Enhancing Understanding of Thiol-X Reactions

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Thiol-X reactions constitute reactions where thiols add to one of many reactive functional groups; notably such reactions include the radical-mediated thiol-ene and the anionic thiol-Michael. These are typically characterized by highly efficient reactions, but the reaction's efficiency comes with the tradeoff of formulation instability and thiols often have an unpleasant odor.

Secondary thiols are reported to possess less offensive odor than their primary thiol counterparts and exhibit longer shelf-lives in thiol-ene formulations, but more information is needed about how the substitution of the thiol affects a variety of thiol-X reactions. This thesis has focused on determining how the thiol substitution affects the thiol-ene, thiol-Michael, and thiol-thioester exchange reactions and materials made from such reactions. To study the thiol-ene and thiol-Michael reactions, model studies were completed using FTIR and NMR spectroscopy.

It was found that for all three substitutions implemented in thiol-ene reactions, there was no significant change in the reaction rate at standard polymerization conditions and at reduced conditions, the reaction rate decreased with increasing substitution, and while most substitutions did not differ greatly in rate, the amount of change in rate is highly dependent on the alkene comonomer.

In thiol-Michael propagation limited reactions (mercaptopropionates), the secondary thiol could be as much as 60% faster due to the increased reactivity of the thiolate anion, though increased steric interactions can override this increased reactivity. In chain transfer limited

systems (alkyl thiols) primary thiols were up to 55% faster due to the lower pKa and ease of deprotonation.

Analogous thiol monomers with the corresponding substitutions were then obtained for polymerization studies. It was found that for thiol-ene and thiol-Michael systems, the polymerizations typically followed the pattern seen in model reactions. However, thiol-Michael polymerizations of greater average functionality of the monomer system became more dependent on the substitution and sterics of the monomer. In these cases secondary thiols that were faster in model studies became more limiting.

Finally, the thiol-thioester exchange reaction is a useful method for enhancing thiol-X derived materials by developing covalent adaptable networks and the effect from substitution was observed here as well.

Dedication

To my mother and father, whose sacrifices and lessons allowed me to get where I am today. I could not have done this without them, and I am incredibly proud to be their daughter.

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To begin, I would like to thank my advisor, Christopher Bowman, who took me in his lab as a bright-eyed, eager student and helped guide me to become the skilled researcher that I am today. Chris's success and achievements are undoubtably linked to his passion and ingenuity, qualities that I hope to bring with me as I launch my career in organic chemistry. From the moment I first sat in his office he has challenged me to foster my independence, to seek answers, and to grow my voice in science. It was a curious way that I found myself in that polymer engineering lab, but I have no regrets. I would not be where I am today without him.

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Dr. Brady Worrell, Dr. Jasmine Sinha, and Dr. Benjamin Fairbanks have all been there to help me with whatever lab mishap comes my way.

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I have found myself in the presence of some pretty incredible friends. Katie Rainey has been there for me through thick and thin, and has been a motivational force in helping me succeed. When times are dark and scary, she helps me find some sunshine. Helen Tanner is a beautiful soul who has been cheering me on from across the pond. I can always count on her for her loyalty and friendship that has always been delivered in a wonderful British accent.

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Finally, my incredible family. Pawpaw and Grandma Anne have always encouraged my education, and I wish they could be here today to see it come to completion. I'm incredibly grateful that my parents, Monica and Millard, raised me with qualities that helped me succeed – perseverance, empathy, and ambition. Nobody, and absolutely nobody, said getting a PhD would be easy, or even normal. People called me crazy, but my parents were there every step of the way and when I asked for help, did everything in their power to get me back up again. Then there's my sister, Lizzy. She has the biggest capacity to love and care out of any other human being I know. Despite of all of our differences over the years, I know I can always count on her.

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Chapter 1: Introduction

1.1 History and Introduction of Polymers

Polymers are a ubiquitous class of materials, both of synthetic and natural origin. While nature has made these unique materials since before the existence of DNA, polymers created from synthetic processes have a much shorter history. Frenchmen Henri Braconnot and Théophile Jules Pelouze were the first to attempt nitrating starch and cellulose in 1833 to produce Xyloïdine and Pyroxilin, respectively[1]. Even though these two scientists were making polymers, they did not have a clear understanding of what polymers were. Jöns Jakob Berzeliuz, a Swedish chemist, was actually the first to use the word "polymer" in the literature in 1833, but his definition was different than the accepted modern definition. He defined polymers as compounds of the same chemical composition that exhibited different chemical properties[2]. This definition was so broad that it included isomers, homologues, and polymorphisms and did not take into account molecular weight, an obviously key concept in the understanding of what polymers represent today.

In 1846, Swiss scientist Christian Schönbein developed and pioneered a stable method to treat cellulose, ironically by accident. He was known for doing experiments in his own kitchen and famously spilled concentrated acid on a table. He used a cotton apron to clean up the mess and hung the apron to dry[3]. Once dry, it promptly ignited into flames and one can only

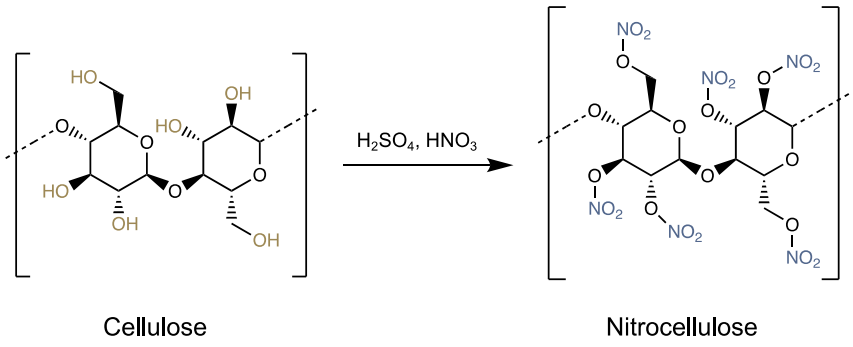

Figure 1. Repeating forms of cellulose reacting with sulfuric acid and nitric acid to produce cellulose trinitrate or nitrocellulose.

assume he had to come up with an awkward explanation for his wife, as it was also her apron. His stable method used a mixture of sulfuric acid and nitric acid to create a product known as guncotton, *Schiesswolle*, or nitrocellulose[4]. These semi-synthetic materials were the first modern examples of polymer science.

Nitrocellulose is what is known now as a linear polymer, or a polymer made up of long chains or strings of repeating units, commonly compared to a bowl of spaghetti. The polymer chains entangle and are attracted to each other due to secondary intermolecular interactions, and they can range in their structure from linear, to lightly or highly branched, to dendritic systems. Dendrimers are star-shaped macromolecules with arms of repetitive molecules that branch out from the center. Linear and branched polymers are often referred to as thermoplastics because of their ability to flow; at higher temperatures, the chains slide past one another and the polymer can be reshaped, reprocessed or recycled.

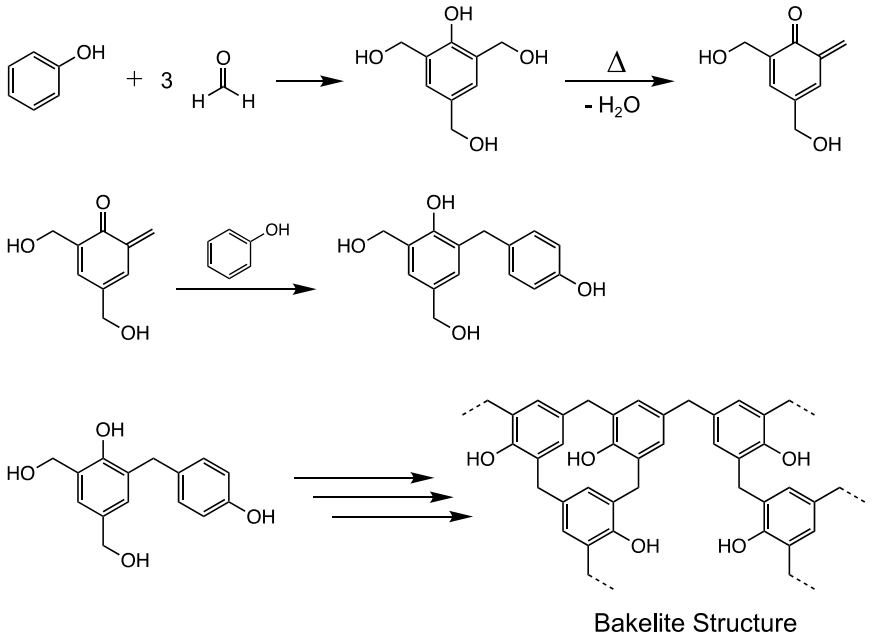

Figure 2. Synthesis and structure of Bakelite, the first fully synthetic polymer, adapted from stc-clips.org[5]. This is an example of a thermoset material.

In 1907 Leo Baekeland created the first fully synthetic polymer, Bakelite, a product of the polycondensation of phenol and formaldehyde[6]. Unlike nitrocellulose, Bakelite is not a linear polymer, but a thermoset. Instead of linear or branched chains, the repeat units form more than two bonds, creating a network similar to the structure of a fishing net. Thermosets do not have the same recyclability because the way these polymers are structured does not allow them to flow at higher temperatures, and once they are set, or cured, cannot be reshaped.

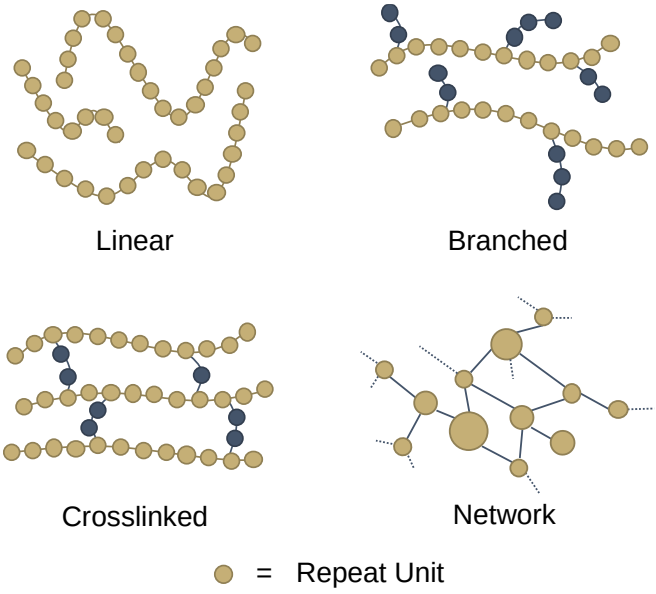

Figure 3. Schematic representation of Linear, Branched, Crosslinked, and Network polymer structures. The black circles represent repeat units, or monomers, of the main chain, whereas the red circles represent additions to the main chain. The red lines of the network polymer are bonds.

Polymer research continued to grow over the years. In 1920 Hermann Staudinger began his research on larger molecular weight molecules, researching synthetic polymers such as polyoxymethylene, polystyrene, and polyethylene oxide[7, 8]. Later, he was awarded the Nobel Prize in 1953[9] for his discoveries in macromolecular chemistry. He classified polymers as a class of macromolecules, consisting of small molecules that were linked together by covalent bonds[7, 10]. This revolutionary idea gave birth to the field of polymer chemistry.

From there, polymers and plastics continued to gain popularity during the Second World War. Polymers became valuable alternatives for materials that became allocated for military use or scarce to come by. Polyamide became a silk substitute, what we know today as nylon, and used as rope or parachutes[11]. Cellulosics, acrylic, and polyethylene materials became valuable

alternatives to precious metals and rubber. In fact, polytetrafluoroethylene proved instrumental in ending World War II. American chemist, Dr. Roy J. Plunkett accidentally discovered the material, but this material was insoluble, unaffected by chemical corrosion, and impervious to high temperatures – perfect for the purification of UF_6 for the atomic bomb and would later become known as Teflon[12]. Following the World War, the polymer industry saw continued growth, as it began to replace many other man-made materials, such as the steel in cars, the wood in furniture, and paper and glass packaging.

Today, plastics are ubiquitous in daily life. Polyvinylchloride (PVC), a linear polymer, is used to makes food wrap, water resistant materials like rain coats, and piping[13]. Products including CDs, the lens in reading glasses, and bulletproof glass are all forms of polycarbonate, also a linear polymer. Modern thermoset polymers include Teflon, polyurethane, and many epoxies. Many of these reactions include a radical mediated process, which offers spatial and temporal control with a light based initiation process, meaning when a light is shone on a monomer solution, that solution will only react *where* the light shines and *when* the light shines, forming a solid polymer.

Typical radical-based polymerizations of today involve acrylate homopolymerizations, more commonly known as acrylics or polyacrylates. The reaction follows a chain growth mechanism, where a monomer adds to the growing chain one monomer at a time. In network polymerizations, materials will gel at lower conversions. As the reaction progresses, the molecules that are present are either unreacted monomer or long polymer chains.

Other polymerizations follow a step-growth mechanism. In this mechanism, two different functional groups react together to form dimers, and subsequently multimers react together (or with unreacted monomer in the solution) to build up higher molecular weight structures.

Therefore, in network polymerizations, higher conversions are required to achieve gelation. Essentially, all monomers have equal probability to react with one another and as a result, large amounts of the monomer is consumed early in the polymerization prior to the development of high molecular weight species.

The field of polymer science grows astoundingly with each passing year, with new chemistries to make the polymer, new monomers to change the mechanical properties, and new solutions for age-old problems. Advancing technologies have led to materials that respond to various stimuli[14] (e.g. heat[15], light[16, 17], humidity[18], pH[19], electric fields[20], and more) pioneering fields such as shape memory, biocompatibility, and smart materials. Thiol-X chemistries have emerged as part of the ever-improving and ever-changing field of polymer chemistry.

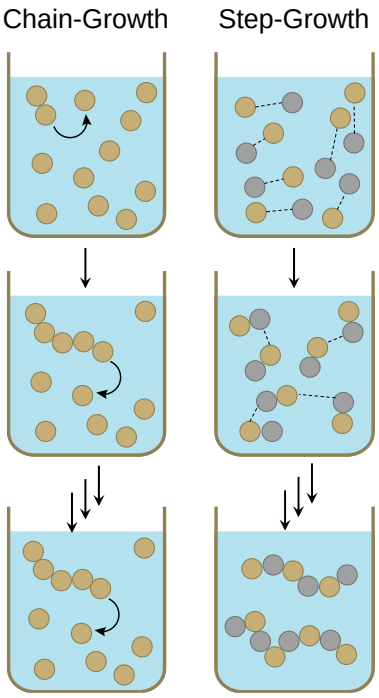

Figure 4. Schematic depicting differences between chain-growth (left) and step-growth (right) polymerizations. In chain growth mechanisms, repeat units add to an active chain one at a time, whereas in step-growth mechanisms, repeating units can combine with other unreacted monomers, oligomers, or with polymer chains.

1.2 The Thiol-X Reactions

Thiol-X chemistries involve reactions of thiols with alkenes, alkynes, epoxies, isocyanates, and other functional groups[21]. The more common reactions include the radical thiol-ene, and anionic thiol-Michael[22]. These reactions have been of great interest in polymerization, synthetic, and functionalization applications as many of these reactions exhibit advantages such as high yield with few, if any, side products, regio- and stereo-selectivity, benign reaction conditions followed by little to no purification steps. Other chemistries that fall under the thiol-X umbrella include the thiol-

isocyanate[23], thiol-epoxy[24], and the newly published thiol-benzoxazine[25] reactions. Additionally, the thiol-thioester exchange reaction has received increased attention in the realm of thiol-X chemistries due to its ability to incorporate labile chemical bonds into thiol-X polymer materials. This thesis will focus on these three reactions: the thiol-ene, thiol-Michael, and thiol-thioester exchange.

1.2.1 The Thiol-Ene Reaction

The thiol-ene reaction was first reported in 1905 by Posner from the Universität Greifswald[26], and consists of a free-radical mediated addition of a thiol to an alkene. This reaction has been used extensively in polymer and materials science because of the advantages offered by thiol-x chemistries. Conventional radical polymerizations have some disadvantages due to their chain-growth mechanism. Even though chain-growth mechanisms gel at lower conversions, the polymerization continues after the material has formed, and this leads to volumetric shrinkage of the material and consequently significant shrinkage stress. Additionally, many of these classic radical polymerizations are plagued by inhibition by oxygen[27, 28]. The dioxygen molecule has a biradical ground state that easily reacts with carbon-centered radicals to yield peroxy radicals at rates that are typically much higher than that of typical propagation rates of polymerizations[29].

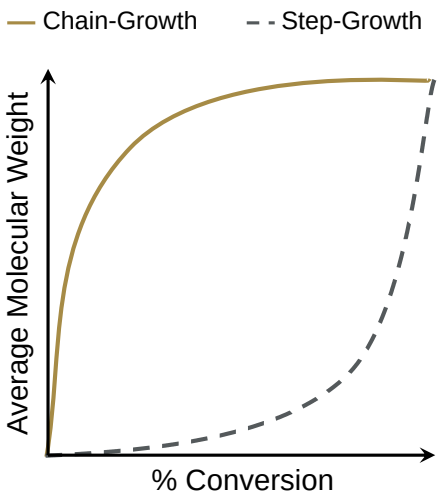

Figure 5. Graphic representation of the average molecular weight of a polymer as the conversion of the polymerization progresses. Chain-growth networks achieve a gelled network at lower conversions, and longer reaction times do not significantly affect the average molecular weight. Step-growth mechanisms require higher conversions to gel polymer networks.

In contrast to these typical radical polymerizations, thiol-ene networks react via a step-growth mechanism. Step-growth polymer networks gel at higher molecular weights, and this delayed gelation reduces the shrinkage stress. Step-growth mechanisms have rapid loss of monomer at the beginning and little to no unreacted monomer species left at the end of the reaction (Figure 5). Additionally, thiol-ene reactions are not sensitive to oxygen, form homogenous networks, and the alkenes used in traditional thiol-ene systems, such as vinyl ethers, allyl ethers, norbornenes, and vinyl siloxanes, do not typically homopolymerize and have simplified kinetics[30, 31]. The mechanism of this reaction is further discussed in Chapter 3.

1.2.2 The Thiol-Michael Reaction

Michael reactions were defined in the literature by Arthur Michael as reactions where an enolate ion nucleophilically adds to the β-carbon of an α,β-unsaturated carbonyl[32]. Later, this definition was expanded to include other nucleophiles[33-35]. The thiol-Michael addition was first reported by Allen et al. in the 1960's and comprises the anionic addition of a thiol to the β-carbon of an α,β-unsaturated carbonyl[36]. The thiol-Michael polymerization also follows a step-growth reaction, and in many ways is considered an anionic analog of the thiol-ene reaction. The weak sulfur-hydrogen bond allows the reaction to proceed under mild, solventless conditions using a variety of mild catalysts and results in high yields. Additionally, the employment of a photolabile base lends both spatial and temporal control to such reactions[37]. The mechanism of the thiol-Michael reaction is further discussed in Chapter 4.

1.2.3 The Thiol-Thioester Exchange

Transesterification is a well-known process and widely used in organic and polymer chemistry[38-41]. It involves the reversible exchange of an alkyl R-group of an ester with that of a different R-group in an alcohol and can be catalyzed with an acid or base (Figure 6a)[42].

Typically, harsh conditions are required for such exchanges to occur. However, the thiol-thioester exchange mechanism (Figure 6b) occurs readily at room temperature using either a base or nucleophilic catalyst[43]. The mechanism of this reaction is further discussed in Chapter 5.

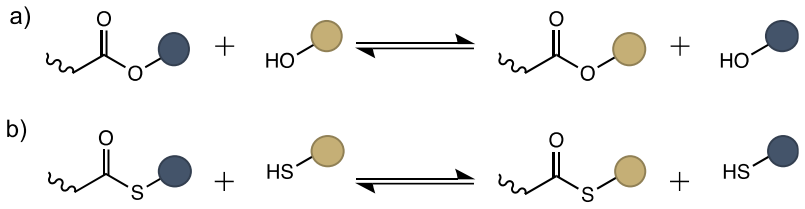

Figure 6. Representation of the transesterification (a) exchange, where an alkyl group of an ester exchanges with the alkyl group of an alcohol, and the thiol-thioester (b) exchange where the alkyl group of a thioester exchanges with the alkyl group of a thiol.

Incorporating these dynamic chemistries into the backbone of the polymer allows for rearrangement of the bonds after the polymer has been made. Such polymers belong to a class of materials called Covalent Adaptable Networks (CANs) [44, 45]. These materials have the mechanical benefits of traditional, cross-linked networks, but the reversibility aspect of those crosslinking strands enables them to respond to various stimuli and alter their structure, properties, or shape.

1.4 Overview of Present Work

In the present thesis, I have sought to determine how increasing the substitution of the thiol in these reactions affects the kinetics as well as the mechanical properties. A preliminary thiol-ene investigation by Li et al. found that secondary thiol monomers address two significant drawbacks to the thiol-ene reaction[46]. Firstly, thiol and alkene mixtures are unstable at room temperature and can react prematurely by a variety of mechanisms – initiation due to the base-catalyzed addition of the thiol to an alkene[47], initiation of free-radicals due to the decomposition of peroxide impurities, generation of thiyl radicals from the reactions of hydroperoxide impurities, and the generation of radicals though a ground-state charge-transfer complex formed

between thiol and alkene functional groups in the monomer mixture[48, 49]. However, the secondary thiol monomers Li et al. used proved to be far more stable at room temperature, where primary thiol monomer mixtures gelled within 12 hours and the secondary thiol monomer mixtures remained stable for up to 20 days. Additionally, there is a strong, unpleasant odor that commonly accompanies thiols, but in this study, the secondary thiols were reported to have little to no odor.

