by the ring-opening polymerization of anhydrosugars. These five-membered forms are more flexible than the naturally occurring sugars, and this flexibility is thought to aid in their binding to HIV. The Yoshida group synthesized sulfated furanose forms of L-arabinose and D-xylose through the ring-opening polymerization of silyl-protected anhydro-forms of the sugars, followed by deprotection and sulfonation (Figure 1.12).[36] They studied the anti-HIV activity of these sugars versus the sulfated form of naturally occurring 6-membered xylose and found that the non-natural furanan forms showed superior anti-

HIV activity compared to the 6-membered polycarbohydrates for similar levels of sulfonation. Recently, they have looked into the synthesis of interesting carbohydrate structure for similar purposes.[37]

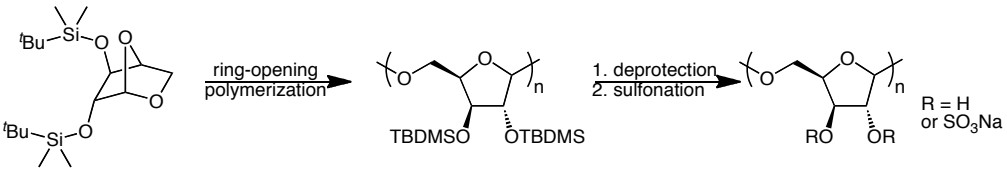


Figure 1.12 Synthesis of sulfated furanan polymers

1.2.3 Polyacetal networks for tissue engineering

Much like drug delivery systems, polyacetals are interesting materials for the field of tissue engineering because of their lack of acidic degradation products. However, tissue engineering materials need to be mechanically sound, whereas many polyacetals have limited mechanical strength and low T_gs. The Fisher group has created cyclic acetals, which may be crosslinked with acrylate end-groups (Figure 1.13) to achieve the necessary mechanical integrity while maintaining the degradation profile of acetals.[38] The properties of this system have been tuned by the incorporation of PEG functionality[39] and co-crosslinking with other diacrylates. They have been shown to be successful tissue repair scaffolds for orbital floor regeneration. A recent review by the group highlights these advances in greater detail.[40]

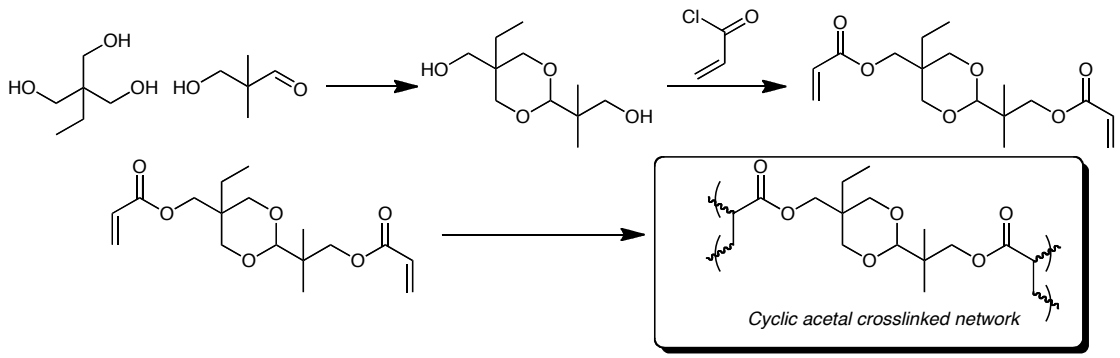


Figure 1.13 Acetal crosslinked networks for tissue engineering applications

1.3 Biodegradable commodity materials

Recently, a significant amount of research efforts have been invested in the development of biodegradable polymers with useful properties to rival current commodity plastics like polyolefins, polyurethanes, and other petroleum-derived polymers. Although these polymers have excellent physical properties and are inexpensive, there are two major drawbacks to their use. First, being derived from petroleum sources, there is a finite availability of the monomer feedstock. As the supply of crude oil diminishes, the price of these common plastics will rise accordingly. Additionally, with increased competition for the same source material as common fuels, the supply of plastics could be limited as well. Approximately 7% of worldwide oil and gas consumed is converted into synthetic plastics,[41] which are ubiquitous in society in applications ranging from packaging and structural materials to complex electronic and biomedical devices.

Secondly, considering the amount of these materials we consume, the problem of waste disposal and storage is a significant concern as well. Although recycling programs can reclaim some plastic material, the vast majority ends up in landfills or

even in the environment. A disturbing example of this immediate problem of plastic waste is in the North Pacific Subtropic Gyre, a massive area of ocean between Hawaii and California where a mass of waste flotsam primarily comprised of discarded plastic has been accumulating for the last 50 years.[42] Because of these concerns, there has been a concerted effort in the field of polymer science to develop biodegradable materials with similar properties to replace petroleum-based polymers.[43] Additionally, many of the biodegradable polymers may be accessed from biorenewable sources, moving away from the reliance on petroleum for the field.

Polyesters have taken the lead in the field of biodegradable and biorenewable replacement materials, particularly the corn-derived poly(lactic acid).[7] Polyesters are typically hard, often semi-crystalline polymers, whereas most polyacetals are amorphous with low T_g. Therefore, most polyacetals are more suited to replace non-biodegradable polyethers, which generally have similar properties.

1.3.1 Acetal soft-block for biodegradable polyurethanes

Polyurethanes are widely used polymers with utility in plastic foams, rubbers, adhesives, and paints. Annual production was estimated to be 8 million tons in 2005.[44] The typical synthesis involves the polyaddition of flexible diol or triols with diisocyanates. Most commonly, these diols are formed from polyethers like PEG or poly(propylene glycol), but unfortunately, the polyethers are not biodegradable.

Two groups have recently investigated the use of polyacetals in place of the polyethers in polyurethanes. The Hashimoto group synthesized an acetal-functionalized polyurethane[45] by first diol polyacetal by self-polymerization of an AB-

type alcohol-vinyl ether monomer end-capped with a diol. This prepolymer was combined with a diaryldiisocyanate to form the product polyurethane with M_n = 49,000 g/mol (Figure 1.14). The properties were compared to the polyurethane formed from the analogous ether-based polymer, poly(butanediol), which had properties consistent with commercial materials. The properties of the polyacetal urethane compared favorably to that of the polyether-linked version in relation to tensile stress versus strain and dynamic viscoelastic properties. Additionally, they demonstrated that polyacetal-urethane was completely degraded in dilute acid, whereas the polyether-urethane was unaffected. This advance could lead to development of biodegradable, or possibly recyclable commercial polyurethanes.

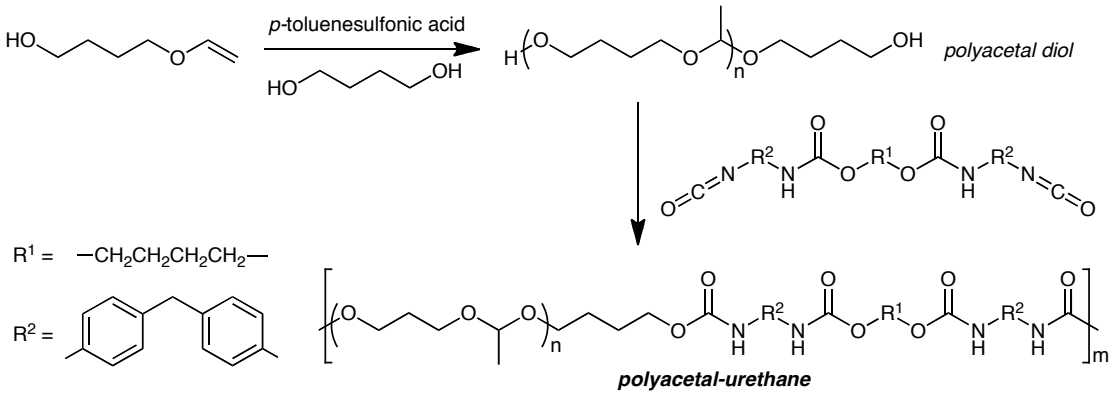


Figure 1.14 Synthesis of polyacetal diol and reaction with diisocyanate to form polyacetal-urethanes

More recently, the Ionescu group has shown similar results using polyacetal-triols as the chain extender for urethane synthesis (Figure 1.15).[46] These materials also compared favorably to commercial urethanes and were shown to have properties

necessary for use as elastomeric urethane foams, while still retaining their biodegradability.

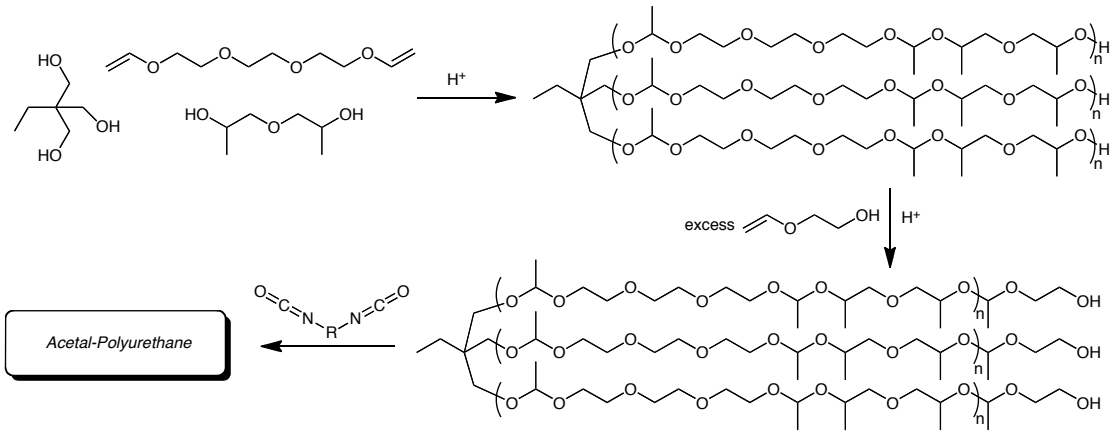


Figure 1.15 Synthesis of biodegradable polyacetal-urethanes from polyacetal triols

1.3.2 Polyacetals from biorenewable resources

Although using polyacetals in polyurethanes is superior to non-degradable polyethers, the polyacetals described in the previous sections were derived from petroleum sources. However, a recent report described the use of α,α-D-trehalose, a symmetric disaccharide generated through the fermentation of starch as a biorenewable feedstock for the synthesis of polyacetals.[47] Starch is an attractive renewable resource because of its availability and has already been investigated as a polymer component.[48]

The polymerization takes place via the direct regioselective acetalization of trehalose with *p*-phthaldehyde or *p*-phthaldehyde bis(dimethyl acetal) (Figure 1.16) High yield was possible, and molecular weights up to M_n = 3800 g/mol were attained. The polymer is a solid, although it shows no thermal transitions before its degradation at 325 °C.

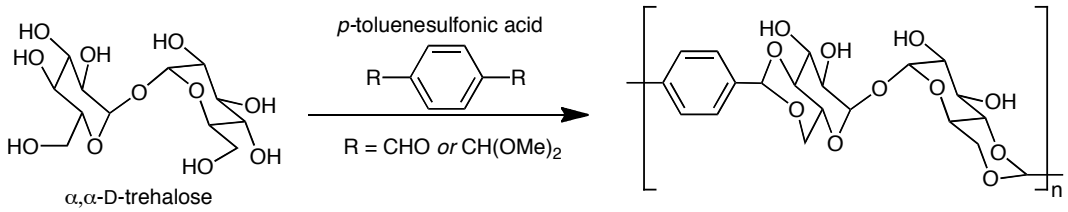


Figure 1.16 Condensation of starch-based α,α-D-trehalose to form a polyacetal

1.4 Other applications

In addition to the examples described previously, polyacetals and polyketals are finding applications beyond the fields of biomedical research and biodegradable materials. As methods for their controlled synthesis continue to become more refined, it can be expected that even more applications for polyacetals and polyketals will be discovered.

1.4.1 Polyacetals as acid-etchable materials for 157 nm photolithography

In attempts to create semiconductor devices with increasingly smaller feature sizes, vacuum ultraviolet lithography was developed that makes use of the F_2 excimer laser with a wavelength of 157 nm.[49] However, this creates the need for functional materials that are highly transparent at this wavelength. Because polyacetals quickly degrade in acid, they were investigated by the Nishikubo group for possible use as transparent polymers that can be photodepolymerized with an appropriate photoacid generator.[50]

They synthesized three different polyacetals by the addition of diols to a divinylether of fluorinated bisphenol A (Figure 1.17). All of the materials were found to be acceptably transparent at 157 nm for 0.1 μm thick films. Their depolymerization

was studied using irradiation and 5% of a photoacid generator. The polymers derived from aliphatic diols depolymerized under irradiation alone. The polymer with all bisphenol A did not depolymerize under only irradiation, but it was completely degraded upon irradiation followed by heating. This was thought to be a function of the relatively high T_g (87 °C) of the polymers.

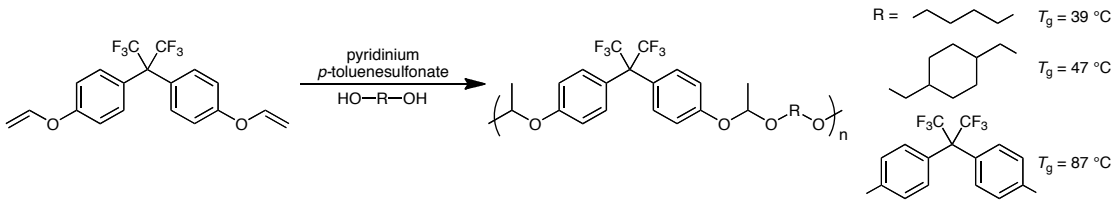


Figure 1.17 Synthesis of polyacetals that are transparent at 157 nm

1.4.2 Polyacetals for cation coordination in solid superbases

Superbases are strongly basic salts with an appropriate ligand that complexes the alkaline metal cation, separating it from the basic anion, therefore enhancing its reactivity. Organic ligands such as crown ethers are able to do this, but they are typically soluble in numerous solvents. Recently, Trofimov and coworkers investigated the use of highly oxygen-containing polyacetals as a polymeric ligand for solid superbases.[51] Despite their degradation in acid, polyacetals are quite stable under basic conditions.

Divinyl monomers with acetal linkages were synthesized, then polymerized cationicly to form a crosslinked polyacetal-poly(vinyl ether) network (Figure 1.18). The polymer was complexed with KOH or CsOH to form the solid superbase, and was tested as a catalyst for the addition of acetylene to acetone to form 2-methyl-3-butyn-2-ol. The new polymeric superbase showed good activity for the transformation.

Additionally it was shown that the solid superbases could be reused for the reaction multiple times without additional KOH.

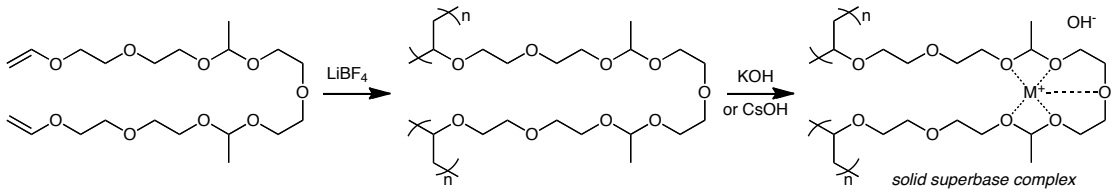


Figure 1.18 Synthesis of polyacetal-poly(vinyl ether) networks for solid superbases

1.4.3 Polyacetals for controlled release of fragrance

Although the degradability of polyacetals and polyketals has been exploited as a means for the release of bioactive pharmaceuticals, the same principles can be applied to fields that also require controlled release of substrates. Many aldehydes and ketones are fragrance molecules that are used in numerous applications such as detergents and hygiene products. Ideally, scent in these applications should remain over a long period of time, but due to their inherent volatility, ketones and aldehydes evaporate and disperse relatively quickly, leading to the loss of scent.

Employing the drug-delivery concept of embedding functionality as part of the degradable backbone, a recent report incorporated the fragrance aldehyde, lilial as the acetal-linkage in a polyacetal via condensation with PEG diols (Figure 1.19).[52] Release studies of the polymers were investigated. As expected, under acidic conditions aldehyde was released relatively quickly, but at pH = 7 less than 2% of aldehyde was released after 140 hours. Additionally, the rate of aldehyde release could be tuned based on the size of the PEG diols, with longer-chain length PEG segments leading to significantly increased degradation and release.

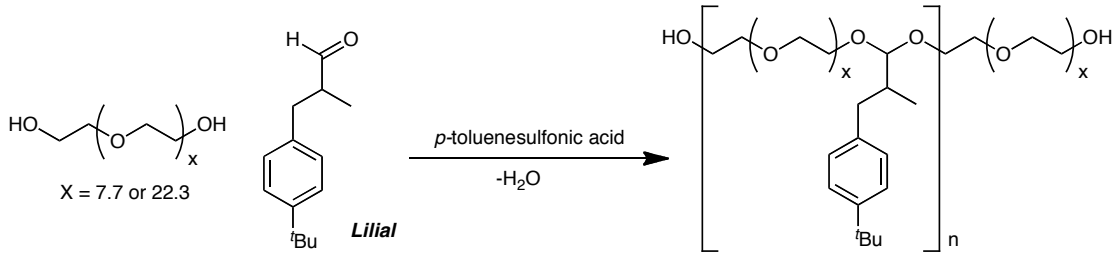


Figure 1.19 Polyacetal containing fragrance aldehyde lillial

1.5 Conclusions

Although polyacetals and polyketals are by no means new materials, investigations into many of the discussed applications are relatively recent developments, with a large number of major discoveries realized within the last ten years. One trend of note is that typically new polyacetal or polyketal systems were developed on a case-by-case basis, often requiring completely new synthetic methodologies. As the field matures, it is likely that the most successful polymers and syntheses will become established. This should streamline the future study of these polymers as well as provide a roadmap for new studies. Because of their unique and desirable properties, it is likely that interest in polyacetals and polyketals will continue to increase in the next decade of research and beyond.

References

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CHAPTER TWO

High Molecular Weight Cyclic Polyketals Synthesized by Ring-Opening Polymerization of Bicyclic Ketals

2.1 Introduction

Polyesters such as poly(lactic acid), poly(glycolic acid), and poly(ε-caprolactone) have great potential as drug-delivery vehicles because they are biocompatible and degrade to innocuous small molecules, which are subsequently metabolized or removed by the body[1]. However, polyesters degrade by hydrolysis of the ester linkages, thus forming significant quantities of organic acid. These acidic species lower local pH in and around the degrading polyester,[2,3] which can aggravate inflammation in the recipient tissue.[4,5] Additionally, the acidic degradation products may damage or destroy a drug that is being delivered.[6] Because of these limitations, there has been recent interest in the synthesis of alternative biodegradable polymers with neutral degradation products.

