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Ruthenium Hydride Catalyzed Silylvinylation of Terminal and Internal Alkynes and Synthesis of Poly(trimethylenecarbonate) and Poly(dimethylacrylamide) Block Copolymer

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Executive Summary

Organic chemistry is an area of chemistry that deals with understanding and utilizing compounds that contain carbon, oxygen, nitrogen, hydrogen, and any other elements deemed non-metals which are found in the right-hand region of the periodic table. Synthesis is an important aspect of organic chemistry, as this provides a 'recipe' for creating one or more desired compounds (products) from other compounds (starting materials or reactants). Synthesis details which starting materials are to be combined such that they react to form the desired products and defines the conditions (temperature, time of reaction) the reaction requires to most efficiently yield these products.

The two areas of chemistry involved in my synthesis research are organometallic chemistry and polymer chemistry. Organometallic chemistry is chemistry that deals with the organic compounds that contain transition metals, which are elements found in the center region of the periodic table. Organometallic compounds are often used as catalysts, which are additives that speed up a chemical reaction. Catalysis is an important aspect of synthetic chemistry (i.e., chemistry that deals with synthesis) because it is a way to increase reaction efficiency, both in reaction time and in product yield. Reaction time is the time required for a reaction to take place, and product yield is the amount of product that is obtained after the reaction is complete with respect to the amount of starting material used. A short reaction time, on the order of minutes to a few hours, and a high product yield, anywhere from 85-100%, are the most valued features of a synthetic scheme. Polymer chemistry is an area of chemistry that typically deals with organic compounds that combine in such a way that they create repeating units of the same compound. In other words, a molecule of a given compound combines with another molecule of itself to create a chain of the same molecules, deemed a polymer.

My research in organometallic chemistry and in polymer chemistry has ultimate applications to medicine. For example, my research in organometallic chemistry seeks to assist in the synthesis of future drug molecules. Often times, a molecule found in nature is known to exhibit healing or medicinal properties. This natural substrate cannot be distributed to the public due to the eventual shortage that would result after the amount supplied by nature is gone. Medicinal chemists (chemists who synthesize drug molecules) seek to fix this problem by developing a synthesis for such natural substrates and related materials which may eventually be useful as pharmaceuticals.

Synthesizing molecules found in nature is a very difficult task. One complication that arises in attempting to replicate natural substrates arises from a concept called stereochemistry. Stereochemistry describes the spatial orientation of the atoms (or parts) that constitute a whole molecule. For example, a compound found in nature may have a nitrogen atom found below a carbon atom when viewed from a certain position. If viewed from this same position on a different molecule of the same compound, the nitrogen atom still needs to be found below the carbon atom. It cannot be found above the carbon atom, as this indicates the identity of the molecule has changed. This second molecule may be considered a stereoisomer of the other molecule, as it has the same chemical components (number and types of atoms) but a different spatial orientation.

Thus my research in organometallics seeks to synthesize dienes (a type of compound that contains two adjacent carbon-carbon double bonds) with defined stereochemistry: in other words, it attempts to synthesize one stereoisomer of a diene. Diene structures are commonly found in nature, and methods to easily replicate the stereochemistry found in these structures are highly desired. A molecule containing an alkyne, or carbon-carbon triple bond, located three

carbon atoms away from an oxygen-silicon group was subjected to bond reorganization using a ruthenium hydride catalyst (an organometallic compound containing a ruthenium metal atom) to create this diene, or adjacent carbon-carbon double bond structure, in a five-membered ring. These rings can be easily opened through additional reactions to isolate the diene and functionalize the remainder of the molecule. My research dealt with the attempting to isolate these five-membered rings containing specific diene stereochemistry.

My research in polymer chemistry has ultimate applications to drug delivery. Polymers are chains of repeating molecules, as mentioned previously. They make up common materials such as plastics. They have useful potential applications as materials to create nanoparticles, and these nanoparticles could eventually deliver drugs within the body.

The simplest polymer chain is made up of one repeating unit of the same molecule. Such a polymer, built from only one molecule, will have distinct properties such as its melting point. There are various ways to diversify polymer chains by adding additional molecules in different orders and sequences. This variety causes the physical properties of the original polymer chain to change, such that a polymer can be 'tailor-made' to melt at a desired temperature and behave a particular way simply by introducing this variation.

There are many ways to introduce such variation. My project explored the efficacy of two methods, Ring Opening Polymerization (ROP) and Reversible Addition-Fragmentation Chain Transfer (RAFT) polymerization, to introduce a second monomer (dimethylacrylamide or DMAA) into a polymer chain that the research group had previously synthesized and characterized by novel catalytic methods (trimethylcarbonate or TMC). The reason for addition of dimethylacrylamide to the poly(trimethylcarbonate) (pTMC) polymer is owed to a desire to increase the melting point of the polymer: it was found that pTMC melted at a temperature below

that of the human body, and that this would not serve its purpose well as a nanoparticle (which

needs to maintain rigidity) delivering drugs within the human body.

Acknowledgements

Table of Contents

Chapter I. Ruthenium Hydride Catalyzed Silylvinylation of Terminal Alkynes

Abstract

Various propargyl alcohols were synthesized via Grignard reactions. These alkynic alcohols are tethered with dimethyl and biphenyl silicon tethers. These terminal alkyne substrates are reacted with RuHCl(CO)(H$_2$IMes)(PPh$_3$) as a catalyst under high pressure (80 psi) ethylene atmosphere to afford the 5-*exo-dig trans*-silylvinylation product in poor yield. Internal alkyne substrates are found to be much more efficiently transformed into the silylvinylation product, favoring one cycloisomer product over the other.

Introduction

Ethylene is a gaseous, inexpensive, and readily available material that is currently used to ripen bananas. It is the simplest alkene with approximately 150 million pounds produced per day.[1] It is believed that ethylene can assist in the construction of unique molecules found in nature that organic chemists are trying to replicate. Successful synthesis of these molecules will benefit the pharmaceutical industry and consumer goods market directly. The use of ethylene as an additive in transition-metal catalyzed transformations is currently being explored, showing success in the Mizoroki-Heck[2,3] transformation, in enyne metathesis,[4] and in hydrovinylation[5,6,7] reactions. Ethlyene's utility in the silylation of alkynes is an under-investigated area that merits closer attention due to the highly functionalized products that result from this regio- and stereospecific reaction.

Silylvinylation is the reaction between an internal alkyne with a tethered silicon molecule possessing a vinyl group to form a five- or six-membered oxasilacycle (isomers **A** and **B**, respectively) as shown in Figure 1. The Clark research group has found that this reaction is

[1] Saini, V.; Stokes, B. J.; Sigman, M. S., *Angew. Chem. Int. Ed.* **2013,** *52* (43), 11206-11220.
[2] Saini, V.; Sigman, M. S., *J. Am. Chem. Soc.* **2012,** *134* (28), 11372-11375.
[3] Plevyak, J. E.; Heck, R. F., *J. Org. Chem.* **1978,** *43* (12), 2454-2456.
[4] Kitamura, T.; Mori, M., *Org. Lett.* **2001,** *3* (8), 1161-1163.
[5] Rajan Babu, T. V., *Synlett* **2009,** *2009* (06), 853-885.
[6] Yi, C. S.; Lee, D. W.; Chen, Y., *Organometallics* **1999,** *18* (11), 2043-2045.
[7] Mans, D. J.; Cox, G. A.; RajanBabu, T. V., *J. Am. Chem. Soc.* **2011,** *133* (15), 5776-5779.

catalyzed by ruthenium hydride catalyst **1** in the presence of methyl vinyl ketone (MVK) additive. This reaction yields a highly selective *trans*-silylvinylation product **A**, which can be carried on to various other chemical reactions, as evidenced in Figure 2, such as fluoride-mediated silicon group removal for **6**, addition of methyl lithium reagent for **7**, selective hydrogenation of the terminal olefin for **8**, or diene metathesis products for **9** and **10**.[8]
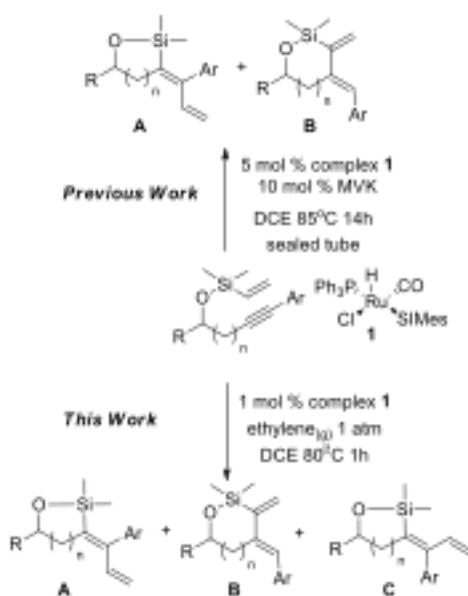
Figure 1. Silvlvinylation of internal alkynes with MVK and ethylene.