These two problems, limited shelf-life and odor, have been addressed in the past by using radical inhibitors to extend the shelf-life and either using high molecular weight thiol monomers or by oligomerizing monomers to reduce the volatility and thus, reduce odor. However, these methods require additional resources to optimize formulations for use, and it would be advantageous if both of these problems could be solved by using a different choice of thiol. This thesis seeks to expand upon this study with a thorough kinetic evaluation that includes tertiary thiols, and a study that expands to the thiol-Michael and thiol-thioester exchange reactions. This endeavor began with model, monofunctional thiols to use in small molecule chemistry – chemistries that do not have the added complexities of polymerizations but are otherwise identical in scope[31, 50, 51]. Fourier Transform Infrared (FT-IR) spectroscopy was used to analyze rate changes as well as conversion and NMR spectroscopy was used to reaffirm conversion, as well as measure exchange concentrations for thiol-thioester systems. The effect from substitutional changes was then observed in polymer kinetics, using novel secondary thiol analogs of the more commonly used thiol monomers in thiol-X literature. Mechanical differences between films made with either primary or secondary thiols were evaluated using Dynamic Mechanical Analysis (DMA), gathering information about the storage and loss moduli, as well as

the glass transition temperature of these films. Finally, rheometry was used to measure viscosity at different time points, to gather information about the conversion over time.

The information obtained from this research will improve the applicability of the thiol-ene, thiol-Michael, and thiol-thioester exchange reactions, since the odorous component of thiols can be very detrimental to certain applications. Consequently, this exploration will also lead to significant technical development for applications beyond the scope of this research.

Chapter 2: Objectives

2.1 Overview

Thiol-X chemistries include reactions involving the efficient additions of thiols to various functional groups. This thesis focuses on two of these reactions: the thiol-ene (radical addition), thiol-Michael (anionic addition) and also focuses on the thiol-thioester exchange which can be incorporated into thiol-X materials. The efficiency of these reactions makes them very desirable for uses that range from small molecule synthesis to polymerization methods. However, as advantageous as these reactions are, the thiol monomers are accompanied by a foul odor. Additionally, thiol and alkene monomer mixtures can be quite unstable and in certain cases react as soon as they are mixed. While secondary thiols have been proposed to address both issues, there is very limited information as to how the substitution of the thiol affects the thiol-ene, thiol-Michael, and thiol-thioester exchange kinetics and mechanical properties.

The objectives of this thesis are to enhance the overall understanding of these thiol-X chemistries with systematic studies of primary, secondary, and tertiary thiols. These studies include analysis of reaction rates and conversion using FT-IR and NMR spectroscopies, mechanical studies using DMA, and rheological studies to measure the shelf-life stability of the monomer mixtures.

2.2 Specific Aim 1: Investigating how the substitution of the thiol affects the thiol-ene reaction kinetics and polymer network mechanical properties.

The purpose of this aim is to characterize the effects of the degree of substitution of the thiol on reaction kinetics by evaluating model reactions of monofunctional small molecules. Studying small molecules allows us to model how the reactions will behave in polymeric systems. Additionally, analogous primary, secondary, and tertiary monomers were synthesized

to explore the effects of the substitution of the thiol on polymerization kinetics and mechanical properties. Subsequently, rheological studies were completed to observe the shelf-life stability of monomer mixtures at room temperature.

2.3 Specific Aim 2: Investigating how the substitution of the thiol affects the thiol-Michael reaction kinetics.

In this aim, model reactions using monofunctional isomers of butane thiol were assessed using FT-IR to gather kinetic and conversion data. Additionally, secondary analogs of the most common thiol monomers used in thiol-Michael studies were selected for further polymer kinetic studies and shelf life tests. Since the product of both the thiol-ene and thiol-Michael reactions are the same thioether bond, no additional mechanical studies were necessary, but shelf life stability tests of the monomer mixtures were conducted.

2.4 Specific Aim 3: Investigating effect of thiol on thiol-thioester exchange reaction

Thioester moieties can be readily incorporated into thiol-X materials as a method to introduce labile chemical bonds. This aim sought to further develop our scientific knowledge of thioester linkages that allow for dynamic exchange by exploring the substitution of the thiol and thioester to understand the capabilities and limitations of these structures. To evaluate the effect of the substitution of the thiol on the thiol-thioester exchange reaction, preliminary studies with ^{1}H NMR were completed using a protic and polar-aprotic solvent, and base and nucleophilic catalysts. Then, 4-oxo-4-[[3-oxo-3-(2-propen-1-yloxy)propyl]thio]-, 2-propen-1-yl ester butanoic acid and its secondary thioester counterpart were synthesized and incorporated into polymer networks. These networks were tested using a dynamic mechanical analyzer for stress relaxation and glass transition behavior, and assessed for self-healing properties. This project was done in

collaboration with Nicholas Bongiardina, who conducted all of the mechanical studies and assisted in collecting NMR data. My role in this project consisted of synthesizing the primary and secondary thioester molecules, as well as the secondary thiol used in this study. Additionally, I collected and interpreted NMR data for the calibration curves and base exchange values.

2.5 Summary of Work

The work detailed in this thesis advances the applications of thiol-X reactions and will enrich the knowledge base of thiol-X chemistries by providing new information as to how the structure of the thiol affects thiol-X reactions. This thesis expands the type of thiols encountered in the thiol-X reaction by providing information about how such secondary and tertiary thiols behave in these reactions. Additionally, this thesis makes thiol-X reactions more applicable by suggesting solutions to the two significant drawbacks. All of these provide additional tools for future research endeavors to optimize properties of thiol-X reactions and materials.

Chapter 3: The Effects of 1°, 2°, and 3° Thiols on Thiol-ene Reactions: Polymerization Kinetics and Mechanical Behavior[1]

3.1 Abstract

The effect of thiol substitution in radical thiol-ene reactions has been studied using model, monofunctional thiols as well as multifunctional thiol monomers along with the assessment of their subsequent polymerization reactions and polymer mechanical behavior. FT-IR was used to monitor the polymerization rate and quantify the overall conversion. While the total conversion was observed to range from 70-100%, the polymerization rate was found to decrease by as much as 10-fold as the thiol substitution was changed from primary to tertiary. Analogous multi-thiol monomers of similar structure but varying substitution were synthesized to observe the effect of substitution type on polymerization kinetics and polymer behavior. Methylation at the α-carbon was varied from primary to tertiary to observe these differences. Mechanical properties were assessed using dynamic mechanical analysis and water sorption experiments, where the glass transition temperatures were found to be within 1-2°C as thiol substitution varied. Furthermore, primary thiol films absorbed 1-3% more water than secondary thiol films. Resin shelf stability experiments were performed using rheometry to measure storage time-dependent viscosity changes, and it was found that secondary thiol films remained relatively stable for up to 100 times longer than their primary counterparts. It was concluded that, while there are differences under relatively slow initiation conditions, at typical initiation rates all three thiol substitutions may be made to react at similar rates for both monofunctional and polymeric systems.

[1] Appears in *Macromolecules*, **2020**, 53 (14), 5805-5815. doi.org/10.1021/acs.macromol.0c00369

3.2 Introduction

The thiol-ene reaction has been widely utilized across a variety of areas in polymer science and across other fields as well. It is an important member of the polymer scientist's toolbox because it enables features including insensitivity to oxygen[52, 53], rapid kinetics, high conversions, solventless conditions, optical clarity, uniform network formation, facile polymer functionalization, highly efficient reaction characteristics, and low polymerization stress. Numerous individuals have characterized thiol-ene reactions as "click" reactions due to these desirable characteristics. Though there are conditions where the thiol-ene reaction deviates significantly from this click behavior depending on initiator concentration as well as functional group type and concentration[54], with proper experimental setup the thiol-ene reaction certainly follows click characteristics[55, 56]. In addition to small molecule synthesis[57, 58], these features provide the thiol-ene reaction with remarkable flexibility in regard to starting materials for numerous applications including high performance protective polymer coatings[59], optical and biomedical materials[60, 61], dendrimer synthesis[62], and surface functionalization[63].

These unique polymerization and polymer network properties are largely due to the step-growth polymerization mechanism[30, 31]. The radically-catalyzed thiol-ene mechanism (Figure 7) proceeds from radical generation, commonly from either thermal or photoinitiation. Once radicals are formed, alternation of propagation and chain transfer reactions occur with the thiyl radical propagating through the alkene to generate a secondary alkyl radical. It should be noted that in thiol-ene literature, the propagation step refers to this addition of a thiyl radical to a carbon-carbon double bond and this terminology differs somewhat from the classical propagation which defines a step in free radical polymerizations[55]. The alkyl radical then chain

transfers to a thiol by abstracting a hydrogen atom to produce the thiol-ene product and regenerate a new thiyl radical[64-66]. Ideally, this reaction is purely step-growth and no homopolymerization of the alkene occurs through the alkyl radical. However, despite widespread use and distinct advantages, there are drawbacks to this system. It is well known that thiols are often accompanied by offensive odors which make them prohibitive for certain cases[67]. Furthermore, the shelf life of thiol and alkene monomer mixtures is limited and has previously been controlled with the use of inhibitors that serve also to slow the reaction[30]. Previous work by Li and coworkers found when using a secondary thiol monomer, the monomer mixtures were stable for at least 20 days, whereas monomer mixtures containing primary thiols gelled within 12 hours[46]. In addition, the secondary monomer was less offensive in odor and could be incorporated into new polymeric materials, as both the primary and secondary monomers were highly reactive. Despite these observations, there is little additional or systematic information on the effects of the degree of thiol functionalization with particularly little regarding tertiary thiol structures in thiol-ene reactions.

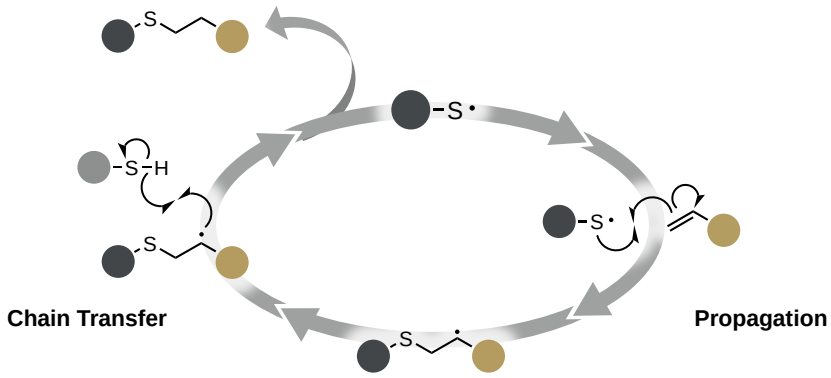

Figure 7. Mechanism of the thiol-ene reaction. A thiyl molecule radically adds to the alkene in an anti-Markovnikov addition (propagation step). The resulting carbon centered radical then chain transfers by abstracting a hydrogen from a new thiol molecule, generating the thioether product as well as a new thiyl radical.

Little research is available to indicate how thiol substitution affects thiol-ene radical reactions. In particular, a thorough kinetic analysis is necessary to evaluate the practicality of secondary and tertiary thiols as monomers in thiol-ene polymerizations, particularly including an understanding of how different thiol and ene reactants may be affected differently by substitution. This work aims to understand how the structure of the thiol affects the reaction kinetics and conversion through small molecule studies using Fourier Transform Infrared (FT-IR) and ^{1}H NMR analysis. Small molecule studies were used both as polymerization models and because of the importance of thiol-ene reactions in molecular synthesis as these model reactions are not complicated by diffusion limitations and viscosity changes that generally occur in polymerizations, particularly bulk photopolymerizations. Polymerizations were also performed on monomers of varying substitution to elucidate the effects of substitution type on the polymerization behavior. Dynamic mechanical analysis (DMA) and water sorption tests were used to evaluate differences mechanical properties and polymer characteristics that result from addition of methyl groups to the polymer backbone. Lastly, this work addresses potential shortcomings from instability of monomer resin by observing changes in apparent solution viscosity over time.

3.3 Experimental

3.3.1 Materials

The molecules, n-butanethiol (NBT), 2-methyl-2-propanethiol (TBT), the photoinitiator 2,2-dimethoxy-2-phenylacetophenone (DMPA), the inhibitor butylated hydroxytoluene (BHT), and solvent diethylene glycol diethyl ether (DEGDE) were purchased from Sigma Aldrich. Sec-

butyl mercaptan (SBT) was purchased from VWR Chemicals, and divinylbenzene was purchased from Alfa Aesar.

The monomers, pentaerythritol tetrakis(3-mercaptopropionate (PETMP-1), triethylene glycol divinyl ether (TEG), trimethylolpropane diallyl ether (TMAE), and 1,3,5-triallyl-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (TTT), were purchased from Sigma Aldrich and used without any further purification. 1,3-divinyltetramethyldisiloxane was purchased from Fisher Scientific. Tris[2-(3-mercaptopropionyloxy)ethyl]isocyanurate (TTTSH-1) was purchased from Alfa Chemistry. Pentaerythritol tetrakis(3-mercaptobutanonate) (PETMP-2), and 1,3,5-tris[2-(3-mercaptobutanoyloxy)ethyl]-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (TTTSH-2), also known as KarenzMT^{TM} PE1 and KarenzMT^{TM} NR1 respectively, were samples generously donated by Showa Denko America Inc.

All molecules, monomers, and solvent were used as received.

3.3.2 Procedures

Monomer Synthesis

Synthesis of 1,4-bis(1-bromoethyl)benzene

Divinylbenzene (13.19 g, 100 mmol), was dissolved in n-hexanes (100 mL) under anhydrous conditions and cooled to -3°C. Under constant stirring, 33 wt% HBr in acetic acid (38.52 mL, 220 mmol HBr) was added to the flask dropwise. After stirring for 24 hrs, the solvent was removed under vacuum, and the crude product was recrystallized in n-hexanes to yield white, needle-like crystals. (9.43 g, 32% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.44 (s, 4H), 5.22 (q, J = 7.0 Hz, 2H), 2.06 (d, J = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 143.30, 127.19, 48.85, 26.72.

Synthesis of 1,4-bis(1-mercaptoethyl)benzene (D2SHB)

Thiourea (16.74 g, 220 mmol) was added to a 250 mL flask containing ethanol (67 mL), brought to reflux with vigorous stirring and allowed to dissolve. Following, 1,4-bis(1-bromoethyl)benzene (29.20 g, 100 mmol) was added and refluxed at least overnight while monitoring with TLC. After the reaction was complete, the solvent was evaporated under vacuum, and the remaining solid was washed repeatedly with 500 mL hexanes. The crude product was used without further purification.

The crude material was added to DI water (50 mL) and KOH (12.34g, 220 mmol). The mixture refluxed for 3 hours. The solution was then cooled and maintained at room temperature while 1M HCl was slowly added until a pH of 1 was reached. The mixture was extracted with ethyl acetate (3 x 100 mL). The organic layer washed with brine, dried with Na_2SO_4, and concentrated. The product was purified with column chromatography using a dichloromethane gradient (0-25%) in hexanes to yield (13.49 g, 68% yield) a suitably pure target (>98%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 (s, 4H), 4.22 (qd, *J* = 7.0, 5.1 Hz, 2H), 1.99 (d, *J* = 5.1 Hz, 2H), 1.66 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 144.71, 126.65, 38.38, 26.04.

Synthesis of 1,4-bis(1-mercapto-1methylethyl)benzene (D3SHB)

The synthesis of D3SHB was adapted from a procedure for synthesizing RAFT agents[68]. First, α,α,α‘,α‘-tetramethyl-1,4-benzenedimethanol (15.00 g, 77.2 mmol) and thiourea (13.50 g, 177.6 mmol) were slowly added to a round bottom flask containing 48 wt% HBr in water (195.0 mmol 21.84 mL). The slurry was heated to 50 °C for 5 minutes, and the slurry solidified into a white solid. The solid was cooled to room temperature, filtered and washed with 0.1 M aq. HBr.

The resulting precipitate was dried under high vacuum and crushed into a fine powder. The powder was added to a round bottom with a 12.4M NaOH solution (60 mL) and allowed to stir for 24 hours. The solution was then acidified with 1M HCl until pH of 1 and then extracted with DCM (3 x 100 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was then purified with column chromatography gradient from 0-50% ethyl acetate in hexanes to achieve a 43% yield. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.51 (s, 4H), 2.25 (s, 2H), 1.82 (s, 12H). ^{13}C NMR (101 MHz, Chloroform-d) δ 211.51, 146.89, 125.40, 45.66, 34.49.

Polymer Synthesis

Polymer films were made by dissolving DMPA (either 1.0 or 0.1 wt%, based on total weight of solution) in thiol, followed by the addition of alkene maintaining a 1:1 functional group stoichiometry. The solution was mechanically mixed while being careful not to expose to sources of light. The solution was sandwiched between two glass slides treated with RainX, and spacers were used to maintain equal thickness (0.75mm for water absorption samples, 0.25 mm for DMA samples). The samples were then exposed to 365 nm irradiation of 20-30 mW/cm^2 at the surface of the sample, irradiation was monitored using a radiometer (model IL 1400A equipped with a GaAsP detector and a quartz diffuser). Each side was treated with irradiation for 15 minutes, and then post cured in an oven 40°C above the glass transition temperature of the polymer. This step is necessary as it ensures consistent curing between samples and that no additional curing will occur during the DMA examination of the sample.

FTIR Characterization

FTIR studies were completed using a Nicolet 6700 FTIR combined with a vertical light cable. Series scans were conducted in real time, taking spectra at a rate of 0.87 sec/scan. The FTIR chamber was constantly purged with dry air, and the samples were irradiated until the reaction was either complete, as indicated by a flat-line of the functional group absorbance spectra, or a reaction time of 30 minutes. The thiol conversion was monitored by observing the S-H absorption peak at 2570 cm^{-1}, and the alkene conversions were monitored by observing the C-H stretch around 3100 cm^{-1}. All reactions were performed under ambient conditions.

The sample mixtures were placed between NaCl crystals. In all cases no spacer was used. The reaction was initiated with a 365 nm light and irradiation intensities were measured with a radiometer (model IL 1400A equipped with a GaAsP detector and a quartz diffuser).

All kinetic rates are reported in conversion %/sec for normalized comparison across all thiols and alkenes. The initial concentrations of all solutions have been provided in case the reader would like to calculate the rates in mol/L•s. Any side reactions or impurities from DMPA are assumed to be insignificant due to the low concentration of DMPA relative to the thiol and ene functional groups (see supplementary info for concentrations).

Dynamic Mechanical Analysis (DMA)

The glass transition temperature (T_g) was measured using a TA RSA-G2. The samples were cut into rectangular dimensions (L x W x Th, 10 mm x 4 mm x 0.25 mm) and were tested in the multi-frequency strain mode by applying a sinusoidal stress of 1 Hz frequency at a temperature ramp rate of 3°C/min.

Water Sorption/Desorption Test

The water sorption procedures were adapted from Podgórski *et al.*[69] Polymer films, prepared as described above, were dried in an oven at 37°C until a constant mass was reached (m_i). The samples were then submerged in DI water at room temperature. At 24 h time intervals, the samples were removed, and excess water blotted with a Kimwipe. The mass was recorded, and the samples were returned to water. When there were no longer any significant changes in mass the equilibrium saturation mass (m_s) was recorded. Then, the saturated samples were dried in an oven at 37°C. The mass was recorded at 24 h time intervals until there were no significant changes in mass, and this final mass was noted as the desorption mass (m_d). The following equations were used to calculate the equilibrium water sorption, *s*, and equilibrium water desorption, *d*. The experiments were performed in triplicate.

$$s = \frac{m_s - m_i}{m_i}, \; d = \frac{m_s - m_d}{m_s} \qquad \text{Equations (1 \& 2)}$$

Shelf-Life Stability

The shelf life of the materials was evaluated by preparing 10.0 g mixtures of thiol and alkene monomers without any exposure to UV radiation. The samples were stored in brown, UV-resistant vials at room temperature. Apparent viscosity measurements were taken using 0.05 mL aliquots for each time point using a rheometer (TA Ares G2 4010-0778). The rheometer measured the viscosity with 20 mm stainless steel parallel plates and a 0.2 mm gap. The temperature was maintained at 22°C, and the apparent viscosity was measured against a sheer rate ramp from 10-1000 s^{-1} over a period of 120 seconds.

^{1}H NMR Conversion Studies

Proton NMR spectra were recorded on a Bruker Avance-III 400 MHz spectrometer. All proton spectra are reported in ppm (δ) relative to internal tetramethylsilane (δ 0.0). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants [Hz], integration). All NMR data were collected at 25°C.

The samples were prepared by dissolving DMPA (0.1wt%) in thiol and alkene model molecules in a 1:1 functional group ratio (i.e. small molecule synthesis). An inhibitor, BHT, was added in a 1:10 BHT:DMPA molar ratio. An initial NMR was collected for each sample. The samples were then tested by injecting the sample into a glass slide – silicone rubber – glass slide sandwich where the silicone rubber sheet had a biopsy hole punched through it. This ensured that none of the volatile components of the mixture evaporated during irradiation. The samples were irradiated with a 365nm light at 10 mW/cm^2 light intensity for a period of time that was 5 minutes longer than the amount of time it took to reach full conversion, as measured by FTIR. The sample was removed and injected into an NMR tube with deuterated chloroform and a spectra was immediately taken.

Each sample was prepared 3 times, and 4 measurements were taken from each sample for a total of 12 replications per monomer mixture. All tests were conducted at ambient conditions.

Conversions were calculated by recording an initial and final spectrum and observing the change in integration of the alkene peaks (~d 6.5) and the thiol peak (~d 1.5-2) using solvent peaks as an internal standard d 3.52 (q, J = 7.0, 4H).