Polyketals are promising vehicles for drug delivery to pH-sensitive targets because they biodegrade into neutral ketone and diol species upon hydrolysis. Examples such as poly(1,4-phenyleneacetone dimethylene ketal) (PPADK)[7] and poly(cyclohexane-1,4-diyl acetone dimethylene ketal) (PCADK)[8,9] have recently emerged as new materials for delicate applications such as delivery to inflammation-sensitive targets like heart and lung tissue.[10]

Both PPADK and PCADK are synthesized by step-growth condensation of a diol with 2,2-dimethoxypropane (Figure 2.1, top two). Step-growth condensation polymerizations require very high conversions to achieve high molecular weights, necessitating extremely precise monomer ratios as well as heat and/or vacuum to drive the reaction and remove stoichiometric small molecule byproducts.[11,12] As a result the highest M_n reported for PPADK is 2.7 kg/mol and for PCADK is 4.2 kg/mol. Polymer

molecular weight can play an important role in its degradation and drug release profiles,[13,14,15] therefore, the ability to synthesize a broad range of molecular weights is desirable. Additionally, the enhanced permeability and retention (EPR) effect – the specific accumulation of macromolecular species in tumors or damaged tissue due to enhanced vascular permeability[16] – requires relatively high molecular weight polymers, typically in the range of 20–200 kg/mol.[17]

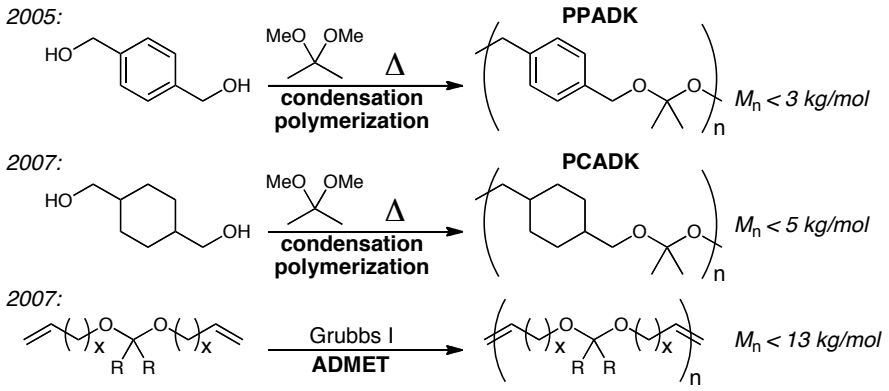


Figure 2.1 Polyketals synthesized by step-growth polymerizations

A recent review of biodegradable polymers for drug delivery cited low molecular weights as one of the primary disadvantages of polyketals and polyacetals.[18] Polymerization techniques that form bonds other than the ketal linkage have been able to generate higher molecular weights than the aforementioned ketal polycondensations. Polyketals synthesized by acyclic diene metathesis had M_n up to 13 kg/mol (Figure 2.1, bottom).[19] Although they contain non-ketal linkages as well, Frechét and coworkers recently had success using diamine-functionalized ketals for the synthesis of alternating polyketal-urethanes or polyketal-ureas with M_n as high as 42 kg/mol.[20]

A new class of biodegradable cyclic polyketals synthesized via Lewis acid-catalyzed polymerization of epoxide-ketones has recently been reported (Figure 2.2, top).[21] In addition to the degradation products being non-acidic, they show promise as cellular antiproliferation agents.[22] Unlike PPADK and PCADK, these cyclic polyketals are formed by a chain-growth mechanism. The proposed enchainment process is activation of the monomer, followed by intramolecular cyclization, then enchainment of the next monomer. Sequential monomer addition to the growing polymer and the lack of small molecule byproducts frees this process from the limitations of step-growth polymerizations. Although the reported molecular weights exceeded those achieved in the PPADK or PCADK systems, the highest M_n reported was only 13 kg/mol. In addition, reaction times were quite long (2-3 d).

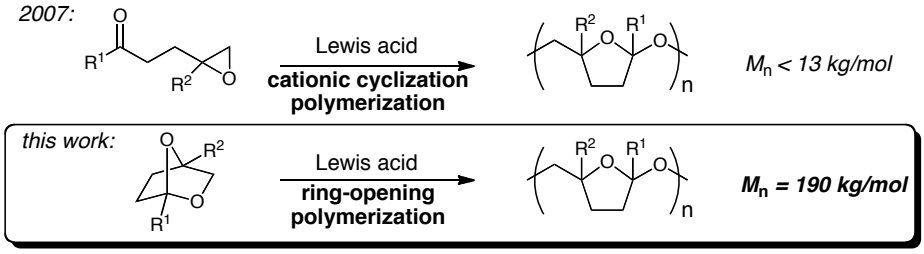


Figure 2.2 Cyclic polyketals synthesized by chain-growth polymerizations

Because of these synthetic limitations, we decided to investigate a more efficient polymer synthesis that might yield higher molecular weight material. An alternative pathway to the same cyclic polyketals is through the ring-opening of the corresponding bicyclic ketal (Figure 2.2, bottom). The cationic polymerization of analogous bicyclic acetals[23] and ortho-esters[24] is established and is capable of producing polymers with very high molecular weights (up to 500 kg/mol).[25] We

hypothesized that synthesis and subsequent ring-opening of bicyclic ketals could produce polyketals with significantly greater molecular weights than have been previously reported.

2.2 Results and Discussion

Bicyclic ketals have been synthesized previously by acid-catalyzed rearrangement of epoxide-ketones.[26,27] Inoue demonstrated that porphyrin aluminum chloride species ring open epoxides by coordination and subsequent nucleophilic attack by chloride. This reactivity resulted in the living polymerization of epoxides.[28] Because these polymerizations are inherently slow, we proposed that intramolecular attack on the ketone moiety might occur before epoxide enchainment, leading to a hemiacetal species, which could ring-close and eliminate chloride to form the bicyclic acetal as well as regenerate the catalyst (Figure 2.3). We found that the Lewis acid *meso*-tetra(4-chlorophenyl)porphyrinato aluminum chloride (ClTPPAl-Cl) was active and selective for the cyclization-rearrangement of 5,6-epoxyhexan-2-one (**1a**) to 1-methyl-2,7-dioxabicyclo[2.2.1]heptane (**2a**). The use of 1,2,4-trichlorobenzene (b.p. = 214 °C) as a solvent allowed for the facile removal of product **2a** from the reaction mixture by vacuum transfer. The same catalyst and conditions also rearranged 1,2-epoxy-5-methylhexan-2-one (**1b**) to 1,4-dimethyl-2,7-dioxabicyclo[2.2.1]heptane (**2b**). Catalyst ClTPPAl-Cl was also able to rearrange 4,5-epoxy-1-phenyl-pentan-1-one (**1c**) to complete conversion, but the product, 2,7-dioxa-1-phenylbicyclo[2.2.1]heptane (**2c**), was unstable as a pure compound at ambient

temperature. For this reason, **2c** was purified by crystallization at -37 °C and used directly for polymerization.

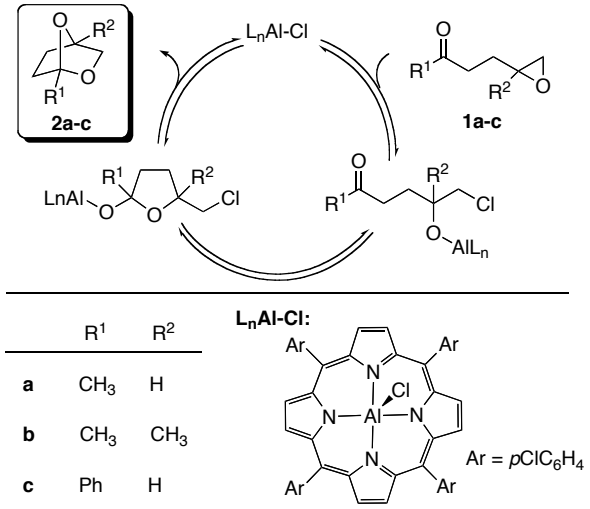
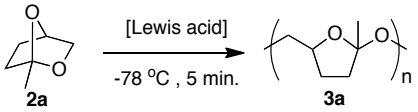


Figure 2.3 Rearrangement of epoxide-ketones to bicylic ketals catalyzed by Lewis acid ClTPPAl-Cl

Using bicyclic ketal **2a** as the model substrate, several Lewis acids were screened for the polymerization reaction (Table 2.1). $Zn(OTf)_2$ produced the highest molecular weight polymer in the epoxide-ketone polymerizations,[21] but it did not produce any polymer under the conditions tested (entry 1). $TiCl_4(THF)_2$ showed some activity, but generated only oligomers (entry 2). However, the strong Lewis acid BF_3•OEt_2 was very active for the polymerization, achieving high molecular weight and high yield in five minutes at -78 °C (entry 3).

Table 2.1 Lewis acid catalyzed ring-opening polymerization of **2a** to **3a**[a]



2a **3a**

entry	catalyst	yield (%)	M_n (kg/mol) [b]	M_w (kg/mol) [b]	M_w/M_n
1	$Zn(OTf)_2$	-	-	-	-
2	$TiCl_4(THF)_2$	17	<1	<1	-
3	BF_3•OEt_2	79	27	36	1.3

[a] Polymerization conditions: 2 mmol monomer, 10 μmol catalyst (200:1 monomer:catalyst), 0.4 mL CH_2Cl_2, -78 °C, 5 minutes. [b] Determined by GPC, in THF, calibrated with polystyrene standards.

Using BF_3•OEt_2 as the catalyst, the bicyclic ketals were polymerized under a variety of loadings (Table 2.2). As a control, epoxide-ketone **1a** was subjected to the polymerization conditions (entry 1) but no polymer was isolated. Using **2a** (entries 2–6), polymers with a range of molecular weights were synthesized. High monomer to catalyst loadings produced high molecular weight polymer, and a maximum M_n of 190 kg/mol was achieved (entry 6). This represents a nineteen-fold increase over the highest previously reported molecular weight for a polyketal. As seen in entries 5 and 6, this methodology is scalable, capable of producing multi-gram batches of polymer. An additional benefit is the rapid rate of the polymerization, reaching high conversions at -78 °C in minutes. The same conditions were successful for the polymerization of monomers **2b** and **2c** as well. As seen in entries 7 and 8, the dimethyl derivative **2b** was polymerized with BF_3•OEt_2 to good molecular weights (up to M_n = 58 kg/mol), although lower yields were isolated compared to monomer **2a**. Finally, despite the inability to isolate the phenyl ketal **2c** in pure form, it was possible to polymerize it to

3c with moderate molecular weight (M_n = 15 kg/mol, entry 9). In comparison, the highest M_n previously reported for **3c** was 1.1 kg/mol.

Table 2.2 Polymerization results using BF_3•OEt_2 as catalyst[a]

entry	mono -mer	mmol monomer	monomer: BF_3•OEt_2	CH_2Cl_2 (mL)	time (min.)	yield (%)	M_n (kg/mol)[b]	M_w/ M_n
1	**1a**	2.0	200:1	0.40	5	0	-	-
2	**2a**	2.0	15:1	0.40	5	70	7.8	1.4
3	**2a**	2.0	40:1	0.40	5	60	12	1.6
4	**2a**	3.8	1500:1	0.76	10	63	67	1.6
5	**2a**	66	2500:1	13.2	15	71	110	1.7
6	**2a**	66	4000:1	13.2	10	n.d.[c]	190	2.0
7	**2b**	1.5	1000:1	0.30	20	31	38	1.3
8	**2b**	2.0	2000:1	0.40	5	24	58	1.5
9	**2c**	1.1	500:1	0.28	30	40	15	2.0

[a] All polymerizations performed at -78 °C. [b] Determined by GPC, in THF versus polystyrene standards. [c] Yield not determined due to limited solubility of high molecular weight material.

It is possible for the polyketals synthesized from the ring-opening of bicyclic ketals to be comprised of 5-membered furanose or 6-membered pyranose rings dependant on which ketal oxygen the ring-opening occurs (Figure 2.4, top). A study of the Lewis acid catalyzed addition of nucleophiles to an analogous bicyclic acetal system had selectivity for 5-membered furan rings,[29] which was analogous to the cationic polymerization of the same monomer.[30] Applying the same reaction conditions to **2a** resulted in the formation of a *cis*/*trans* mixture of a 5-membered furan ring (Figure 2.4, bottom). By analogy, the polyketals synthesized are likely a random *cis*/*trans* mixture of furanose rings, although direct spectroscopic characterization of the polymers themselves was unsuccessful because of a lack of

distinguishing features that could be definitively assigned to either structure. The identity of the small molecule **2a'** as furan ring isomers was identified by 2D ROESY experiment, which showed correlations between the methine and methyl resonances at 4.10 and 1.21 ppm, respectively and the methine and allyl methylene resonances at 4.06 and 2.26 ppm respectively (Figure 2.5).

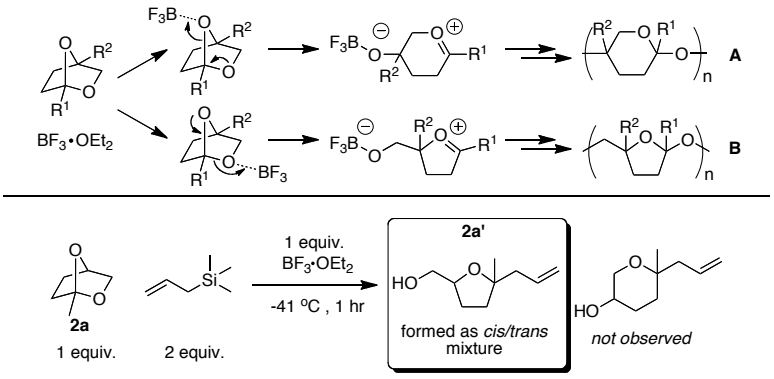


Figure 2.4 Two possible ring-opening possibilities for the polymerization of bicyclic ketals and model study of Lewis acid ring-opening of **2a** to **2a'**

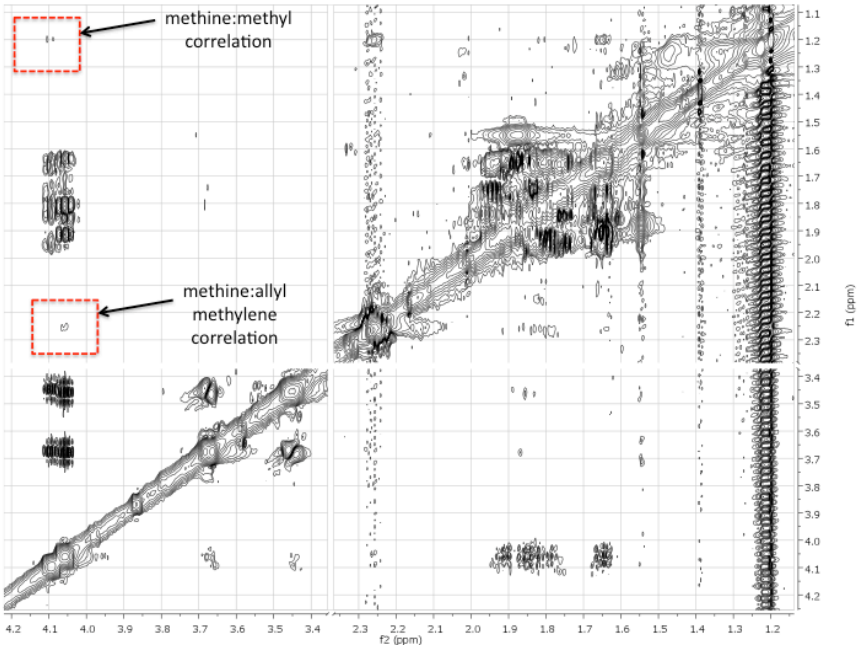


Figure 2.5 600 MHz ROESYAD spectrum of **2a'**

The thermal properties of the synthesized polyketals are shown in Table 2.3. Because the polyketals are relatively hygroscopic, their glass transition temperatures (T_g) decreased upon exposure to moist air. This caused inconsistencies measuring T_g from sample to sample. The reported thermal data was recorded with polymers immediately following precipitation from hexanes and drying under vacuum. Polymers **3a** and **3b** were amorphous with relatively low T_gs (entries 1 and 2). Polymer **3c** had a higher T_g and also showed a melting transition, although it was only seen on the first heating (entry 3).

Table 2.3 Thermal transitions for polymers **3a-c** determined by DSC

entry	polymer	T_g (°C)	T_m (°C)
1[a]	**3a**	23	-
2[a]	**3b**	37	-
3[b]	**3c**	47	(144)[c]

[a] Samples measured from -80 °C to 100 °C with heating rate of 10 °C/min. [b] -80 °C to 150 °C at 10 °C/min. [c] Melting transition seen only on first heat.

2.3 Conclusion

We demonstrated an efficient synthesis of cyclic ketal polymers with unprecedented molecular weights (M_n up to 190 kg/mol) through the rearrangement of epoxide-ketones to bicyclic ketals and subsequent ring-opening polymerization. This represents a significant increase over previously reported polyketal systems. We believe the ability to select for molecular weight will lead to greater control over properties such as degradation and release profile, as well as enhance uptake by the

EPR effect. Further studies will investigate mechanical properties and degradation as well as the synthesis of copolymers.

2.4 Experimental

General Considerations. All manipulations of air and water sensitive compounds were carried out under dry nitrogen using a Braun Labmaster glovebox or standard Schlenk line techniques. ^{1}H NMR spectra were recorded on a Varian Mercury (^{1}H, 300 MHz), Varian INOVA 400 (^{1}H, 400 MHz) or Varian INOVA 600 (^{1}H, 600 MHz) spectrometer and referenced with residual non-deuterated solvent shifts ($CHCl_3$ = 7.24 ppm). ^{13}C NMR spectra were recorded on a Varian Mercury (^{13}C, 75 MHz) or Varian INOVA (^{13}C, 125 MHz) spectrometer and referenced to chloroform, 77.23 ppm. Gel permeation chromatography (GPC) analyses were carried out using a Waters instrument, (M515 pump, 717+ Autosampler) equipped with a Waters UV486 and Waters 2410 differential refractive index detectors, and three 5 μm PSS SDV columns (Polymer Standards Service; 50 Å, 500 Å, and Linear M porosities) in series. The GPC columns were eluted with tetrahydrofuran at 40 °C at 1 mL/min and were calibrated using 20 monodisperse polystyrene standards.

Differential scanning calorimetry of polymer samples was performed on a Mettler-Toledo Polymer DSC instrument equipped with liquid nitrogen cooling system and automated sampler. Typical DSC experiments were made in aluminum pans under nitrogen with a heating rate of 10 °C/min from -80 °C to 100 °C or -80 °C to 150 °C. Data was processed using StarE software.

Materials. HPLC grade dichloromethane was purchased from Fisher Scientific and purified over solvent columns and degassed by three sequential freeze-pump-thaw cycles. 1,2,4-Trichlorobenzene (≥ 99%, anhydrous) was purchased from Aldrich and stored over 3Å molecular sieves. 5,6-Epoxyhexan-2-one (**1a**) and 5,6-epoxy-5-methylhexan-2-one (**3a**) were provided by Medtronic, Inc. and purified by fractional distillation. They were then dried over CaH_2, redistilled, and degassed by three sequential freeze-pump-thaw cycles and stored under inert atmosphere at -37 °C. 4,5-Epoxy-1-phenyl-pentan-1-one (**2a**) was provided by Medtronic, Inc. and purified by crystallizing away polar impurities from toluene. Solvent was then removed by rotary evaporation and resulting oil was recrystallized from hexanes:acetone (9:1). Crystalline material was dried by vacuum overnight and stored under inert atmosphere at -37 °C. Catalyst complex ClTPPAl-Cl was prepared according to reported literature procedure.[31] All other materials were purchased from commercial sources and used without further purification.

Monomer Synthesis.

1-Methyl-2,7-dioxabicyclo[2.2.1]heptane (2a): 5,6-Epoxyhexan-2-one (**1a**) (5.0 g, 44 mmol) was dissolved in 1,2,4-trichlorobenzene (40 mL) in a 200 mL Schlenk bomb. ClTPPAl-Cl (0.48 g, 0.59 mmol) was added and reaction mixture was stirred at 23 °C until all epoxide had been consumed as determined by ^{1}H NMR. Product was removed from reaction mixture by vacuum transfer to dry Schlenk bomb in liquid nitrogen (room temperature bath). Product was stirred over CaH_2 for 24 hours, vacuum transferred to dry Schlenk bomb then degassed by three freeze-pump-

thaw cycles. 2.8 g isolated (56% yield). Stored monomer in glovebox at -37 °C. ^{1}H NMR ($CDCl_3$): δ 4.68 (m, 1H), 3.62 (m, 1H), 3.56 (pseudo d, J = 6.3 Hz, 1H), 1.91-1.75 (m, 2H), 1.70-1.61 (m, 2H), 1.60 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 108.33, 77.01, 71.30, 36.51, 29.46, 18.38. HRMS (EI) calculated for $C_6H_{10}O_2$: 114.0681; measured 114.0689.