To further functionalize the scope of obtainable products of the Ruthenium hydride catalysis, the silylvinylation reaction is performed under ethylene gas atmosphere. Ethlyene serves as an additive and allows for the formation of the oxasilacycle with terminal terminal alkynes, thus increasing the substrate scope of ruthenium-catalyzed silylvinylation chemistry. An assembly of

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[8] O'Malley, S. J.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2001**, 40, 2915−2917.

variously functionalized terminal alkynes with vinyl silicon tethers will be subjected to this

silylvinylation reaction with catalyst **1** under high-pressure ethylene gas additive. It is expected

that these reaction conditions will allow for a reversal of the stereochemistry obtained with

MVK. This would make isomer **C**, shown in Figure 1, accessible to the synthetic organic

chemist. This isomer can be taken on to further chemical reactions to yield a set of stereospecific

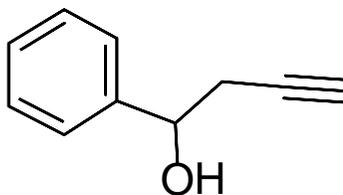products analogous to those formed from **6-10** in Figure 2.
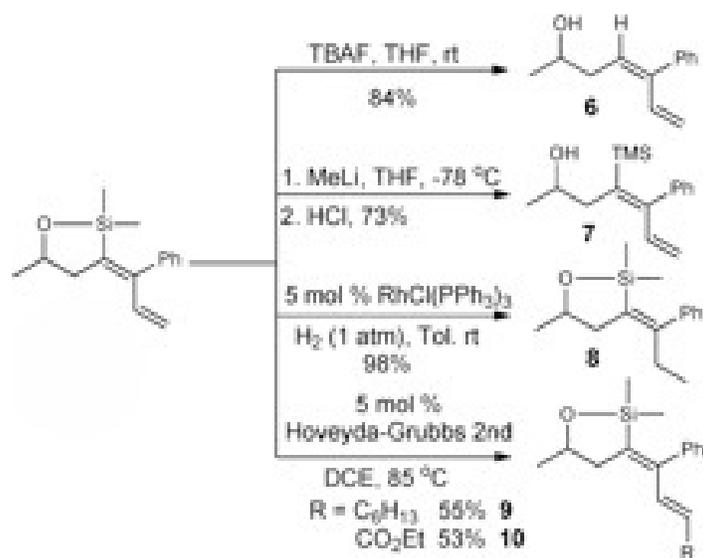
Figure 2. Substrate scope of *trans*-silylvinylation product

Experimental Methods

General procedure for homopropargylic alcohol formation via Grignard addition:

(1-phenyl-3-butyn-1-ol)

12

To a flame-dried 3-neck 250 mL round bottom flask with large magnetic stir bar was added Mg^0

(0.6 g, 25 mmol, 1.5 equiv), $HgCl_2$ (0.046 g, 0.17 mmol, 0.01 equiv), and 1 iodine chip heated

under vacuum until a pink cloud formed. The mixture was cooled to room temperature, placed

under argon atmosphere, then covered with Et_2O (13 mL). Propargyl bromide (1.88 mL, 1.58

g/mL, 2.97 g, 25 mmol, 1.5 eq) was added drop-wise for 5 minutes as a solution in Et_2O (21 mL)

to maintain reflux conditions. The reaction was stirred for an additional hour at reflux. Solution

changes color from clear to whitish or dark gray. After 1 h, mixture was titrated with L-menthol

(1 mmol) and 1,10-phenanthroline (spatula tip) to give a 0.47 M solution. Reaction was then

cooled to -40 °C (dry ice/acetone) and benzaldehyde (11.28 mmol, determined from titration)

was added drop-wise over 5 minutes. Milky white suspension allowed to stir and warmed to

room temperature. Two h after addition of the aldehyde, the reaction was quenched with HCl (50

mL) at 0 °C. Organic layer washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to

give a dark yellow oil (1.44 g, 87%). Spectroscopic data corresponded to data found in the

literature.

General procedure for attaching silicon tether to homopropargylic alcohol:

($C_{14}H_{18}OSi$)
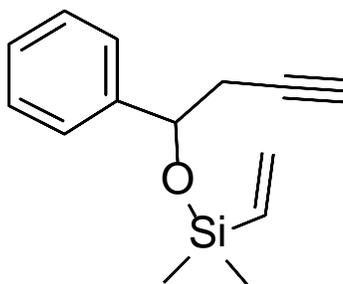
To an oven-dried and flame-dried 100 mL round bottom flask with magnetic stir bar was added

homopropargylic alcohol (0.67 g, 3 mmol, 1 equiv), imidazole (0.409 g, 6 mmol, 2 equiv),

DMAP (0.073 g, 0.6 mmol, 0.2 equiv), and DCM (20 mL, 0.15M) under an argon atmosphere. The yellow solution was cooled to 0 °C (ice/water bath) and either dimethyl or biphenyl vinyl chloro silane (3.6 mmol, 1.2 equiv) was added drop-wise for 5 minutes. The light yellow solution was stirred for 1.5 h with completion confirmed by thin layer chromatography. Reaction was then quenched with NH_4Cl (40 mL, sat. aqueous) then the aqueous layer was extracted with DCM (30 mL) 3 times. The combined organics were dried over $MgSO_4$, filtered, and concentrated to give a dark yellow oil. The residue was purified via flash column chromatography (silica gel 4 x 14 cm; eluted with 2% ether/hexane (250 mL), 4% ether/hexanes (100 mL) to give the desired silyl ether as a clear oil (0.63 g, 68%). Spectroscopic data corresponded to data found in the literature.

General procedure for diene formation:

($C_{14}H_{18}OSi$)
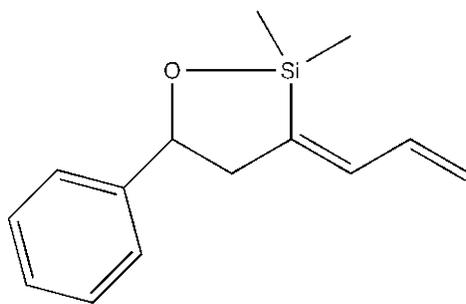
To a Fischer-Porter bottle with magnetic stir bar in an argon filled glovebox was added RuHCl(CO)(H_2IMes)(PPh$_3$) (9.18 mg, 0.0125 mmol, 0.05 equiv) and silyl-tethered alkyne (57.6 mg, 0.25 mmol, 1 equiv) in toluene (1 mL, 0.25 M). The sealed reaction vessel was removed from the glovebox and the Swagelok apparatus was attached. The light orange solution was purged with ethylene (80 psi) 3 times then placed under ethylene atmosphere (80 psi) and stirred at 80 °C (preheated silicone oil bath) for 16 h. TLC analysis indicated complete consumption of

starting material. The dark brown solution was allowed to cool to room temperature and the

system was vented open to air. The solution was filtered through a plug of silica gel, eluted with

ether, and then concentrated *in vacuo* to give a whitish yellow flaky solid or clear oil. The

residue was purified via flash column chromatography (silica gel 2.5 x 15 cm; eluted with 2%

ether/hexanes (300 mL)) to give clear oil. Spectroscopic data corresponded with data reported in

literature.

Results

Table 1. Homopropargylic alcohols formed via Grignard addition.