3.4 Results and Discussion

3.4.1 Monofunctional Studies

Secondary and tertiary thiol monomers have been shown to address certain drawbacks to the thiol-ene reaction, yet little is known as to how the substitution of the thiol affects the reaction kinetics. To understand this effect, a thorough kinetic study was completed using monofunctional low molecular weight molecules as model compounds. These model compounds should proceed chemically in a manner nearly identical to that which happens during polymerization while eliminating complicating factors such as the conversion-dependent diffusion and viscosity changes that occur as a typical polymerization progresses[31, 50, 51]. Therefore, at low conversions in the thiol-ene reaction, the small molecule kinetics and the polymerization kinetics are expected to be similar, but towards the end of the reaction we would expect substantial differences due to the diffusion and viscosity changes taking place in polymerization reactions as the high molecular weight or crosslinked polymer forms. In addition to the similarities to low conversion polymerizations, these studies also serve to inform small molecule synthesis via the thiol-ene reaction, by forming small molecules rather than the polymeric product.

Following Cramer *et al.,* three different alkenes were selected – each with a different rate determining step (RDS) in the alternating propagation-chain transfer mechanism of the thiol-ene reaction[70]. It is understood that for the vinyl siloxane and the allyl ether, the rate-determining steps are propagation and chain transfer, respectively, while the rates for both steps are comparable for the vinyl ether. When the reaction is propagation limited, it was hypothesized that the least stable thiyl radical would react more rapidly with an alkene, facilitating propagation but inherently slowing chain transfer. Therefore, the primary thiol, which is least able to stabilize

a radical, would have the fastest kinetic rate, followed by secondary and then tertiary thiols. For the chain transfer limited case, the most stable thiyl radical would form the most rapidly because less energy is required to form the thiol-ene product upon hydrogen abstraction. Therefore, it was hypothesized that the tertiary thiol, which has the greatest capacity to stabilize a radical, would react the fastest, followed by secondary and then primary thiols. When the propagation rate is about equal to the chain transfer rate, the order of reactivity depends on whether the effect of substitution is greater on propagation or chain transfer, or if there is a similar effect on both.

Steric hindrance of a molecule has a dramatic effect on the reaction kinetics, and therefore it was necessary to observe, from a preliminary standpoint, whether substitution of the alpha-carbon in secondary or tertiary thiols would have an adverse effect on reaction rate. The sterics of the thiol, rather than the electronics, are expected to play a larger role because in alkane thiols the S-H bond have near similar bond dissociation energies and reactivity regardless of substitution, thus there is a greater effect from sterics[71]. FT-IR was used to measure the thiol-ene reaction kinetics for all three substitutions. The initial assessment of thiol substitution included three isomers of butanethiol: n-butane thiol (NBT), sec-butanethiol (SBT), and tert-butanethiol (TBT) (Figure 8). A divinyl ether monomer (TEG) was used as the complementary reactive group because vinyl ethers typically do not homopolymerize during thiol-ene reactions[15]. A divinyl siloxane (DVSiO) and allyl ether (TMAE) were also evaluated because of their differing RDSs. The initiator for all reactions was 2,2-dimethoxy-2-phenyl acetophenone (DMPA), a radical photoinitiator that cleaves upon exposure to 365 nm light.

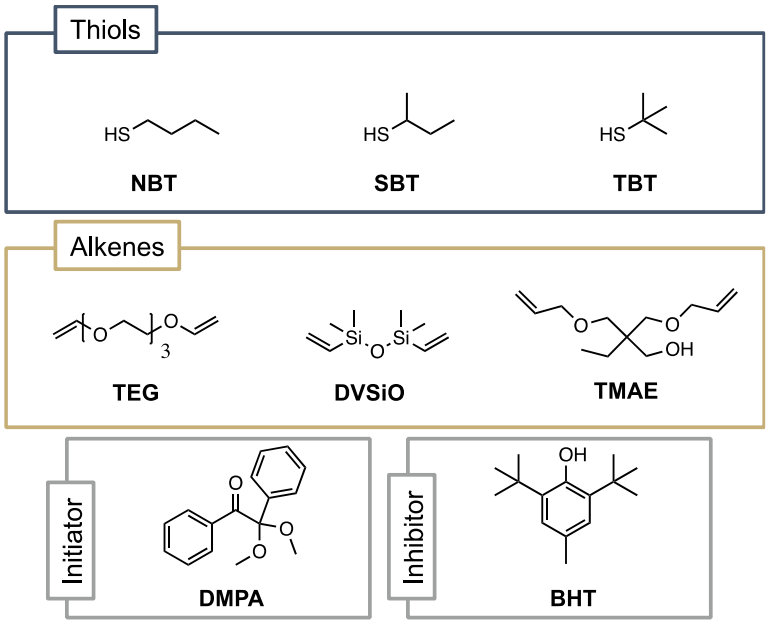

Figure 8. Chemical structures of monofunctional thiols (NBT, SBT, and TBT), alkene monomers (TEG, DVSiO, and TMAE), photoinitiator (DMPA), and radical inhibitor (BHT) used in this study.

The results show that under typical initiation conditions (1.0 wt% DMPA, 365 nm, 30 mW/cm^2) the reactions for all three thiols reacted with the vinyl ether were extremely rapid with relatively small differences in the rapid reaction rates (Figure 9). This behavior suggested that for these model reactions, the substitution of the thiol had a small effect on the reaction rate of the thiol-ene reaction and could readily be incorporated without significant decreases in the rate expected.

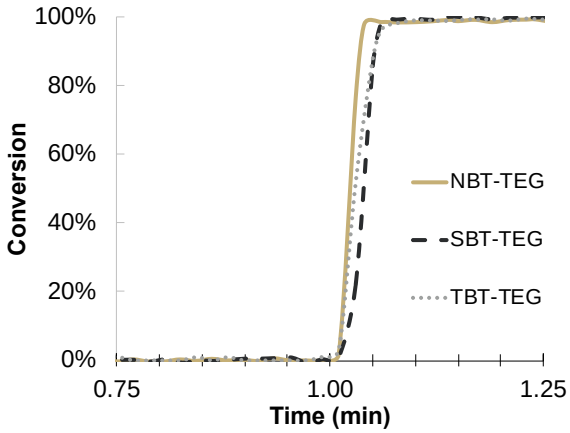

Figure 9. Experimental data for the alkene conversion vs time at standard initiation conditions for n-butane thiol (NBT), sec-butanethiol (SBT), and tert-butanethiol (TBT) with the vinyl ether monomer (TEG), used in a 1:1 functionality of thiols and alkenes. Samples contain 1.0 wt% of DMPA and are irradiated with 40 mW/cm^2 light intensity with a 365 nm filter. Irradiation began at t = 1 minute and the sample was held in the dark prior to that time to observe any dark polymerization that might occur.

The reactions were too fast to observe the relative substitution effects on the reaction under these conditions. To investigate the kinetics further, the initiation rates were significantly reduced (0.1 wt% initiator, 365 nm, 10 mW/cm2). For all of the alkenes studied under these conditions, the primary thiol was faster than the secondary which was faster than the tertiary, albeit to different extents depending on the alkene that was used. For the vinyl ether TEG monomer specifically, reduced initiation rates emphasize that despite with the increase in substitution, the conversion of the reaction went to quantitative conversion. This behavior was confirmed by both ^{1}H NMR and IR measurements (Table 1). Since the conversions of the thiol and alkene are nearly identical, it is assumed that the alkene and thiol monomers are reacting on a 1:1 ratio, and therefore only alkene conversions are shown in Figure 10 for each alkene. Small differences in conversion between the alkene and the thiol can be attributed to difficulty in observing the thiol peak in the IR spectra and NMR peak overlap.

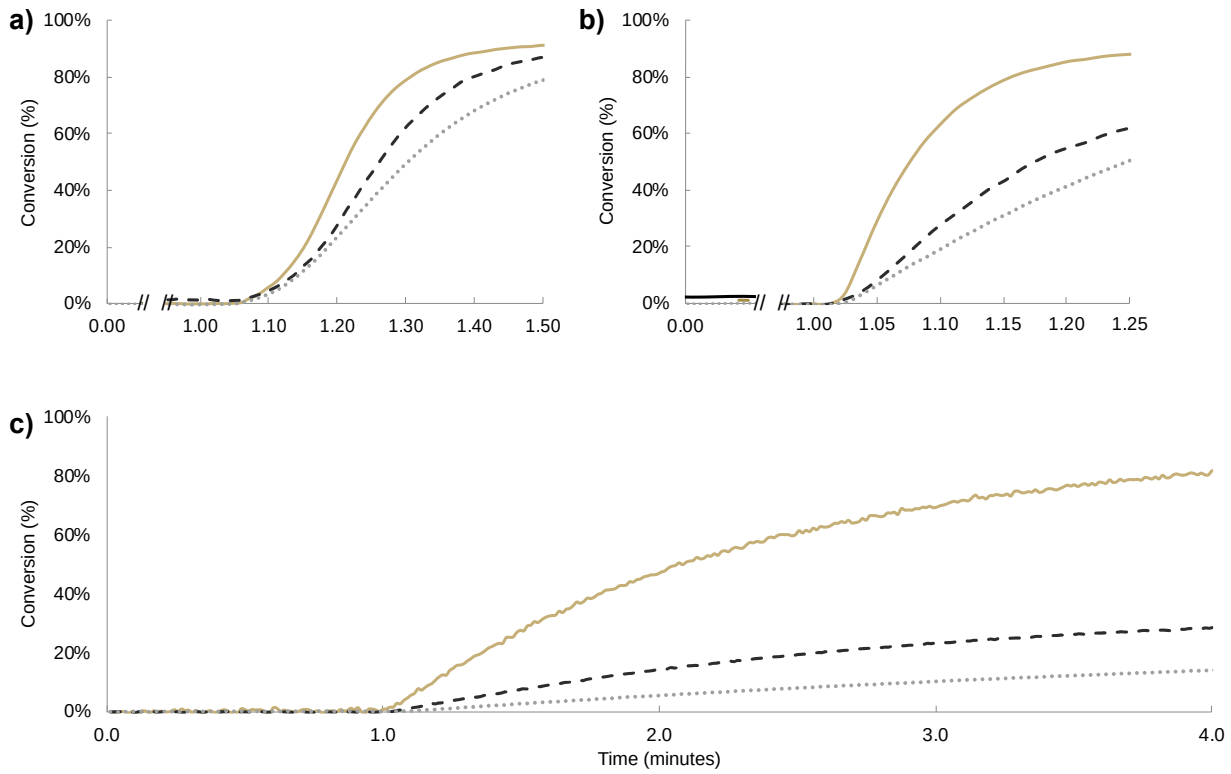

*Figure 10. Experimental data for the alkene conversion vs time of the n-butane thiol (solid line) (NBT), sec-butanethiol (dashed line) (SBT), and tert-butanethiol (dotted line) (TBT) with **a)** the vinyl ether monomer (TEG), **b)** the divinyl siloxane (DVSiO), and **c)** the diallyl ether (TMAE). A 1:1 functionality of thiol to alkene functional groups was used. Samples contain 0.1 wt% of DMPA and are irradiated with 10 mW/cm^2 light intensity with a 365 nm filter. The lamp was turned on at t = 1 minute.*

For TEG (Figure 10a), the primary thiol reacts the fastest, followed by the secondary and then tertiary thiols; however, all of the reaction rates are of the same order of magnitude (Table 1) with only approximately a 50% decrease in rate from the primary to tertiary thiol. For the vinyl silane DVSiO (Figure 10b), the final conversion is not affected by substitution and all three thiols went to full completion in both NMR and FTIR though for the NMR conversion of the n-butane thiol, quantitative assessment of the conversion was not possible due to peak overlap (Table 1). The relative rates for DVSiO reactions followed the trend of the TEG with the primary thiol being the fastest followed by secondary and then tertiary thiols. However, the kinetic rate for DVSiO was more impacted by the increase in substitution than for TEG with an approximately 70% decrease in the reaction rate when comparing the tertiary thiol with the

primary thiol. Cramer et al. reported that the rate of the thiol-ene reaction is dependent on the electron density of the alkene and vinyl silanes are some of the more electron dense alkenes[31]. Even though the molecule could have some steric interference from the additional methyl groups, it is unlikely that this effect is playing a significant role considering the alkene is monosubstituted, terminal, and has a trigonal planar shape.

Table 1. Reaction rates and final percent conversion values found in IR and NMR analysis for the divinyl ether (TEG), divinyl siloxane (DVSiO) and diallyl ether (TMAE) alkenes (0.1wt% DMPA, 365 nm, 10 mW/cm^2). All reactions were completed at room temperature.

	Divinyl Ether					
	Rate (s^{-1})		IR Final Conv.		NMR Final Conv	
	Alkene	Thiol	Alkene	Thiol	Alkene	Thiol
NBT	8.1% ± 1.2 %	8.7% ± 0.5%	93% ± 2%	95% ± 8%	91% ± 7%	92% ± 3%
SBT	5.2% ± 0.3%	4.7% ± 0.5 %	83% ± 2%	93% ± 2%	98% ± 2%	90% ± 3%
TBT	4.0% ± 0.2%	2.9% ± 0.3%	98% ± 2%	98% ± 1%	95% ± 6%	94% ± 1%

	Divinyl Siloxane					
	Rate (s^{-1})		IR Final Conv.		NMR Final Conv	
	Alkene	Thiol	Alkene	Thiol	Alkene	Thiol
NBT	11.9% ± 0.5%	9.4% ± 1.3%	92% ± 6%	95% ± 2%	100% ± 0%	Unavail.
SBT	4.3% ± 1.5%	4.7% ± 0.5 %	92% ± 4%	99% ± 0%	99% ± 2%	97% ± 1%
TBT	3.0% ± 0.1%	2.9% ± 0.2%	93% ± 3%	98% ± 1%	97% ± 2%	86% ± 0%

	Diallyl Ether					
	Rate (s^{-1})		IR Final Conv.		NMR Final Conv	
	Alkene	Thiol	Alkene	Thiol	Alkene	Thiol
NBT	0.0088% ± 0.0004%	0.0072% ± 0.0004%	96% ± 3%	92% ± 6%	94% ± 1%	Unavail.
SBT	0.0011% ± 0.0001%	0.0019% ± 0.0002%	83% ± 4%	89% ± 3%	74% ± 2%	80% ± 1%
TBT	0.00011% ± 0.00002%	0.00023% ± 0.00010%	43% ± 3%	58% ± 6%	32% ± 2%	47% ± 3%

The diallyl ether (TMAE) is affected the most by the thiol substitution (Figure 10c). The reaction rate decreased by an order of magnitude with each additional substitution of the thiol,

and each decrease in rate was accompanied by a decrease in the final conversion achieved, as measured at the 20 minute mark. The appearance of higher thiol conversion for the secondary and tertiary thiol-ene systems is attributed to evaporation of the low boiling point thiols, where the longer reaction times lead to greater amounts of evaporated thiol. The reaction rate and subsequently conversion for TMAE are more dramatically impacted than TEG and DVSiO because the steric interactions increase the activation energy of the chain transfer step – where the alky radical abstracts a hydrogen from the S-H bond[72]. Allyl ethers are known to have a chain transfer rate limiting step and would show this increase in activation energy as a reduction in rate. In addition, allyl ethers are known to react more slowly in the thiol-ene reaction than vinyl ethers and vinyl siloxanes[30], which is also a likely explanation for why the reaction rate and conversion were more affected by substitution compared to TEG and DVSiO.

For all three alkene monomers, increasing substitution resulted in a decrease in the reaction rate, as shown in Table 1 and Figure 10. This trend was expected for reactions that were propagation limited (DVSiO), whereas the opposite tend might have been expected for the chain transfer limited reactions (TMAE). Given that TEG also followed this trend, it is apparent that steric hinderance is also driving the reduction in reaction rate as the thiol is increasingly substituted in addition to the electronic effects on the radical stability.

3.4.2 Polymerization Kinetics

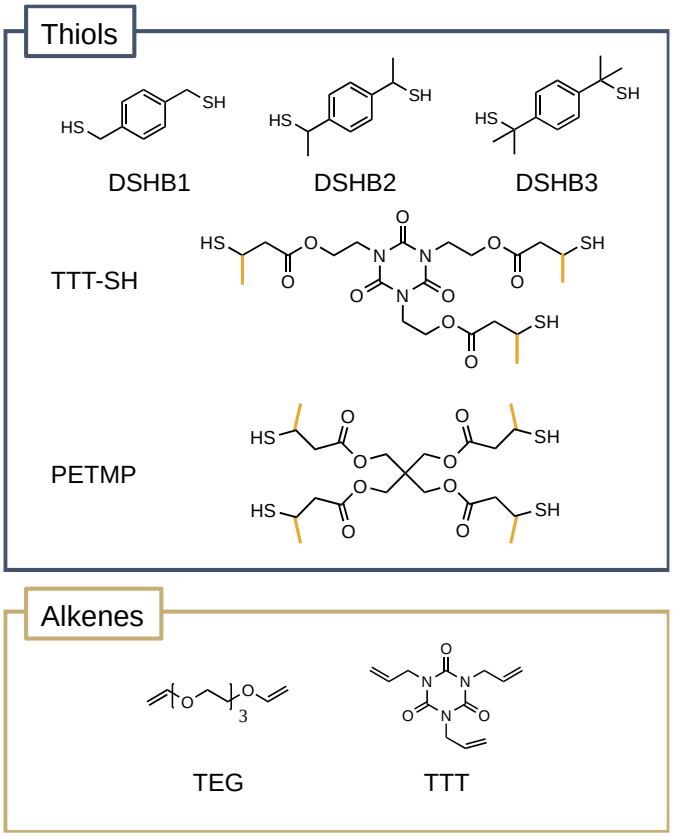

Figure 11. Chemical structures of thiol and alkene monomers used in polymeric kinetic and mechanical studies. Rate studies were conducted with primary, secondary, and tertiary difunctional benzylic thiols as well as primary and secondary analogs of both trifunctional and tetrafunctional thiol monomers commonly used in the thiol-ene literature. The primary and secondary analogs were also used for mechanical studies. The alkenes used are trifunctional and difunctional alkenes also commonly used in thiol-ene literature.

To study the effect of substitution on polymerization kinetics, analogous primary, secondary, and tertiary benzyl thiol monomers were synthesized. Structures for these monomers are shown in Figure 11. Thiol-ene mixtures were then prepared to assess how the different substituted monomers behave in polymerizations that form crosslinked polymers (Figure 12). It should be noted that under certain circumstances, the addition of the first thiol to a multifunctional monomer can result in changes in rate for the remaining, unreacted thiols due to secondary interactions such as pi-pi stacking[73]. In these experiments, it is assumed that the difference in rate between the addition of multiple functional groups is negligible due to the fact that that our functional groups are well-spaced and unlikely to be affected electronically by the reacted state of any other functional group.

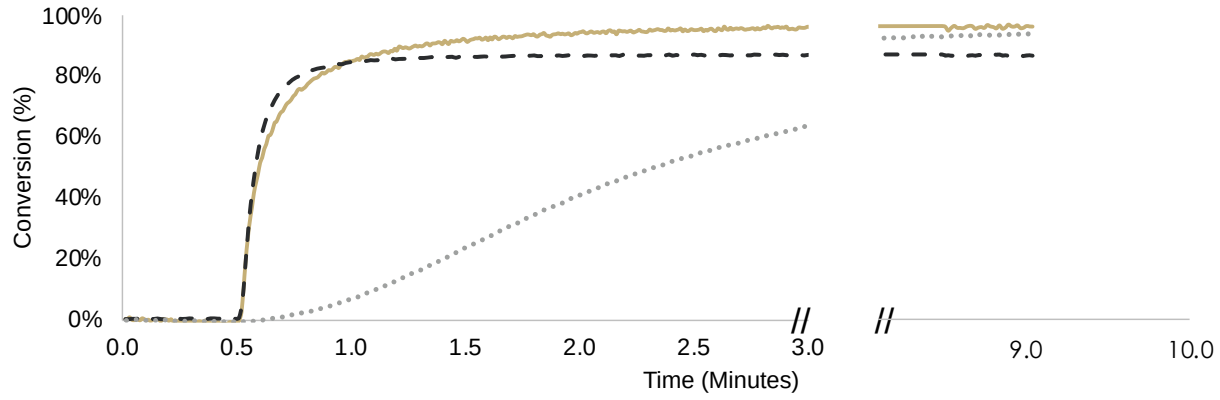

Figure 12. Experimental data for the alkene conversion vs time of D1SHB (•), D2SHB (□), and D3SHB (+) with the TTT, used in a 1:1 functionality of thiols and alkenes. Samples contain 1.0 wt% of DMPA and are irradiated with 30 mW/cm^2 light intensity with a 365 nm filter. Reactions were conducted at 40 °C.

The primary and secondary thiol react at similar rates, but the primary thiol reaches a slightly higher conversion than the secondary thiol. The tertiary thiol exhibited a much slower rate than the less substituted thiol monomers, but still reaches full conversion after 9 minutes. The significant decrease in rate, as compared to the model compounds, for the tertiary thiol monomer is hypothesized to be due to the steric hinderance of the methyl groups near the thiol, especially given that the thiol is adjacent to a benzyl group. Even though the each monomer has the same benzene group, the addition of methyl groups does not result in a linear decrease in rate. The addition of each methyl group to an alkyl halide results in rate decreases by orders of magnitude for SN2 reactions, and even though our reaction is different, there is potentially a similar pattern in rate[74]. The benzene group on the beta carbon lends additional steric hinderance, and the rigidity of the monomer would restrict the movement of the polymer as it is forming. It is interesting that the effects observed in the model compound are exaggerated here in the polymerizing systems.

Further studies were completed using primary and secondary thiol monomers that are commonly used in thiol-ene polymerizations – one with a pentaerythritol core (PETMP-1 and

PETMP-2) and another with a triazine-trione core (TTTSH-1 and TTTSH-2) as shown in Figure 11[55].

Table 2. Summary of Polymerization Rates and Conversion for Primary and Secondary PETMP and TTTSH.