1,4-Dimethyl-2,7-dioxabicyclo[2.2.1]heptane (2b): 5,6-epoxy-5-methylhexan-2-one (**1b**) (2.6 g, 20 mmol) was dissolved in 1,2,4-trichlorobenzene (10 mL) in 200 mL Schlenk bomb. ClTPPAl-Cl (82 mg, 0.1 mmol) was added and reaction mixture was stirred at 23 °C until all epoxide had been consumed as determined by ^{1}H NMR. Product was removed from reaction mixture by vacuum transfer to dry Schlenk bomb in liquid nitrogen. Product was stirred over CaH_2 for 24 hours, vacuum transferred to a dry Schlenk bomb then degassed by three freeze-pump-thaw cycles. 2.3 g isolated (87% yield). Stored monomer in glovebox at -37 °C. ^{1}H NMR ($CDCl_3$): δ 3.63 (d, J = 6.2 Hz, 1H), 3.35 (dd, J = 6.2 Hz, J = 3.4 Hz, 1H), 1.95 (m, 1H), 1.78 (m, 2H), 1.66 (m, 1H), 1.59 (s, 3H), 1.48 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 108.67, 84.35, 75.83, 37.82, 35.21, 18.85, 17.65. HRMS (EI) calculated for $C_7H_{12}O_2$: 128.0837; measured 128.0846.

2,7-Dioxa-1-phenylbicyclo[2.2.1]heptane (2c): 4,5-epoxy-1-phenyl-pentan-1-one (**1c**) (1.0 g, 5.7 mmol) was dissolved in dichloromethane (28 mL) in a 200 mL Schlenk tube. ClTPPAl-Cl (23 mg, 0.28 mmol) was added and reaction mixture was stirred at 23 °C until all epoxide had been consumed as determined by ^{1}H NMR. Reaction mixture was concentrated to 5 mL by removing dichloromethane by vacuum using Schlenk line. Mixture was dissolved in 25 mL dry hexanes added and then

cooled to 0 °C. The solution was canula-filtered away from insoluble residual catalyst to a dry Schlenk tube and concentrated by vacuum to ~10 mL. Liquor was moved to glovebox freezer and stored at -37 °C until crystals formed. Mother liquor was decanted and material was immediately dissolved in dichloromethane and used for polymerization: ~0.45 g isolated (45% crude yield). ^{1}H NMR ($CDCl_3$): δ 7.59 (m, 2H), 7.41-7.34 (m, 3H), 4.93 (m, 1H), 3.83-3.77 (m, 2H), 2.33-2.25 (m, 1H), 2.10-1.99 (m, 2H), 1.90-1.82 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 129.02, 128.45, 126.25, 109.39, 71.70, 37.44, 29.45. HRMS (EI) calculated for $C_{11}H_{12}O_2$: 176.0837; measured 176.0838.

Polymer Synthesis

Polyketal 3a: In glovebox, **2a** (228 mg, 2.0 mmol) was added to flame-dried Schenk tube and dissolved in 0.30 mL CH_2Cl_2, and the tube was sealed with a rubber septum. BF_3•OEt_2 (1.4 mg, 10 μmol) was dissolved in 0.1 mL CH_2Cl_2 and taken up by syringe and the needle was placed into a rubber septum. Under N_2 backflow on Schlenk line, monomer solution was cooled to -78 °C by dry ice/acetone bath. BF_3•OEt_2 solution was injected and reaction was stirred for 5 minutes. The polymerization was then quenched with a dilute solution of triethylamine in THF and warmed to ambient temperature. Hexanes was added (20 mL) and tube was cooled to -78 °C to precipitate polymer. Solvent was subsequently decanted. This process was repeated 4 times. Polymer was dissolved in CH_2Cl_2 and pipetted to tared vial. Solvent was removed in Schlenk line until vacuum gage read baseline: 180 mg polymer was isolated (79% yield). ^{1}H NMR ($CDCl_3$): δ 4.24-4.00 (1H), 3.62-3.21 (2H), 2.20-1.55 (4H), 1.46-1.32 (3H). ^{13}C NMR ($CDCl_3$): δ 108.42-107.62, 80.48-77.98, 66.09-63.39,

39.14-37.35, 28.88-27.11, 23.58-21.98.

Polyketal 3b: In glovebox, **2b** (256 mg, 2 mmol) was added to flame-dried Schenk tube and dissolved in 0.3 mL CH_2Cl_2, and the tube was sealed with a rubber septum. BF_3•OEt_2 (0.14 mg, 1 μmol) was dissolved in 0.1 mL CH_2Cl_2 and taken up by syringe and the needle was placed into a rubber septum. Under N_2 backflow on Schlenk line, monomer solution was cooled to -78 °C by dry ice/acetone bath. BF_3•OEt_2 solution was injected and reaction was stirred for 5 minutes. The polymerization was then quenched with a dilute solution of triethylamine in THF and warmed to ambient temperature. Hexanes was added (20 mL) and tube was cooled to -78 °C for 20 minutes until polymer precipitated, followed by decanting excess solvent. This process was repeated 2 times. Polymer was dissolved in CH_2Cl_2 and pipetted to tared vial. Solvent was removed in Schlenk line until vacuum gage read baseline: 61 mg polymer was isolated (24% yield). ^{1}H NMR ($CDCl_3$): δ 3.46-3.08 (2H), 2.21-1.53 (4H), 1.46-1.32 (3H), 1.29-1.08 (3H). ^{13}C NMR ($CDCl_3$): δ 108.44-107.55, 84.87-83.91, 69.04-67.76, 39.74-36.99, 35.00-33.98, 26.17-22.53 (2C).

Polyketal 3c: In glovebox, **2c** (~200 mg, 1.1 mmol) was dissolved in 0.28 mL CH_2Cl_2 and added to flame-dried Schenk tube, and the tube was sealed with a rubber septum. BF_3•OEt_2 (0.3 mg, 2.2 μmol) was dissolved in 0.1 mL CH_2Cl_2 and taken up by syringe and the needle was placed into a rubber septum. Under N_2 backflow on Schlenk line, monomer solution was cooled to -78 °C by dry ice/acetone bath. BF_3•OEt_2 solution was injected and reaction was stirred for 30 minutes. The polymerization was then quenched with a dilute solution of triethylamine in THF and warmed to ambient temperature. Hexanes was added (20 mL) and tube was cooled to -

78 °C to precipitate polymer. Powdery polymer was condensed by centrifugation and decanting solvent. This process was repeated 2 times. Polymer was dissolved in CH_2Cl_2 and pipetted to tared vial. Solvent was removed in Schlenk line until vacuum gage read baseline: 80 mg polymer was isolated (40% yield). ^{1}H NMR ($CDCl_3$): δ 7.63-7.37 (2H), 7.37-7.08 (3H), 4.53-4.04 (1H), 3.78-2.94 (2H), 2.46-1.43 (4H). ^{13}C NMR ($CDCl_3$): δ 142.34-141.31, 128.79-128.08, 128.00-127.49, 126.89-125.89, 81.81-78.18, 67.13-63.51, 42.13-39.52, 29.51-26.86.

Structural assignment

Synthesis of 2a' for structural characterization: In glovebox, **2a** (114 mg, 1.0 mmol) was dissolved in 10 mL dry CH_2Cl_2 in a 100 mL Schlenk tube. Allyltrimethylsilane (228 mg, 2 mmol) (distilled over CaH_2, freeze/pump/thaw x3) was added. Reaction mixture was cooled to -41 °C in dry ice/acetonitrile bath under N_2 backflow from Schlenk line. BF_3•OEt_2 (142 mg, 1 mmol) was diluted with CH_2Cl_2 then pulled into a syringe that was stoppered with a rubber septum. The BF_3•OEt_2 solution was injected to the reaction mixture, which was stirred at -41 °C for 1 hour. Reaction was quenched by addition of $NaHCO_3$, which was extracted three times with ethyl acetate. Organic layer was washed twice with saturated brine and then dried over Na_2SO_4 and removing solvent under reduced pressure the product **2a'** was isolated by flash chromatography (1:1 ethyl acetate:hexanes). 5-Membered structure was ascertained by NMR through 2D ROESY experiment, which showed correlation between the methine proton either the methyl or allyl methylene resonances, indicative

of their close proximity in the five-membered structure. Additional peak resolution between *cis* and *trans* isomers was achieved with HSQC.

2a' (methine proton *cis* to methyl group): ^{1}H NMR ($CDCl_3$) δ 5.87-5.76 (1H), 5.10-5.03 (2H), 4.10 (1H), 3.71-3.65 (1H), 3.50-3.40 (1H), 2.30-2.22 (2H), 1.93 (1H), 1.85 (1H), 1.79 (1H), 1.65 (1H), 1.21 (3H). ^{13}C NMR ($CDCl_3$): δ 134.6, 117.7, 83.0, 78.6, 65.0, (46.0/45.6), 36.3, 27.3, (26.9/26.3).

2a' (methine proton *trans* to methyl group): ^{1}H NMR ($CDCl_3$) δ 5.87-5.76 (1H), 5.10-5.03 (2H), 4.06 (1H), 3.71-3.65 (1H), 3.50-3.40 (1H), 2.30-2.22 (2H), 1.93 (1H), 1.85 (1H), 1.79 (1H), 1.65 (1H), 1.21 (3H). ^{13}C NMR ($CDCl_3$): δ 134.6, 117.7, 83.0, 78.6, 65.0, (46.0/45.6), 36.3, 27.3, (26.9/26.3).

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CHAPTER THREE

Synthesis of Cyclic Anhydride-Alcohol AB Monomers and Their Polymerization to Pendant Acid Polyesters

Research performed in part, in collaboration with John Rowley

3.1 Introduction

Polyesters are an important class of polymers traditionally synthesized by condensation polymerization of diols and carboxylic acid derivatives. However, this method is limited by the need to remove small molecule byproducts and requires very careful reagent stoichiometric ratios to reach high conversions necessary for high molecular weights.[1] Modern catalytic syntheses based on chain-growth ring-opening polymerization of cyclic esters[2,3] or copolymerization of epoxides and cyclic anhydrides[4] have been shown to be efficient alternatives to condensation and enabled the controlled synthesis of a large variety of polyesters. However, due to interference with catalysts, certain functional groups are difficult to obtain with these methods, such as pendant carboxylic acids.

Polymers bearing pendant carboxylic acid functional groups are attractive synthetic targets because they are pH-responsive materials that are neutral species at low pH, but exist as polyanions at higher pH. This ability has been utilized in the past to form pH-sensitive micelles,[5] stabilize enzymes,[6] and form polyelectrolyte complexes with polycations.[7] Additionally, after deprotonation, it is possible to incorporate metal ions into the polymer, forming ionic crosslinks between pendant carboxylates. These ionic crosslinks can impart significant durability, impact strength, and enhanced barrier properties.[8]

Polyesters with carboxylic acid functionality are intriguing materials because, in addition to the advantages pendant carboxylic acids, they would have the potential to act as biodegradable materials. Poly(malic acid) is a example of a pendant-acid polyester that has garnered significant attention recently because of its attractive

physical properties and that it degrades to benign hydrolysis products.[9] Pendant-acid polyesters are accessible via ring-opening polymerization, however, this method requires protection of the acid functionality of the monomer and subsequent post-polymerization deprotection to form the free acid.

An interesting alternative synthesis of pendant acid polymers would be the self-condensation ring-opening polymerization (SCROP) of cyclic acid anhydrides-alcohols with rigid or lengthy linkers to preclude internal cyclization (Figure 3.1). SCROP is a method where AB monomers with a nucleophile and a strained heterocycle react by ring-opening, eliminating the need to drive off small molecule side-products.[10] Typically, the ring-opening step during these polymerizations liberates a new nucleophile, so that they function as masked AB_2 monomers, creating hyperbranched polymer.[11] However, on reaction with alcohols, anydrides form an ester bond and liberate a pendant carboxylic acid. It is possible that the generated acid could act as an electrophile for attack by another monomer, forming hyperbranched material. However, carboxylic acids are significantly less reactive than comparable anhydrides, so the polymerization would likely lead to primarily linear polyesters. Supporting this theory is the Frechét group's proton-transfer ring-opening polymerization, in which basicity differences between alcohols and phenols leads to only linear polyethers.[12]

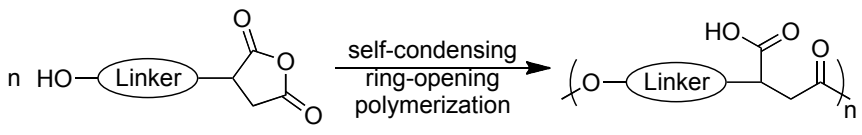


Figure 3.1 Self-condensation ring-opening polymerization of anhydride-alcohols

Few examples of anhydride-alcohols are known, mostly because the typical synthetic protocols for cyclic anhydrides limit their formation. Cyclic anhydrides are typically formed under harsh conditions, such as intramolecular condensation of diacids or Alder-ene reaction of maleic anhydride with alkenes, which are unsuitable when alcohols are present due to their reactivity towards anhydrides. A small number of examples exist,[13] but their polymerization behavior has never been investigated.

Our group has recently reported the catalytic synthesis of cyclic anhydrides by the ring-expansive double carbonylation of epoxides,[14] which occurs under conditions mild enough for the inclusion of alcohol functionality. We felt this methodology would be an ideal vehicle for the production of a library of interesting polyesters with pendant carboxylic acids, which would be inaccessible by other synthetic methods. Dr. As shown previously, the epoxide-alcohol **1a** to can be converted to anhydride-alcohol **2a** by catalytic double carbonylation (Figure 3.2). Dr. John Rowley investigated the polymerization behavior of **2a**, showing that it could be efficiently polymerized thermally to acid-functionalized polyester **3a** (Figure 3.2) as well as showing that the polymer could be modified by ionic crosslinking.[15]

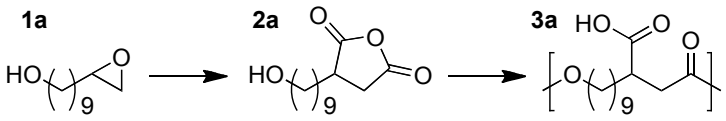


Figure 3.2 Synthesis of anhydride-alcohol **2a** by catalytic carbonylation and its subsequent polymerization to carboxylic acid-appended polyester **3a**

Dr. Rowley was also able to synthesize anhydride-alcohol **2b** based on the biorenewable, sugar-based feedstock[16] isosorbide (Figure 3.3). Additionally, synthesis

of enantiomerically pure **(*S*)-2b** facilitated the growth of single crystals and a structure was generated by X-ray diffraction (Figure 3.3). The structure confirmed the inversion of epoxide stereochemistry as well as the anhydride-alcohol structure, of which there are limited number of examples that have been characterized by X-ray crystallography.[17,18,19,20,21]

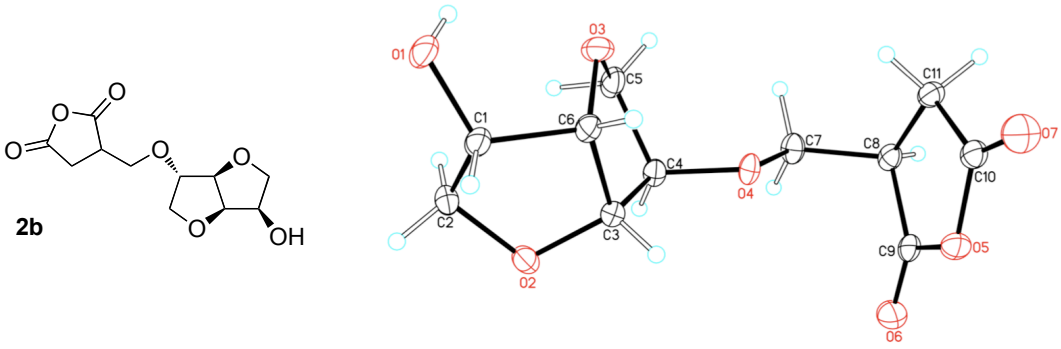
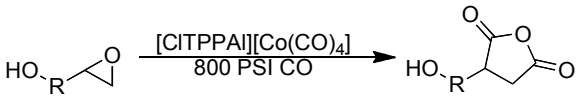


Figure 3.3 Isosorbide-based anhydride-alcohol **2b** and solid-state structure of **(*S*)-2b** with displacement ellipsoids drawn at 40% probability level

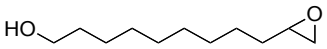
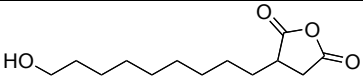
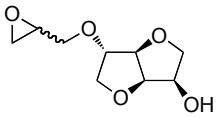
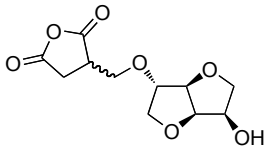
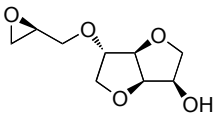
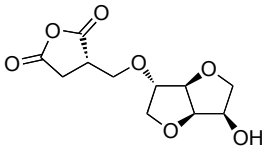
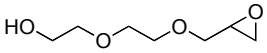
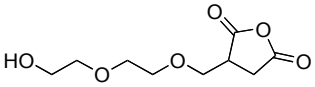
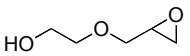
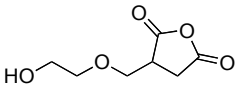
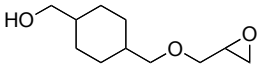
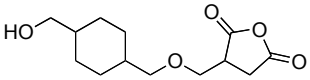
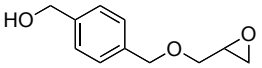
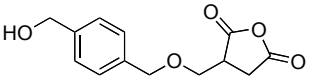
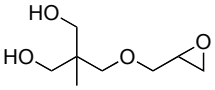
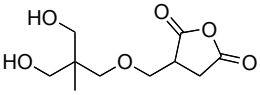
3.2 Results and Discussion

To expand this methodology, we synthesized a number of epoxide-alcohol starting materials, which were converted with a modified double carbonylation protocol using the previously reported *meso*-tetra(4-chlorophenyl)porphyrinato aluminum cobalt tetracarbonyl ([ClTPPAl][Co(CO)$_4$]) catalyst to the corresponding anhydride-alcohols (Table 3.1). Although all reactions proceeded to complete conversion as measured by ^{1}H NMR, isolated yields were significantly reduced, most likely due to losses from the polymerization of the anhydride-alcohols during the reaction as well as their instability on silica gel.