Entry	Aldehyde/Ketone	Product	Yield
1			87%
2			83%
3			74%
4			84%
5			60%
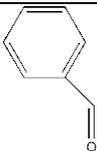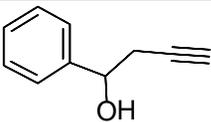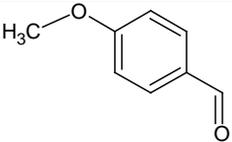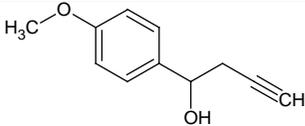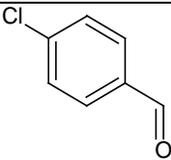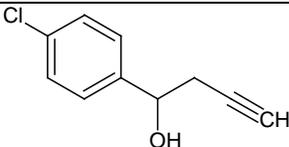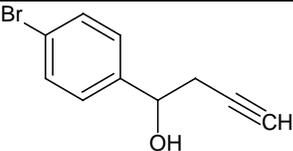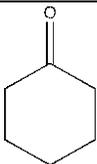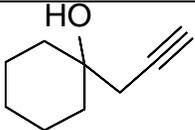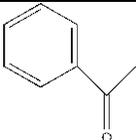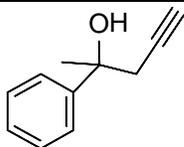
| 6 | | | 85% |
| 7 | | | 45% |

Table 2. Silicon tethered homopropargylic alcohols.
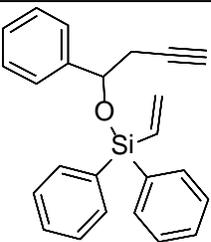
Entry	Product	Yield
1		68%
2		68%
3		58%
4		68%
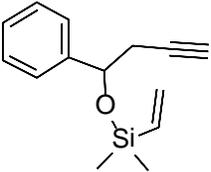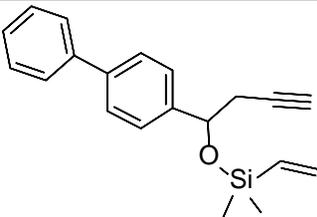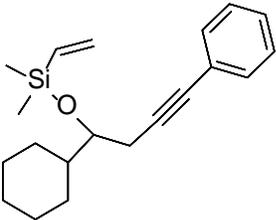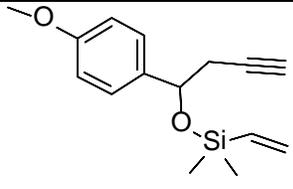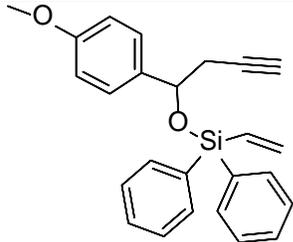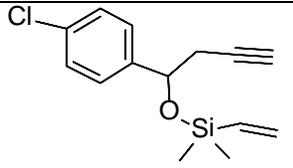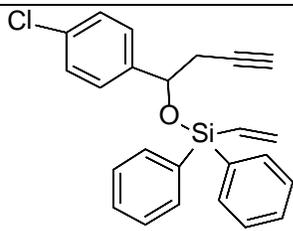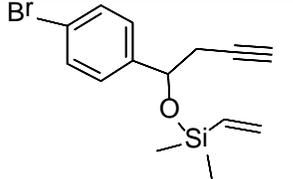
5		49%
6		38%
7		82%
8		85%
9		73%
10		43%
11		71%
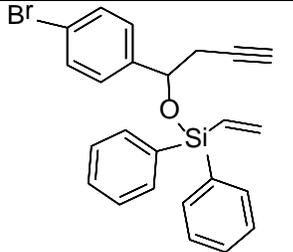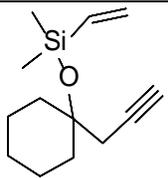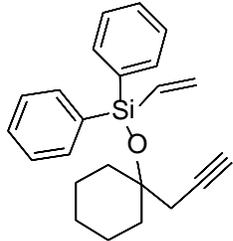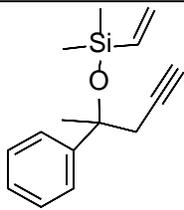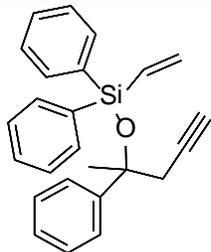
12		39%
13		73%
14		55%

Table 3. Diene systems synthesized by RuH catalysis.
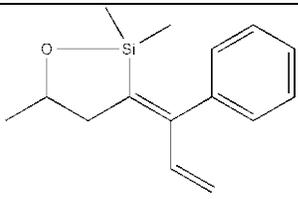
Entry	Product	Yield
1		59%
2		48%
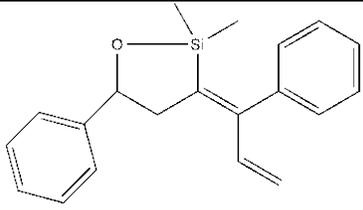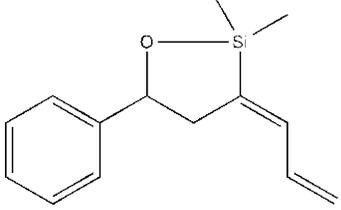
3		NA

Discussion

A series of homopropargylic alcohols were synthesized from corresponding Grignard reactions of propargyl bromide and different ketones and aldehydes (Table 1) to broaden the substrate scope of the silylvinylation reaction. Entry 1 incorporates a phenyl group in 87% yield, entry 2 incorporates a para-methoxy benzene group in 83% yield, entry 3 incorporates a para-chloro benzene goup in 74% yield, entry 4 incorporates a para-bromo benzene group in 84% yield, entry 5 incorporates a cyclohexane group in 60% yield, entry 6 incorporates a methyl and benzene group from the corresponding ketone at 85% yield and entry 7 incorporates a para-benzyl benzene group in 45% yield. It can be seen from these results that the greatest yield is obtained from the unsubstituted benzyladehyde from entry 1. Para-halo-substituted benzaldehydes afford products in exceptionally good yield (i.e., greater than 74%) as seen in entries 3 and 4, along with the para-methoxy-substituted benzaldehyde from entry 2. Methylbenzyl ketone also worked exceptionally well in this reaction as seen in entry 6. Entries 5 and 7, utilizing cyclohexanone and para-benzyl benzaldehyde, report poor yields of 60% and 45% respectively.

The poor yield in entry 5 is likely due to lack of the appropriate electronic effects found for all other entries, owed to the simple use of a cyclohexane group rather than a benzene group. For example, the efficient yields of entries 3 and 4 are likely due to the mild electron withdrawing properties of the para-substituted halogen on the benzene ring, thus activating the carbonyl for attack by the Grignard reagent to form the product. Without the ability to activate

the carbonyl due to alkyl substituents lacking a pi-electron system, the Grignard reaction affords a relatively poor yield as seen in entry 5. Entry 7 supports this idea, where the para-benzyl group serves as an electron donating group which would in turn deactivate the carbonyl for Grignard attack, thus explaining its poor yield. It is anomalous, however, that entry 2 should afford such a relatively high yield despite the presence of the para-methoxy group which is electron donating. It is expected that the entry 2 should report a lower yield in accordance with the yield found in entry 7, as both the benzene and methoxy group are electron donating and subsequently deactivate the carbonyl. The additional phenyl ring present in entry 7 may account for this low yield, as the product would not be very soluble in the reaction solvent and thus would not be isolatable from the byproducts.