	Polymerization Rates Measured by IR			
	Primary (1°)		Secondary (2°)	
	Alkene Rate (s^{-1})	Thiol Rate (s^{-1})	Alkene Rate (s^{-1})	Thiol Rate (s^{-1})
PETMP:TTT	0.32 ± 0.02	0.28 ± 0.02	0.14 ± 0.00	0.11 ± 0.00
PETMP:TEG	0.17 ± 0.02	0.16 ± 0.01	0.23 ± 0.08	0.20 ± 0.07
TTTSH:TTT	0.10 ± 0.2	0.12 ± 0.01	0.09 ± 0.003	0.08 ± 0.01
TTTSH:TEG	0.17 ± 0.01	0.17 ± 0.02	0.13 ± 0.01	0.12 ± 0.01

	Ultimate Conversions Measured by IR			
	Primary (1°)		Secondary (2°)	
	Alkene Conversion	Thiol Conversion	Alkene Conversion	Thiol Conversion
PETMP:TTT	79% ± 2%	72% ± 4%	69% ± 1%	60% ± 6%
PETMP:TEG	102% ± 1%	100% ± 0%	102% ± 13%	93% ± 12%
TTTSH:TTT	60% ± 5%	74% ± 5%	70% ± 3	60% ± 6%
TTTSH:TEG	89% ± 1%	100% ± 4%	98% ± 0%	102% ± 0%

The kinetic rates and conversion for primary and secondary thiols were evaluated using TEG and TTT monomers, which are two alkene monomers commonly used in thiol-ene polymerizations[4]. Similarly to the monofunctional studies, where the polymerization was performed at 1.0 wt% initiator and 20 mW/cm^2 light intensity, the rates for the primary and secondary monomers were nearly identical. These conditions again were reduced to 0.1 wt% initiator and 10 mW/cm^2 light intestity, and the results of these studies are summarized in Table 2. Even at such reduced conditions, the thiol monomers reacted with the TEG alkene at similar

rates and reach quantitative conversion. The difference in rate was about 0.04 s^{-1} for both PETMP:TEG and TTTSH:TEG systems. The TTT monomer typically reacted more slowly than the TEG monomer, but the overall trend remains that networks derived from primary thiol monomers react faster than the corresponding secondary thiol monomers. The conversions for this system were slightly lower and did not reach full conversion. This behavior is likely due to the fact that PETMP-TTT networks are glassy at room temperature (Figure 13, which is discussed in the following section), which limits the mobility of active radicals upon vitrification, and reducing the final conversion. This can be overcome by thermal post-curing or curing at elevated temperatures, neither of which was performed for this kinetic analysis.

3.4.3 Polymer Mechanics and Characteristics

Polymer systems were evaluated to provide an overview of any differences in the physical properties of materials derived from primary and secondary thiols. The mechanical parameters of thiol-ene films are well documented – narrow glass transition temperatures and homogeneous network compositions being two important highlights of typical thiol-ene behavior[30]. This study examined whether the thiol substitution impacts these desirable mechanical properties. The same commercially available thiols that were used in the previously described kinetic studies are also common in thiol-ene polymerizations. Polymers formed from these primary thiols and their secondary analogs were used for DMA, shelf life, and water absorption evaluation.

The T_g, as defined by the peak of the tan(δ), and storage modulus are shown in Figure 13a and Figure 13b, respectively. In all cases, both T_g and storage modulus differed only slightly

between the primary and secondary thiol-based materials, and the width of the tan(δ) peak itself was unchanged for each thiol-alkene pair.

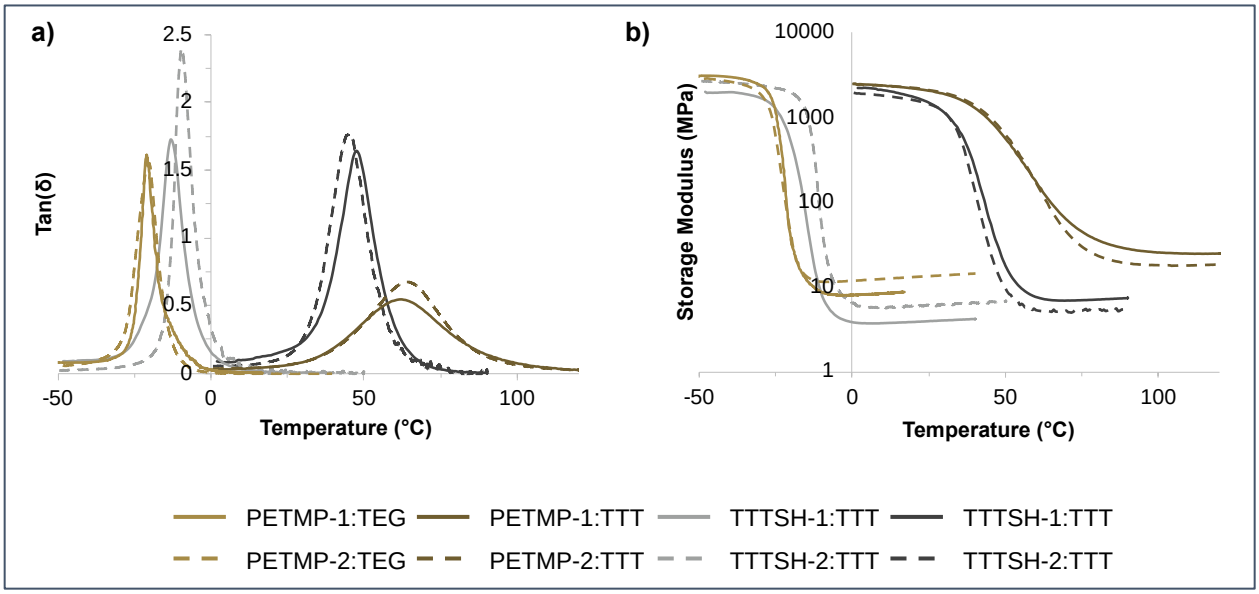

Figure 13. Glass transition temperature (7a) and storage modulus (7b) results. For the tri and tetrafunctional thiols with both TTT and TEG, solid lines correspond to the primary thiols and dashed correspond to the secondary thiols. The samples were prepared using 1.0wt% initiator, and cured using 365nm light and 40 mW/cm^2 light intensity. All polymer films were post-cured at 40°C above the glass transition temperature of the film.

Thiol-ene materials have been proposed as alternatives for (meth)acrylate-based photopolymerized resins for coatings, dental composites and numerous other applications where water uptake and degradation are important considerations[69, 75]. Water absorption, the maximum mass of water per unit volume at saturation, and water desorption, the equilibrium amount of water per unit volume in dried samples, are shown in Figure 14. The polymer films with primary thiol formulations generally absorbed more water than the polymer films with the secondary thiol formulations (as calculated by Equation 1). For these TEG-based materials, the primary thiol-based network absorbed about 2 times and 1.3 times more water than the PETMP and TTTSH systems, respectively. The TTT-based films made from primary thiols absorbed similar

amounts of water when compared to the secondary thiol polymers. The low T_g, and therefore increased diffusion rates due to looser crosslinking, of TEG-based films resulted in greater water absorption than that of the TTT-based materials.

The differences in desorption values between materials made with different thiol-substitution were calculated by Equation 2 but typically the primary thiol films have slightly higher desorption values than the films made with secondary thiols. The differences between the primary and secondary thiol films are greater for the TEG systems than the TTT systems, and this behavior is again attributed to the differences in T_g. Overall, these differences in absorption and desorption are very similar, differing by a percentage or two if at all.

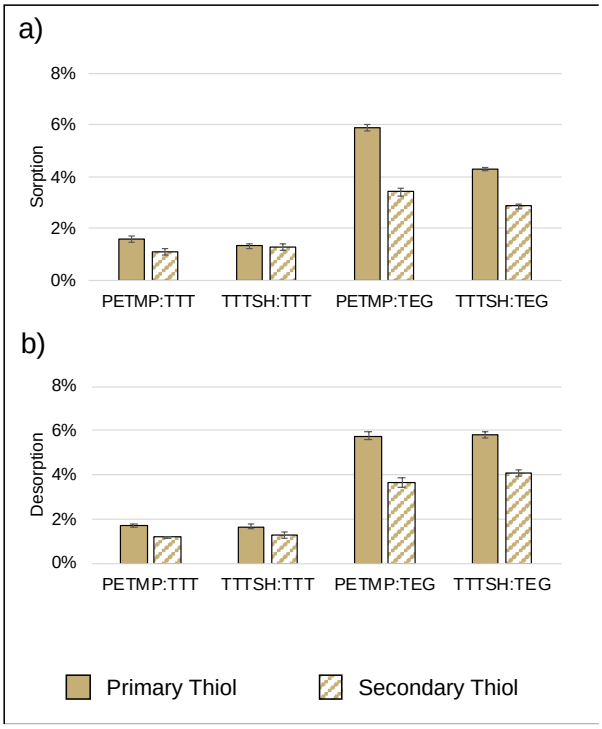

Figure 14. Absorption (a) and desorption (b) values ($\mu g/mm^3$) from water sorption tests. The polymer films were prepared using 1.0wt% initiator, and cured using 365nm light and 40 mW/cm^2 light intensity. All polymer films were post-cured at 40°C above the glass transition temperature of the film. All experiments were completed at room temperature.

Thiol-ene resins have long suffered from self-initiation, which limits the shelf-life stability of pre-mixtures of the thiol and alkene monomers. This phenomenon is due to several factors including the base catalyzed addition of a thiol to the double bond where the base is presumably introduced as an impurity in one of the monomers, generation of radicals through a

ground-state charge-transfer complex, or decomposition of impurities that produce free radicals or the thiyl radical that then initiate the reaction[48, 49], depending on the specific alkene and thiol. While this complication can be at least partially offset by inhibitors and acidic buffers, the substitution of a secondary thiol could extend the shelf-life of thiol-ene solutions without these additives[76]. To demonstrate this aspect, shelf-life studies were completed by measuring the apparent viscosity of the pre-polymer resin over time.

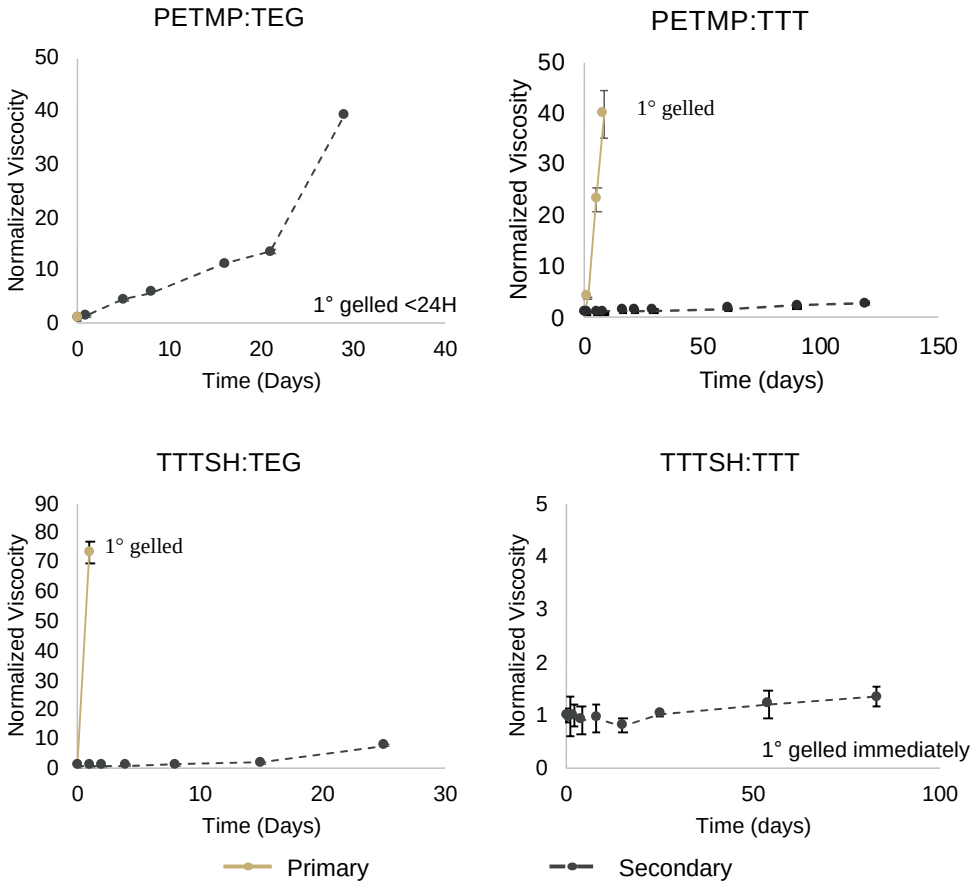

Figure 15. Rheological experiments for primary (solid line) and secondary (dashed line) thiol monomer mixtures with TEG and TTT alkenes. The primary PETMP:TEG sample gelled within the first 24 hours, and the primary TTTSH:TTT sample gelled immediately upon the mixing of the thiol and alkene. The primary TTTSH:TEG sample gelled between day 1 and day 2, and the primary PETMP:TTT sample gelled after day 8.

The shelf life studies clearly demonstrated the advantage of secondary thiols in thiol-ene resins. As noted in Figure 15, the primary thiol resins gelled before the secondary thiol samples

in every case, usually in dramatically shorter periods of time. The PETMP-1:TEG monomer mixture gelled within 24 hours, and despite being a reactive vinyl ether, the PETMP-2:TEG mixture did not gel until after the 30th day time point. In the case of the PETMP-2:TTT monomer mixture, it maintained a viscosity near its initial viscosity for more than 120 days. The TTTSH-1 monomer mixtures all gelled before the TTTSH-2 monomers. The TTTSH-1:TEG monomer mixture gelled before day 2, while the TTTSH-2:TEG monomer mixture maintained a normalized viscosity between 1-2 and gelled after the 25th day time point. Additionally, the TTTSH-1:TTT monomer mixture gelled as soon as the alkene component was added, and the TTTSH-2:TTT also maintained on a small increase in the normalized viscosity for more than 80 days.

3.5 Conclusions

Overall, increasing the substitution of the thiol does not affect the kinetic rate of the thiol-ene reaction at typical polymerization conditions, and lower initiation conditions are required to observe a difference in the reaction rate for differently substituted thiols. Even at these reduced conditions, most reactions go to full completion as seen with the vinyl ether TEG and vinyl silane DVSiO monomers. The significantly decreased rate for the allyl ether TMAE is likely due to the fact that the increased sterics of the thiol increases the activation energy of the chain transfer step of the reaction. Since the allyl ether thiol-ene reaction is chain transfer rate limited, this alkene is more affected by the substitution of the thiol[72]. In all cases, the primary thiol reacted the most rapidly, followed by the secondary then tertiary thiols, which is attributed to steric effects from increased substitution.

Polymeric systems with the difunctional benzyl centered monomers followed the same trend as the monofunctional systems, and despite a slower reaction speed for the tertiary thiol,

the tertiary system still reached quantitative conversion. These data suggest that other substituted thiols will follow this pattern.

Finally, commercially available primary and secondary thiols were polymerized into films for assessment of the mechanical properties. The glass transition temperature and storage modulus did not differ greatly between the primary and secondary thiol. However, shelf life studies demonstrated that secondary thiol-based mixtures exhibit far superior stability of the monomer resins compared to analogous primary thiol-based mixtures.

The information in this study demonstrates that more substituted thiols can be incorporated into thiol-ene reactions without any significant drawbacks in terms of kinetic rate, conversion, or adverse effects on basic material properties. Additionally, with the added benefits of an extended shelf life, secondary thiols have demonstrated many of the attributes that make the thiol-ene reaction so popular in material science – fast, efficient kinetics with few side products, narrow glass transition with homogenous networks, and highly-tunable mechanical properties. The amount of deviation from the primary thiol's properties is ultimately dependent on the type of alkene used.

3.6 Acknowledgements

The authors gratefully acknowledge Showa Denko America Inc. for providing the secondary thiol monomers PETMP-2 and TTTSH-2. Funding was also provided by the National Institutes of Health Dental and Craniofacial Research Fellowships 5 F31 DE027880-02 and 1 F31 DE027861-01A1 , as well as support through the 1U 01DE023777-01.

Chapter 4: The Effects Of Thiol Substitution On The Kinetics And Efficiency Of Thiol-Michael Reactions And Polymerizations

4.1 Abstract

The kinetic effects of the substitution and functionality of the thiol in thiol-Michael reactions were investigated using model monofunctional thiols and multifunctional thiols used in various cross-linking polymerizations. Differences in kinetic rates and final conversions were observed via FT-IR. The shelf life of these polymers and their mechanical properties were analyzed using a rheometer to measure viscosity changes over time. It was concluded that for monofunctional systems, the reaction rate is dependent on both electronic and steric interactions. For systems with a propagation rate limiting step (i.e., the propionate) the secondary thiol was faster than the primary thiol due to increased reactivity of the thiolate anion, by as much as much as a 60% increase in rate. However, more sterically hindered internal alkenes resulted in primary and secondary rates about equal to each other. For systems with a chain-transfer rate limiting step, (alkyl thiol) the rate was dependent on the pKa of the thiol and ease of deprotonation, and in these cases the primary thiol was the fastest. Though primary and secondary thiols had relatively mild differences in rates, reactions of tertiary thiols were slower than either of the others. For polymerizing systems using multifunctional thiols the results varied depending on the substitution and functionality. When reacting with a difunctional alkene, the secondary thiol was 74-95% faster than the primary thiol, depending on the type of thiol assessed, and as the functionality of the alkene increased, the rates became more comparable. In the tetrafunctional alkene systems the primary thiol was 57% faster than the secondary thiol. The shelf-life of the systems produced varied results. Typically, in systems with the difunctional thiol, the primary

thiol formulation was significantly less stable and gelled more rapidly than the resin with the corresponding secondary thiol. However, in the tetrafunctional thiol systems, the resin containing the secondary thiol gelled more rapidly than that containing the primary thiol. All systems typically gelled within 30 days regardless of substitution, although no additional formulation adjustments were made to stabilize any of these systems beyond changing the thiol structure.

4.2 Introduction

The thiol-Michael click reaction was first noted in the 1960's[36], and exhibits many exceptional characteristics that make this reaction desirable for a variety of applications including dendrimer synthesis[77, 78], surface functionalization[79, 80], hyperbranched polymers[81] and polymer synthesis[82, 83]. These characteristics – rapid kinetics with few side products, high functional group conversion, lack of oxygen inhibition, and mild reaction conditions that can proceed solventless or using environmentally benign solvents[55] – arise from the mechanism of the reaction and have led to this reaction being considered, under appropriate conditions, a click reaction[84]. This addition reaction takes place between thiols and electron deficient alkenes, rapidly reaching high quantitative conversions, and being readily catalyzed by either basic or nucleophilic initiators[85]. When using a base catalyst, the base abstracts a hydrogen from a thiol to generate the thiolate anion. During nucleophilic initiation, the nucleophile first adds to the double bond of the Michael acceptor, generating an enolate that then abstracts a hydrogen from a thiol to generate the thiolate anion (Figure 16).

In both the basic and nucleophilic mechanisms, the thiolate then acts as the Michael donor, attacking the electron deficient β-carbon of the alkene during the propagation step of this reaction (Figure 16). The generated enolate anion then abstracts a proton from a thiol, regenerating the thiolate anion to continue the cycle of this reaction. Past research has shown that

the thiol-Michael reaction is affected by solvent polarity, thiol basicity, base strength, and the electron deficiency of the vinyl group[86]. Additionally, the steric hindrance of the reactants affects the thiol-Michael reaction – the larger the substituents at the α and β positions on the Michael acceptor, the slower the reaction[87]. Additionally, if the steric hindrance around the nucleophile increases, so does its reactivity[88].

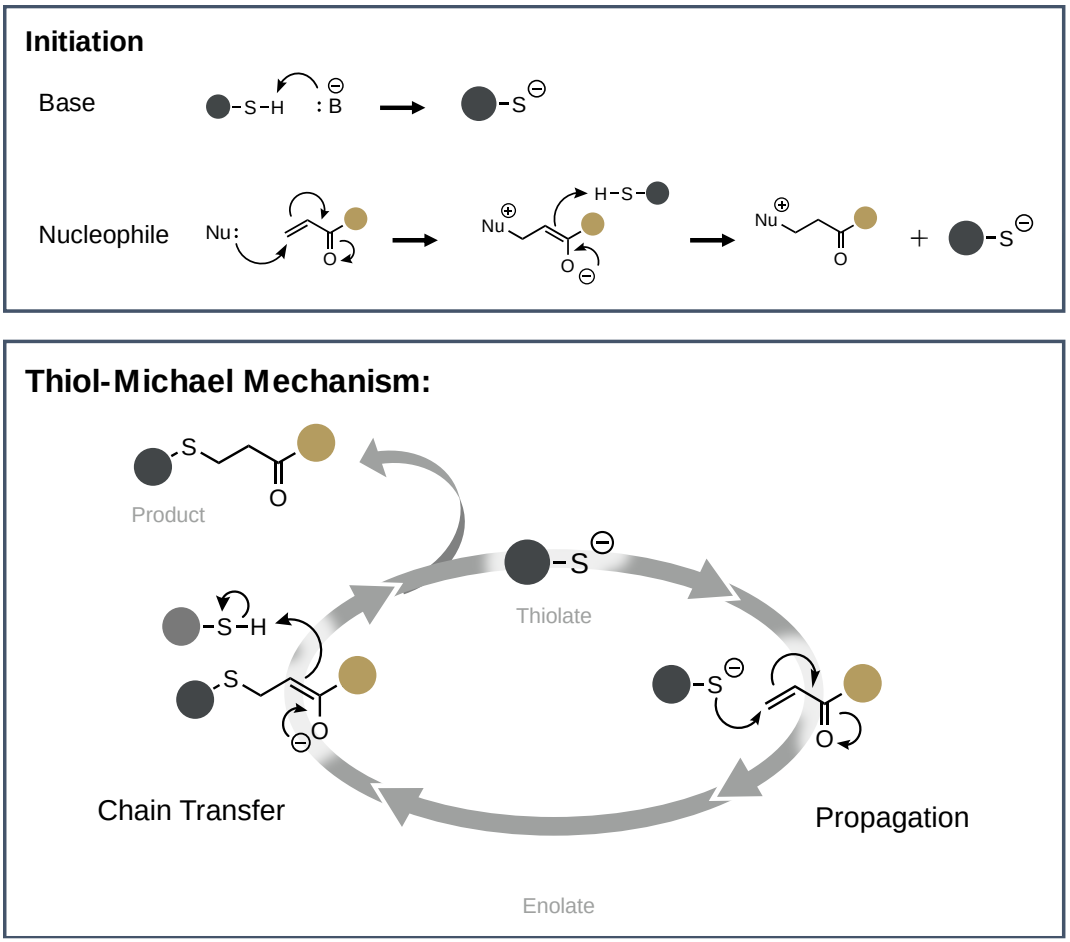

Figure 16. Initiation and the thiol-Michael mechanism. For base catalyzed reactions, a base abstracts a hydrogen yielding a thiolate anion, which proceeds directly into the thiol-Michael reaction. For nucleophile-catalyzed reactions, a nucleophile attacks the unsaturated β-carbon of the Michael acceptor. The resulting enolate then abstracts a hydrogen from a thiol to generate the thiolate anion. The leftover product from the catalyst's nucleophilic attack is an inherent side product. The thiolate anion attacks the attacks the unsaturated β-carbon of Michael acceptor generating a negatively charged enolate. The enolate then abstracts a hydrogen from a new thiol, reproducing the thiolate anion, as well as the thioether product.