Table 3.1 Double carbonylation of epoxide-alcohols to the corresponding anhydride-alcohols



1a-h **2a-h**

entry	epoxide-alcohol	anhydride-alcohol	isolated yield
1[a]	**1a** 	**2a** 	72%
2[a]	**1b** 	**2b** 	68%
3[a]	**(*R*)-1b** 	**(*S*)-2b** 	-
4	**1c** 	**2c** 	56%
5	**1d** 	**2d** 	17%
6	**1e** 	**2e** 	57%
7	**1f** 	**2f** 	16%
8	**1g** 	**2g** 	13%

[a] From previous studies[15]

This methodology is able to synthesize anhydride-alcohol monomers that are hydrophobic (entries 1, 6, 7), hydrophilic (entries 2-5, 8), have rigid ring systems (entries 2, 3, 6, 7), and a dialcohol AB_2-type monomers for the synthesis of hyperbranched polymers (entry 8). The anhydride-alcohols **2b** and **(*S*)-2b** are derived

from the biorenewable resource isosorbide, a sugar derivative. It is also possible to add the epoxide functionality with epichlorohydrin, which can be renewably produced from glycerol. The anhydride-alcohols were all isolated as solids, except for the ethylene glycol-based molecules **2c** and **2d**, which were viscous oils.

Unlike many other self-condensation ring-opening polymerizations, the cyclic anhydride is reactive enough to condense with the alcohol functionality simply by heating, eliminating the need for external catalysts or stoichiometric reagents. This condensation polymerization was studied using differential scanning calorimetry (DSC) of the anhydride-alcohol monomer **1e** (Figure 3.4). As can be seen, the solid undergoes an endothermic melting transition at 78 °C, which is followed by a broad exothermic peak from 90 °C to 160 °C corresponding to heat generated by the polymerization. Upon a second heating cycle neither the melting nor exothermic transitions are present, and the only remaining feature is polymer glass transition temperature (T_g) at 44 °C. This DSC polymerization method was used to study the anhydride-alcohol monomers as well and the results are shown in Table 3.2.

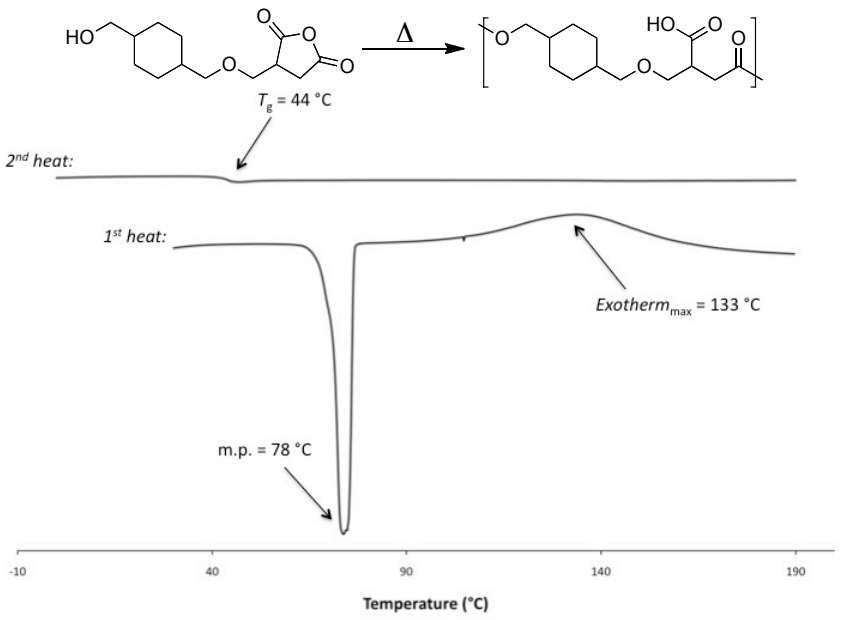
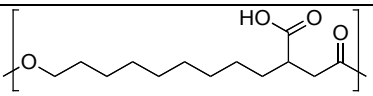
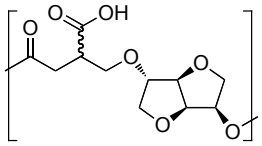
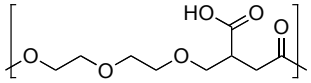
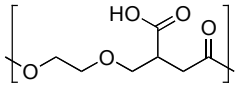
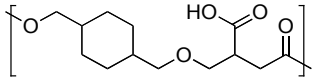
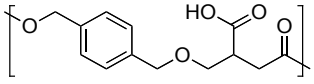
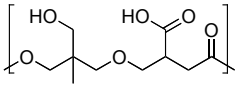


Figure 3.4 DSC polymerization of monomer **1e**

Table 3.2 Study of the polymerization of anhydride-alcohol monomers by DSC

entry	anhydride -alcohol	polymer	monomer m.p. (°C)	exotherm max (°C)	polymer T_g (°C)
1[a]	**2a**	**3a** 	48	130	-7
2[a]	**2b**	**3b** 	107	>200	67
3	**2c**	**3c** 	n/a	84	-18
4	**2d**	**3d** 	n/a	n/a	15
5	**3e**	**3e** 	74	133	44
6	**3f**	**3f** 	95	145	43
7	**2g**	**3g** 	86	128	54

[a] From previous studies[15]

The isosorbide-based monomer **2b** did not show an appreciable exotherm below 200 °C, most likely due to the secondary alcohol being a weaker nucleophile. It and the enantiopure version, **(*S*)-2b** were also polymerized with harsher conditions (150 °C, 16 hours) to achieve high conversions. The harsher conditions resulted in polymer **3b** with T_g = 77 °C and **(*S*)-3b** with T_g = 87 °C.[15]

3.3 Conclusion

We have reported the synthesis of a library of anhydride-alcohol monomers, which can be polymerized thermally to afford carboxylic acid-appended polyesters. A range of backbones was accessible with this methodology, including starting materials derived from biorenewable sources. This system is very interesting as a method for accessing acid-functionalized polyesters that would be synthetically challenging by other means.

3.4 Experimental

General Considerations. All manipulations of air and water sensitive compounds were carried out under dry nitrogen using a Braun Labmaster glovebox or standard Schlenk line techniques. High-pressure reactions took place in a custom-made, stainless steel 6-well reactor as described previously[22] or a 100 mL stainless steel Parr reactor. ^{1}H NMR spectra were recorded on a Varian Mercury (^{1}H, 300 MHz), Varian INOVA 400 (^{1}H, 400 MHz) or Varian INOVA 600 (^{1}H, 600 MHz) spectrometer and referenced with residual non-deuterated solvent shifts ($CHCl_3$ = 7.24 ppm, acetone = 2.05 ppm). ^{13}C NMR spectra were recorded on a Varian Mercury (^{13}C,

75 MHz) or Varian INOVA (^{13}C, 125 MHz) spectrometer and referenced to chloroform (77.23 ppm) or acetone carbonyl (206.68 ppm).

Differential scanning calorimetry of polymer samples was performed on a TA Instruments Q1000 instrument or a Mettler-Toledo Polymer DSC instrument equipped with liquid nitrogen cooling system and automated sampler. Typical DSC experiments were made in crimped aluminum pans under nitrogen with a heating rate of 10 °C/min from -80 °C to +200 °C.

Materials. Carbon monoxide was purchased from Matheson Trigas or Airgas in aluminum cylinders (99.99% min. purity) and was used as received. HPLC-grade tetrahydrofuran, dichloromethane, and hexanes were purchased from Fisher Scientific and purified over solvent columns and degassed by three freeze/pump/thaw cycles. 1,4-Dioxane was dried over sodium/benzophenone and then vacuum transferred and degassed by three freeze/pump/thaw cycles. *Meso*-tetra(4-chlorophenyl)porphyrinato aluminum cobalt tetracarbonyl ([ClTPPAl][Co(CO)$_4$]),[14] 9-hydroxynonylsuccinic anhydride (**2a**),[14] and 5-hydroxymethyl-2,2,5-trimethyl-1,3-dioxane[23] were prepared according to reported literature procedures.

Additionally, synthesis of 2-*O*-(methylsuccinic anhydride)isosorbide (**2f**) and (*S*)-2-*O*-(methylsuccinic anhydride)isosorbide (***S*-2f**) and pertinent crystallographic information and refinement has been reported here.[15]

Epoxide-alcohol synthesis.

***O*-allyldiethyleneglycol (1c precursor)**: Sodium hydride (1.2 g, 50 mmol) was slurried in dry THF and added to a 200 mL Schlenk tube with a magnetic stir bar

and then cooled to -78 °C. While open to nitrogen bubbler, diethylene glycol (9.5 mL, 100 mmol) was added slowly by syringe. The reaction was slowly warmed to 25 °C and stirred until gas evolution ceased. It was then cooled to -78 °C again, and allyl bromide (2.9 mL, 33 mmol) was added by syringe. The reaction was warmed to 25 °C, then heated at 50 °C for 24 hours. The reaction mixture was filtered through celite and solvent was removed *in vacuo.* Residue was dissolved in diethyl ether and extracted 3 times with deionized water. Water was washed 3 times with diethyl ether, and then extracted 5 times with a large excess of dichloromethane, which was then dried over Na_2SO_4. Solvent was removed *in vacuo* to afford product as a colorless oil: 4.3 g isolated (79% yield). ^{1}H NMR ($CDCl_3$): δ 5.90 (ddt, J = 17.3, 10.5, 5.7, 1H), 5.26 (dq, J = 17.2, 1.6, 1H), 5.17 (dq, J = 10.4, 1.3, 1H), 4.01 (dt, J = 5.7, 1.4, 2H), 3.77 – 3.55 (m, 8H), 2.39 (t, J = 6.2, 1H).

***O*-glycidyldiethyleneglycol (1c)**: *O*-allyldiethyleneglycol (4.3 g, 27 mmol) was dissolved in dichloromethane (30 mL) in a roundbottom flask with a stirbar and cooled to 0 °C. MCPBA (9.0 g, 40 mmol) was added slowly and the reaction was warmed to 25 °C for 24 hours. Solid was filtered away and solvent was removed *in vacuo*. Residue was dissolved in diethyl ether and extracted 3 times with deionized water. Water was washed 3 times with diethyl ether, and then extracted 5 times with a large excess of dichloromethane, which was then dried over Na_2SO_4. Solvent was removed *in vacuo* to afford product as a colorless oil: 2.47 g isolated (52% yield). ^{1}H NMR ($CDCl_3$): δ 3.80 (dd, J = 11.7, 2.9, 1H), 3.75 – 3.57 (m, 8H), 3.41 (dd, J = 11.7, 5.9, 1H), 3.15 (ddt, J = 5.8, 4.1, 2.8, 1H), 2.78 (dd, J = 5.0, 4.2, 1H), 2.59 (dd, J = 5.0, 2.7, 1H).

***O*-glycidylethyleneglycol (1d)**: Allyloxyethanol (5.1 g, 50 mmol) was dissolved in dichloromethane (50 mL) in a roundbottom flask with a stirbar and cooled to 0 °C. MCPBA (15.5 g, 70 mmol) was added slowly and the reaction was warmed to 25 °C and stirred for 24 hours. Solid was filtered away and solvent was removed *in vacuo*. Residue was dissolved in diethyl ether and extracted 3 times with deionized water. Water was washed 3 times with diethyl ether, and then extracted 5 times with a large excess of dichloromethane, which was then dried over Na_2SO_4. Solvent was removed *in vacuo* to afford product as a colorless oil: 2.96 g (50% yield). ^{1}H NMR ($CDCl_3$): δ 3.81 (dd, J = 11.7, 2.8, 1H), 3.72 (dd, J = 8.2, 4.0, 2H), 3.69 – 3.51 (m, 2H), 3.43 (dd, J = 11.7, 5.8, 1H), 3.15 (ddt, J = 5.6, 4.2, 2.7, 1H), 2.79 (dd, J = 4.9, 4.2, 1H), 2.62 (dd, J = 5.0, 2.7, 1H), 2.17 (s, 1H).

***O*-glycidyl-*trans*-1,4-cyclohexanedimethanol (1e)**: *trans*-1,4-cyclohexanedimethanol (3.6 g, 25 mmol) was dissolved in dry dichloromethane (25 mL) in a Schlenk tube equipped with a stirbar and cooled to -78 °C. Epichlorohydrin (1.47 mL, 19 mmol) and boron trifluoride diethyl etherate (0.17 mL, 1.25 mmol) were added by syringe and the reaction was warmed to 25 °C, then heated to 50 °C for 3 hours. Sodium hydroxide (1.0 g, 25 mmol) in water (25 mL) was added to the dichloromethane mixture and the reaction was stirred and heated at 50 °C overnight. Aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with saturated ammonium chloride solution once and brine twice and then dried over Na_2SO_4. Residue was purified by flash chromatography (60% EtOAc:40 % hexanes) was isolated as a colorless oil: 1.83 g (49% yield). ^{1}H NMR ($CDCl_3$): δ δ 3.69 (dd, J = 11.6, 3.0, 1H), 3.43 (t, J = 5.8, 2H), 3.38 – 3.22 (m, 4H),

3.12 (ddt, J = 5.8, 4.2, 2.9, 1H), 2.77 (dd, J = 5.0, 4.2, 1H), 2.58 (dd, J = 5.0, 2.7, 1H), 1.81 (ddd, J = 10.9, 5.7, 2.5, 4H), 1.60 – 1.36 (m, 2H), 1.25 (t, J = 5.5, 1H), 1.02 – 0.83 (m, 4H).

***O*-allyl-1,4-benzenedimethanol (1f precursor)**: Sodium hydride (0.52 g, 22 mmol) was slurried in dry THF and added to a 200 mL Schlenk tube with a magnetic stir bar and then cooled to -78 °C. Under strong flow of nitrogen, 1,4-benzenedimethanol (6.0 mL, 43 mmol) was added added. The reaction was slowly warmed to 25 °C open to nitrogen bubbler. Because of the relative insolubility of 1,4-benzenedimethanol, the reaction was warmed to 50 °C until gas evolution ceased. The mixture was then cooled to -78 °C again, and allyl bromide (1.25 mL, 15 mmol) was added by syringe. The reaction was warmed to 25 °C, then heated at 50 °C for 24 hours. The reaction mixture was filtered through celite and solvent was removed *in vacuo*. The residue was purified by flash chromatography (10% acetone:90% dichloromethane) and isolated as a colorless oil: 2.0 g (78% yield). ^{1}H NMR ($CDCl_3$): δ 7.33 (s, 4H), 5.94 (ddt, J = 17.2, 10.4, 5.6, 1H), 5.24 (ddq, J = 35.2, 10.4, 1.5, 1H), 4.66 (d, J = 5.6, 2H), 4.51 (s, 2H), 4.01 (dt, J = 5.6, 1.4, 2H), 1.75 (t, J = 5.8, 1H).

***O*-glycidyl-1,4-benzenedimethanol (1f)**: *O*-allyl-1,4-benzenedimethanol (see below for synthesis) (2.0 g, 11 mmol) was dissolved in dichloromethane (15 mL) in a roundbottom flask with a stirbar and cooled to 0 °C. MCPBA (4.3 g, 19 mmol) was added slowly and the reaction was warmed to 25 °C for 24 hours. Solid was filtered away and solvent was removed *in vacuo*. Residue was purified by flash chromatography (10% acetone:90% dichloromethane) and product was isolated as a colorless oil: 1.35 g (62% yield). ^{1}H NMR ($CDCl_3$): δ 7.33 (s, 4H), 4.67 (s, 2H), 4.57

(q, J = 12.0, 2H), 3.75 (dd, J = 11.4, 3.0, 1H), 3.41 (dd, J = 11.4, 5.9, 1H), 3.17 (ddd, J = 7.0, 5.9, 2.9, 1H), 2.87 – 2.73 (m, 1H), 2.60 (dd, J = 5.0, 2.7, 1H).

2-((Allyloxy)methyl)-2-methylpropane-1,3-diol (1g precursor): Sodium hydride (1.6 g, 69 mmol) was slurried in dry THF and added to a 200 mL Schlenk tube with a magnetic stir bar and then cooled to -78 °C. While open to nitrogen bubbler, 5-hydroxymethyl-2,2,5-trimethyl-1,3-dioxane (9.1 g, 57 mmol) in THF was added slowly by syringe. The reaction was slowly warmed to 25 °C and stirred until gas evolution ceased. It was then cooled to -78 °C again, and allyl bromide (5.4 mL, 63 mmol) was added by syringe. The reaction was warmed to 25 °C, then heated at 50 °C for 24 hours. Reaction mixture was filtered through celite and solvent was removed *in vacuo*. 5-((Allyloxy)methyl)-2,2,5-trimethyl-1,3-dioxane was purified by vacuum distillation. The acetone protecting group was removed by heating 5-((allyloxy)methyl)-2,2,5-trimethyl-1,3-dioxane with 16 mL 1M HCl in THF at 45 °C for 14 hours, followed by removal of all volatiles by vacuum to afford product as a colorless oil: 8.3 g (91% yield). ^{1}H NMR ($CDCl_3$): δ 5.86 (ddd, J = 22.7, 10.8, 5.5, 1H), 5.20 (dddd, J = 13.2, 10.4, 3.0, 1.4, 2H), 3.96 (d, J = 5.5, 2H), 3.63 (dd, J = 46.3, 10.9, 4H), 3.42 (s, 2H), 2.36 (s, 2H), 0.81 (s, 3H).

2-Methyl-2-((oxiran-2-ylmethoxy)methyl)propane-1,3-diol (1g): 2-((Allyloxy)methyl)-2-methylpropane-1,3-diol (see below for synthesis) (3.15 g, 20 mmol) was dissolved in dichloromethane (20 mL) in a roundbottom flask with a stirbar and cooled to 0 °C. MCPBA (6.2 g, 28 mmol) was added slowly and the reaction was warmed to 25 °C for 24 hours. Solid was filtered away and solvent was removed *in vacuo*. Residue was dissolved in diethyl ether and extracted 3 times with

deionized water. Water was washed 3 times with diethyl ether, and then approximately 50% water was removed by vacuum. The remaining aqueous mixture was extracted 5 times with a large excess of dichloromethane, which was then dried over Na_2SO_4. Solvent was removed *in vacuo* to afford product as a colorless oil: 1.92 g (55% yield). ^{1}H NMR ($CDCl_3$): δ 3.84 – 3.34 (m, 8H), 3.13 (ddt, J = 5.4, 4.2, 2.7, 1H), 2.83 – 2.74 (m, 1H), 2.62 (dd, J = 5.0, 2.8, 1H), 0.80 (s, 3H).

General procedure for carbonylation of epoxide-alcohols.

Substrate and catalyst were dissolved in dioxane in glovebox and added to a 100 mL Parr reactor with magnetic stir bar. Reactor was pressured to at least 800 PSI CO. Reactor was heated in oil bath with stirring to 50 °C, then the temperature was ramped to 90 °C. The reactor was then cooled in dry ice for 5 minutes before CO was released. ^{1}H NMR was taken for crude conversion. Solvent was removed by vacuum and residue was purified by crystallization or flash chromatography.

(**(2-(2-Hydroxyethoxy)ethoxy)methyl)succinic anhydride (2c):** Substrate: *O*-glycidyldiethyleneglycol **(1c) (**0.36 g, 2 mmol), [ClTPPAl][$Co(CO)_4$]: 0.087 g, 0.08 mmol, 4 mol%. Dioxane: 10 mL (0.2 M). Temperature: 50 °C for 2 hours, 90 °C for 24 hours. Chromatography: 80% EtOAc:20% hexanes to 100% EtOAc. 0.26 g isolated (56% yield). ^{1}H NMR ($CDCl_3$) δ 3.98 (dd, J = 9.3, 3.4, 1H), 3.74 – 3.50 (m, 9H), 3.25 (ddt, J = 9.3, 6.3, 3.2, 1H), 3.12 – 2.93 (m, 2H).