Silicon tethers were then coupled to each of the terminal alkynic homopropargylic alcohols as listed in Table 2. Two silicon tethers were used, the dimethyl and the biphenyl, in an attempt to significantly broaden substrate scope and evaluate effects of the tether. Entry 1 consists of the phenyl substituted alcohol (table 1, entry 1) with the biphenyl tether, produced in 68% yield, and entry 2 consists of the same alcohol with the dimethyl tether, also produced in 68% yield. Entry 3 consists of the para-benzyl benzyl substituted alcohol (table 1, entry 7) with the dimethyl tether, produced in 58% yield. Entry 4 consists of an alcohol not synthesized in Table 1, coupled with the dimethyl there in 68% yield. Entry 5 consists of the para-methoxy benzyl substituted alcohol (table 1, entry 2) with the dimethyl tether, produced in 49% yield, and entry 6 consists of the same alcohol with the biphenyl tether, produced in 38% yield. Entry 7 consists of the para-chloro benzyl substituted alcohol (table 1, entry 3) with the dimethyl tether, produced in 82% yield, and entry 8 consists of the same alcohol with the biphenyl tether produced in 85% yield. Entry 9 consists of the para-bromo benzyl substituted alcohol (table 1,

entry 4) with the dimethyl tether, produced in 73% yield, and entry 10 consists of the same alcohol with the biphenyl tether, produced in 43% yield. Entry 11 consists of the cyclohexane substituted alcohol (table 1, entry 5) with the dimethyl tether, produced in 71% yield, and entry 12 consists of the same alcohol with the biphenyl tether produced in 73% yield. Entry 13 consists of the methyl benzyl alcohol (table 1, entry 6) with the dimethyl tether, produced in 73% yield, and entry 14 consists of the same alcohol with the biphenyl tether, produced in 55% yield. It is interesting to note the general trend of the biphenyl tether leading to decreased yields, such as those seen in entries 6, 10, 12, and 14, compared to those of the dimethyl tethers. This is likely due to steric factors, with the more sterically hindered silyl chloride providing lower yields of the desired products.

These silicon-tethered alcohols were then subjected to RuH catalysis under high pressure (80 psi) ethylene atmosphere to produce the 5-*exo-dig trans*-silylvinylation products listed in Table 3. In practice only the phenyl substituted dimethyl tethered alkyne (table 2, entry 2) was subjected to this catalysis treatment and afforded no quantifiable yield as listed in table 3, entry 3. Treatment of other terminal alkynes to the high pressure RuH catalysis did not afford any desired products. This may be due to the rapid dimerization of the silylvinylation product formed from the terminal alkyne that does not occur with internal alkynes, due to the presence of more stable/less reactive substituents than hydrogen (i.e, the inevitable substituent of a terminal alkyne). Entries 1 and 2 in table 3 used internal alkynes with phenyl group termini and methyl and phenyl homopropargylic respective substitution; these produced acceptable yields of 59% and 48%, respectively

Thus internal alkynes proved to be good substrates for the silylvinylation reaction with ethylene as an additive, as seen in table 3, entries 1 and 2. This reaction was explored further in

Wilson et. al., in a publication of another member of the laboratory in which my research was conducted. It was found that when the RuH catalysis reaction takes place under ethylene atmosphere, the ethylene is indeed incorporated into the final silylvinylated product. Internal alykens bearing aryl and alkyl substituents worked equally as well in this reaction. Increased pressure of ethylene was found to favor a specific silylvinylation isomer over the other, and almost entirely excluded the cycloisomerization product, thus providing a defined use for the protocol attempted in my research which failed to produce reliable results for terminal alkynes. The specific isomeric products formed from this protocol can be taken on to epoxidations and enone formation reactions, which provide useful synthetic applications to the products of the internal alkyne RuH catalysis reactions.[9]

Conclusion

Grignard reactions were used to synthesize various propargyl alcohols. These were then elaborated with dimethyl and biphenyl vinylsilicon tethers. These tethered alkynes were treated with ruthenium hydride catalyst under high pressure (80 psi) ethylene atmosphere to afford the 5-*exo-dig trans*-silylvinylation product in poor yield. Tethered terminal alkynes were found to undergo silylvinylation catalysis to afford a single cycloisomer product in high yield and are more suited for these reaction conditions. Further experimentation is required to develop conditions that produce a single cycloisomer of the tethered terminal alkynes.

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Chapter II. Synthesis of Poly(trimethylenecarbonate) and Poly(dimethylacrylamide) Block Copolymer in Two Synthetic Routes

Abstract

Two synthetic routes toward a diblock copolymer containing pTMC and pDMAA were completed from ROP and RAFT polymerization. The first route involved two separate polymerization reactions, and the second route involved two simultaneous polymerization reactions. The success of this synthesis was indeterminable by the analytical methods used, which included ^{1}H NMR spectroscopy with a 500 MHz Bruker instrument and Size Exclusion Chromatography with samples dissolved in chloroform. Further analytical techniques such as Mass Spectrometry and IR spectroscopy are required to assess the formation of the desired pTMC and pDMAA diblock copolymer.

Introduction

Polymerization chemistry is an important area of research, lending itself to applications in material science and specifically to the development of drug delivery systems.[1] Polymers, or molecules containing a chain of at least one repeating unit, have many unique properties determined by their composition. Alteration of the polymeric composition can thus change the polymer's properties, such as freezing point, elasticity, and solubility, and this allows for the design of a polymer with unique and specific properties. Some unique properties of polymers are its glass transition temperature (T_g) and its melt transition temperature (T_m), during the former of which a polymer goes from a glass-like structure to a more amorphous structure and during the later of which a polymer loses its crystallinity and becomes melted or molten.

A copolymer is a polymer that contains at least two distinct polymer units. The arrangement of these units is telling of the copolymer's properties. Such arrangements include an alternating copolymer, periodic copolymer, and block copolymer, in which there is simple and consistent alternation of the polymer units, to alternation of repeating polymer units of different lengths, to completely separate units of polymer units of a single length, respectively. To create a

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[1] Jérôme, C.; Lecomte, P. "Recent advances in the synthesis of aliphatic polyesters by ring-opening polymerization" *Advanced Drug Delivery Reviews*. **2008**; 60. 1056-1076.

block copolymer, controlled polymerization techniques may be used. Such techniques include ring-opening polymerization (ROP), reversible addition-fragmentation chain transfer (RAFT), and atom transfer free radical polymerization (ATRP) and work by allowing chain growth to begin at approximately equal times and also by allowing chain growth to terminate at the same time (therefore allowing for a controlled polymerization reaction). Controlled polymerization is preferable because it allows for the formation of polymer chains of consistent length and for control over end groups of the final polymer. The chain lengths of the various polymer molecules that are present in a given polymer sample are described by a polymer's polydispersity, which can be obtained from Size Exclusion Chromatography (SEC) analysis, and is defined below

$$D = \frac{M_w}{M_n} \qquad [1]$$

where D represents the polydispersity index of a polymer, M_w represents the weight average molecular weight – a number obtained by averaging the mass of the chains in a sample, and M_n represents the number average molecular weight – a number obtained by averaging the number of atoms detected in a sample.

As M_w and M_n approach the same number, the polydispersity approaches 1, which indicates that all polymer chains are equivalent in mass and number of atoms, and are therefore the same length. This is ideal and typically only obtained in biological processes. Synthetic chemistry aims for polydispersities of 1, but accepted values lie in the range of 1 to 1.5, as these indicate sufficiently equivalent polymer chain lengths in the sample molecule. M_w and M_n values are also be obtained from SEC.

One polymer of interest is poly(trimethylenecarbonate), abbreviated pTMC. This polymer is easily formed by the ring-opening polymerization (ROP) of trimethylene carbonate (TMC), which has amassed much discussion in previous literature (Figure 1).[2,3,4,5,6]
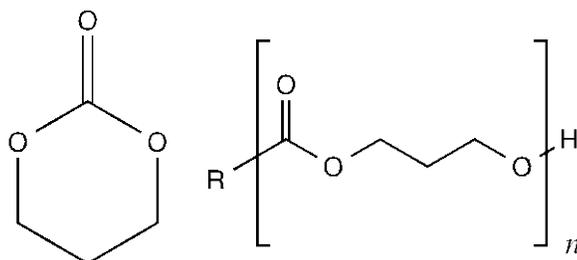
Figure 1. TMC, left, may be polymerized to pTMC, right, by a ROP reaction. The lower-case n denotes the number of repeating TMC units that are present in the pTMC molecule.