However, it has been shown that in thiol-ene reactions, where a thiol adds radically to an alkene[30], increasing the steric hindrance around the thiol molecule does not imbue dramatic

decreases in reaction rate, and in some conditions, any difference in kinetic rate was negligible[89]. This behavior could be due to the large atomic radius of the sulfur atom and the increased nucleophilicity, any changes in sterics have relatively reduced effects when compared to the size of the larger sulfur atom. Additionally, secondary thiol and alkene mixtures were found to have a longer shelf life, and the secondary thiol monomers were reported not to have any odor[46]. Therefore, this work seeks to determine how more substituted thiols will affect the thiol-Michael reaction, as there are few, if any, literature sources that discuss how the substitution of the thiol affects the thiol-Michael reaction. Consequently, model reactions using monofunctional thiols were completed to observe the effect of increased substitution in thiol-Michael systems without added complexities from polymerizations, such as gelation and diffusion limitations. Fourier Transform Infrared (FTIR) Spectroscopy was used to observe the reaction kinetics and conversion changes in real time. Additionally, secondary analogs of the most common thiol monomers used in thiol-Michael studies were selected for further polymerization kinetic analysis and shelf life assessments of the resin stability. The findings of this study provide foundational understanding of thiol reactivity in thiol-Michael reactions.

4.3 Experimental

4.3.1 Materials

The thiols, n-butylthiol (NBT) and tert-butylthiol (TBT), and alkenes, ethyl vinylsulfone and hexyl acrylate, were purchased from Sigma Aldrich. Sec-butylthiol (SBT) was purchased from VWR International. The alkene, pentaerythritol tetraacrylate, was purchased from Tokyo Chemical Industry (TCI). 1,4-butanediol diacrylate was purchased from Fisher Scientific. The photobase, 2-(2-nitrophenyl)propyloxycarbonyl-1, 1, 3, 3-tetramethylguanidine (NPPOC-TMG), was synthesized in the lab, following the reaction proposed by Zhang *et al.*[90] Diethyl fumarate

was obtained from Alfa Aesar and 1,4-butanediol bis(mercaptoproprionate) was purchased from Wako Chemical. All deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc.

Pentaerythritol tetrakis(3-mercaptopropionate) (PETMP-1) was purchased from Sigma Aldrich. 1,3-divinyltetramethyldisiloxane, and 1,3,5 trimethoxybenzene were purchased from Fisher Scientific. Tris[2-(3-mercaptopropionyloxy)ethyl]isocyanurate (TTTSH-1) was purchased from Alfa Chemistry. Pentaerythritol tetrakis(3-mercaptobutanonate) (PETMP-2), 1,3,5-tris[2-(3-mercaptobutanoyloxy)ethyl]-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (TTTSH-2), and 1,4-Bis(3-Mercaptobutyryloxy)butane also known as KarenzMT^{TM} PE1, KarenzMT^{TM} NR1, and KarenzMT^{TM}BD1, respectively, were samples generously given to the lab by Showa Denko America Inc.

All molecules, monomers, and solvent were used as received.

4.3.2 Procedures

FTIR Characterization

Samples were prepared by mechanically mixing NPPOC-TMG (2.5 wt% of the total solution for monofunctional experiments, 2.0 wt% for polymeric solutions) with the thiol and alkene which were present in a 1:1 functional group ratio. The sample mixture was deposited onto NaCl plates in a laminated configuration. A Nicolet 6700 FTIR with a vertical light cable was used for all FTIR experiments. The samples were placed in a chamber purged with dry air, and then irradiated using a 365nm UV light at 10 mW/cm^2 at ambient temperature. A radiometer (model IL 1400A equipped with GaAsP detector and a quartz diffuser) was used to measure the irradiation intensities. A series of scans taking spectra at a rate of 0.87 sec/scan was used to

monitor the alkene peak area (~3030-3100 cm^{-1}) and the thiol peak area (~2480-2520cm^{-1}) in real time for conversion and kinetic analysis.

^{1}H NMR Conversion Studies

Conversion was determined by taking before and after proton spectra of the reaction mixtures and monitoring the change in integration for an alkene peak between δ 6.4-6.8 and a thiol peak at δ 1.3-1.5 for the alkyl thiols and 1.7-1.8 for the mercaptopropionates. All proton NMR spectra were recorded on a Bruker Avance-III 400 MHz spectrometer at 25 °C, and are reported in ppm (δ) relative to internal tetramethylsilane (δ 0.0). All samples were diluted with deuterated chloroform.

Reaction mixtures were first prepared by dissolving the photobase, NPPOC-TMG (2.5 wt %) in the appropriate thiol and alkene mixture at a 1:1 functional group ratio. An initial NMR spectrum was recorded before the samples were injected into a glass slide – silicone rubber – glass slide sandwich in which the silicone had a hole punched through it. The samples were irradiated with 365 nm light at 10 mW/cm^2 on each side for a period of time 5 minutes longer than it took to reach full conversion, as reported by FTIR. The sample was then removed from the sandwich and prepped for a final NMR spectrum.

Each thiol and alkene mixture was prepared a total of three different times and three samples were taken from each solution for a total of nine trials.

Shelf-Life Stability

Samples of 10.0g mixtures of resins containing thiol and alkene monomers were prepared and then stored in amber glass vials at room temperature, with careful precautions taken against any exposure to UV radiation. Viscosity measurements were taken at various time points using a rheometer (TA Ares G2 4010-0778). The rheometer used 0.05 mL aliquots and measured

viscosity with a 20 mm stainless steel parallel plate and 0.2 mm gap at a constant temperature of 22°C. The sheer rate was ramped from 10-1000 s^{-1} over a period of 120 seconds.

4.4 Results

4.4.1 Model Monofunctional Compounds Studies

Despite significant progress on the understanding and implementation of thiol-Michael addition reactions and step-growth polymerization strategies[84], it is still unclear how the thiol substitution affects the kinetics and efficiency of thiol-Michael addition reactions. To investigate thiol substitution effects, a kinetic study was conducted using monofunctional alkyl thiols, and difunctional mercaptopropionates (with monofunctional alkenes) as model compounds. Ideally, the small molecule, monofunctional reactions are chemically nearly identical to those in a polymerization and lend great insight into kinetic aspects without additional complicating factors associated with diffusion, polarity and viscosity changes, all of which accompany the reaction during polymerization[70]. Fourier Transform Infrared spectroscopy (FT-IR) was used to observe how three different isomers of butane thiol, i.e. n-butane thiol (NBT), sec-butylthiol (SBT), and tert-butylthiol (TBT), reacted under typical thiol-Michael reaction conditions.

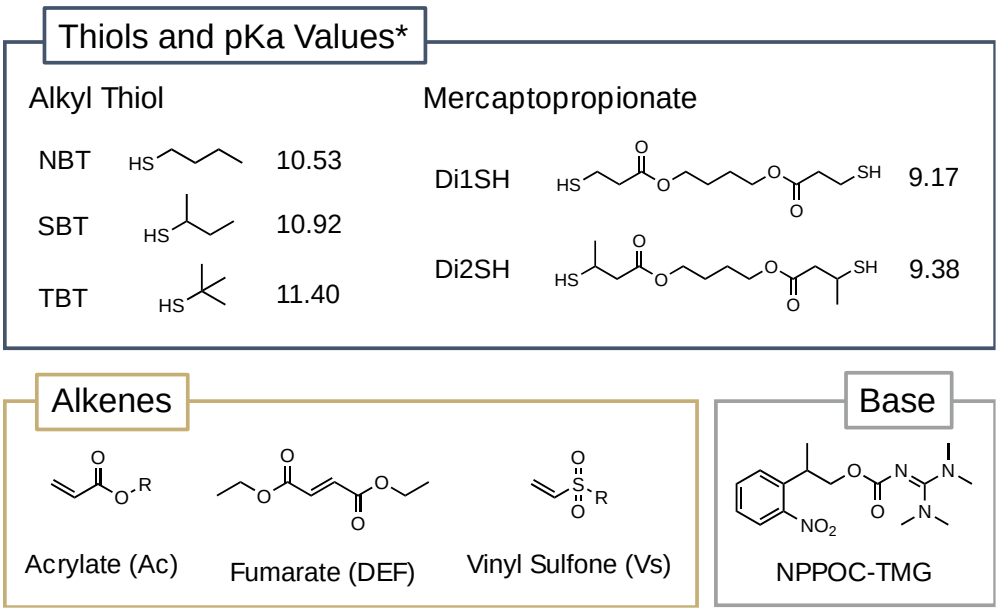

Figure 17. Structures of compounds used in monofunctional studies, including the monofunctional alkyl thiols (NBT, SBT, and TBT) and mercaptopropionates (Di1SH and Di2SH), the alkenes (Ac, DEF, and VS), and the photobase (NPPOC-TMG). The pKa values listed are reported from SciFinder's Advanced Chemistry Development (ACD/Labs) prediction software[91].

Three alkenes, with different reactivities in thiol-Michael reactions, were selected. The more electron deficient alkene typically has a faster kinetic rate so, comparing alkenes in this experiment, the divinyl sulfone was the most reactive with all three thiols, followed acrylate, and then the fumarate which additionally lends insight to differences between terminal and internal alkenes. Structures and pKa values of these compounds are shown in Figure 17. Not all of the thiol compounds used in these experiments have experimentally measured pKa values from literature, and simulation and experimental data are not necessarily comparable. In order to systematically compare all thiols used in these experiments, software associated with SciFinder was used to calculate pKa[91].

Table 3. Reaction Rates in (%/s) and final percent conversions found using FT-IR analysis for the acrylate (Ac), vinyl sulfone (Vs), and fumarate (DEF) alkenes all with 2.5 wt% photoinitiator NPPOC-TMG exposed to 365nm at an intensity of 10 mW/cm^2. All reactions were completed at room temperature.

	Acrylate (Ac)					
	Rate (s^{-1})		IR Final Conversion (%)		NMR Final Conversion (%)	
	Alkene	Thiol	Alkene	Thiol	Alkene	Thiol
NBT	2.4 ± 0.2	2.2 ± 0.3	98 ± 8	92 ± 5	100 ± 0	92 ± 4
SBT	1.0 ± 0.2	0.9 ± 0.2	91 ± 8	86 ± 14	98 ± 1	97 ± 1
TBT	0.02 ± 0.00	0.04 ± 0.01	31 ± 4	47 ± 1	58 ± 10	54 ± 12
Di1SH	0.9 ± 0.2	0.8 ± 0.2	100 ± 2	94 ± 9	98 ± 2	95 ± 3
Di2SH	1.1 ± 0.1	1.2 ± 0.1	91 ± 3	100 ± 8	98 ± 2	95 ± 3

	Vinyl Sulfone (Vs)					
	Rate (s^{-1})		IR Final Conversion (%)		NMR Final Conversion (%)	
	Alkene	Thiol	Alkene	Thiol	Alkene	Thiol
NBT	2.9 ± 0.8	2.4 ± 0.2	100 ± 5	101 ± 5	100 ± 0	99 ± 1
SBT	2.0 ± 0.6	1.6 ± 0.3	99 ± 14	97 ± 4	100 ± 1	96 ± 1
TBT	0.9 ± 0.2	0.9 ± 0.2	80 ± 12	90 ± 11	95 ± 5	97 ± 4
Di1SH	1.1 ± 0.2	1.1 ± 0.2	94 ± 4	95 ± 3	99 ± 1	97 ± 2
Di2SH	2.8 ± 0.6	2.6 ± 0.3	98 ± 3	95 ± 5	100 ± 0	98 ± 2

	Fumarate (DEF)					
	Rate (s^{-1})		IR Final Conversion (%)		NMR Final Conversion (%)	
	Alkene	Thiol	Alkene	Thiol	Alkene	Thiol
NBT	0.53 ± 0.13	0.53 ± 0.15	93 ± 9	96 ± 9	99 ± 0	97 ± 1
SBT	0.32 ± 0.04	0.31 ± 0.03	87 ± 7	90 ± 6	93 ± 2	87 ± 2
TBT	0.03 ± 0.01	0.07 ± 0.04	22 ± 8	51 ± 10	36 ± 13	34 ± 16
Di1SH	0.59 ± 0.09	0.54 ± 0.08	93 ± 9	86 ± 10	94 ± 2	93 ± 1
Di2SH	0.68 ± 0.14	0.56 ± 0.13	79 ± 9	72 ± 9	98 ± 2	93 ± 7

There is a difference in trend if one is looking at the alkyl thiols or looking at the mercaptopropionate. For the alkyl thiols, the increase in thiol substitution causes a decrease in reaction rate across all three alkenes used. In the case of the vinyl sulfone, the reaction rate decreased about 1.0 s^{-1} with each increase in substitution (about 30%). The acrylate and the fumarate saw about a 50% decrease in rate from the primary to secondary thiol and the tertiary thiol reaction with either of these alkenes resulted in a very slow rate, less than 0.05 s^{-1}. (Table 3). The final conversion for primary and secondary thiols of all alkenes, and also the tertiary thiol reacting with the vinyl sulfone typically reached high conversions of 80% or higher. This was confirmed using IR and NMR spectroscopies (Table 3). The tertiary thiol reacting with either the acrylate or the fumarate exhibited reduced conversions, as well as discrepancies between the thiol and acrylate conversion. The slightly elevated thiol conversion over the alkene is attributed to the slow nature of the reaction and the long UV light exposure, possibly resulting in the self-initiation of the thiol and formation of disulfides (Figure 18).

For the mercaptopropionate, the secondary thiol reacted more rapidly than the primary thiol for the acrylate and vinyl sulfone alkenes, and at about the same rate for the fumarate (Figure 18). The secondary thiol was about 0.03 s^{-1} (62%) faster when reacting with the acrylate, and 1.6 s^{-1} (311%) faster when reacting with the vinyl sulfone. Both primary and secondary thiols reached high conversions with the acrylate and vinyl sulfone alkenes; however, even though the rates were very similar, for the fumarate, the secondary thiol reaction had slightly lower conversions as measured by IR.

The differences in rate are attributed to the fact that alkyl thiols and mercaptopropionates have different rate determining steps, as reported by Huang et al.[92] The more basic alkyl thiolate anion allows for increased nucleophilicity, resulting in a chain transfer rate limiting step. In this

case, the increased steric hindrance would slow the enolate deprotonating the thiol. The resulting trend is that the tertiary thiol is the slowest and the primary thiols are the fastest. However, for mercaptopropionates, the conjugate base has a lower nucleophilicity than that of the alkyl thiols, and they, additionally, are more acidic and have a more reactive chain transfer step. This means that mercaptopropionates have a propagation rate limiting step, and in this step, the less stable thiolate anion is going to react more rapidly – i.e. the one with the higher pKa. In this case, the primary thiol is slower than the secondary. In the case of the fumarate, it is likely that the steric interactions from the additional methyl group of the secondary thiol and the internal alkene override the electronic differences, resulting in near similar rates.

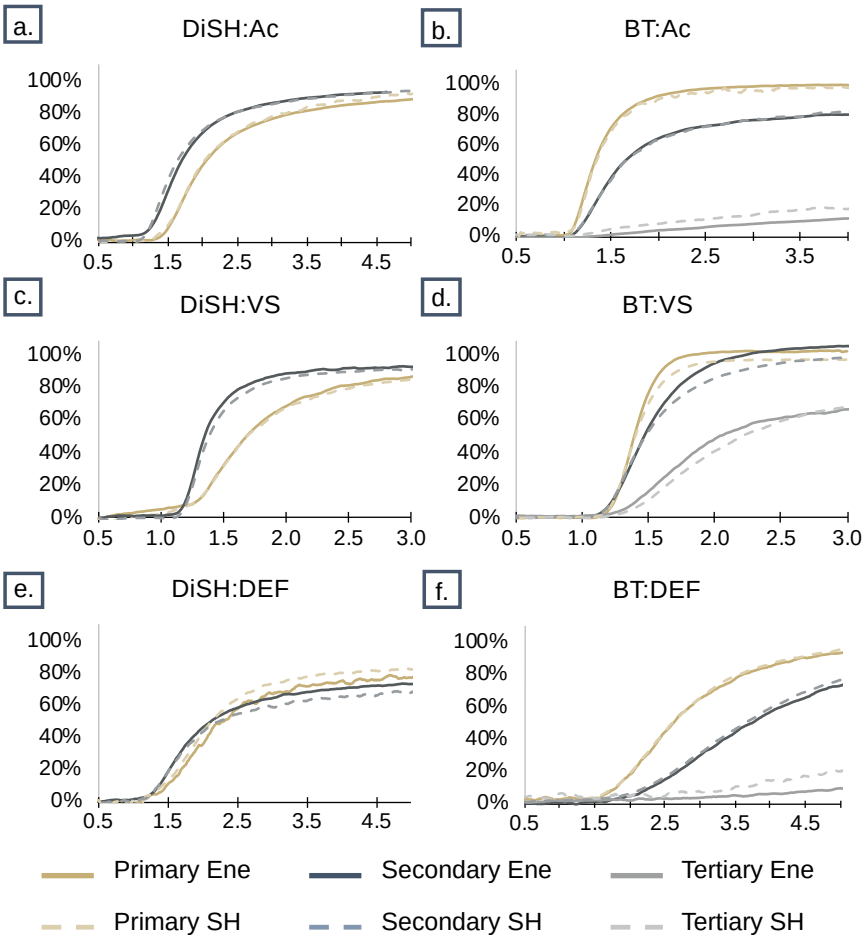

Figure 18. Alkene (solid) and thiol (dashed) conversion over time for reactions with acrylate (a. and b.), vinyl sulfone (c. and d).), and diethyl fumarate (e. and f.) with the propionate (DiSH) and alkyl (BT) thiols. All reactions were completed using a 1:1 functionality of thiols to alkenes, and resins contain 2.5 wt% NPPOC-TMG. Reactions proceeded using a 365nm light to cleave the photo-protected base at 10 mW/cm^2 light intensity.

4.4.2 Thiol-Michael Crosslinking Systems

The effect of the substitution of the thiol was further studied in polymer network forming resins comprised of either primary or secondary thiols since the tertiary thiol demonstrated poor reactivity and low reaction yields. Primary and secondary analogs with varying numbers of thiol functional groups of some of the more commonly used thiol monomers were selected.

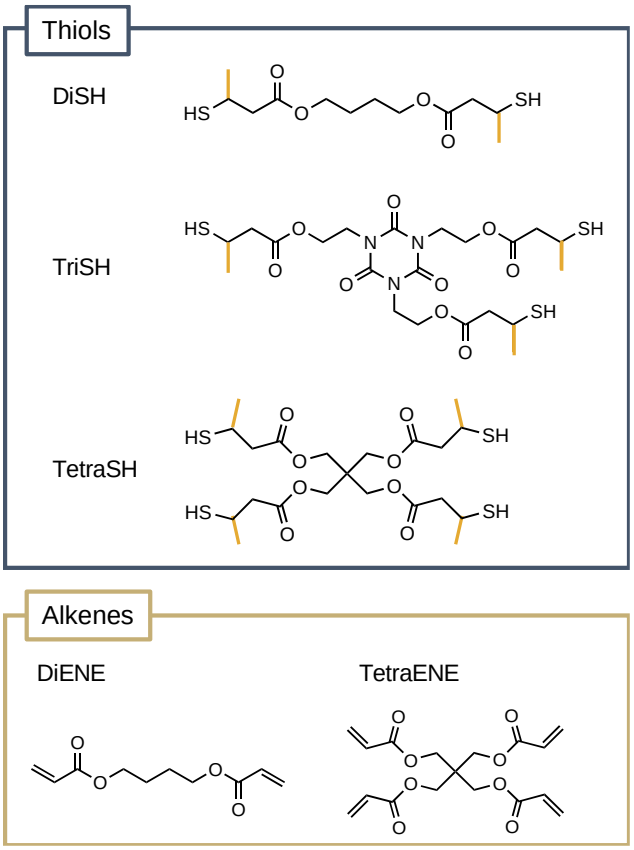

Figure 19. Structures of compounds used in polymerization kinetic studies including the primary thiols (1DiSH, 1TriSH, and 1TetraSH), the secondary thiols indicated by the methyl groups in yellow (2DiSH, 2TriSH, and 2TetraSH), and a difunctional (Diene) and a tetrafunctional (Tetraene) alkenes. The photoinitiator used in all of these studies was the photobase NPPOC-TMG pictured in Figure 17.

The compounds selected were chosen based off of the substitution and functionality of the thiol (Figure 19). As such, the effects of both the number of thiol functional groups and the degree of thiol substitution on the conversion and polymerization kinetics with either a difunctional or tetrafunctional alkene were investigated and compared.