(**(2-Hydroxyethoxy)methyl)succinic anhydride (2d):** Substrate: *O*-glycidylethyleneglycol **(1d) (**0.35 g, 3 mmol), [ClTPPAl][$Co(CO)_4$]: 0.066 g, 0.06 mmol, 2 mol%. Dioxane: 6 mL (0.5 M). Temperature: 50 °C for 2 hours, 80 °C for 8

hours. Chromatography: 80% EtOAc:20% hexanes to 100% EtOAc. 0.091 g isolated (17% yield). ^{1}H NMR ($CDCl_3$) δ 3.98 (dd, J = 9.4, 3.4, 1H), 3.71 (dd, J = 9.0, 3.5, 3H), 3.60 (t, J = 4.3, 2H), 3.35 – 3.22 (m, 1H), 3.04 (d, J = 7.7, 2H).

(((4-(hydroxymethyl)cyclohexyl)methoxy)methyl) succinic anhydride (2e): Substrate: *O*-glycidyl-*trans*-1,4-cyclohexanedimethanol **(1e) (**0.32 g, 1.4 mmol), [ClTPPAl][$Co(CO)_4$]: 0.046 g, 0.04 mmol, 3 mol%. Dioxane: 7 mL (0.2 M). Temperature: 50 °C for 3 hours, 80 °C for 24 hours. Chromatography: 80% EtOAc:20% hexanes. Recrystallized from diethyl ether at -40 °C. 0.182 g isolated (57% yield). M.P. = 78 °C, ^{1}H NMR ($CDCl_3$) δ 3.86 (dd, J = 9.2, 3.2, 1H), 3.58 (dd, J = 9.2, 3.0, 1H), 3.44 (s, 2H), 3.30 – 3.19 (m, 3H), 3.01 (d, J = 7.6, 2H), 1.89 – 1.62 (m, 4H), 1.41 (s, 2H), 1.23 (s, 1H), 1.05 – 0.81 (m, 4H). HRMS (ESI) calculated for $C_{13}H_{21}O_5^+$ (M + H+): 257.1389; measured 257.1393.

(((4-(hydroxymethyl)benzyl)oxy)methyl) succinic anhydride (2f): Substrate: *O*-glycidyl-1,4-benzenedimethanol **(1f)** (1.35 g, 7 mmol), [ClTPPAl][$Co(CO)_4$]: 0.23 g, 0.2 mmol, 3 mol%. Dioxane: 14 mL (0.5 M). Temperature: 45 °C for 2 hours, 90 °C for 38 hours. Chromatography: 10% acetone:90% dichloromethane. Recrystallized from EtOAc:diethyl ether (~1:10): 0.22 g isolated (17% yield). M.P. = 95 °C ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J = 8.0, 4H), 4.68 (d, J = 5.2, 2H), 4.53 (q, J = 12.1, 2H), 3.90 (dd, J = 9.2, 3.4, 1H), 3.61 (dd, J = 9.2, 3.1, 1H), 3.29 – 3.18 (m, 1H), 3.00 (d, J = 7.7, 2H).

3-((3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy)methyl) succinic anhydride (2g): Substrate: 2-methyl-2-((oxiran-2-ylmethoxy)methyl)propane-1,3-diol **(1g)**: **(**0.44 g, 2.5 mmol), [ClTPPAl][$Co(CO)_4$]: 0.082 g, 0.07.5 mmol, 3 mol%.

Dioxane: 25 mL (0.1 M). Temperature: 50 °C for 3 hours, 90 °C for 24 hours. Chromatography: 10% acetone:90% dichloromethane to 50% acetone:50% dichloromethane. Recrystallized by dissolving residue in 1 mL EtOAc and slo diffusion of diethyl ether at -40 °C. 0.078 g isolated (16% yield). M.P. = 86 °C, ^{1}H NMR (acetone) δ 3.88 (dd, J = 9.2, 3.4, 1H), 3.76 (s, 1H), 3.69 (dd, J = 9.2, 3.1, 1H), 3.60 (s, 1H), 3.54 – 3.35 (m, 7H), 3.23 (dd, J = 18.4, 10.0, 1H), 2.98 (dd, J = 18.4, 4.7, 1H), 1.01 – 0.62 (m, 3H). ^{13}C NMR (acetone) δ 174.94, 172.62, 75.18, 70.86, 66.84, 43.82, 42.81, 33.11, 17.60.

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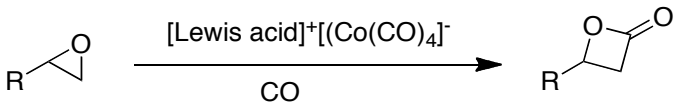
CHAPTER FOUR

Aluminum Lewis Acids with Donor-Appended Salalen Ligand Frameworks for Epoxide Carbonylation

4.1 Introduction

β-Lactones are a class of molecules that are useful small molecule synthetic intermediates[1,2] as well as active monomers for synthesis polyhydroxyalkanoates (PHAs).[3] PHAs are a class of naturally occurring polyesters that are used by bacteria for energy storage.[4] They have garnered significant interest recently because they are biodegradable and biocompatible polymers. Additionally, some PHAs have interesting materials properties that make them plausible biodegradable replacements for petroleum-derived plastics. For example, poly(3*R*-hydroxybutyrate) has a high T_m (> 170 °C) and similar properties to that of isotactic polypropylene.[5]

Ring-expansive epoxide carbonlyation is an efficient, atom-economical approach to the synthesis of β-lactones. Although epoxide carbonylation was first reported in a 1994 patent by Drent and coworkers,[6] it had a very narrow substrate scope, the mechanism of action was unclear, and attempts to reproduce the results indicated the major product of the reaction was actually polymer.[7] However, the discovery of the Lewis acid/cobalt(tetracarbonyl) ($Co(CO)_4$) catalyst system provided a discrete, homogeneous, active catalyst system for epoxide carbonylation (Figure 4.1).[8,9] Changes to the Lewis acid component of this system results in dramatic changes in reactivity, and improved Lewis acids led to increased substrate scope,[10,11] increased activity,[12] and advantages like low pressure carbonylation.[13]



Scheme 4.1 Epoxide carbonylation by homogenous Lewis acid/ $Co(CO)_4$ catalysts

Investigation into the mechanism of epoxide carbonylation with aluminum-based Lewis acids identified that the ring-closure step to form lactone and regenerate the active catalyst was the turnover-limiting step.[14] Additionally, a first-order rate dependence on donating solvent, such as THF, was discovered. This can be attributed to the change in coordination of the aluminum center as it transitions from a 5-coordinate neutral aluminum species to a 6-coordinate cationic aluminum species. As such, epoxide carbonylation with aluminum Lewis acids was particularly slow in nonpolar, non-donating solvents such as hexanes and toluene.

We were intrigued by the idea of increasing the rate of ring-closure through the covalent-modification of the Lewis acid ligand with its own donating moiety, thus removing the need for donating solvent. As well as being an interesting proof of concept, such a catalyst could be useful for the carbonylation of epoxides with side-chain functionalities reactive to the cobalt-acyl resting state.

Additionally, it was shown that in the double carbonylation of epoxides to succinic anhydrides, the second carbonylation from lactone to anhydride had an *inverse* first order relationship with polar, donating solvent.[11] Therefore, while the coversion of epoxide to lactone occurred fastest in THF, it was very slow in toluene, and the conversion of lactone to anhydride occurred fastest in toluene, but it was slowest in THF. It was proposed that the use of a two-catalyst system with a donor-appended catalyst for the first step and a porphyrin catalyst for the second would allow for fast double carbonylation of epoxides in toluene.

4.2 Results and Discussion

We investigated different ligands on which to append our donating group and settled on the hybrid salalen framework. Aluminum salalens have been used for catalytic enantioselective sulfur oxidation[15] and hydrophosphonation of aldehydes.[16] It is similar to the Salph ligand already successfully used for epoxide carbonylation.[8,13] The singly-reduced salalen framework gives us a synthetic handle with which to append a single donor (Figure 4.2), as it is probable that donors bound to both faces of the aluminum catalyst would prevent it from binding and activating epoxide substrate.

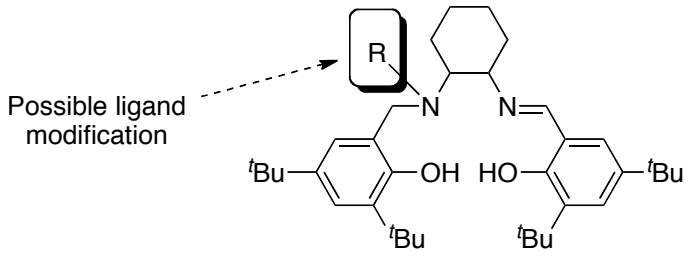


Figure 4.2 The salalen ligand framework and proposed modification point

We decided to test two different groups for ability as the axial donor, strongly Lewis basic pyridine and weakly Lewis basic furan. The synthesis was designed based on our group's prior success building non-symmetric salen ligands by starting with mono-protonated diaminocyclohexane. The 2-substituted aromatic aldehydes of the proposed donors were attached by reductive amination. The two phenolic donors were attached by imine condensation and Mannich condensation, respectively to generate the pyridine-appended salalen (**1a**) and the furan-appended salalen (**1b**) (Figure 4.3).

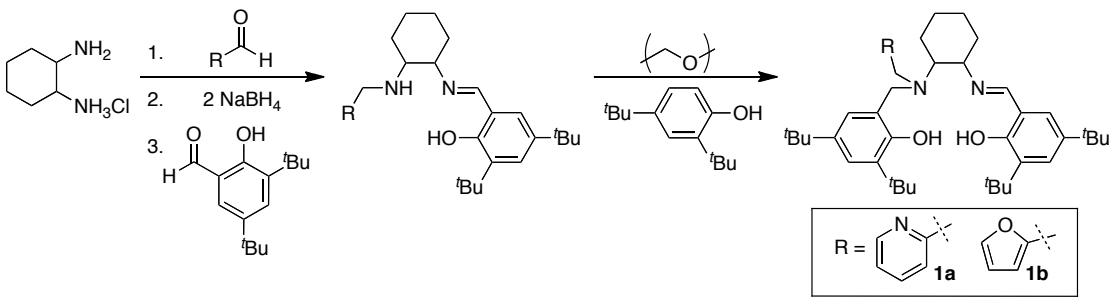


Figure 4.3 Synthetic methodology to access donor-appended salalen ligands

Metallation and salt metathesis to generate the [cationic aluminum] [cobalt tetracarbonyl] complex were carried out using standard protocol yielding complexes **2a** and **2b** (Figure 4.4). In all carbonylation catalysts our group has synthesized, the Lewis acid is coordinated by two THF solvent molecules. By ^{1}H NMR, This was true in the case of the furan-appended **2b**, but the pyridine-strapped **2a** had only one bound THF, providing evidence for pyridine binding to the cationic aluminum center.

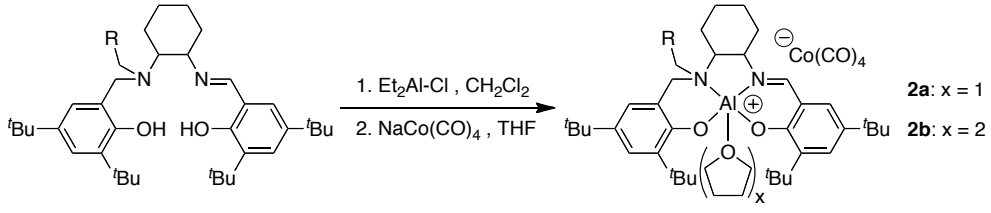
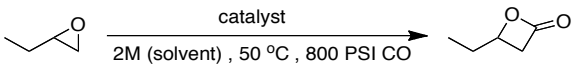


Figure 4.4 Metallation and salt metathesis to form bimetallic complexes

With the catalysts in hand, we tested their reactivity for epoxide carbonylation activity in different solvents along with the most closely related carbonylation catalyst $[(Salph)Al(THF)_2][Co(CO)_4]$[8] (SalphAl) (Table 4.1). 1,2-Epoxybutane was used as a model epoxide and typical carbonylation conditions were used for all reactions.

Table 4.1 Carbonylation of 1,2-epoxybutane using appended salalen catalysts **2a** and **2b** compared to SalphAl in a variety of solvents



entry	catalyst	epoxide:catalyst	solvent	time (min.)	conversion[a]	TOF (hr^{-1})
1	**2a**	400:1	THF	60	56%	170
2	**2a**	400:1	hexanes	60	33%	130
3	**2a**	400:1	toluene	60	95%	310
4	**2a**	400:1	neat	60	25%	100
5	**2a**	400:1	DME	60	45%	180
6	**2a**	1000:1	dioxane	60	81%	810
7	**2b**	400:1	THF	60	11%	44
8	**2b**	400:1	hexanes	60	< 1%	-
9	**2b**	400:1	toluene	60	< 1%	-
10	**2b**	400:1	neat	60	12%	48
11	SalphAl	400:1	THF	60	72%	290
12	SalphAl	200:1	hexanes	50	5%	12
13	SalphAl	200:1	toluene	50	11%	26
14	SalphAl	400:1	neat	60	23%	90
15	SalphAl + 2-picoline	200:1	toluene	50	3%	8

[a] Measured by ^{1}H NMR

As seen from entries 1-6 the pyridine-appended catalyst **2a** is active for epoxide carbonylation in all solvents tested. As expected, the donating moiety greatly increased the rate in non-donating solvents like hexanes and toluene (entries 2, 3) compared to the original SalphAl catalyst, which had very low activity (entries 12, 13). Interestingly, the rate of the pyridine catalyst in toluene is actually higher than in the donating solvents THF and DME (entries 1, 5), possibly because of competitive binding of THF versus epoxide to the aluminum center. The pyridine catalyst was fastest in the donating but nonpolar 1,4-dioxane. As opposed to the success of **2a**, the furan-appended catalyst **2b** had limited activity in THF and neat epoxide (entries 7, 10) and showed no activity in non-donating solvents hexanes and toluene (entries 8,

9). Most likely the furan moiety is too weak of a donor to assist the ring-closing of lactone. The relative inactivity of **2b** is a useful control, however, to show that there is no inherent advantage in the salalen ligand framework compared to salen, and in fact it appears to be significantly worse in the absence of a strong appended donor. This offers evidence that the additional binding of pyridine in **2a** is primarily responsible for its significantly increased activity. Additonally, a control experiment was conducted by mixing a 1:1 ratio of 2-picoline and SalphAl and testing its activity under the same conditions (entry 15) to determine if addition of external pyridine would also increase the rate in non-polar solvents. Interestingly, this system showed very little activity

Because the use of THF as a solvent seemed to inhibit the reaction, we tested the turnover frequency of **2a** as a function of added THF. Carbonylations with **2a** were run using hexanes:THF mixtures 3:1, 1:1, and 1:3 to supplement. This was also compared to the SalphAl system (Figure 4.5). Unlike SalphAl, which has been shown previously to have a first-order dependence of donating THF to its rate, **2a** reached a maximum TOF in a 1:1 mixture of THF hexanes, after which additional THF slowed the reaction. At none of the amounts of THF was **2a** as active as in toluene or dioxane or salphAl in THF.

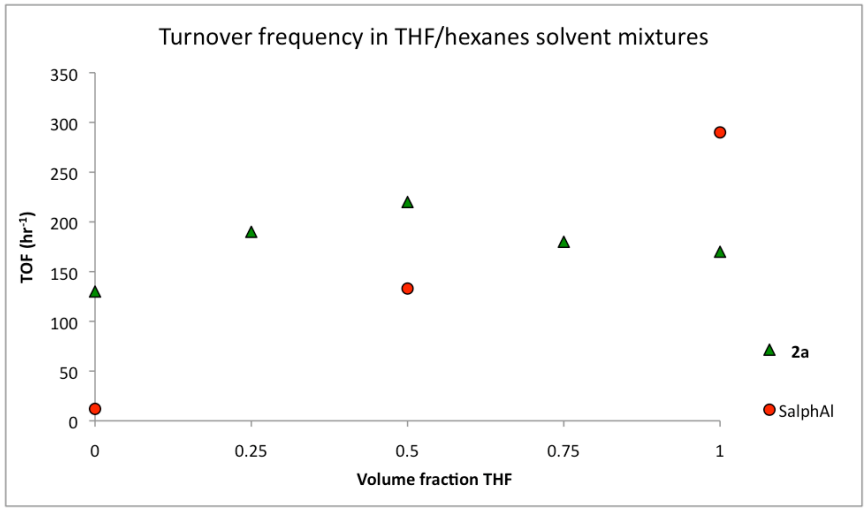
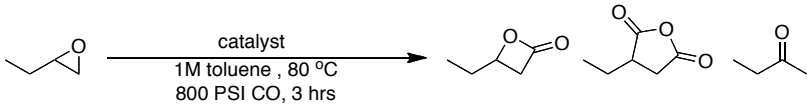


Figure 4.5 Turnover frequency as a function of added THF in hexanes for SalphAl and **2a**

Because of the expected rate increase of **2a** in toluene, the two-catalyst protocol for anhydride synthesis in toluene was attempted. **2a** (0.25 mol%) and *meso*-tetra(4-chlorophenyl)porphyrinato aluminum cobalt tetracarbonyl ([ClTPPAl][$Co(CO)_4$]) (0.25 mol%) were tested for the conversion of 1,2-epoxybutane to ethylsuccinic anhydride versus the use of [ClTPPAl][$Co(CO)_4$] (0.5 mol%) alone (Table 4.2). Unfortunately, despite the increased activity of **2a** in toluene, the reaction overall went to lower conversion than the same mole percent of aluminum using only [ClTPPAl][$Co(CO)_4$]. However, the porphyrin catalyst in toluene also generated a significant amount of the unwanted ketone side product formed by β-hydrogen elimination from the cobalt alkyl species. The two-catalyst system generated less ketone than the porphyrin alone, however, it still produced more than the typical double carbonylation conditions using 1,4-dioxane as solvent.[11]

Table 4.2 Double carbonylation of 1,2-epoxybutane by two-catalyst system



entry	catalyst 1	catalyst 2	epoxide	lactone	anhydride	ketone
1	0.25 mol% [ClTPPAl][Co(CO)$_4$]	0.25 mol% **2a**	<1%	52%	41%	7%
2	0.50 mol% [ClTPPAl][Co(CO)$_4$]	–	<1%	25%	51%	24%

The failure of the 2-catalyst system to generate anhydride faster than solely the porphyrin system likely has to do with the mechanism and rates of the two elementary reactions. The conversion of epoxide to lactone has been shown to have zero order in epoxide,14 leading to a linear conversion to lactone until the reaction completes. Therefore, even with the slower rate of the porphyrin in toluene, the reaction proceeds to complete conversion in a linear fashion. Secondly, the second carbonylation of lactone to anhydride is slower than the first.[11]11 In the two-catalyst system, the pyridine-appended catalyst showed no activity for anhydride formation, therefore only 50% of total catalyst is active for the slwer step. The porphyrin system, however, has 100% of its catalyst active for the slower second carbonylation, and therefore proceeded to higher overall conversion.

4.3 Conclusion

We report the design and synthesis of a new class of carbonylation catalyst based on the salalen ligand framework with an appended donating group in the hopes of increasing its activity in non-donating solvents. The pyridine-appended catalyst was active for the carbonylation of 1,2-epoxybutane in a wide variety of solvents and, as

predicted, was much more active in non-donating solvents like hexanes and toluene than previously reported catalysts.

4.4 Experimental

General Considerations. All manipulations of air and water sensitive compounds were carried out under dry nitrogen using a Braun Labmaster glovebox or standard Schlenk line techniques. High-pressure reactions took place in a custom-made, stainless steel 6-well reactor as described previously[8] or a 100 mL stainless steel Parr-type reactor. ^{1}H NMR spectra were recorded on a Varian Mercury (^{1}H, 300 MHz), Varian INOVA 400 (^{1}H, 400 MHz) or Varian INOVA 600 (^{1}H, 600 MHz) spectrometer and referenced with residual non-deuterated solvent shifts ($CHCl_3$ = 7.24 ppm, benzene = 7.16 ppm). ^{13}C NMR spectra were recorded on a Varian Mercury (^{13}C, 75 MHz) or Varian INOVA (^{13}C, 125 MHz) spectrometer and referenced to chloroform (77.23 ppm) or benzene (128.39 ppm).