ROP historically required a cyclic carbonate or ester, such as TMC, an initiating nucleophilic compound, such as an alcohol, appropriate solvent, such as 1,4-dioxane, with conditions of elevated temperature and an organometallic catalyst. The organometallic catalysts used often contained tin and other metals which could not be removed entirely from the final product. For drug delivery systems and other biomedical applications of polymers, the presence of these metals was not acceptable due to potential health complications and biological

[2] Nederberg, F.; Lohmeijer, B.; Leibfarth, F.; Pratt, R.; Choi, J.; [1], A.; Waymouth, R.; Hedrick, J. "Organocatalytic Ring Opening Polymerization of Trimethylene Carbonate" *Biomacromolecules*. **2007**; 8. 153-160.
[3] Yu, Y.; Shin, S.; Ko, K.; Yu, W.; Youk, J. "One-pot synthesis of poly(vinyl alcohol)-based biocompatible block copolymers using a dual initiator for ROP and RAFT Polymerization" *Polymer*. **2013**; 54. 5595-5600.
[4] Matuso, J.; Sanda, F.; Endo, T. "Cationic ring-opening polymerization behavior of an aliphatic seven-membered cyclic carbonate, 1,3-dioxepan-2-one" *Macrolmol. Chem. Phys.* **1998**; 199. 97-102.
[5] Matsuo, J.; Aoki, K.; Sanda, F.; Endo, T. "Substituent Effect on the Anionic Equilibrium Polymerization of Six-Membered Cyclic Carbonates" *Macromolecules*. **1998**; 31. 4432-4438.
[6] Yu, F.; Zhuo, R. "Synthesis and Characterization of OH-Terminated Poly(trimethylene carbonate)s by Alcohol-Initiated Ring-Opening Polymerization in Melt Bulk without Using Any Catalyst" *Polymer Journal*. **2004**; 36(1). 28-34.

interactions. The use of novel, purely organic catalysts (often called green chemistry) was sought after for this and other polymerization techniques. It was determined that a carbene catalyst stored with a CO_2 adduct that easily deteriorates upon heating was just as effective as organometallic catalysts for ROP, allowing for 'Metal Free ROP.'[7]

The mechanism through which ROP takes place is straight forward and is pictured in Figure 2. Activation of the carbene species by loss of the CO_2 adduct begins the reaction. This carbene then deprotonates the initiator, leaving a nucleophilic species. This nucleophile adds to the carbonyl group of the cyclic carboxylate, displacing the previously bound oxygen of the carboxylate group so that it then becomes a nucleophilic species, which then adds to another molecule of the cyclic carboxylate, opening that ring and releasing another nucleophilic species. The reaction eventually terminates when exposed to air, where the nucleophilic species become capped by protons from water and form a polymer with a hydroxyl end group, as evidenced in Figure 1.[2]

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[7] Connor, E.; Nyce, G.; Myers, M.; Möck, A.; Hedrick, J. "First Example of N-Heterocyclic Carbenes as Catalysts for Living Polymerization: Organocatalytic Ring-Opening Polymerization of Cyclic Esters" *Journal of the American Chemical Society*. **2002**; 124(6). 914-915.
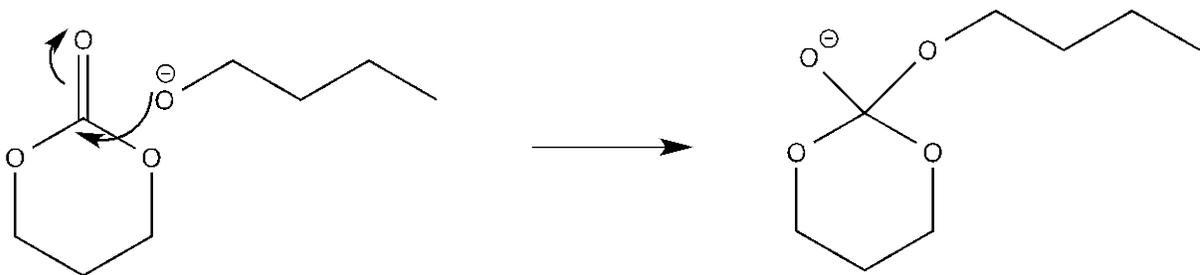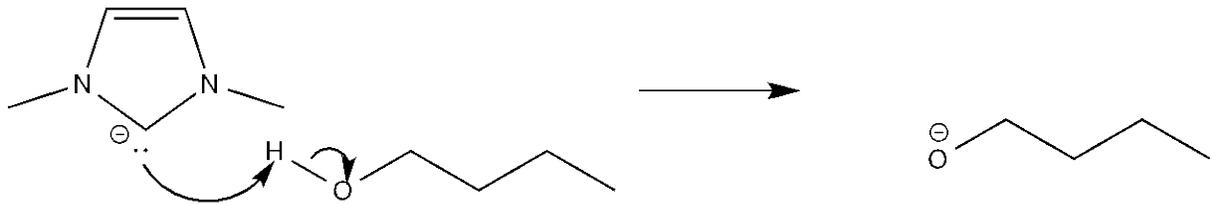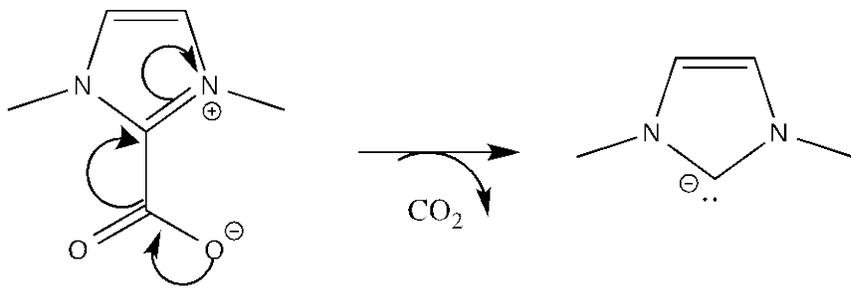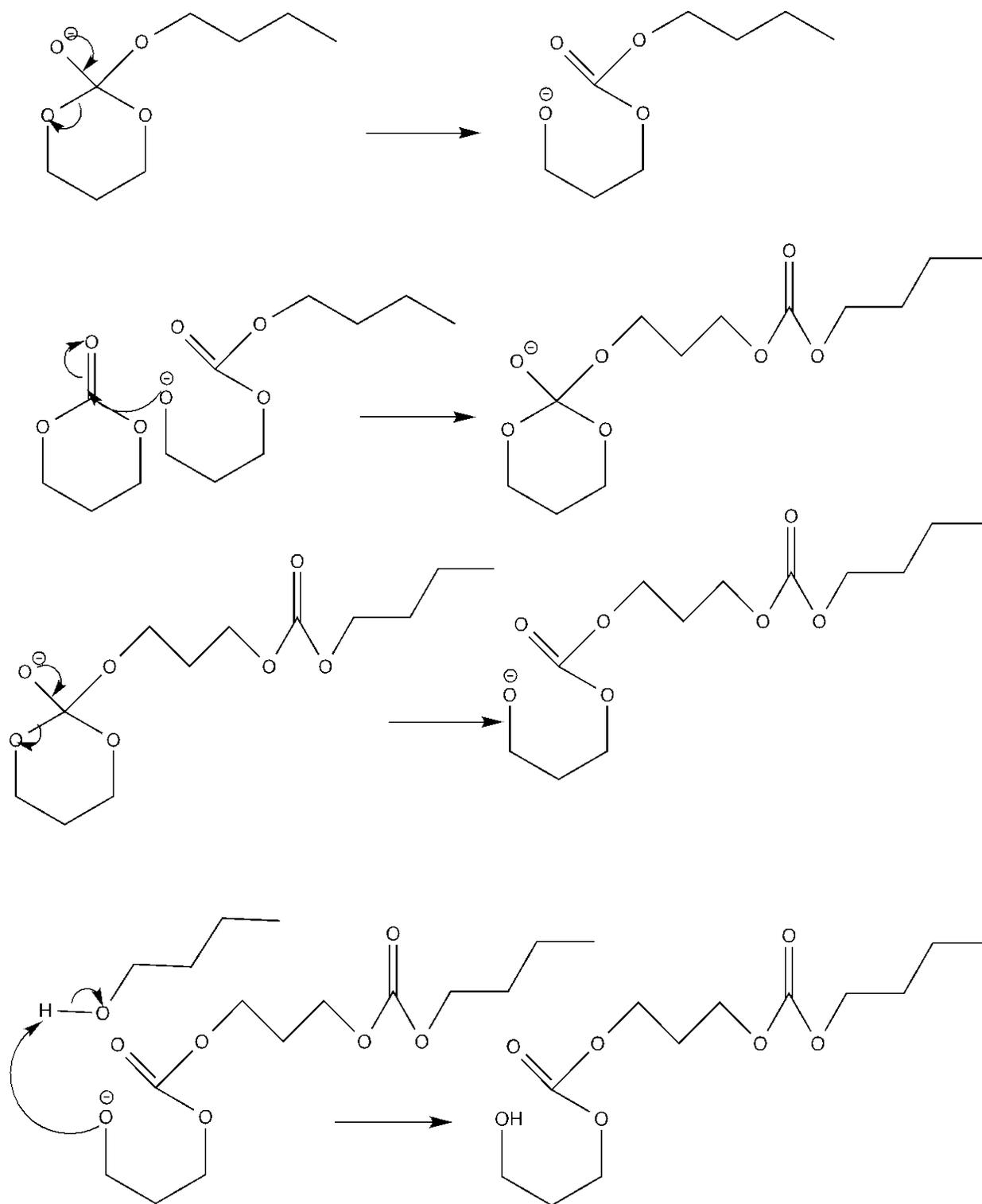
Figure 2. Mechanism for ROP (pages 4 and 5).