Table 4. Kinetic Rates (s-1) and final percent conversions of thiol-Michael polymer reactions found using FT-IR analysis for the primary and secondary thiol monomers. (2.0 wt% initiator, 365nm, 10 mW/cm2). All reactions were completed at room temperature. The term "Slow" refers to the polymers that had less than 30% conversion over a minimum of 10 minutes.

	Polymerization Rates Measured by IR			
	Primary (1°)		Secondary (2°)	
	Alkene Rate (s-1)	Thiol Rate (s-1)	Alkene Rate (s-1)	Thiol Rate (s-1)
DiSH:Diene	0.6 ± 0.4	0.6 ± 0.4	2.3 ± 0.4	2.3 ± 0.4
DiSH:Tetraene	0.15 ± 0.01	Slow	3.3 ± 1.4	1.0 ± 0.2
TriSH:Diene	0.9 ± 0.2	0.9 ± 0.3	1.0 ± 0.2	1.0 ± 0.6
TriSH:Tetraene	0.3 ± 0.1	0.1 ± 0.1	0.4 ± 0.2	0.4 ± 0.3
TetraSH:Diene	2.3 ± 0.6	2.2 ± 0.5	1.0 ± 0.2	1.0 ± 0.2
TetraH:Tetraene	1.2 ± 0.7	0.7 ± 0.6	1.2 ± 0.1	0.72 ± 0.4

	Ultimate Conversion Values Measured by IR			
	Primary (1°)		Secondary (2°)	
	Alkene Conversion	Thiol Conversion	Alkene Conversion	Thiol Conversion
DiSH:Diene	99% ± 5%	79% ± 9%	96% ± 2%	94% ± 1%
DiSH:Tetraene	85% ± 4%	17% ± 3%	96% ± 11%	90% ± 4%
TriSH:Diene	96% ± 6%	88% ± 15%	94% ± 9%	88% ± 16%
TriSH:Tetraene	75% ± 11%	45% ± 13%	72% ± 20%	60% ± 18%
TetraSH:Diene	95% ± 4%	98% ± 2%	92% ± 4%	90% ± 4%
TetraH:Tetraene	86% ± 17%	42% ± 27%	88% ± 8%	65% ± 15%

From the results, several trends are seen in the data. As the thiol functionality increases for the primary thiol reacting with either a diene or a tetraene, the polymerization reaction rate increases. For the diene, the alkene reaction rate increased from 0.58 ± 0.4 s^{-1} to

0.92 ± 0.2 s^{-1} to 2.3 ± 0.6 s^{-1} for the difunctional, trifunctional and tetrafunctional thiols, respectively. Similarly, for the tetraene, the rate increased from 0.15 ± 0.01 s^{-1} to 0.27 ± 0.1 s^{-1} to 1.2 ± 0.7 s^{-1} as the thiol functionality increased (Table 4). The opposite trend was observed for the reaction kinetic experiments with secondary thiols where the rates decreased with increasing thiol functionality. This behavior most likely is due to the fact that with higher substitution and higher functionality, the thiolate becomes less accessible, thus increasing the propagation step of the polymerization process. Interestingly, for the secondary trifunctional thiol reacting with the tetraene it had a reaction rate of 0.43 ± 0.2 s^{-1}, and when compared to the secondary tetrafunctional thiol reacting with the tetraene, it had a reaction rate of 1.2 ± 0.1 $s^{-1.}$ As such, for secondary thiols, the trifunctional thiol ended up having the slowest rate.· In addition, for the diene polymers, both substitution and functionality do not appear to have a pronounced effect on the final conversion of the polymer. However, for the tetraene reaction with the trifunctional and tetrafunctional thiols, the conversion was incomplete. This result is most likely due to acrylate homopolymerization since the final conversions for the alkenes were higher than those of the corresponding thiols. Moreover, the difunctional and tetrafunctional polymers had higher conversions than the trifunctional system which is attributed to structures of the compounds slowing conversion. It is important to note that for all of the samples, they were all gelled and formed solid polymers prior to removal from the IR.

When comparing primary versus secondary thiols, the secondary thiol often reacts faster than the primary thiol, as seen with the DiSH:Diene, and DiSH:Tetraene resins (Figure 20), but the differences in reactivities seem diminish with increasing thiol functionality. The trifunctional thiol had similar rates between the primary and secondary thiols - the diene kinetic rate being 0.92 ± 0.2 s^{-1} to 1.0 ± 0.2 s^{-1} for the primary and secondary thiols,

respectively, and the tetraene kinetic rate being $0.27 \pm 0.1\ s^{-1}$ to $0.43 \pm 0.2\ s^{-1}$ for the primary and secondary thiols, respectively. The tetraSH-diene resin found the primary thiol being faster ($2.3 \pm 0.6\ s^{-1}$) than the secondary thiol ($0.98 \pm 0.2\ s^{-1}$) and the TetraSH-tetraene resin showed comparable rates. This trend generally indicates that with lower average monomer functionality, the secondary thiols have a faster rate than the primary thiols. As the average monomer functionality increases, the primary thiol's rate increases while the secondary thiol's rate decreases. This phenomenon may be due to mechanistic changes with changes in crosslink density. In less densely crosslinked or linear systems, i.e., systems with a lower average monomer functionality, the inherent chemical reactivity is largely controlling the polymerization rate whereas as the crosslink density increases, other factors, including changes to the mobility of the system, become limiting.

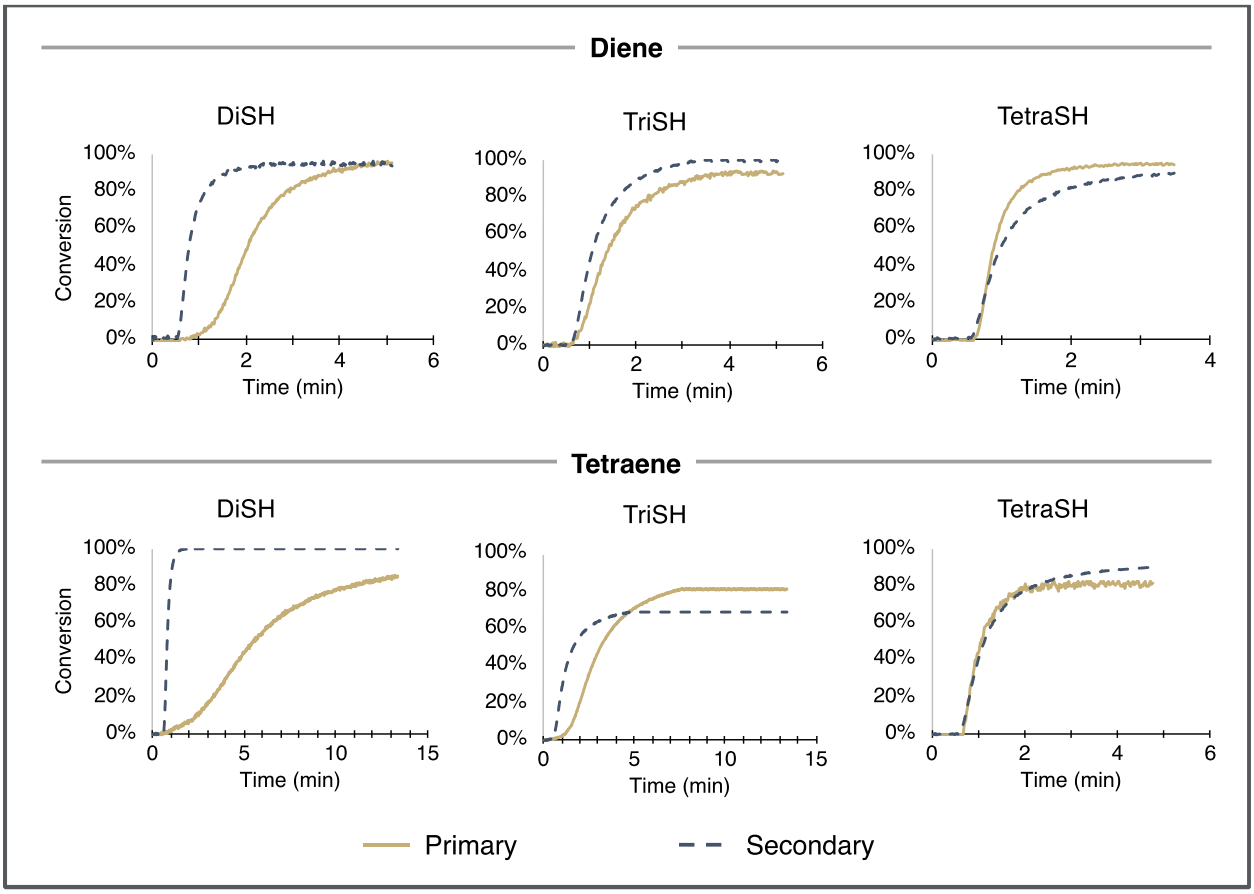

Figure 20. Alkene conversions over time for reactions with the diene and tetraene alkenes and primary (solid line) and secondary (dashed line) thiols: DiSH (left), TriSH (Middle), and TetraSH (right). All reactions were completed using a 1:1 functionality of thiols to alkenes, and contain 2.0 wt% NPPOC-TMG. Reactions proceeded using a 365nm light to cleave the photo-protected base at 10 mW/cm^2 light intensity.

4.4.3 Shelf Life Studies

The highly reactive thiol-Michael reaction is often prone to spontaneous self-initiation, thus limiting the shelf-life of a premixed thiol and alkene resin. It has been reported that some alkenes in thiol-Michael reactions, particularly those that are highly electron deficient such as maleimides, are not stable for long periods of time reacting spontaneously in short periods of time[11]. This instability could potentially be offset by using Bronsted acids such as methanesulfonic acid, though this approach is often not viable as a long-term strategy[93]. Secondary thiols have been shown to increase the stability of radically polymerizable thiol-ene

resins for long periods of time when compared to their primary counterparts, and in some cases the secondary thiol and alkene resins remained un-gelled for three months longer than the primary thiol and alkene resins[89]. Therefore, this work sought to determine if a similar effect is observed for thiol-Michael resins.

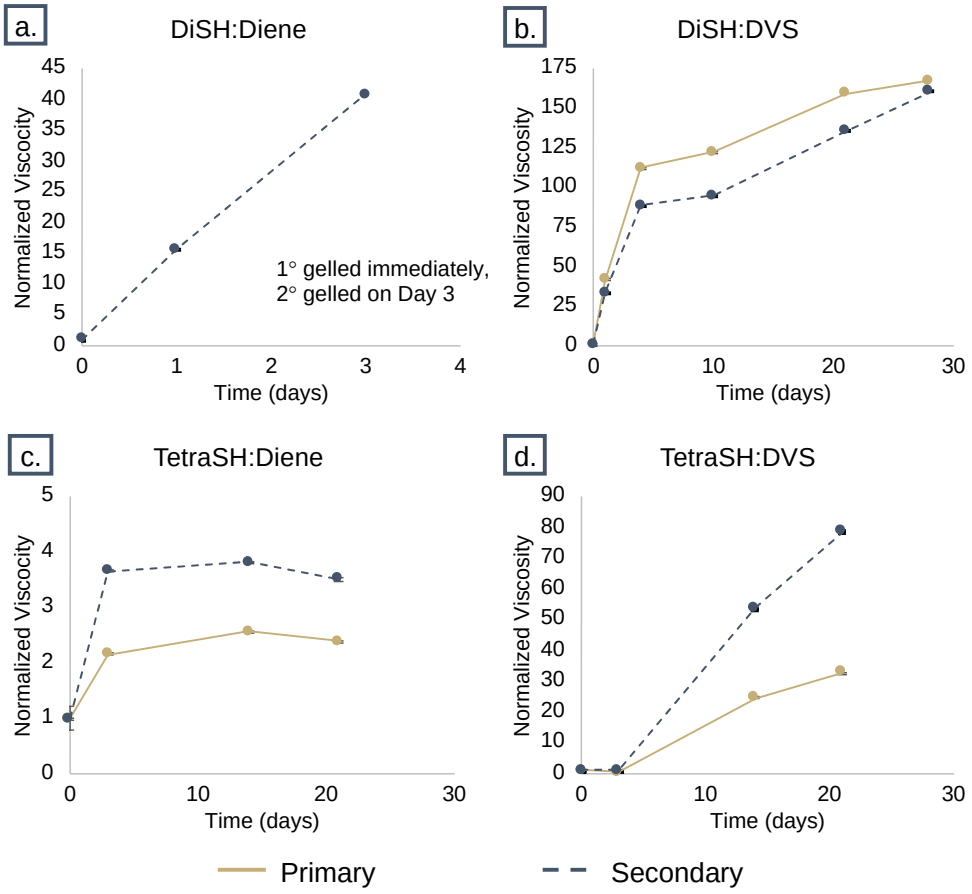

Figure 21. Rheological shelf-life experiments for the primary (solid line) and secondary (dashed line) thiols when mixed with either Diene or DVS alkenes. The primary DiSH and Diene mixture gelled immediately, while the secondary resin gelled after day 3. The rest of the experiments were conducted for 28 days at room temperature. The resin mixtures were stored in amber vials in a box and only opened under yellow light.

Accordingly, shelf-life studies were completed using the rheometer to measure the viscosity of stoichiometric thiol and alkene resins over time. According to Figure 21, some resins were more stable with secondary thiols. When the primary DiSH was mixed with the diene, the resin gelled before any significant rheological data could be collected while the corresponding secondary DiSH:Diene resin lasted for 3 days before gelation (Figure 21a). Additionally, the

secondary DiSH:DVS resin maintained a similar or potentially slightly lower viscosity over a 28 day time period than the primary DiSH:DVS resin (Figure 21b). It is interesting that this phenomenon occurred because the secondary DiSH thiol had a higher reaction rate than the primary DiSH thiol when mixed with the Diene. The primary and secondary DiSH:DVS solution gelled after the 28th day.

Resins incorporating the TetraSH did not follow the same pattern. The primary TetraSH solutions maintained a lower viscosity than the secondary TetraSH for both the Diene and DVS solutions, though it should be noted that all of these solutions gelled after the 21st day (Figure 21c and Figure 21d). This behavior is likely due to the fact that the secondary TetraSH thiol had a higher reaction rate with the Diene than primary TetraSH thiol.

4.5 Conclusion

In monofunctional thiol-Michael addition systems comprised of model thiol and ene compounds, the changes in reaction rate of the thiol were due to both steric and electronic interactions. For alkyl thiols, which have a chain transfer limiting step, steric interactions slowed the deprotonation of the thiol (1° > 2° > 3°). For propionates, which have a propagation limiting step, the thiol with the higher pKa and thus, more reactive thiol had the faster rate (2° > 1°), except in the case where steric interactions appeared to override the electronic effects, as seen with the internal alkene of the fumarate. Notably, the tertiary thiol showed slower rates and much lower conversions when compared to the primary and secondary thiols. Only primary and secondary thiols were studied in polymeric studies because of the significantly reduced rate in the tertiary thiols.

In polymeric systems, whether or not the primary thiol was faster than the secondary thiol was dependent on the functionality of the system. In systems where the combined monomer

functionality was the lowest (i.e. difunctional alkenes with difunctional thiols), the secondary thiol was faster than the primary thiol, and as the monomer functionality increased, the reaction rates of the two types of thiols became more comparable. In tetrafunctional thiol and alkene systems the primary thiol had the faster reaction rate, and the secondary thiol was slower.

In shelf stability assessments, for the DiSH systems, typically the primary thiol was more unstable, but all of the solutions gelled within a month. In the TetraSH systems, the primary thiol generally maintained a lower viscosity over time, but these solutions also gelled within a month.

4.6 Acknowledgements

The authors gratefully acknowledge Showa Denko America Inc. for providing the secondary thiol monomers DiSH, TriSH, and TetraSH. Funding was also provided by the National Institutes of Health Dental and Craniofacial Research Fellowships 5 F31 DE027880-02 and the National Science Foundation through grant CHE 1808484.

Chapter 5: Substituted Thiols in Thiol-Thioester Exchange

This chapter is an ongoing project authored by Katelyn Long and Nicholas Bongiardina of the Bowman Lab with the intention to submit to publication upon completion. Katelyn Long was responsible for the synthesis of the novel secondary thioester compounds and the secondary mercaptopropionate, as well as the synthesis of other compounds used in this project. Additionally, she collected and processed the NMR data used to determine equilibrium extents of reaction. She will continue to collect and process the data until the project is finished. Nicholas Bongiardina also helped with the synthesis of compounds, and also conducted the material analyses, including those with the dielectric and DMA. He also contributed to the thiol-ene anhydride research. He will be submitting this work as first author, and Katelyn Long will be listed as second author. Both authors have written their respective contributions to this chapter, as well as co-authored the introduction and abstract. The conclusion was authored by Katelyn Long and the entire document has been heavily edited by both authors.

5.1 Abstract

The thiol-thioester reaction has emerged as a promising method for developing covalent adaptable networks (CANs) due to its ability to exchange under low temperature conditions in a number of solvents, orthogonality amongst other functional groups, and tunability. In this work, experiments were conducted to determine how secondary versus primary thiols affect the thiol-thioester exchange reaction. NMR exchange experiments were conducted using small molecule compounds to model how polymers of similar components would behave, and it was determined that the K_{eq} generally trends towards 1, regardless of whether a basic or nucleophile catalysts were used. Though slower, exchange occurred at room temperature, even if no catalyst was

present. Dielectric spectroscopy and DMA were used to determine the material dynamics and stress relaxation of the thioester networks derived from thiol-ene films, respectively.

5.2 Introduction

Covalent adaptable networks (CANs) are a class of thermosetting polymer materials that contain dynamic chemical functionalities that enable rearrangement of what would normally be considered a static network. This dynamic character combines the mechanical robustness and chemical stability of thermosets with the processability and recyclability of thermoplastics. As such, these hybrid materials enable a unique array of material behaviors that are typically unattainable for thermosets and opening applications for which weaker thermoplastic materials may be unsuitable.

The basic principle for producing CANs is the incorporation of labile chemical bonds that are triggered by the application of an external stimulus, such as light or heat. Depending on the general choice of chemistry, the dynamic bonds either: i) break-and-reform via reversible addition or a dissociative mechanism as is the case for the Diels-Alder reaction[94, 95], or ii) may interconvert from one topology to another via reversible exchange or an associative mechanism as observed for transesterification[96], disulfide exchange[97], and thiol-thioether exchange[43, 98]. Recently, thiol-thioester exchange (TTE) (Figure 22) has received increased attention because of its low activation energy (~20 kJ/mol), exchange rates that are tailored by the choice and concentration of a basic or nucleophilic catalyst, and facile incorporation of thioesters into thiol-X materials[40, 43, 98, 99]. This exchange moiety has shown great potential for peptide synthesis[100, 101], dissolvable sealants[102], pressure sensitive adhesives[103], and nanocomposites[103, 104].

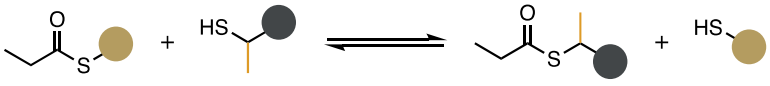

Figure 22. Schematic of thiol-thioester exchange reaction for primary and secondary (gold line) thiols.

While substantial work has been done to characterize TTE for thiols common in materials synthesis[43], the effect of the thiol substitution on TTE has seen little attention. More recently, substitution of the thiol on the thiol-X processes has seen attention from Li and coworkers, who observed that increasingly substituted thiols have a longer shelf life and less odor than typical primary thiols[105], and Long and coworkers, who have shown that secondary and tertiary thiols can be used in thiol-ene[106] and thiol-Michael[107] addition polymerizations with little practical effects on reaction kinetics or conversion at relevant polymerization conditions, while improving shelf life stability. This behavior has important implications for many thiol-X materials because they often cannot be pre-mixed and stored due to their high reactivity. As such, it is also useful to understand the effects of thiol substitution on TTE to further broaden the utility of this important dynamic chemistry.

Here, experiments were performed to assess any advantages or disadvantages to using secondary thiols in TTE materials, both from a mechanistic and mechanical standpoint. Model molecules, analogous to the monomers used in subsequent polymer studies, were synthesized and equilibrium experiments, as described by Worrell and Coworkers[43], ^{1}H NMR experiments were conducted to determine the relative extent of reaction of the primary and secondary thiols at equilibrium. The impact of substituted thioesters was then evaluated on thiol-ene networks containing thioester moieties modeled after those used by Worrell and coworkers[43]. The differences in the dynamic character of the primary and secondary TE-containing networks were then evaluated using dielectric analysis (DEA) and compared to conventional static mechanical measurements from dynamic mechanical analysis (DMA).

5.3 Experimental Section

5.3.1 Materials

Pentaerythritol tetrakis(3-mercaptopropionate) (PETMP), methyl 3-mercaptopropionate (1SH), 1,4-diazabicyclo[2.2.2]octane (DABCO), 4-(dimethylamino)pyridine (DMAP), allyl succinic anhydride (ASA), Quinuclidine (QN), 1,3,5-trimethoxybenzene (TMB), triethylamine (TEA), Omnicure 819, 2,2-dimethoxy-2-phenylacetophenone (DMPA), and 1,1,3,3-tetramethylguanidine (TMG) were purchased from common stock chemical suppliers (Sigma Aldrich, Fischer Scientific, TCI Chemicals) and used as delivered. Pentaerythritol tetrakis(3-mercaptobutyrate) (PETMB) was generously provided by ShowaDenko and used as delivered. All deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and used as received.