Materials. Carbon monoxide was purchased from Matheson Trigas or Airgas in aluminum cylinders (99.99% min. purity) and was used as received. HPLC-grade tetrahydrofuran, toluene, dichloromethane, diethyl ether, and hexanes were purchased from Fisher Scientific and purified over solvent columns and degassed by three freeze/pump/thaw cycles. 1,2-Dimethoxyethane and 1,4-dioxane were dried over sodium/benzophenone and then vacuum transferred and degassed by three freeze/pump/thaw cycles. 1,2-Epoxybutane was stirred over CaH_2 for three days, vacuum transferred, and degassed by three freeze/pump/thaw cycles. *Trans*-1,2-diaminocyclohexane•HCl[17], N,N′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-

benzenediamine aluminum cobalt tetracarbonyl (SalphAl)[8] and *meso*-tetra(4-chlorophenyl)porphyrinato aluminum cobalt tetracarbonyl ([ClTPPAl][$Co(CO)_4$])[11] were prepared according to reported literature procedures. All other materials were purchased from commercial sources and used without further purification except where noted.

Catalyst synthesis.

1a Half-ligand precursor: *Trans*-1,2-diaminocyclohexane•HCl (1.5 g, 10 mmol) was dissolved in MeOH (10 mL) in roundbottom flask with stirbar. 2-Pyridinecarboxaldehyde (0.95 mL, 10 mmol) was added by syringe and the reaction was stirred at 25 °C for 2 hours. The flask was cooled in an ice water bath, followed by careful addition of sodium (0.83 g, 22 mmol) and warmed to 25 °C for 2 hours. Residual sodium borohydride was quenched with a few drops of water. 3,5-Di-*tert*-butylsalicylaldehyde (2.34 g, 10 mmol) was added and the reaction mixture stirred overnight. Solvent was removed *in vacuo* and residual material was dissolved in dichloromethane and distilled water. The aqueous layer was extracted twice with dichloromethane and the combined organic layers were washed twice with distilled water and once with saturated brine, then dried over Na_2SO_4. Dichloromethane was removed *in vacuo* and the residue was dissolved in chloroform and layered with methanol to crystallize out the major impurity: N,N′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine. After filtration to remove the salen impurity, chloroform was removed *in vacuo* to afford a viscous green oil: 3.17 g (75%). ^{1}H NMR ($CDCl_3$): δ

(2-pyridylmethyl)salalen 1a: **1a Half-ligand precursor** (3.00 g, 7.1 mmol), paraformaldehyde (0.21 g, 7.1 mmol), and 2,4-di-*tert*-butylphenol (1.47 g, 7.1 mmol) were dissolved in benzene (7 mL) in a 20 mL scintillation vial with a magnetic stir bar. The vial was sealed with a Teflon-lined cap and secured with electrical tape, then heated to 100 °C for 24 hours. Benzene was removed *in vacuo* and the resulting oil was purified by flash chromatography (CH_2Cl_2). After isolation and solvent removal, **1a** was recrystallized from hot acetonitrile as a fine yellow powder: 1.62 g (36 %). ^{1}H NMR ($CDCl_3$): δ 13.61 (s, 1H), 8.40 (s, 1H), 7.36 (t, J = 4.2, 1H), 7.29 (m, 1H), 7.07 (d, J = 2.4, 1H), 6.25 (m, 1H), 6.10 (d, J = 3.1, 1H), 3.75 (q, J = 14.8, 3H), 2.99 (m, 1H), 2.65 (m, 1H), 2.08 (d, J = 13.7, 2H), 1.74 – 1.16 (m, 6H), 1.44 (s, 9H), 1.27 (s, 9H).

1b Half-ligand precursor: *Trans*-1,2-diaminocyclohexane•HCl (1.21g, 8 mmol) was dissolved in MeOH (20 mL) in roundbottom flask with stirbar. 2-furfuraldehyde (0.66 mL, 8 mmol) was added by syringe and the reaction was stirred at 25 °C for 2 hours. The flask was cooled in an ice water bath, followed by careful addition of sodium (0.64g, 17 mmol) and warmed to 25 °C for two hours. Residual sodium borohydride was quenched with a few drops of water. Di-*tert*-butylsalicylaldehyde (1.87 g, 8 mmol) was added and the reaction mixture was stirred overnight. Solvent was removed *in vacuo* and residual material was dissolved in dichloromethane and distilled water. The aqueous layer was extracted twice with dichloromethane and the combined organic layers were washed twice with distilled water and once with saturated brine, then dried over Na_2SO_4. Dichloromethane was removed *in vacuo* and the residue was dissolved in chloroform and layered with

methanol to crystallize out the major impurity: N,N′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine. After filtration to remove the salen impurity, chloroform was removed *in vacuo* to afford a viscous geen oil: 2.34 g isolated (70% yield). ^{1}H NMR ($CDCl_3$): δ 13.61 (s, 1H), 8.40 (s, 1H), 7.37 (d, J = 2.4, 1H), 7.29 (m, 1H), 7.07 (d, J = 2.4, 1H), 6.26 (m, 1H), 6.12 (m, 1H), 3.72 (m, 2H), 2.99 (m, 1H), 2.65 (m, 1H), 2.13 (m, 2H), 1.77 – 1.17 (m, 6H), 1.44 (s, 9H), 1.28 (s, 9H).

(2-furfurylmethyl)salalen 1b: **1b Half-ligand precursor** (1.72 g, 4.2 mmol), formalin (0.34 mL, 4.2 mmol), and 2,4-di-*tert*-butylphenol (0.87 g, 4.2 mmol) were dissolved in methanol (4 mL) in a 20 mL scintillation vial with a magnetic stir. The reaction was sealed and heated at 60 °C for 120 hours. Methanol was removed *in vacuo* and the resulting oil was purified by flash chromatography (CH_2Cl_2). After isolation and solvent removal, **1b** was washed with hot MeOH and isolatedas a fine off-white powder: 0.43 g (16 % yield). ^{1}H NMR ($CDCl_3$): δ 13.43 (s, 1H), 10.22 (s, 1H), 8.32 (s, 1H), 7.37 (d, J = 2.4, 1H), 7.34 (s, 1H), 7.11 (d, J = 2.3, 1H), 7.02 (d, J = 2.4, 1H), 6.84 (d, J = 2.2, 1H), 6.32 (m, 1H), 6.22 (d, J = 3.1, 1H), 4.04 (d, J = 13.9, 1H), 3.66 (m, 3H), 3.32 (m, 1H), 3.00 (m, 1H), 1.93 – 1.02 (m, 8H), 1.49 (s, 9H), 1.29 (s, 9H), 1.25 (s, 9H), 1.11 (s, 9H).

Metallation and salt metathesis general procedure: Ligand (1 equiv.) was added to a dry Schlenk tube with a stir bar and was dried under vacuum for at least 1 hour, then dissolved in dry dichloromethane. Diethylaluminum chloride (1.8M in heptanes, 1.2 equiv.) was added by syringe while open to nitrogen bubbler and the mixture was stirred for at least 3 hours. Solvent was removed by vacuum on Schlenk line and the reaction tube was brought to the glove box. Sodium cobalt tetracarbonyl

(1 equiv.) was added and dry THF was added. The reaction was stirred overnight and THF was removed on Schlenk line. The residue was brought to the glovebox where it was dissolved in a minimum of THF and filtered through a syringe filter. The filtrate THF was removed on the Schlenk line.

[**(2-pyridylmethyl)salalen aluminum][cobalttetracarbonyl] 2a**: 0.39 g, 0.55 mmol. Complex was recrystallized from dry diethyl ether affording yellow powder: 0.17 g, 34% yield. ^{1}H NMR (C_6D_6): δ 8.85 (d, J = 5.4, 1H), 7.95 (s, 1H), 7.82 (s, 1H), 7.63 (d, J = 8.4, 1H), 7.44 (d, J = 9.2, 1H), 7.11 (s, 1H), 6.85 (m, 2H), 6.44 (s, 1H), 5.26 (d, J = 18.2, 1H), 3.80 (m, 3H), 3.58 (s, 4H), 3.26 (d, J = 13.6, 0H), 3.04 (d, J = 13.3, 1H), 2.47 (s, 9H), 1.72 (s, 9H), 1.38 (s, 9H), 1.32 (s, 9H), 1.27 (s, 12H), 0.60 (m, 1H), 0.12 (m, 1H). IR: ($\nu_{C=O}$) = 1875 cm^{-1}

[**(2-furfurylmethyl)salalen aluminum][cobalttetracarbonyl] 2b**: Starting material: 0.17 g, 0.24 mmol. Complex was too soluble in common dry organic solvents and was used directly as a yellow powder: 0.050 g, 21% yield. ^{1}H NMR (C_6D_6): mostly insoluble: *alkyl* region: δ 2.0 – 0.9 (42H), THF peak: δ 3.58 (8.65 H) (~2.2 THF/Al) IR: ($\nu_{C=O}$) = 1880 cm^{-1}

General carbonylation procedure: In the glovebox, catalyst was weighed to 8 mL scintillation vials with magnetic stir bars and dissolved in the desired solvent. Epoxide was added and the vials were loaded into the 6-well high-pressure reactor, which was sealed and removed from the glovebox and pressured to 800 PSI CO. The reactor was then heated to the desired temperature and magnetically stirred. After the

reaction time the reactor was cooled in dry ice for 5 minutes followed by CO release. Conversions were measured by ^{1}H NMR.

Addition of 2-picoline to SalphAl procedure: 2-Picoline was dried over 3Å molecular sieves for 3 days, dissolved in dry toluene, and degassed by sparging the solution with nitrogen prior to use. In the glovebox, SalphAl and toluene were added to 100 mL Parr reactor with magnetic stir bar. After removal from the glovebox, reactor the reactor was attached to carbon monoxide line, and a septum was attached over the injection valve behind a flow of 5 PSI CO. The picoline solution was injected and allowed to stir with SalphAl briefly. 1,2-Epoxybutane was then injected in the same manner, the injection valve was sealed, and the reactor was charged to 900 PSI CO. It was heated in an oil bath at 50 °C for 50 minutes with magnetic stirring, then cooled in dry ice for 5 minutes at which point CO was released and conversion was measured by ^{1}H NMR spectroscopy.

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CHAPTER FIVE

Zinc Dipyrromethenes: New Catalysts for β-Lactone Polymerization

5.1 Introduction

Poly(4-hydroxybutyrate) (PHB) and its relatives, poly(4-hydroxyalkanoates) (PHAs) are naturally occurring polyesters which are biodegradable, biocompatible, and have interesting mechanical properties.[1] They have therefore garnered a significant amount of attention recently as an environmentally friendly alternative to classic commodity plastics such as polyethylene and polypropylene. It is possible to obtain PHAs by bacterial fermentation, but the process is energy-intensive and there is limited tolerance for different functional side-chains.[2] By chemical routes, PHAs are inaccessible by traditional condensation polymerization of β-hydroxycarboxylic acids because of the propensity to eliminate water forming the α,β-unsaturated products instead. However, the polymer may be successfully synthesized via the ring-opening polymerization of β-lactones (Figure 5.1).[3]

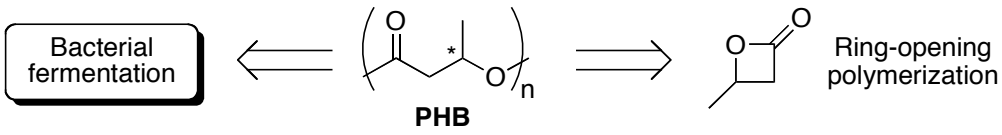

Figure 5.1 Synthetic routes to poly(3-hydroxybutyrate)

Naturally occurring PHB exists as the all (*R*) stereoisomer and is a semicrystalline polymer with a T_m > 170 °C and has been investigated for its excellent physical properties.[4] Atactic PHB from the polymerization of racemic β-butyrolactone, however, is an amorphous polymer with a T_g = 4 °C with no mechanical integrity. Although it is possible to synthesize the naturally occurring isomer from the polymerization of enantiopure lactone, the limited availability of

starting material would render this method prohibitively expensive for most applications.

As a result, there has been interest in the stereoselective polymerization of β-lactones to provide facile access to these exciting materials from a viable, synthetic chemical pathway. The first reported isoselective catalysts were generated from heterogeneous methaluminoxane systems,[5,6] which are known to generate asymmetric coordination sites from the studies of isoselective olefin polymerizations. These systems produce various tacticities of PHB, owing to the numerous different active polymerization sites, but isotactic material can be obtained by fractionation. While aluminoxane systems gave polymer with similar isotacticities to the bacterially produced material, they suffered from broad molecular distributions ($M_w/M_n > 4$), long reaction times, and the need to isolate isotactic fractions from atactic and syndiotactic material. Most recently, PHB with [m] diads as high as 85% and narrow molecular weight distributions was synthesized from silicate-supported rare-earth catalysts, although the polymer was limited to low molecular weights (M_n <12 kg/mol).[7]

Homogeneous catalysts have had success generating partially isotactic PHB. Aluminum-based catalysts with chiral salen or porphyrin scaffolds are able to generate iso-enriched PHB, but the molecular weights and tacticity is limited.[8] Reaction of metal salts with chiral diols allowed the kinetic resolution polymerization of β-butyrolactone, however, like the heterogeneous systems, both isotactic and syndiotactic polymer was produced.[9] An achiral salen chromium(III) catalyst that is thought to polymerize through a bimetallic enchainment mechanism was able to achieve isotacticities with [m] diads of 60-70%.[10] However, this system requires high

reaction temperatures (100 °C) and also suffers from very broad molecular weight distributions (M_w/M_n = 5-10) as well as showing secondary melting points indicative of syndiotactic PHB.

One of the difficulties in the isoselective polymerization of PHB is the fact that the ring-opening polymerization of β-lactones has a tendency to produce syndioenriched material by chain-end control.[11] Recently, the Carpentier group has used this innate reactivity to their advantage, creating highly syndioselective yttrium(III) catalysts for β-lactone polymerization.[12] The chain-end bias for syndiospecific enchainment must be overcome by the ligand in an isoselective catalyst.

In the past, the Coates group has investigated the β-diiminate zinc isopropoxide cataysts for the polymerization of β-lactones.[3] These zinc-based catalysts are active at reasonable temperatures, and are living for β-butyrolactone polymerization to PHB. However, the BDI ligand system is achiral and produces only atactic polymer from racemic monomers.

We proposed a catalyst based on the dipyrromethene (DPM) ligand framework, which can be synthesized from the condensation with pyrroles and aldehydes followed by oxidation (Figure 5.2). Like BDI, DPM is a monoanionic ligand that forms a 6-membered nitrogen-bound metallocycle when complexed. We hoped this analogous structure would allow us to synthesize a zinc alkoxide catalyst with the same inherent reactivity as BDIZnO^{i}Pr, while allowing us to alter the ligand geometry to form an isoselective catalyst.

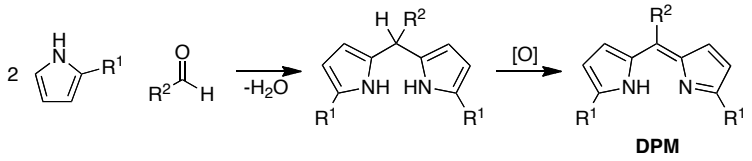

Figure 5.2 The dipyrromethene (DPM) ligand framework

Dipyrromethenes can be thought of as one half-porphyrin systems, and their coordination behavior has been studied with a variety of metals, including iron[13,14] and zinc.[14] They are, however, relatively unstudied as catalyst ligand frameworks. One reason for this may be due to the limited availability of 2-substituted pyrroles, hindering the ability to tune the sterics and electronics of the DPM framework. A recent report by the Sadighi group showed the efficient synthesis of 2-aryl pyrroles via cross-coupling.[15] This method allows the introduction of asymmetric aryl groups into the DPM framework in the hopes of forming a chiral pocket for catalysis to take place (Figure 5.3). We proposed to synthesize a series of these DPM zinc alkoxides and tested their activity and stereoselectivity for the polymerization of β-butyrolactone to PHB.

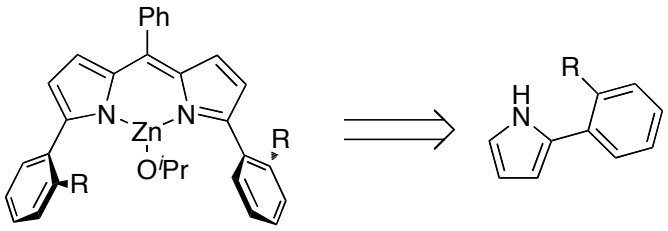

Figure 5.3 Proposed chiral DPM catalysts from 2-arylpyrroles

5.2 Results and Discussion

Using the Sadighi protocol, we synthesized a series of 2-aryl pyrroles with varying substitutions (Figure 5.4). Aryl halides are the precursors described in the original report, but *o*-alkylaryl halides were not easily available. Instead we converted phenols to the corresponding aryl triflates, which were also active for the cross-coupling conditions. The unsubstituted and 2-phenyl substituted pyrroles were isolated in good yield. The bulky 2-*tert*-butyl and 2,4,6-triisopropyl substituted pyrroles were isolated in lower yield, which is consistent with the observations made by Sadighi.

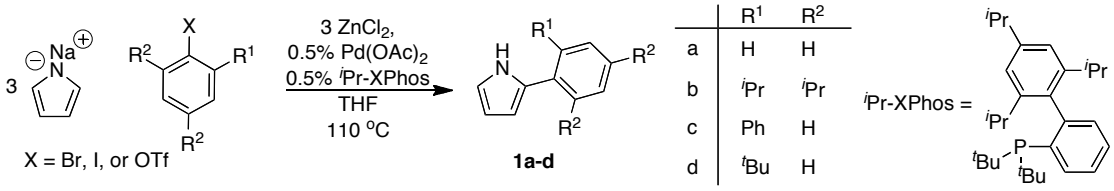

Figure 5.4 Synthesis of 2-aryl substituted pyrroles

With aryl pyrroles **1a-d** in hand, we synthesized the DPM ligands by a literature procedure.[14] Pyrroles **1a-d** were condensed with benzaldehyde dimethyl acetal to the corresponding dipyrromethanes. Without isolation, they were oxidized by 2,3-dichloro-5,6-dicyanoquinone to generate dipyrromethenes **2a-d** (Figure 5.5).

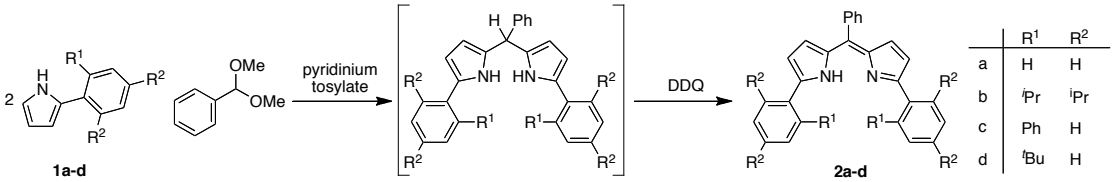

Figure 5.5 Pyrrole condensation to form dipyrromethanes followed by DDQ oxidation to afford dipyrromethene free ligand

Following isolation of the DPM ligands **2a-d**, we attempted to metallate them following the same protocol as the BDI zinc system.[3] Deprotonation and metallation was attempted with bis(bis(trimethylsilyl)amido) zinc followed by exchange for isopropoxide to form the active catalysts. The BDI ligands based on 2,6-diisopropylphenylaniline require metallation in refluxing xylenes for 48 hours. The DPM ligands on the other hand were deprotonated and metallated in 8 hours at 80 °C in toluene. Unfortunately, metallation of the unsubstituted **2a** with bis(bis(trimethylsilyl)amido) zinc did not yield the desired product, but instead formed the bis-ligated species, most likely due to the lack of steric bulk. However, the DPMs with *ortho*-aryl substituents formed the desired mono-ligated species. After reaction of the zinc amide intermediates with isopropanol, the alkoxide catalysts **3b-d** were formed (Figure 5.6).