ROP is just one of many polymerization methods currently used today. Another such

polymerization technique is Reversible Addition-Fragmentation chain Transfer (RAFT). This

polymerization technique also utilizes green chemistry, utilizing a selection of trithicarbonate

catalysts.[8] These trithiocarbonate catalysts are known as RAFT Agents, as they facilitate the

polymerization process. These compounds can be synthesized in appreciable yield[9]. One such

RAFT Agent, 2-dodecylsulfanylthiocarbonylsulfanyl-2-methylpropionic acid, denoted CTA-2

and used for RAFT diblock copolymer formation, allows for the insertion of a polymer unit on

its carboxylic acid end group (Figure 3 and Figure 4). In addition to the RAFT Agent and

monomer under consideration, a radical initiator such as azobisisobutyronitrile is required for

RAFT polymerization, as well as an appropriate solvent such as 1,4-dioxane and conditions of

elevated temperature.
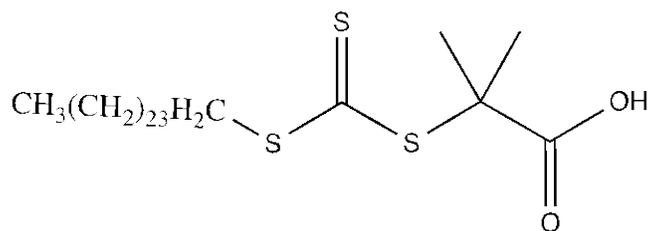
Figure 3. CTA-2 (DMP) RAFT Agent for Diblock Copolymer Synthesis.

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[8] Chiefari, J.; Chong, Y.K.; Ercole, F.; Kristina, J.; Jeffery, J.; Le, T.; Mayadunne, R.; Meijs, G.; Moad, C.; Moad, G.; Rizzardo, E.; Thang, S. "Living Free-Radical Polymerization by Reversible Addition-Fragmentation Chain Transfer: The RAFT Process" *Macromolecules*. **1998**; 31. 5559-5562.

[9] Haraguchi, K.; Kubota, K.; Takada, T.; Mahara, S. "Highly Protein-Resistant Coatings and Suspension Cell Culture Thereon from Amphiphilic Block Copolymers Prepared by RAFT Polymerization" *Biomacromolecules*. **2014**; 15. 1992-2003.
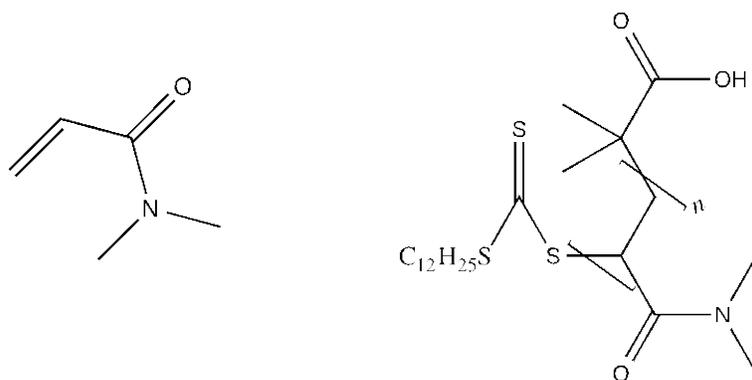
Figure 4. The monomer dimethylacrylamide (DMAA), left, and the polymer

poly(dimethylacrylamide) (pDMAA) within the diblock copolymer RAFT agent.

The mechanism for RAFT polymerization is shown below in Figure 5. RAFT

polymerization begins by decomposition of the radical initiator. In the case of

azobisisobutyronitrile, the initiator decomposes to N_2 gas and two equivalent radical species.

This decomposition is preferable due to the stability of the triple bond obtained from the creation

of N_2, as well as the ability of the tertiary carbon to support the radical. This radical begins to

react with a molecule of monomer, such as dimethylacrylamide, by breaking the pi-bond of the

monomer's double bond, forming a new radical monomer species that is bonded to the initiator

and contains a lone electron (i.e., radical). This radical then reacts with the trithiocarbonate

species of the RAFT Agent, breaking the double bond of thiocarbonyl group to form a new bond

to the sulfur species from the place of the radical electron and placing a radical electron on the

carbon connecting the trithio-species. This placement is stable due to the three adjacent sulfur

atoms' ability to support electrons given their high polarizability. This species eventually forms

an equilibrium with a RAFT Agent that loses one of its end groups, in the case of DMP it is the

end group containing the tertiary carbon due to its ability to support radical formation, and one in

which the end group is retained and the radical monomer-initiator species is lost.[10] Further

reaction takes place with the displaced radical end group, ideally reacting with monomer the

same way the radical initiator had done and forming chains of monomer groups such that a

sufficient polymer radical is created. The radical of this polymer product then reacts with the

trithiocarbonate, displacing the monomer-initiator species and forming the end product

trithiocarbonate polymer shown in Figure 4.