5.3.2 Methods

(A) 3-mercaptobutanoic acid: To a 250mL round-bottomed flask with a magnetic stir bar was added ~80mL of concentrated aqueous HCl (80 mL). Then 2-PETMP (10g, 0.018 mol) was added *via* syringe. The mixture was heated to 110°C and allowed to stir at reflux overnight (~16 hours). After this period, the flask was removed from reflux and subjected to ice bath to cool. Once cooled, the mixture was transferred to a 250mL separatory funnel. This product was extracted with ethyl acetate (2x50mL) which was neutralized with $NaHCO_3$ (2x15mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting product was used directly with no further purification. (7.1 grams; 83% yield); yellow oil; ^{1}H NMR (800 MHz, $CDCl_3$) δ 11.40 (s, 1H), 3.36 (m, 1H), 2.65 (m, 2H), 1.85 (d, 1H), 1.41 (d, 3H).

(C) Thioester diacid (2-TDA): To a 250mL round-bottomed flask with a magnetic stir bar was added 45mL of anhydrous MeCN and 5mL of pyridine (9:1 ratio). Then 4.16 grams of

succinic anhydride (4.16g, 0.04 mol) was added to the flask. This mixture was allowed to stir for 5 minutes. Then, 3-mercaptobutyric acid (5g, 0.041 mol) was added *via* syringe, followed by 4-(dimethylamino) pyridine (0.25g, 5mol%). The flask was then capped and allowed to stir overnight at room temperature. After this period, the mixture was concentrated *in vacuo*, then dissolved in ethyl acetate (100mL). The mixture was acidified with 1M HCl to a pH of ~1, then added to a 250mL separatory funnel, where it was extracted with ethyl acetate (2x25mL). The organic layers extracted were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then dissolved in 40mL of DCM solution, and precipitated out with 60mL of hexanes. The solution was then allowed to cool in a freezer overnight. After this period, the precipitate was filtered and rinsed with chilled hexanes (15mL). The resulting product was used directly with no further purification (7.3 g, 81% yield). ^{1}H NMR (800 MHz, CD_3OD) δ 3.89 (m, 1H), 2.84 (t, 2H), 2.61 (m, 4H).

(E) Thioester Diene (2-TE): To a 250mL round-bottomed flask with a magnetic stir bar was added 70mL of toluene. Then, the diacid thioester (5.0 g, 0.023 mmol) was added *via* syringe, along with Na_2SO_4 (7.0 g, 0.049 mol) and 0.4 grams of TsOH-H_2O (0.4 g, 2.27mmol). This product was allowed to mix well into a slurry. Then, 6.18mL of allyl alcohol (5.27 grams, 0.091 mol) was added all at once *via* syringe. The mixture was then attached to a reflux condenser, heated to 85°C, and allowed to stir at reflux overnight. After this period, the mixture was filtered, and the filter cake rinsed with toluene (15mL). The filtered mixture was then concentrated *in vacuo* and heated to 60°C to ensure the complete removal of excess allyl alcohol. This crude product was submitted to column chromatography and concentration *in vacuo* of selected samples gave the desired product. This product was used directly with no further

purification. (4.5 grams; 66% yield) ^{1}H NMR (800 MHz, $CDCl_3$) δ 5.89 (m, 2H), 5.24 (m, 4H), 4.59 (d, 4H), 3.94 (m, 1H), 2.86 (t, 2H), 2.67 (m, 4H) 1.38 (d, 3H).

(B), (D) General methylation of carboxylic acids: In a round bottom flask containing 140 mL of toluene, the carboxylic acid of interest (30 mmol), sodium sulfate (16.4 g, 66 mmol), and para-toluene sulfonic acid (1.1 g, 3.3 mmol) were added. The resulting solution was mixed well into a slurry. The methanol (3.8 g, 120 mmol) was added all at once. The solution was heated to 85°C and allowed to react overnight. After, the mixture cooled to room temperature, was filtered and concentrated *in vacuo* to a yellow oil. The oil was purified by column chromatography.

NMR Studies

^{1}H NMR were recorded in CDCl3 (internal standard: 7.26 ppm) and in DMSO-d6 (internal standard: 2.50 ppm, 1H) on a Bruker DRX-400 MHz spectrometer. Chemical shifts (δ), reported in parts per million (ppm), had the following abbreviations used to identify the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad.

Calibration Curves for NMR Exchange Studies: Calibration was performed by first preparing separate stock solutions of each of the different thioesters (0.30 M) and the internal standard 1,3,5-trimethoxybenzene (0.12 M) using a deuterated solvent ($CDCl_3$ or DMSO-d_6). The stock solutions were prepared fresh each day, capped, and vortexed thoroughly until fully homogeneous. Varying amounts of each of the stock solution were added to the NMR tube according to Table 5 below, followed by the deuterated solvent to properly dilute each sample using a calibrated pipette. The NMR tube was capped, thoroughly mixed using a vortex mixer, and an ^{1}H NMR immediately taken. Three replicates of each sample were taken.

Table 5. Stock solution amounts to create varying concentrations for NMR calibration curves.

Sample Percentage	Thioester	Internal Standard	Solvent	Total
100%	400 µL	200 µL	0 µL	600 µL
75%	300 µL	200 µL	100 µL	600 µL
50%	200 µL	200 µL	200 µL	600 µL
25%	100 µL	200 µL	300 µL	600 µL

The calibration graphs were calculated by integrating the aromatic peak of the internal standard, normalizing to 1.00, and then integrating the acyl peak of the thioester and notating the integral value. The integral ratios of the acyl thioester:internal standard were plotted against the percentages and a linear function was obtained. These steps were repeated for the aliphatic (-OCH_3) peak of the internal standard.

Determining Amount of Exchange: The amount of exchange was calculated by preparing separate stock solutions of each of the different thioesters (1.33 M), each of the different thiols (1.33 M), catalyst (either basic TMG or nucleophilic quinuclidine) (0.13 M), and the internal standard 1,3,5-trimethoxybenzene (0.12 M) using a deuterated solvent ($CDCl_3$ or DMSO-d_6). The stock solutions were prepared fresh for each experiment, capped, and vortexed thoroughly until fully homogeneous. Using a calibrated autopipette, varying amounts of each of the stock solutions were added to the NMR tube according to Table 6 below, in the order of internal standard, thioester, thiol, and base. Additionally, control samples were prepared by adding the same quantity of neat deuterated solvent in place of the catalyst. The NMR tube was capped, thoroughly mixed using a vortex mixer, and an ^1H NMR spectra was collected after 12 hours using a timed auto sampler. Four replicates of each sample were taken. The amount of exchange was then determined by integrating the aromatic peak of the internal standard and normalizing to 1.00, integrating the acyl peak of the thioester, and integrating exchanged peak of the exchanged thioester. The integrations were noted, and the ratio of the acyl thioester:aromatic internal

standard was calculated and plugged into the equations obtained from the calibration curve ([yield]=slope*[experimental ratio]) to solve for the experimental yield. These steps were then repeated using the aliphatic integration of the internal standard (-OCH_3) and the ratio of the acyl thioester/aliphatic internal standard was plugged into the calibration curve integration. The two values obtained for the experimental yield were then averaged and used directly to identify how much, if any, exchange occurred. Four replicates of each solution were performed.

Table 6. Quantities of stock solutions for preparing experimental exchange solutions. Note that for control samples, instead of adding a stock solution with catalyst, the same quantity of neat solvent was added instead.

Solution	1° Thioester	2° Thioester	1° Thiol	2° Thiol	Internal Standard	Catalyst	Total
1	150 µL	-	-	150 µL	150 µL	150 µL	600 µL
2	-	150 µL	150 µL	-	150 µL	150 µL	600 µL

Sample preparation for thiol-ene samples

The monomer resin composed of a tetrathiol (1.0 equivalent PETMP or PETMB monomer), a thioester containing diene (either 1.0 or 2.0 equivalent 1TE-diene or 2TE-diene monomer), 1 wt.% Omnicure 819 photoinitiator, and 4 mol% DABCO in TTE active samples was prepared by first dissolving the photoinitiator and catalyst in the appropriate TE-diene, then mixing in the thiol. Dielectric samples were prepared on Mini-Varicon^{TM} sensors purchased from Lambient Technologies. Sensors were rinsed with acetone and placed in a drying oven to remove adsorbed water and solvent from the surface. The cleaned senor was placed flat on a glass slide and positioned under the curing light source with 250 µm spacers on either side, and the monomer resin was deposited on the metal electrode surface and spread over the entire metal contact surface. A glass slide was placed on top and weighted down on each side with binder clips. The sample was irradiated with 405 nm light at 25 mW/cm^2 for 5 minutes to activate the photoinitiator and cure the sample, which was then allowed to post cure at 60 °C for 1 hour. Samples for DMA and

stress relaxation were prepared by depositing the resin between two glass slides with 250 µm spacers, after which the sample was irradiated with 405 nm at 25 mW/cm^2 for 5 minutes.

Dielectric Analysis

Dielectric analysis was performed on a ModuLab XM Material Test System (AMETEK Scientific Instruments, UK) at various temperatures depending on the material. Isothermal temperature sweeps were performed over a range of 30^{-2} - 10^6 Hz under an applied sinusoidal voltage of 4500 mV in amplitude. Sample were prepared on Mini-Varicon^{TM} sensors as described above.

Dynamic mechanical analysis and stress relaxation

Glass transition temperature (T_g), storage modulus (E'), and loss modulus (E'') were measured on RSA G2 dynamic mechanical analyzer (TA Instruments) using a temperature ramp rate of 3°C/min and a frequency of 1 Hz, with an oscillating strain of 0.03 % and a preload force of 0.40 N. Stress relaxation was performed in tension. A strain of 8% was applied and the resulting isothermal stress was measured over time at various temperatures, then normalized to the initial value.

5.4 Results and Discussion

5.4.1 Synthesis

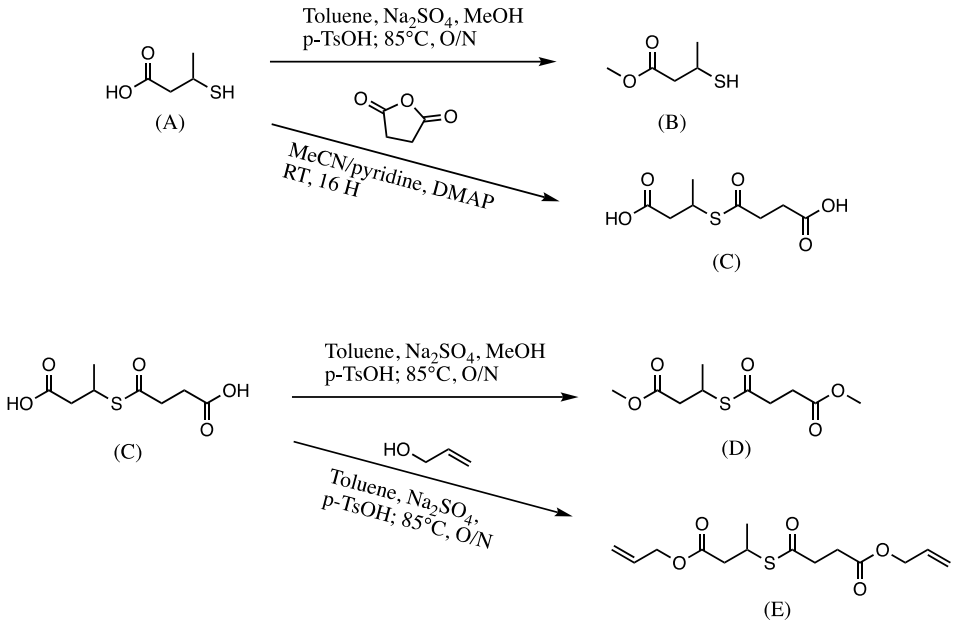

Figure 23. Scheme for the synthesis of secondary thiol and thioester containing compounds.

To investigate the effect from more highly substituted thiols in the TTE reaction, secondary thiol and secondary thioester molecules had to be synthesized (Figure 23). These procedures were adopted from the literature where similar, primary thiols have been synthesized[38, 43]. Compound A was obtained with 83% yield via reverse esterification. This reaction was done under acidic conditions to prevent the formation of disulfides. Compound A could then be methylated to synthesize B for model, monofunctional studies, or it could be converted to thioester C. Compound C was synthesized in an 81% yield via ring opening of succinic anhydride. Compound C was then either methylated (D) for use in model, monofunctional studies, or alkylated with an allyl group to generate a difunctional alkene with the thioester moiety. The analogous, primary versions of these compounds were also synthesized through similar methods.

5.4.2 Model Compounds

NMR Calibration Curves

Quantitative NMR is emerging as an efficient technique to quantify organic molecules present in solution. In these experiments, quantitative NMR was used to determine the concentration of primary and secondary thioesters present at equilibrium. This approach involves the use of either an external or internal standard for absolute concentration determination[108]. In this case, an internal standard was chosen for higher precision and lower uncertainties. The internal standard (IS) in these experiments was 1,3,5-trimethoxybenzene as it is soluble in both $CDCl_3$ and DMSO-d_6, and its protons shifts (~6.1 and 3.7 ppm) did not overlap with the thioester peaks observed.

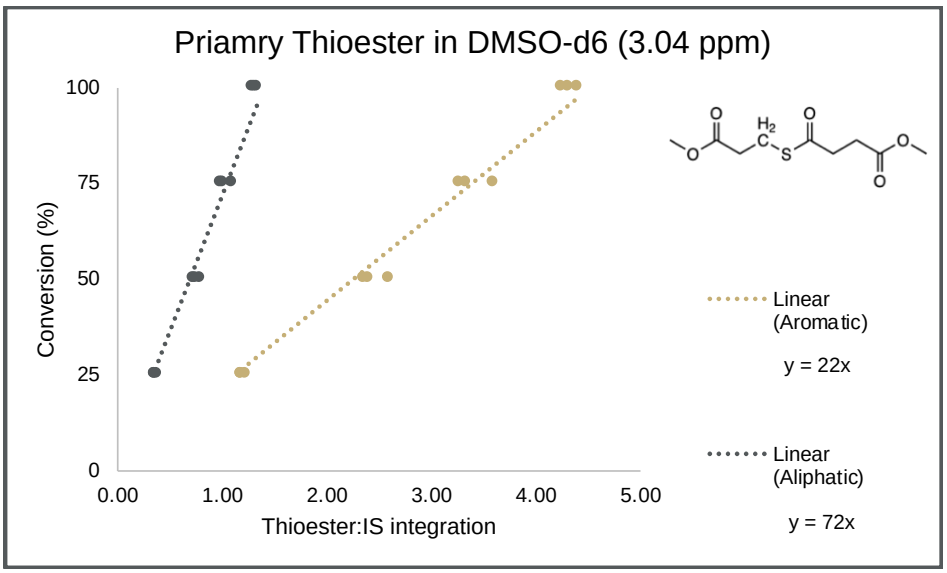

Figure 24. Example calibration curve for the primary thioester in DMSO-d_6 using 1,3,5-trimethoxybenzene as an IS. All experiments were conducted at room temperature. Curves were generated as a function of known concentration versus the ratio of the thioester peak with respect to the two IS peaks – aliphatic (grey) and aromatic (gold).

By maintaining the same concentration of internal standard and varying known concentrations of the thioester, calibration curves were established for the primary and secondary thioesters in both $CDCl_3$ and DMSO-d_6 (Figure 24). This experiment was done by normalizing the IS peak at 6.1 ppm to 1.0, then calculating the ratio of the integrations of the thioester peak to

both the aromatic and aliphatic IS peaks. A plot of thioester concentration versus peak integration ratio was then created, generating a linear $y=mx$ formula, where y is equal to the thioester conversion and x is equal to peak ratio integration. Once these calibration curves were completed, the slope of these graphs, combined with the ratio of peak integrations measured during equilibrium experiments was used to determine the time dependent and equilibrium conversion.

NMR Equilibrium

In their work on the thioester exchange reaction in organic media, Worrell and coworkers[43] determined the equilibrium constants between a variety of thiols and thioesters in a range of solvents to determine: i) the favored products at equilibrium for different thiol/thioester structures and ii) which solvents are conducive to the exchange reaction. Their strategy was adopted here to determine whether primary or secondary thiol/thioester products are favored when a primary thiol reacts with a secondary thioester, and vice versa. The investigation was carried out with the basic catalyst TMG (pKa = 13.6 in water), the nucleophilic catalyst QN (N = 20.5), and without catalyst. These catalysts were selected due to their use in previous studies on TTE reactions. Tests were performed directly in deuterated solvent, DMSO-d_6, to examine the effect of solvent polarity on equilibrium extent of reaction, and the experimental integrations were converted to conversion using the slope value from the calibration curves.

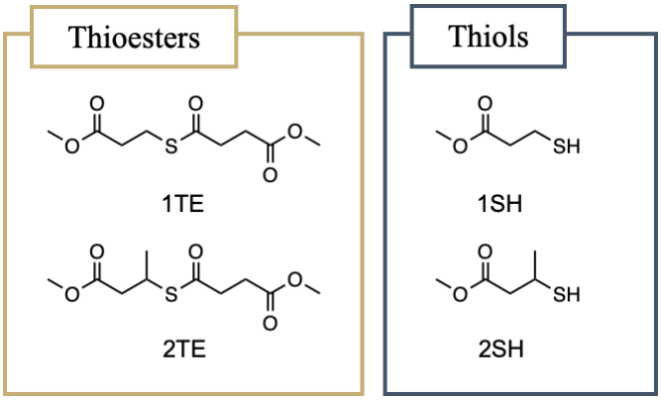

Figure 25. Model primary and secondary thiol and thioester compounds used in NMR studies.

When Worrell and coworkers conducted their equilibrium experiments, methyl 3-mercaptopropionate and 2-(boc-amino)ethanethiol achieved a K_{eq} of 0.82 with methyl 3-mercaptopropionate as the reactant, and a K_{eq} of 0.99 with 2-(boc-amino)ethanethiol as the reactant in DMSO-d_6 with TEA as a catalyst[43]. This system is the most comparable situation for primary and secondary mercaptopropionates, and as such, one would expect the K_{eq} for the studies conducted in these experiments to be of similar value.

Table 7. Summary of K_{eq} values for all solutions studied. These experiments were conducted in DMSO-d_6 at room temperature with 10 mol % catalyst. All reactions used equimolar thiol and thioester reactants and were compared to an internal standard (1,3,5 trimethoxy benzene). Time points were taken for up to 180 hours.

Solution	Reactant	Product	Catalyst	K_{eq}
1a	1° Thioester + 2° Thiol	2° Thioester + 1° Thiol	None	Q = 0.61*
1b	2° Thioester + 1° Thiol	1° Thioester + 2° Thiol	None	Q = 0.85*
2a	1° Thioester + 2° Thiol	2° Thioester + 1° Thiol	TMG	0.90
2b	2° Thioester + 1° Thiol	1° Thioester + 2° Thiol	TMG	1.19
3a	1° Thioester + 2° Thiol	2° Thioester + 1° Thiol	Quinuclidine	1.09
3b	2° Thioester + 1° Thiol	1° Thioester + 2° Thiol	Quinuclidine	0.88

* Reaction did not reach equilibrium

After collecting and organizing the results of the experiment, it should be noted that for the most part, the K_{eq} values are similar to those reported in the literature (Table 7), regardless of whether a base (TMG) or nucleophile (quinuclidine) catalyst was used. For the TMG catalyst, solution 2a and 2b achieved a K_{eq} of 0.90 and 1.19, respectively. For the quinuclidine catalyst,

solution 3a and 3b achieved a K_{eq} of 1.09 and 0.88, respectively. For the most part, these values are similar to 1, suggesting that the reactants and products trend towards 50% each.

The exchange did proceed when no catalyst was present, albeit much more slowly. While the catalyzed reactions typically reached equilibrium within 36 hours, the non-catalyzed reactions continued to react even after 180 hours. However, the curves of these graphs generally trend toward equilibrium values of the catalyzed reactions – Solution 1a and 1b had reaction quotient values of Q = 0.61 and Q = 0.85 respectively.

5.4.2 Thiol-ene materials

An important feature of any CAN material is the rate of exchange when the chemistry is active. While the NMR studies of model compounds do show that neither the primary nor secondary thioester seems to be strongly favored as a product, these experiments tell us little about the exchange rates of the primary thiol/thioester based networks as compared to the secondary analog. To this end, thiol-ene networks based on the previous literature[43, 98] with either primary or secondary thiols/thioester, shown in Figure 26, were made. Here, DABCO was used as a nucleophilic catalyst because of its good nucleophilicity and ease of use in polymer systems. Dielectric and mechanical stress relaxation measurements were used to assess the relative effectiveness of TTE for these primary and secondary thioester materials. It is hypothesized that due to the steric hinderance of the secondary thioester and thiol that the overall dynamics will be slower than for the primary system despite the similar reactivity from an equilibrium standpoint.

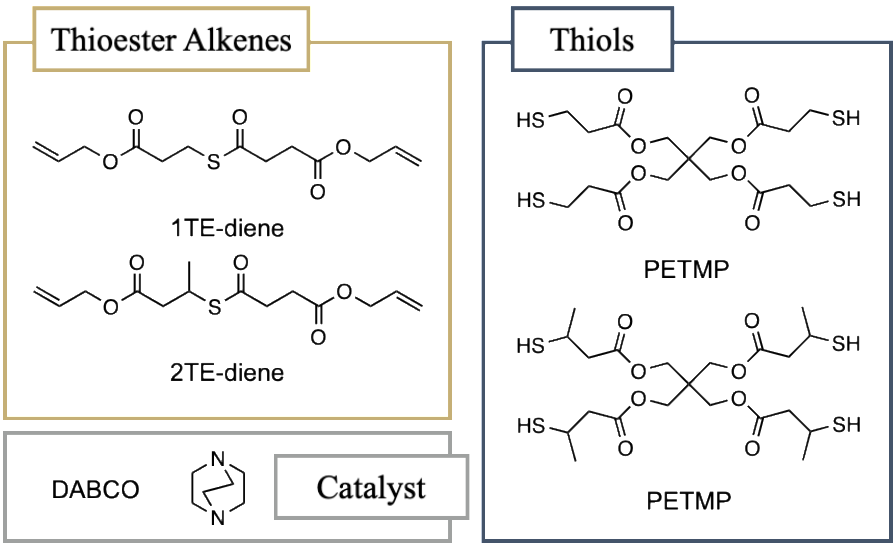

Figure 26. Structures of the thiols, thioesters, and nucleophilic catalyst for thiol-ene films. Samples consisted of either a 2:1 ratio of thiol-to-thioester functionality, with 1 wt% of the visible light photoinitiator I819 and were irradiated at 25 mW/cm^2.