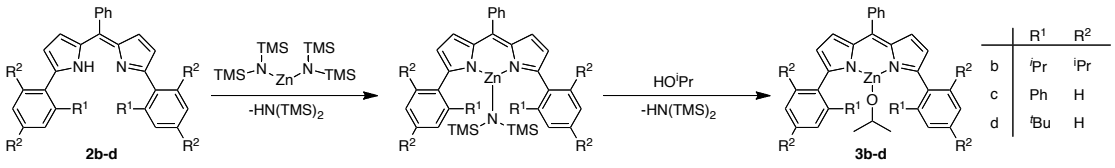

Figure 5.6 Metallation and formation of DPM zinc-alkoxides

With the zinc catalysts synthesized, we tested their activity for β-butyrolactone polymerization to PHB under a variety of conditions (Table 5.1). All three catalysts were active for the polymerization at 50 °C (entries 1, 6-9), but very limited activity was observed at temperatures below 40 °C. Increasing the temperature to 70 °C did not further increase the conversion (entry 4). The most successful polymerization (entry 1) was characterized by gel permeation chromatography (GPC) and was found

to have M_n = 20000 g/mol (theoretical M_n = 16100 g/mol) with a molecular weight distribution (M_w/M_n) of 1.19. The narrow molecular weight distribution and relative agreement between theoretical and observed molecular weight was similar to results using the BDI zinc catalysts, which are living catalysts for β-butyrolactone polymerizations.

Table 5.1 Polymerization of β-butyrolactone using DPMZnO^{i}Pr catalysts

entry	catalyst	monomer: catalyst	T (°C)	time (hr)	solvent	% conv.[a]
1	**3b**	200:1	50	18	toluene (5M)	94
2	**3b**	350:1	25	20	C_6D_6 (1.5M)	1
3	**3b**	400:1	35	21	neat	3
4	**3b**	200:1	40	11	C_6D_6 (0.75M)	33
5	**3b**	200:1	70	19	toluene (5M)	43
6	**3c**	200:1	50	14	toluene (5M)	26
7	**3c**	280:1	50	14	neat	46
8	**3d**	200:1	50	12	C_6D_6 (1M)	33
9	**3d**	100:1	50	19	toluene (5M)	71

[a] Conversion measured by 1H NMR spectroscopy.

However, none of the polymerizations resulted in complete conversion of monomer. The reaction was studied in situ by ^{1}H NMR to probe whether incomplete conversion was a result of short reaction times or catalyst degradation (Table 5.2). No polymerization was observed beyond occurred after 4 hours, indicating that there may be a catalyst deactivation process. Additionally, the ^{1}H NMR showed the emergence

and growth of unidentified peaks and the decrease of the catalyst signal (Figure 5.7), providing additional evidence for the existence of catalyst degradation under the polymerization conditions. There appears to be some degradation even on the first spectrum taken immediately after the reagents were mixed.

Table 5.2 Conversion to PHB versus time[a]

entry	time (hr)	conversion (%)
1	0	1
2	4	33
3	11	33

[a] Conditions: 40 °C, 0.75 M C_6D_6, 200:1 monomer:**3b**, conversion measured by ^{1}H NMR

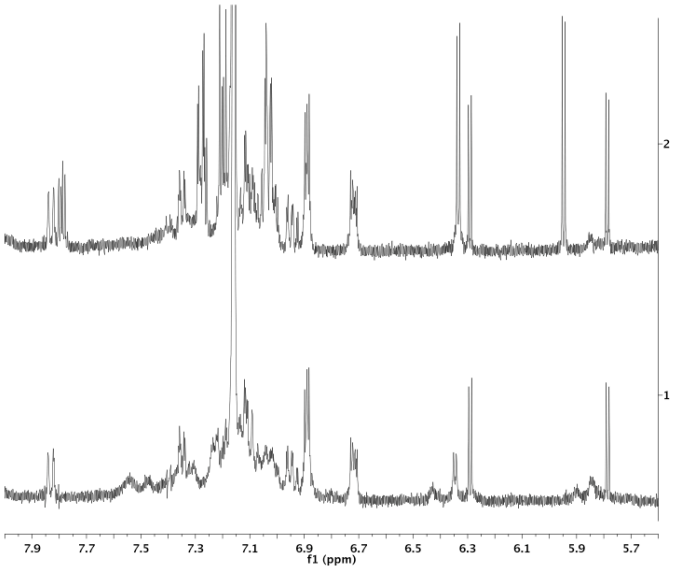

Figure 5.7 ^{1}H NMR of aryl region during β-butyrolactone polymerization after 10 minutes (bottom) and 11 hours (top)

Atactic PHB precipitates as an amorphous slime, but the polymer generated by *ortho*-biphenylDPMZnO^{i}Pr **3b** (Table 5.1, entry 1) precipitated as a flaky powder, raising the possibility that crystalline material had been generated. PHB from entry 1 was analyzed by DSC and found to have a T_g at 4 °C and a broad T_m at 108 °C. Although atactic PHB never shows a melting point, a T_m of 108 °C is more consistent with syndiotactic rather than isotactic PHB. This was confirmed by ^{13}C NMR, which showed the polymer had enriched [r] diads ([r] = 69%) confirming that the polymer structure was in fact syndiotactic, not isotactic (Figure 5.8). Because of this unexpected result, the polymers from other catalysts were tested at well. Polymer from the other *ortho*-monosubstituted *tert*-butylDPMZnO^{i}Pr **3d** (Table 5.1, entry 9) was also shown to be syndio-enriched with [r] = 59%. The hexaisopropylDPM **3c** (Table 5.1, entry 7), however, generated completely atactic polymer. This was somewhat expected as the triisopropyl catalyst is most similar in terms of steric bulk to tetraisopropyl BDI zinc catalysts, which are known to generate only atactic PHB.[3]

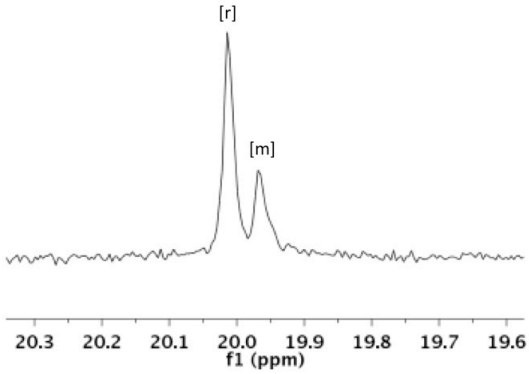

Figure 5.8 ^{13}C NMR (methyl region) of PHB from **3b** shows increased [r] diad content

5.3 Conclusion

A series of zinc dipyrromethene complexes were synthesized and investigated for their activity as catalysts for β-butyrolactone polymerization. The species showed some activity for the polymerization and generated polymers with narrow molecular weight distributions. However, polymerizations never reached complete conversion, as catalyst degradation was competitive with polymerization. Finally, although the DPM ligands were designed in the hopes of imparting isoselectivity to the polymerization, the two 'chiral' catalysts **3b** and **3d** produced only syndio-enriched PHB, most likely by chain end control. Analagous to the BDI zinc catalysts, the bulky achiral DPM catalyst **3c** produced atactic polymer.

5.4 Experimental

General Considerations. All manipulations of air and water sensitive compounds were carried out under dry nitrogen using a Braun Labmaster glovebox or standard Schlenk line techniques. ^{1}H NMR spectra were recorded on a Varian Mercury (^{1}H, 300 MHz), Varian INOVA 400 (^{1}H, 400 MHz) or Varian INOVA 600 (^{1}H, 600 MHz) spectrometer and referenced with residual non-deuterated solvent shifts ($CHCl_3$ = 7.24 ppm, C_6H_6 = 7.16 ppm). ^{13}C NMR spectra were recorded on a Varian Mercury (^{13}C, 75 MHz) or Varian INOVA (^{13}C, 125 MHz) spectrometer and referenced to chloroform, 77.23 ppm. Gel permeation chromatography (GPC) analyses were carried out using a Waters instrument, (M515 pump, 717+ Autosampler) equipped with a Waters UV486 and Waters 2410 differential refractive index detectors, and three 5 μm PSS SDV columns (Polymer Standards Service; 50 Å, 500

Å, and Linear M porosities) in series. The GPC columns were eluted with tetrahydrofuran at 40 °C at 1 mL/min and were calibrated using 20 monodisperse polystyrene standards.

Differential scanning calorimetry of polymer samples was performed on a TA Instruments Q1000 instrument equipped with liquid nitrogen cooling system and automated sampler. Typical DSC experiments were made in aluminum pans under nitrogen with a heating rate of 10 °C/min from -80 °C to 170 °C.

Materials. HPLC grade, tetrahydrofuran, toluene, and hexanes was purchased from Fisher Scientific and purified over solvent columns and degassed by three sequential freeze-pump-thaw cycles. Isopropanol was distilled off of CaH_2 and stored over 3Å sieves. Bis(bis(trimethylsilyl)amido) zinc,[3] β-butyrolactone,[16] sodium pyrrolide,[15] 2-phenyl pyrrole,[15] and 2-(2,4,6-triisopropylphenyl)-pyrrole were prepared by previously reported procedures. All other materials were purchased from commercial sources and used without further purification.

Ligand Synthesis:

General procedure for 2-aryl pyrrole synthesis. In glovebox a 200 mL Schlenk bomb with magnetic stir bar was charged with sodium pyrrolide (3 equiv.) and zinc chloride (3 equiv.) and dissolved in dry THF. The bomb was moved to the Schlenk line and substrate (1 equiv.) was injected. Under a backflow of nitrogen, *tert*-butyl XPhos (0.5%) and palladium acetate (0.5%) were added and the bomb was sealed and heated to 100 °C with stirring for 20 hours. Reaction mixture was dissolved in diethyl ether and water. Water was extracted three times with ether and organic

layer was washed three times with water, and then dried over Na_2SO_4. After solvent removal, resulting material was purified by flash chromatography.

2-([1,1'-biphenyl]-2-yl)-pyrrole 1b: Substrate: [1,1'-biphenyl]-2-yl trifluoromethanesulfonate (0.91 g, 3.0 mmol) – flash chromatography: 2.5% EtOAc: 97.5% hexanes. 0.47 g isolated (71% yield). ^{1}H NMR ($CDCl_3$): δ 7.57 (d, J = 7.8, 1H), 7.52 (br s, 1 H), 7.34 (m, 4H), 7.27 (m, 4H), 6.54 (m, 1H), 6.29 (m, 1H), 6.13 (m, 1H).

2-(2-*tert*-butylphenyl)-pyrrole 1d: Substrate: 2-(*tert*-butyl)phenyl trifluoromethanesulfonate (0.42 g, 1.5 mmol) - flash chromatography: 5% EtOAc: 95% hexanes. 0.13 g isolated (43% yield). ^{1}H NMR ($CDCl_3$): δ 7.97 (s, 1H), 7.49 (m, 1H), 7.32 (m, 2H), 7.16 (ddd, J = 14.4, 7.5, 3.4, 2H), 6.77 (dd, J = 4.1, 2.6, 1H), 6.22 (dd, J = 5.8, 2.9, 1H), 6.12 (td, J = 3.3, 1.5, 1H), 1.19 (s, 9H).

General procedure for dipyrromethene synthesis: Substituted pyrrole (2 eq.) and benzaldehyde dimethyl acetal (1 eq.) were dissolved in dichloromethane (0.2 M pyrrole) and pyridinium tosylate (0.1 eq.) was added. The mixture was stirred at 25 °C for 36 hours. Filtered reaction mixture through plug of silica gel, then diluted to 0.1 M dichloromethane. 2,3-dichloro-4,5-dicyanoquinone (DDQ, 1 eq.) was added and mixture was stirred at 25 °C for 24 hours. Solvent was removed and residue was purified by flash chromatography.

2,2'-diphenyl-*meso*-phenyldipyrromethene (3a): 2-Phenyl pyrrole **2a** (1.41 g, 0.99 mmol) – flash chromatography: 10% EtOAc: 90% hexanes. 0.054 g isolated, (32% yield). ^{1}H NMR ($CDCl_3$): δ 7.92 (m, 4H), 7.48 (m, 11H), 6.83 (d, J = 4.3, 2H), 6.70 (d, J = 4.3, 2H).

2,2'-bis([1,1'-biphenyl]-2-yl)-*meso*-phenyldipyrromethene (2b): 2-([1,1'-biphenyl]-2-yl)-pyrrole **2b** (0.47 g, 2.1 mmol) – flash chromatography: 10% EtOAc: 90% hexanes. 0.37 g isolated, (66% yield). ^{1}H NMR ($CDCl_3$): δ 7.81 (m, 2H), 7.33 (m, 21H), 6.35 (d, J = 4.2, 2H), 5.80 (pseudo-d, J = 4.2, H).

2,2'-bis(2,4,6-triisopropylphenyl)-*meso*-phenyldipyrromethene (2c): 2-(2,4,6-triisopropylphenyl)-pyrrole **2c** (0.25 g, 0.93 mmol) – flash chromatography: 5% EtOAc: 95% hexanes. 0.11 g isolated, (19% yield). ^{1}H NMR ($CDCl_3$): δ 7.66 (m, 2H), 7.46 (m, 3H), 7.00 (s, 4H), 6.61 (d, J = 4.1, 2H), 6.22 (d, J = 4.1, 2H), 2.89 (m, 2H), 2.77 (m, 4H), 1.26 (d, J = 6.9, 12H), 1.07 (d, J = 6.8, 24H).

2,2'-bis(2-*tert*butylphenyl)-*meso*-phenyldipyrromethene (2d): 2-(2-*tert*butylphenyl)-pyrrole **2d** (0.13 g, 0.65 mmol) – flash chromatography: 5% EtOAc: 95% hexanes. 0.080 g isolated, (51% yield). ^{1}H NMR ($CDCl_3$) δ 7.61 (m, 2H), 7.46 (m, 5H), 7.28 (m, 2H), 7.16 (m, 4H), 6.59 (d, J = 4.1, 2H), 6.34 (d, J = 4.1, 2H), 1.25 (s, 18H).

Metallation and formation of isopropoxide species:

Bis(2,2'-Diphenyl-*meso*-phenyldipyrromethene) zinc: 2,2'-Diphenyl-*meso*-phenyldipyrromethene **3a** (0.086 g, 0.23 mmol) was dissolved in C_6D_6 with bis(bis(trimethylsilyl)amido) zinc (0.089 g, 0.23 mmol) and heated to 120 °C. After 24 hours, solvent was removed and product was recrystallized from cold toluene and identified as the bis-ligated species. ^{1}H NMR (C_6D_6): 7.66 (m, 12H), 7.28 (m, 6H), 7.02 (t, J = 7.6, 8H), 6.91 (t, J = 7.4, 4H), 6.57 (d, J = 4.2, 4H), 6.36 (d, J = 4.2, 4H).

2,2'-bis([1,1'-biphenyl]-2-yl)-*meso*-phenyldipyrromethene-bis(trimethylsilyl)amido) zinc (3b precursor): 2,2'-bis([1,1'-biphenyl]-2-yl)-*meso*-

phenyldipyrromethene (0.10 g, 0.19 mmol) was dissolved in 2 mL toluene with bis(bis(trimethylsilyl)amido) zinc (0.073 g, 0.19 mmol) and heated to 78 °C. After 3 hours, solvent was removed and product was washed with hexanes: 0.053 g isolated (37% yield) ^{1}H NMR (C_6D_6): 7.78 (ddd, J = 7.6, 1.4, 0.5, 2H), 7.45 (m, 4H), 7.33 (ddd, J = 7.6, 1.4, 0.5, 2H), 7.28 (td, J = 7.5, 1.4, 2H), 7.16 (m, 8H), 7.02 (m, 3H), 6.90 (m, 2H), 6.37 (d, J = 4.2, 2H), 5.93 (d, J = 4.2, 2H), 0.06 (s, 18H).

2,2'-bis([1,1'-biphenyl]-2-yl)-*meso*-phenyldipyrromethene zinc iso-propoxide (3b): 2,2'-bis([1,1'-biphenyl]-2-yl)-*meso*-phenyldipyrromethene-bis(trimethylsilyl)amido) zinc (0.20 g, 0.26 mmol) was dissolved in 4 mL toluene. Isopropanol (20 μL, 0.26 mmol) was added by syringe and solution was stirred at 25 °C overnight. Precipitate was seen, filtered via canula and washed with hexanes. 0.05g isolated (30% yield) ^{1}H NMR (C_6D_6): δ 8.04 (dd, J = 7.5, 1.2, 2H), 7.20 – 7.03 (m, 21H), 6.52 (d, J = 4.2, 2H), 5.93 (d, J = 4.2, 2H), 4.25 (m, 1H), 0.83 (d, J = 6.0, 6H).

2,2'-bis(2,4,6-triisopropylphenyl)-*meso*-phenyldipyrromethene-bis(trimethylsilyl)amido) zinc (3c precursor): 2,2'-bis(2,4,6-triisopropylphenyl)-*meso*-phenyldipyrromethene (0.10 g, 0.16 mmol) was dissolved in 3 mL toluene with bis(bis(trimethylsilyl)amido) zinc (0.064 g, 0.16 mmol) and heated to 85 °C. After 8 hours, cooled, but no solid formed. Crude NMR showed incomplete conversion. 0.035 g bis(bis(trimethylsilyl)amido) zinc added and heated to 90 °C overnight. Solvent was removed and product was washed with hexanes. 0.10 g isolated (75% yield) ^{1}H NMR (C_6D_6): δ 7.30 (t, J = 4.1, 3H), 7.00 (m, 4H), 6.71 (d, J = 4.1, 2H), 6.48 (d, J = 4.1, 2H), 3.19 (m, 4H), 2.79 (m, 2H), 1.40 (d, J = 6.8, 6H), 1.22 (d, J = 6.9, 6H), 1.08 (d, J = 6.7, 6H), -0.13 (s, 18H).

2,2'-bis(2,4,6-triisopropylphenyl)-*meso*-phenyldipyrromethene zinc isopropoxide (3c): 2,2'-bis(2,4,6-triisopropylphenyl)-*meso*-phenyldipyrromethene-bis(trimethylsilyl)amido) zinc (0.10 g, 0.12 mmol) was dissolved in 4 mL toluene. Isopropanol (10 μL, 0.12 mmol) was added by syringe and solution was stirred at 80 °C. After 4 hrs, cooled and filtered. Crude NMR showed incomplete conversion, so additional 6 μL isopropanol was added and heated to 40 °C overnight. Solvent was removed and oily product was washed with cold hexanes. 0.020 g isolated (20% yield) ^{1}H NMR (C_6D_6): δ 7.38 – 6.87 (m, 9H), 6.71 (d, J = 4.0, 2H), 6.51 – 6.31 (m, 2H), 3.65 – 3.29 (m, 1H), 3.27 – 3.11 (m, 2H), 3.08 – 2.87 (m, 2H), 2.87 – 2.67 (m, 2H), 1.54 – 0.98 (m, 42H).