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[10] Lai, J.; Filla, D.; Shea, R. "Functional Polymers from Novel Carboxyl-Terminated
Trithiocarbonates as Highly Efficient RAFT Agents" *Macromolecules.* **2002**; 35. 6754-6756.
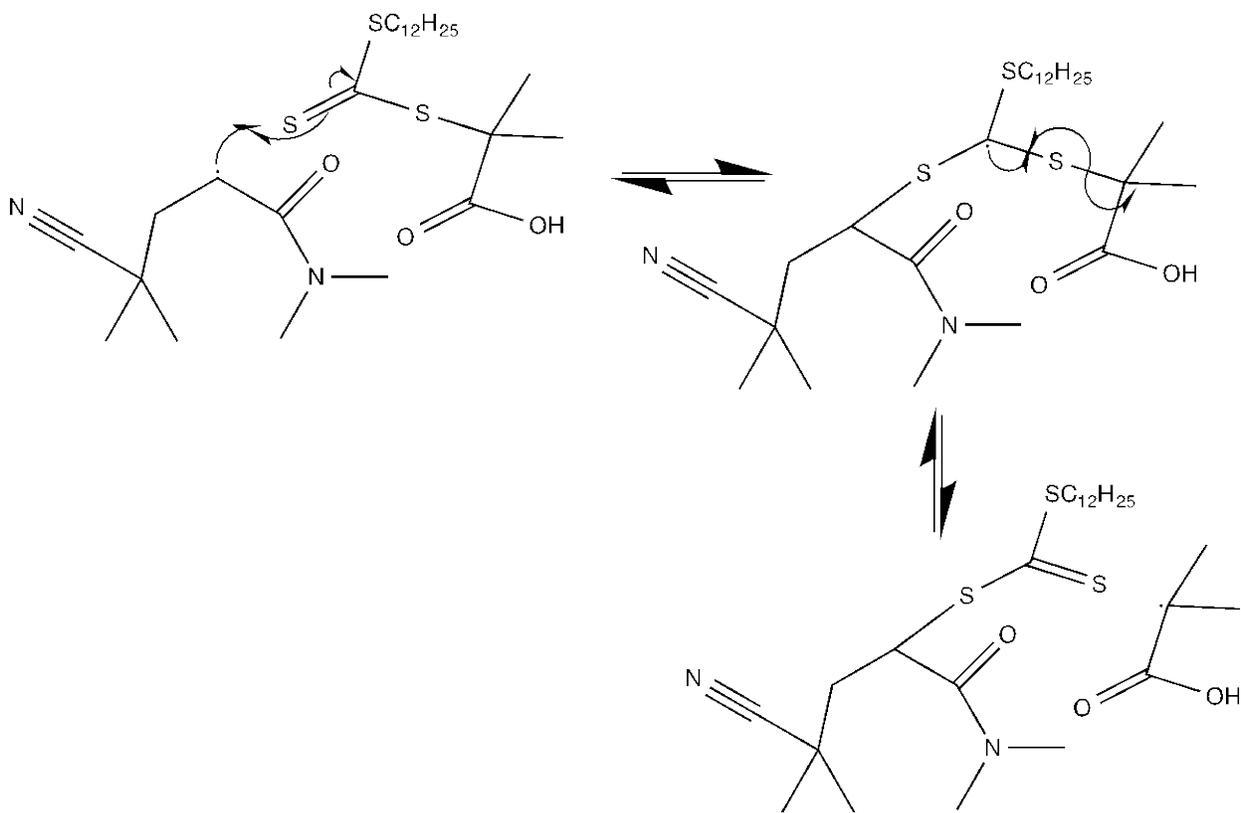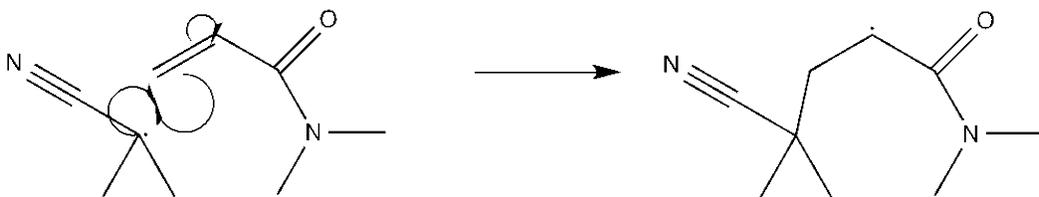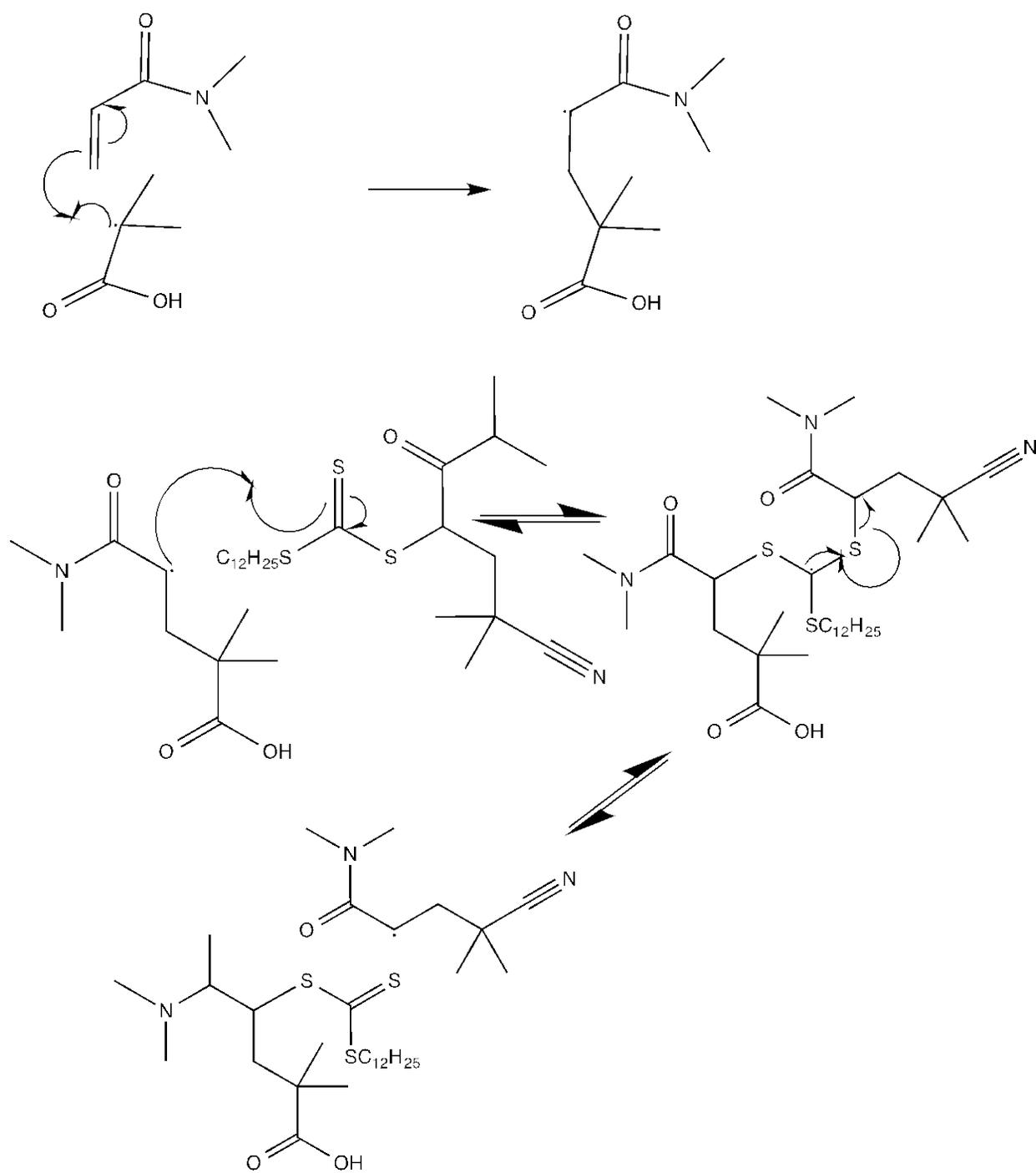
Figure 5. Mechanism for RAFT with DMP as RAFT Agent and DMAA as monomer (pages 8 and 9).

A combination of ROP and RAFT were explored in the following report, to modify the physical properties of the polymer pTMC, specifically its T_g, by incorporating another polymer, pDMAA, or poly(dimethylacrylamide), in a diblock copolymer formation. The goal behind the synthesis of this copolymer is to raise the T_g of pure pTMC, as its current T_g renders it inutile in biomedical applications that require the polymer to withstand higher temperatures and maintain its rigidity.

Experimental Methods

Standard experimental procedures are outlined below, and quantities/molar ratios and yields for all trials are provided in the Results and Discussion section following.

A. Synthesis of pNIPAA
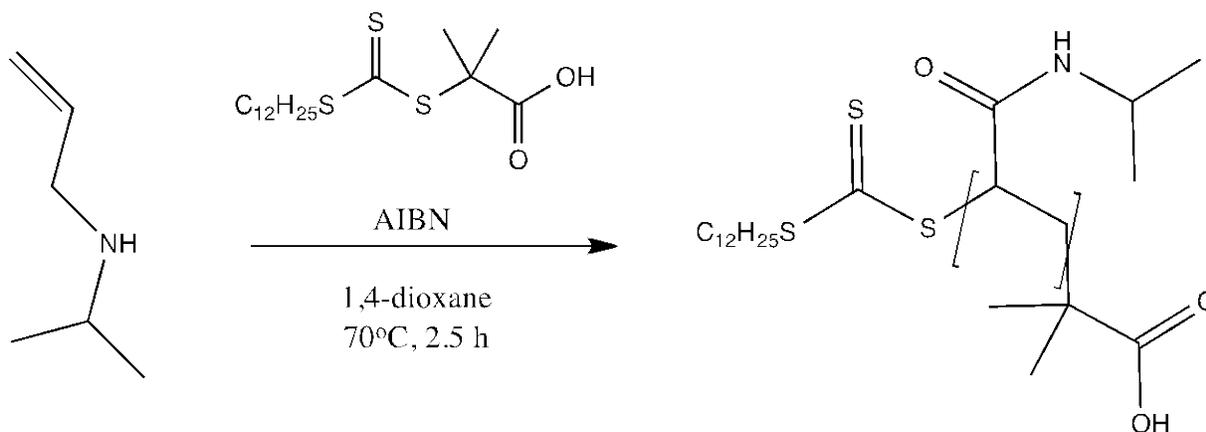
DMP (0.044g, 0.122mmol) and AIBN (0.002g, 0.012mmol) were added to Schlenk tube with magnetic stir bar and plastic septum followed by NIPAAm (0.965g, 8.526mmol). Dried 1,4-dioxane (2.5mL) was added to Schlenk tube and mixture was placed under Argon atmosphere for 20 minutes. Schlenk tube was then placed in preheated oil bath at 70°C. After 2.5 hours reaction ended by submerging Schlenk tube in liquid N_2 bath, allowing the yellow reaction mixture to freeze. The thick yellow oil was allowed to reach room temperature, after which a crude [1]H