Dielectric analysis (DEA) of thiol-ene materials

Dielectric spectroscopy is an important tool in polymer dynamics research due to the unique ability to efficiently probe different chain relaxation modes over a wide temperature and frequency range. To do this, an electric field is applied and interacts with the permanent and induced dipole moments that are built into the structure of the polymer materials. The response and relaxation of these dipoles can then be leveraged to probe the structure and properties of the material of interest. The ability to use an oscillating electric field over a large frequency range enables the materials scientist to observe dynamics at the chain and chain-segment scale in a way that is impractical or impossible by macroscopic mechanical testing, provided that the material of interest possesses polar groups to interact with the applied electric field. A variety of polymer systems have been assessed using DEA, including epoxy-resin systems that are ubiquitous in materials applications[109], natural and synthetic rubbers[110, 111], dental resins[112], and composites to probe filler/resin/interface dynamics[113-115]. However, there has been little work to use DEA to evaluate polymer dynamics in CANs.

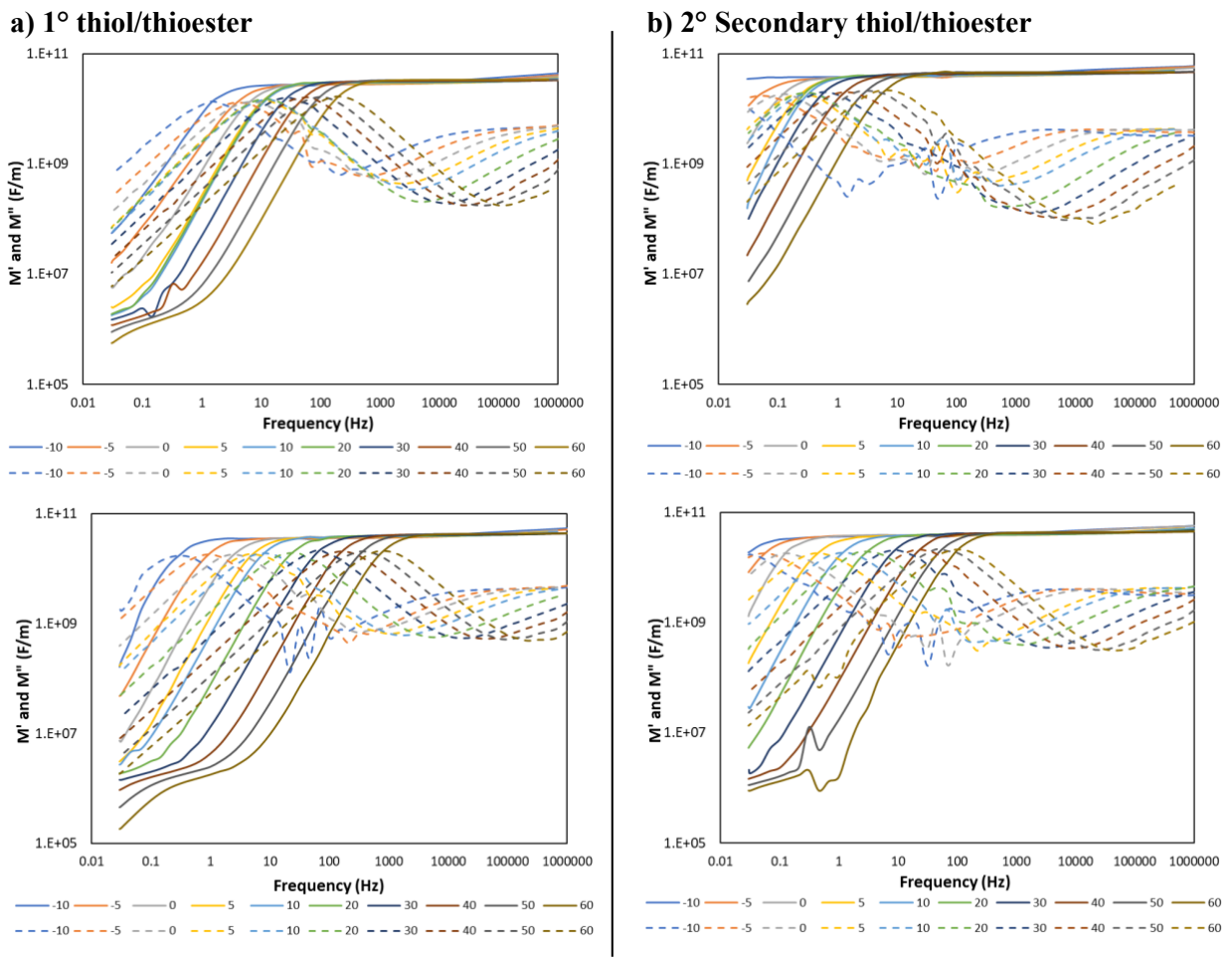

Figure 27. Dielectric spectra for thioester films taken using an interdigital sensor: a) Primary thiol/thioester spectra of sample containing no catalyst (top) and DABCO as a nucleophilic catalyst (bottom), b) Secondary thiol/thioester spectra of sample containing no catalyst (top) and DABCO as a nucleophilic catalyst (bottom). The solid lines denote the real part of the electric modulus, and the dashed lines denote the loss modulus.

The primary and secondary thiol and thioester monomers and the general reaction scheme used to make these films are shown in Figure 27. Here, DEA was used to assess the real ($M^{'}$) and loss ($M^{''}$) electric moduli with respect to the α-relaxation, which is associated with the glass transition, for primary and secondary TTE networks. Figure 27 shows M' and M" for networks that did (bottom) and did not (top) contain the nucleophilic catalyst DABCO.

For both the primary and secondary thioester networks, the α-relaxation occurs at a higher frequency, or a shorter relaxation time, for the catalyzed samples relative to the control due to the

ability of TTE to increase the overall mobility through network rearrangement. At the same time, the peak in the loss modulus for the primary thioester material occurs at a higher frequency at a given temperature, corresponding to a faster relaxation time. A possible explanation for this behavior that the secondary thioester network is less polar than the primary network due to the large number of methyl groups, which is known to decrease the rate of TTE[43]. This decrease in polarity may lead to a decrease in mobility, resulting in a slower relaxation time in otherwise equivalent networks.

5.5 Conclusions

Information gathered from these experiments lends a better understanding as to how the substitution of the thiol and thioester affects the TTE reaction, allowing a wider range of available molecules and methods for tunability for TTE. NMR exchange experiments revealed that exchange still occurs at room temperature, even if no catalyst is present. Regardless of whether a nucleophilic or basic catalyst is used, the K_{eq} generally trends towards a value of 1 in DMSO-d_6 suggesting that it does not favor one substitution over the other. In the thiol-ene networks, the dielectric relaxations demonstrate a faster exchange primary thiol/thioester compared to the secondary analog when the catalyst was present. In addition, α-relaxation time for the primary networks without catalyst was faster than that of the equivalent secondary network, indicating that polarity may play a role in either the dielectric measurements, the exchange rates, or both.

There is however, still more information to gather. NMR equilibrium experiments still need to be conducted in $CDCl_3$. A less polar solvent may reduce the amount of exchange, if exchange occurs at all, so it will be very interesting to learn if one substitution exchanges more than the other. Additionally, the values obtained from the DEA involve new procedures that are

not yet well established in literature, and comparison to conventional mechanical methods, namely stress relaxation, with be crucial to understanding any differences in the dynamics at play.

Chapter 6: Conclusions and Future Directions

6.1 Conclusions

The year 2020 marks the 100th anniversary of Hermann Staudinger's first publication on polymerizations[8], and the field of macromolecular chemistry and polymer science has truly flourished into an expansive and diverse field. This thesis brings new innovations to such a field by enhancing thiol-X chemistries. First, it brought greater understanding as to how the substitution of the thiol affects the thiol-ene for monofunctional and polymerization studies, and analyzed how increasing the substitution would affect the mechanical properties of such films. Next, the mechanism of the thiol-Michael reaction was studied. Finally, the thiol-thioester exchange reaction, a mechanism that incorporates labile chemical bonds in many thiol-X materials, was investigated to determine the effects from increased substitution. The following sections summarize the findings of this work and are followed by recommendations as to where this line of research could continue.

6.1.1 The Thiol-Ene Reaction

The first steps taken to investigate how the substitution of the thiol affects thiol-X reactions began with isomers of butanethiol. The reaction rates were measured using FT-IR spectroscopy for both monofunctional and polymerization reactions. Conversion values for the monofunctional experiments were reaffirmed using ^{1}H NMR spectroscopy. Finally, water sorption and shelf life experiments were completed and mechanical properties were analyzed using DMA. Under standard initiation conditions, it was found that all three of these thiols reacted swiftly, with negligible difference in rate regardless of substitution. It was not until the initiation conditions were significantly reduced that a pattern emerged – as the substitution of the

thiol increased, the rate of the reaction decreased. While this difference in rate was relatively small for most alkenes, it was ultimately dependent on the alkene used in the reaction.

When shifting to polymerization reactions, the rates and conversions followed the same pattern found in the monofunctional experiments. Using novel, benzyl-centered thiol monomers, it was found that the primary and secondary thiols reacted at very similar rates, and while the tertiary thiol reacted almost 10-fold more slowly, it still reached ~95% conversion after 8.5 minutes of irradiation. The increase in substitution also did not appear to greatly affect the T_g, as the values differed by only 1-2°C between films made with either primary or secondary thiol monomers. Additionally, primary thiol films absorbed only 1-3% more water than secondary films, likely due to the additional methyl group increasing the hydrophobicity of the polymer. The most exciting data emerged from the shelf-life studies. All of the thiol-ene mixtures containing primary thiols gelled within a few days, whereas the secondary thiols remained stable for much longer. In fact, after recently checking, the TTTSH-2:TTT and PETMP-2:TTT still had not gelled. The mixtures were made 8 months ago.

The results of these experiments imply that secondary and tertiary thiols can be incorporated into thiol-ene reactions, likely without severe drawbacks to rate or conversion, but users will see a dramatic increase in solution stability.

6.1.2 The Thiol-Michael Reaction

The next thiol-X reaction investigated was the thiol-Michael reaction. Monofunctional model reactions were studied using FT-IR and NMR analysis to determine rate and conversion for these reactions. The rate of the reaction was ultimately dependent on the pKa and reactivity of the thiolate anion, as well as any associated steric interactions. This resulted in a pattern that

was different than that of the thiol-ene reaction – where the rate decreased with increasing substitution regardless of the rate limiting step of the reaction. In the thiol-Michael reaction, propionates typically have a propagation RDS and alkyl thiols have a chain transfer RDS. For propagation limiting systems, the rate was dependent on the reactivity of the thiolate anion resulting in the secondary thiol being faster than the primary. For chain transfer limiting systems, the primary thiols were faster due to the lower pKa and the ease of deprotonation. Tertiary thiols were ultimately slower than either of the others likely due to their increased sterics.

For polymerization studies, only the kinetics and conversion were analyzed. Since the thiol-ene and thiol-Michael reaction share the same thioether bond as a product, the mechanical properties would not change regardless of which reaction was used. The kinetics of the polymer reactions followed the same pattern as the monofunctional experiments in systems of lower average monomer functionality. As the average monomer functionality of the polymerization increased, the rate of the secondary thiol polymerizations decreased – likely due to an effect from the increased sterics of the monomers.

Primary and secondary thiols were then analyzed in shelf-life experiments, which ultimately produced varied results. The solution that gelled faster correlated with whichever had the faster rate in the polymerization studies and was ultimately dependent on the crosslinking density of the mixture as well as the reaction mechanism. There seemed to be no advantage to using one substitution over the other and all systems typically gelled within 30 days.

6.1.3 The Thiol-Thioester Exchange Reaction

Covalent adaptable networks (CANs) are unique materials containing dynamic chemistries to allow for rearrangement of the polymer network[44, 45]. The thiol-thioester reaction is one such example of a CAN and can be easily incorporated into thiol-X materials, so this

reaction was studied as well. Novel secondary thiol and thioester molecules were synthesized and studied using ^{1}H-NMR equilibrium. To accurately quantify the amounts of each thioester species present in solution, calibration curves were created that compared the conversion of the thioester to the ratio of the NMR integration of the thioester peak relative to the IS, 1,3,5-trimethoxy benzene[42]. The amount of exchange was studied under different conditions and it was found that in DMSO-d_6 the K_{eq} generally trended towards 1, suggesting that there is not a high preference for one substitution over the other.

Next, dielectric analysis (DEA) was used to assess the real and loss electric moduli with respect to α-relaxation. DEA applies an oscillating electric field to a material and measures the permittivity, electric modulus, admittance, and impedance[111, 116, 117]. The advantage here lies in the fact that it has a wider frequency range than that of conventional tools (DMA), and it can measure specific chain relaxation mechanisms as long as there is a polar group that can interact with the electric field. Both catalyzed and non-catalyzed samples were tests, and the α-relaxation occurs at a higher frequency for the catalyzed samples when compared to the non-catalyzed samples. This indicated a shorter relaxation time, likely due to the catalyst increasing the ability of the TTE and overall mobility of the network. Primary thioester materials had a faster relaxation time than secondary thioester materials, indicated by the peak in primary thioester material's loss modulus occurring at a higher frequency for a given temperature. This could be due to the reduced polarity of the secondary thioester network.

This project is not yet complete as there is still a lot to learn from the thioester reaction. The polarity of the solvent is known to affect the amount of exchange, so it will be interesting to learn how the K_{eq} changes as we move to a less polar solvent such as $CDCl_3$. Additionally, since DEA has been infrequently used to evaluate polymer dynamics in CANs, it will be necessary to

study these materials with a more conventional tool such as the DMA. In this method, we will be able to learn how the DEA results compare to the DMA results.

6.2 Future Directions

The findings of this work indicate that secondary and even tertiary thiols can be incorporated into two of the most common thiol-X reactions – the thiol-ene and thiol-Michael additions, as well as the dynamic thiol-thioester exchange reaction. The findings of this research provide greater understanding as to how the substitution of the thiol affects these reactions in terms of rate, conversion, and mechanical properties of thiol-x materials, ultimately providing better insight as to how increasing the substitution affects the mechanism of these reactions. Consequently, this exploration will lead to significant technical development for applications beyond the scope of our lab, as both the thiol-ene and thiol-Michael reactions are heavily used in organic and polymer chemistry.

However, the thiol-ene and thiol-Michael reactions are just two of the many thiol-X reactions. The success of these initial findings begs the question: how does the substitution of the thiol affect other thiol-X reactions, and can more substituted thiols be incorporated into those reactions as well?

One such reaction that could incorporate substituted thiols is the thiol-epoxy reaction[24]. The reaction mechanism is similar to that of the thiol-Michael (Figure 28); a base either directly deprotonates the thiol, or a nucleophile indirectly deprotonates the thiol by attacking the epoxide, generating an epoxide anion that swiftly deprotonates the thiol. The thiolate anion then nucleophilically attacks the -CH_2- group of the epoxide causing the ring to open[118]. The alkoxide that is formed then swiftly deprotonates the next thiol, since thiols have a much lower pKa than alcohols (around 16 for alcohols, 10 for thiols). Overall, the reaction is dependent on the

nucleophilicity of the thiolate anion and the ease of deprotonation of the thiol – just as we have seen in the thiol-Michael reaction.

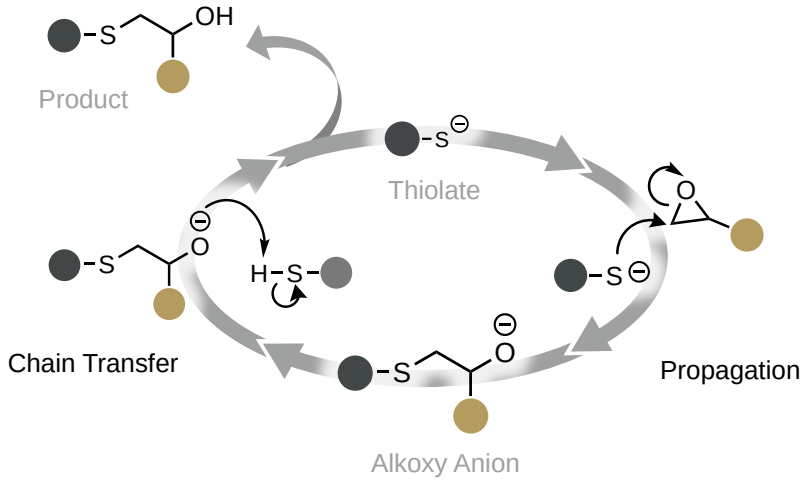

Figure 28. Mechanism for the thiol-epoxy reaction, where the thiolate anion attacks the less substituted side of the epoxide causing the ring to open. The alkoxy anion then deprotonates a new thiol, generating the thioether product as well as a new thiolate anion.

This is a case in which a secondary thiolate anion may react faster than a primary thiolate, as the secondary thiolate anion is more reactive. This would ultimately depend on the rate determining step of the reaction. While this information is not currently known, it may also depend on the pKa of the thiol. As the pKa of the thiol increases, the deprotonation step would slow and, at some point, would become rate limiting.

One difference between the thiol-epoxy and the thiol-Michael could make studying this reaction very interesting; the addition of the thiol to the alkene in the thiol-Michael reaction exists in a quasi-equilibrium state and is reversible, which could affect conversion[119]. For the thiol-epoxy however, this step would be driven forward by the relief of ring strain, which could result in higher conversions for more substituted monomers.

Podgórski and coworkers have studied a variation of the thiol-thioester exchange-based materials by utilizing a mixed-mechanism thiol-anhydride-ene reaction[120]. These unique

materials incorporate two different exchanged reactions– the reversible addition of a thiol to succinic, maleic, and phthalic anhydrides and the reversible thiol-thioester exchange (Figure 29).

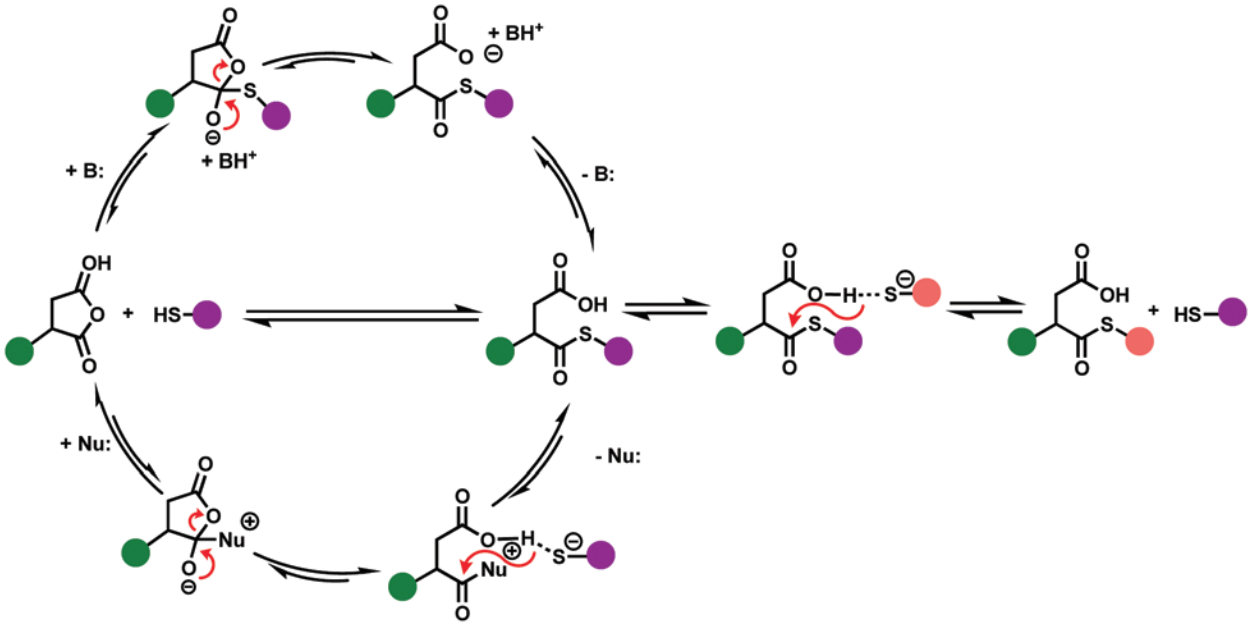

Figure 29. From Podgórski et al[120]. The proposed mechanism for the two dynamic reactions – the thiol and anhydride addition (left) and the thiol-thioester exchange (right).

If one were to incorporate more substituted thiols in these systems, one factor to consider is that secondary and tertiary thiols have increased steric interactions due to the additional methyl groups. We have seen in previous experiments that, while this can reduce the rate of the reaction, sterics often do not affect conversion.

Looking at each dynamic chemistry at play here separately, preliminary thioester studies from Chapter 5 have suggested that in polar environments the rate of exchange does not necessarily favor primary nor secondary thioesters, and exchange proceeds regardless of whether a basic or nucleophilic catalyst is used. It is likely that for the thioester reaction exchange reaction in this mixed mode-context, the trends will be the same or at least, very similar. For the reversible thiol-anhydride reaction , secondary thiols, and even tertiary thiols, will likely add to

the anhydride since planar nature of maleic, succinic, and phthalic anhydride may offset the steric effects from increased substitution. The anhydride addition reaction is designed to be in equilibrium, so the relative concentration of anhydride to thioester at a given temperature may be affected by sterics. It is also likely that the amount of time to reach equilibrium may increase for secondary thiols. Additionally, one might see a slower relaxation time and reduced rate of exchange for films that incorporate secondary thiols.

Chapter 7: Bibliography

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