2,2'-bis(2-*tert*butylphenyl)-*meso*-phenyldipyrromethene-bis(trimethyl-silyl)amido) zinc (3d precursor): 2,2'-bis(2-*tert*butylphenyl)-*meso*-phenyldipyrromethene (0.091 g, 0.19 mmol) was dissolved in 1 mL C_6D_6 with bis(bis(trimethylsilyl)amido) zinc (0.073 g, 0.19 mmol) and was reacted at 25 °C. After 48 hours, solvent was removed. Product residue was very soluble in hexanes and was used directly for isopropanol addition. ^{1}H NMR (C_6D_6): δ 7.38 (m, 5H), 7.13 (m, 7H), 6.64 (d, J = 4.1, 2H), 6.35 (br s, 2 H), 1.36 (br s, 18H), 0.10 (s, 18H).

2,2'-bis(2-*tert*butylphenyl)-*meso*-phenyldipyrromethene zinc isopropoxide (3d): 2,2'-bis(2-*tert*butylphenyl)-*meso*-phenyldipyrromethene-bis(trimethylsilyl)-amido) zinc (~0.13 g, ~19 mmol) was dissolved in 1 mL C_6D_6. Isopropanol (14 μL, 19 mmol) was added by syringe and solution was stirred at 25 °C. Crystals formed after 10 minutes. Filtered and washed with hexanes: 0.033g isolated (28% yield) ^{1}H NMR ($CDCl_3$): δ 7.48 (m, 5H), 7.40 (d, J = 7.8, 2H), 7.17 (dt, J = 7.9, 4.4, 2H), 7.10 (d, J =

4.2, 4H), 6.62 (d, J = 4.0, 2H), 6.34 (d, J = 4.0, 2H), 3.07 (m, 1H), 1.09 (s, 18H), -0.19 (d, J = 5.9, 6H).

Standard polymerization protocol: In glovebox, catalyst was weighed to 8 mL dry scintillation vial with magnetic stir bar, and then dissolved in appropriate solvent. β-butyrolactone was added and the vial was sealed with a Teflon-lined cap, taped, and removed from the glovebox. Samples were heated in an oil bath with stirring. After reaction, aliquot was taken for ^{1}H NMR spectroscopy, and then polymerization was quenched with 1 drop of acetic acid and precipitated into hexanes. NMR polymerizations followed the same protocol except after reaction was mixed and homogenous it was added to a J-Young tube, sealed, and heated in an oil bath without stirring.

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CHAPTER SIX

Applications of Heterocycle Carbonylation

Research performed in part, in collaboration with:

Yanke Liang, Nathan Hnatiuk, John M. Rowley, Paul R. Rablen, Martha Morton, and Amy R. Howell

6.1 Introduction

Catalytic carbonylation of heterocycles is an efficient and atom-economical process for the synthesis of organic chemicals with carbonyl functionality. By using the inherent ring-strain in small molecules such as epoxides as a driving force, carbonylation is an ideal method to access a number of interesting small molecule materials.

6.2 Paper-sizing agents

Paper sizing is the addition of hydrophobic functionality to the hydrophilic cellulose matrix of paper to attenuate its polarity, tuning its adhesion profile as well as its material properties. This process is essential for printing, as otherwise ink would spread and disperse into the paper. However, with too much functionalization of the waxy sizing agent, the polar ink will won't adhere to the paper's surface.[1]

Paper sizing is achieved by treating the hydroxyl groups from cellulose with a hydrophobic electrophile. Historically, this was achieved with rosin under acidic conditions, where the paper hydroxyl groups undergo transesterification with aliphatic acyl groups present in the rosin. Modern paper sizing, however, is performed under basic conditions so as to allow incorporation of calcium carbonate as a filler agent in the paper. Currently, there are only two types of paper sizing agents in widespread use for alkaline conditions: alkyl ketene dimers and aliphatic succinic anhydrides (Figure 6.1).[1]

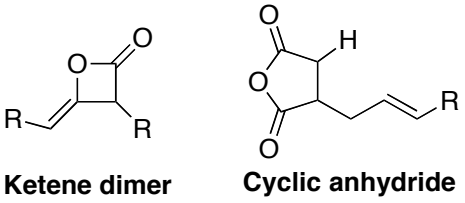


Figure 6.1 Two most common modern classes of basic paper sizing agents

Ketenes are produced by the dehydrohalogenation of acid halides, and they can undergo dimerization to form unsaturated β-lactones (Figure 6.2). The hydrophobic groups necessary for successful paper sizing are result from the use of long-chain fatty acids as a feedstock for the ketene dimers.[2] Therefore, ketene dimers are particularly attractive because the chemical feedstock for their synthesis is biorenewable. In practice, the ketene dimer is relatively unreactive, which eases processing demands because it may be pre-mixed with paper pulp in aqueous mixtures for storage until processing. However, this also creates a need for reactivity enhancement reagents to speed the paper functionalization.[2]

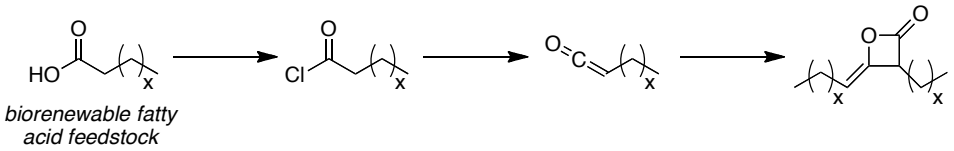


Figure 6.2 Synthetic pathway for ketene dimer paper-sizing agents

The cyclic anhydride paper-sizing agent is synthesized using the pericyclic Alder-ene reaction of maleic anhydride with an allyl-terminated long-chain aliphatic species, resulting in a terminal cyclic anhydride (Figure 6.3). The anhydride paper-sizing agents are significantly more reactive, and don't require the addition of

enhancing agents. However, this reactivity has its disadvantages and anhydride agents cannot be stored with the pulp formulations, instead being added to the paper mixture immediately before processing by an emulsion technique.

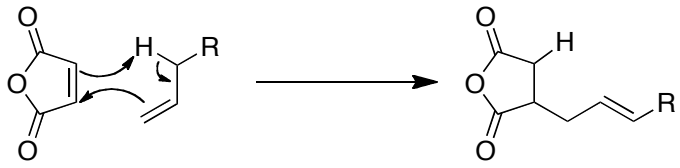


Figure 6.3 Synthesis of aliphatic-functionalized anhydrides via the Alder-ene reaction

Because each of the paper-sizing agents has drawbacks, an interesting material would be a hybrid of the two. The efficacy of the ketene dimer is thought to be the two long-chain aliphatic substituents, whereas the anhydride. It was hypothesized that 1,2-disubstituted cyclic anhydrides could provide the ideal characteristics of each. However, there are no facile synthetic routes to this class of materials from widely available sources.

Heterocycle carbonylation is an ideal candidate for such an endeavor, because it is catalytic, selective, scalable, and atom-economical. Our group has recently shown the efficient synthesis of a variety of cyclic anhydrides via the double carbonylation of epoxides.[3] We decided to investigate the carbonylation of disubstituted substrates for the synthesis of novel paper-sizing agents in collaboration with Hercules Incorporated.

6.3 Results and Discussion

We first investigated a 16 and 18-carbon mixture with a single internal alkene synthesized by isomerization by metal hydrides. This is an attractive target because the source material is readily available and inexpensive as there are limited applications for higher molecular weight olefins. However, after double carbonylation it would lead to disubstituted anhydrides with heptane or nonane average side-chains (Figure 6.4). The alkene was oxidized with peracetic acid to the corresponding internal epoxide mixture. However, upon exposing these mixtures to typical carbonylation conditions with *Meso*-tetra(4-chlorophenyl)porphyrinato aluminum cobalt tetracarbonyl ([ClTPPAl][$Co(CO)_4$]) as catalyst resulted in only partial conversion to anhydride, with significant amounts of inseparable lactone intermediate as well as internal alkenes resulting from the retro 2+2 loss of carbon dioxide from lactones.

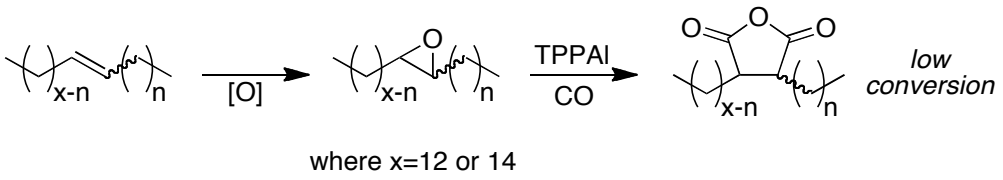


Figure 6.4 Proposed synthetic pathway to disubstituted anhydrides from C16-18 alkene

It is likely that this lack of reactivity it twofold. First, the long hydrophobic side-chains may affect the environment directly around the epoxide. As we have shown in the prior study of aluminum Lewis acid-based carbonylation catalysts, the use of hexanes as a reaction solvent severely retards the reaction,[4] owing from poor

solubilization of the catalyst as well as lacking the donating ability necessary to release lactone product. Second, the alkene starting material is a thermodynamic mixture of alkenes, favoring the *trans* over *cis* configuration. Carbonylation proceeds by the S_N2 attack of the cobaltate anion on the activated heterocycle, resulting in inversion. Therefore the primarily *trans* epoxides give rise to *cis*-substituted lactones. The carbonylation of *cis* lactones proceeds much slower than the corresponding *trans* lactones,[5] most likely due to steric interference of the substituents with the cobaltate attack from both faces of the lactone ring (Figure 6.5).

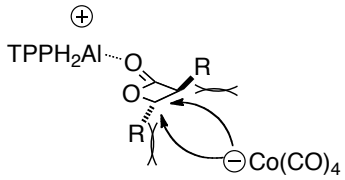


Figure 6.5 Steric interference with cobalt nucleophilic attack from trans disubstituted β-lactones

Owing to the difficulty with the stereochemistry of the C16-18 alkene mixtures, we decided to investigate other routes to long-chain, disubstituted anhydrides. The availability of *cis* alkenes is limited, so we instead turned our attention to one of the existing paper-sizing agent classes, the ketene dimers. One of the classic syntheses of β-lactones is the formation then hydrogenation of ketene dimers. This approach would give us access to lactones with ideal hydrophobic side-chains from the existing paper-sizing agents. Additionally, the hydrogenation is expected to result in primarily *trans*-lactones, hopefully improving their carbonylation.

The ketene dimers Aquapel 203 (MW=364) and Aquapel 364 (MW=505) were hydrogenated with palladium on carbon to the corresponding lactones. After screening, we found conditions that allowed for the complete conversion of the lactones to their anhydride products (Figure 6.6). The primary difficulty in the conversion of the disubstituted lactones was loss of carbon dioxide to form alkenes under the reaction conditions. This was particularly problematic for the higher molecular weight substrate, most likely due to the nonpolar microenvironment around the lactone as a result of its long-chain alkyl branches. The use of 1,4-dioxane as a solvent and dilute substrate and catalyst eliminated alkene formation and allowed complete conversion to disubstituted anhydride species.

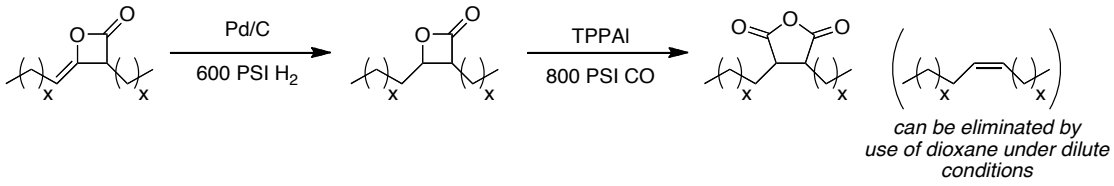


Figure 6.6 Carbonylation of hydrogenated ketene dimers

As a rough test of paper-sizing ability, we reacted the newly synthesized anhydrides with filter paper by dispersing in CH_2Cl_2 and adding to the paper, the storing in 150 °C oven for 24 hours. The imparted hydrophobicity was tested qualitatively by the addition of water droplets by pipet to the unmodified and modified filter paper (Figure 6.7). As can be seen, the anhydride was able to significantly alter the surface properties of the porous filter paper so that it repels the water droplets.

Figure 6.7 Water droplets added to unfunctionalized filter paper (leftmost spot) and filter paper modified by disubstituted anhydride

6.4 Conclusion

Through carbonylation we were able to synthesize a novel class of paper-sizing agents: long-chain hydrophobic disubstituted cyclic anhydrides. These new agents were accessed by hydrogenation then carbonylation of ketene dimers. They showed ability to react with paper surfaces and alter the surface properties.

6.5 β-Lactones as intermediates for synthesis of *psico*-Nucleosides

Oxetanocin A is a nucleoside modified with an oxetane-based sugar (Figure 6.7) that is of great interest due to its strong inhibition of HSV-1, HSV-2, HCMV, and HIV-1.[6] A number of analogs have been synthesized by derivitization of the nucleoside moiety and have shown promising properties. The Howell group proposed a synthesis of oxetanocin analogs bearing the unique oxetane-sugar moiety. A synthesis was imagined from the activation and nucleoside attack on 2-methyleneoxetanes activated by electrophilic fluorine. These methyleneoxetanes can in turn be derived from the methylenation of β-lactones (Figure 6.8).[7]

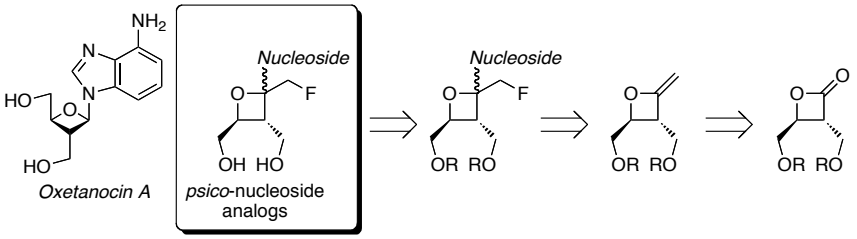
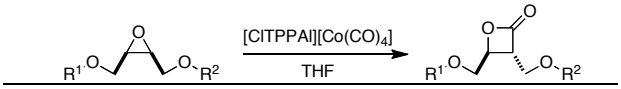


Figure 6.8 Oxetanocin A and strategy for synthesis of *psico*-nucleoside analogs

6.6 Results and Discussion

The Howell group supplied three cis-epoxides with different protecting groups, and they were efficiently carbonlyated to the corresponding β-lactones by epoxide carbonylation (Table 6.1). In the case of the non-symmetric epoxides, two product lactones were produced in roughly equal proportions. Non-identical symmetric protecting groups were used for selective deprotection and addition of groups to enhance anchimeric assistance in the hopes of generating selective attack on the stabilized carbocation (Figure 6.9).

Table 6.1 β-lactones successfully generated from protected epoxides



entry	R_1	R_2
1	Bn	Bn
2	OTBS	OTBS
3	OBn	OTBS

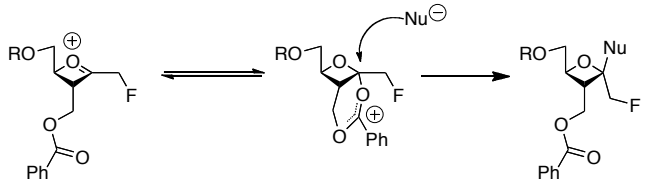


Figure 6.9 Proposed anchimeric assistance for nucleoside attack on ocetanium species

Psico-nucleosides were successfully prepared using this method. Unfortunately, no anchimeric assistance for the nucleoside attack was observed, leading to a mostly statistical mixture of products.[7]

6.7 Conclusion

Disubstituted β-lactones were successfully generated by carbonylation and used for the synthesis of *psico*-nucleoside analogs of Oxetanocin A, although anchimeric assistance was unable to afford diastereoselectivity.

6.8 Experimental

General Considerations. All manipulations of air and water sensitive compounds were carried out under dry nitrogen using a Braun Labmaster glovebox or standard Schlenk line techniques. High-pressure reactions took place in a custom-made, stainless steel 6-well reactor as described previously[8] or a 100 mL stainless steel Parr reactor. ^{1}H NMR spectra were recorded on a Varian Mercury (^{1}H, 300 MHz), Varian INOVA 400 (^{1}H, 400 MHz) or Varian INOVA 600 (^{1}H, 600 MHz) spectrometer and referenced with residual non-deuterated solvent shifts ($CHCl_3$ = 7.24 ppm). ^{13}C NMR spectra were recorded on a Varian Mercury (^{13}C, 75 MHz) or Varian

INOVA (^{13}C, 125 MHz) spectrometer and referenced to chloroform (77.23 ppm). Aquapel 203, 364, and C16-18 alkene were supplied by Hercules Inc and purified by flash chromatography prior to use.

Materials. Carbon monoxide was purchased from Matheson Trigas or Airgas in aluminum cylinders (99.99% min. purity) and was used as received. HPLC-grade tetrahydrofuran, dichloromethane, hexanes, and toluene were purchased from Fisher Scientific and purified over solvent columns and degassed by three freeze/pump/thaw cycles. 1,4-Dioxane was dried over sodium/benzophenone and then vacuum transferred and degassed by three freeze/pump/thaw cycles. *Meso*-tetra(4-chlorophenyl)porphyrinato aluminum cobalt tetracarbonyl ([ClTPPAl][$Co(CO)_4$]), was prepared according to reported literature procedures.[3]

Epoxidation of C16-18 alkenes:

C16-18 alkene mixture was dissolved in dichloromethane and peracetic acid solution was added. The mixture was stirred for 48 hours, and then quenched with $NaHSO_3$. Acidic species were removed with subsequent washes of saturated $NaHCO_3$ and organic layer was dried over Na_2SO_4.

Hydrogenation of ketene dimers:

Ketene dimers Aquapel 203 (MW = 364) or 364 (MW = 504) were dissolved in toluene and added to a stainless steel Parr reactor with glass insert and stirbar. 10% Pd/C was added and the reactor was pressurized with 600 PSI H_2. After 24 hours, gas was vented and palladium was filtered off. Solvent was removed to afford the substituted β-lactones.

Aquapel 203 lactone: ^{1}H NMR ($CDCl_3$) δ 4.53 (ddd, J = 9.4, 6.4, 4.3, 1H), 3.59 (dt, J = 8.8, 6.9, 1H), 1.79 – 1.45 (m, 6H), 1.25 (s, 36H), 0.98 – 0.75 (m, 6H).

Aquapel 364 anhydride: ^{1}H NMR ($CDCl_3$) δ 4.55 – 4.42 (m, 1H), 3.56 (dt, J = 8.9, 7.0, 1H), 1.90 – 1.43 (m, 6H), 1.41 – 1.08 (m, 50H), 0.89 – 0.74 (m, 6H).

General carbonylation procedure:

Substrates were degassed and dried under full vacuum overnight, then stored in the carbonylation solvent of choice over 3Å sieves in the glovebox prior to use. The substrate was loaded into a stainless steel reactor charged with catalyst with a stirbar and additional solvent was added if necessary. The reactor was pressurized with 800 PSI CO and heated and stirred. The reactor was cooled in dry ice, CO was released and solvent was removed by vacuum. Anhydrides were purified by flash chromatography. Lactones were sent to Amy Howell without further purification.

Aquapel 203 anhydride: ^{1}H NMR ($CDCl_3$) δ 2.75 (p, J = 5.8, 2H), 1.91 – 1.58 (m, 4H), 1.51 – 1.01 (m, 38H), 0.86 (t, J = 6.8, 6H).

Aquapel 364 anhydride: ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 2H), 1.96 – 1.59 (m, 4H), 1.56 – 0.97 (m, 52H), 0.87 (d, J = 6.5, 6H).

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