NMR in CDCl$_3$ was taken. The oil was dissolved in 5mL THF and precipitated with 130mL Et$_2$O in a liquid N$_2$/acetone bath. Vacuum filtration afforded a yellow powder.

First Route

B. Synthesis of DMP (RAFT Agent)

$$C_{12}H_{25}SH \xrightarrow[\text{acetone}]{\substack{CS_2, CHCl_3, NaOH \\ \text{aliquat 336}}}$$
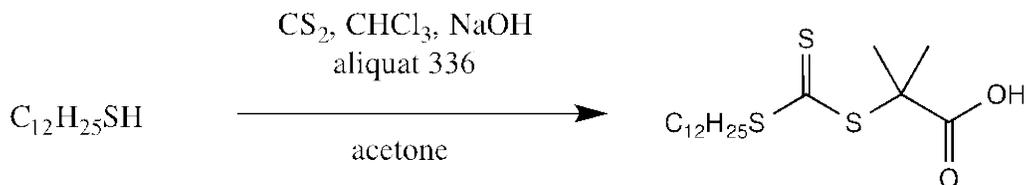
To a 100mL round bottom Schlenk flask with magnetic stir bar and septum was added C$_{12}$H$_{25}$SH (3.767g, 18.6mmol), aliquot 336 (0.323g, 0.8mmol), and acetone (9.58g, 165mmol), with stirring. The reaction was then placed in NaCl/ice/water bath and under Argon atmosphere for 15 minutes. A solution of 50% NaOH (1.677g, 41.9mmol) was then added dropwise to reaction mixture over 5 minutes, forming a white precipitate. After 20 minutes, a solution of CS$_2$ (1.523g, 20mmol) in acetone (2g, 34.4mmol) was added dropwise over 5 minutes. The reaction mixture changed to a white suspension bright yellow and then murky yellow. After 10 minutes, CHCl$_3$ (3.58g, 30mmol) was added neat, followed by dropwise addition of 50% NaOH (8g, 200mmol) over 10 minutes. The reaction was then equipped with Argon balloon, allowed to stir overnight in NaCl/ice/water bath. The following day, 30mL H$_2$O was added to thick red suspension, followed by 5mL concentrated HCl dropwise in a water bath. Argon flowed through reaction mixture until bubbles stopped forming. Once bubbling ended, a red solid was obtained by vacuum filtration. The red solid was taken up in 125mL of 2-propanol to form a suspension. A deep red filtrate was obtained by vacuum filtration, concentrated in vacuo to give a thick

scarlet red paste. Thick scarlet red paste recrystallized from hot n-hexane (20mL). A yellowish

red solid obtained via vacuum filtration.

^{1}H NMR (500MHz, CDCl$_3$): δ 0.88 (t, J = 7 Hz, 3H), 1.26-1.40 (m, 18 H), 1.61-2.17 (m,

8 H), 3.24 (t, J = 7.5 Hz, 1H), 3.36 (t, J = 7.5 Hz, 1H)

C. Synthesis of TMC[5]
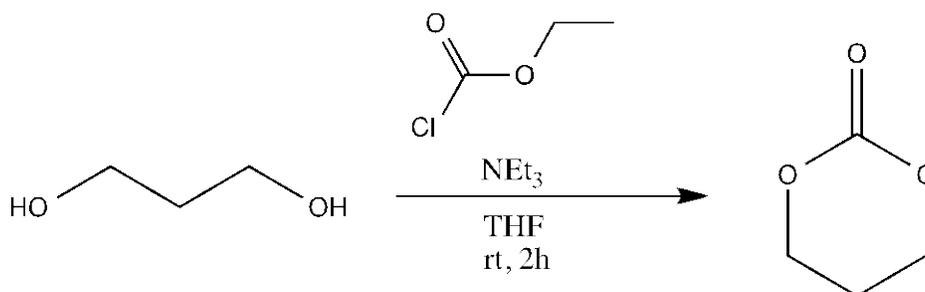
To a 250mL round bottom flask with medium-sized magnetic stir bar and septum was

added 1,3-propanediol (6.711g, 88.2mmol) and ethylchloroformate (19.14g, 176.4mmol) in THF

(100mL). Triethylamine (17.85g, 176.4mmol) in THF (25mL) was added dropwise to the flask

submerged in an ice/water bath, forming a milky white precipitate. The reaction was allowed to

stir at room temperature for 3 hours, after which the reaction mixture was filtered via vacuum

filtration and concentrated in vacuo (rotovaporator) to give orange/brown oil, 10.687g. A white

solid (product) was obtained by flash column chromatography using ethyl acetate/hexanes eluent

(3:1) (visualized with KMnO$_4$ stain) and recrystallized from warm THF (3mL) and Et$_2$O (2mL).

R$_f$ value = 0.4

^{1}H NMR (500MHz, CDCl$_3$): δ 2.11-2.16 (m, 2 H), 4.44 (t, J = 5.5 Hz, 4 H)

D. Synthesis of pTMC
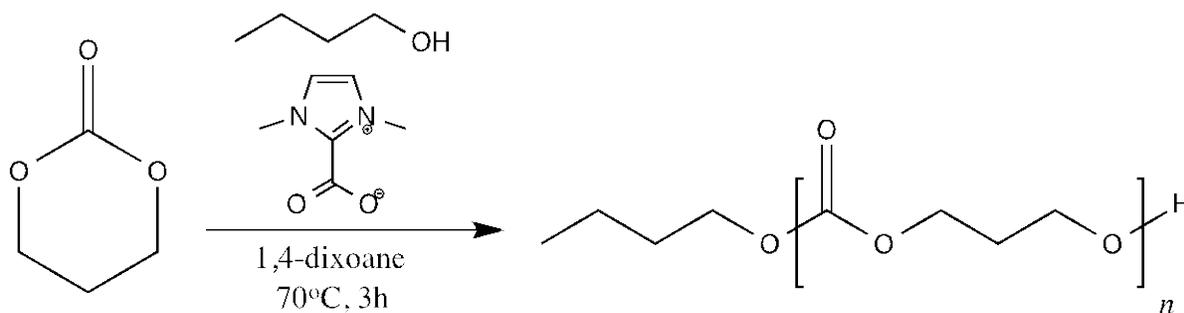
To a flame dried Schlenk tube with thin magnetic stir bar and septum was added TMC (500mg, 4.9mmol) and 1,3-dimethylimidazolium-2-carboxylate (13.7mg, 0.098mmol) under an Argon atmosphere. Dry 1-butanol (7.26g, 0.098mmol) was added followed by dried 1,4-dioxane (5mL, 1M TMC) and the reaction mixture was placed into a preheated oil bath at 70°C. After 3 hours, reaction mixture was concentrated in vacuo (rotovaporator) to give a yellowish oil, after which a crude ^{1}H NMR in CDCl$_3$ was taken. The yellowish oil was dissolved in about 3mL CHCl$_3$ and precipitated with ice cold MeOH. The MeOH was pipetted off and a white powder was obtained after drying in vacuo.

^{1}H NMR (500MHz, CDCl$_3$): δ 1.94 (t, 1H), 4.13 (t, 2.09 H)

E. Esterification of RAFT Agent
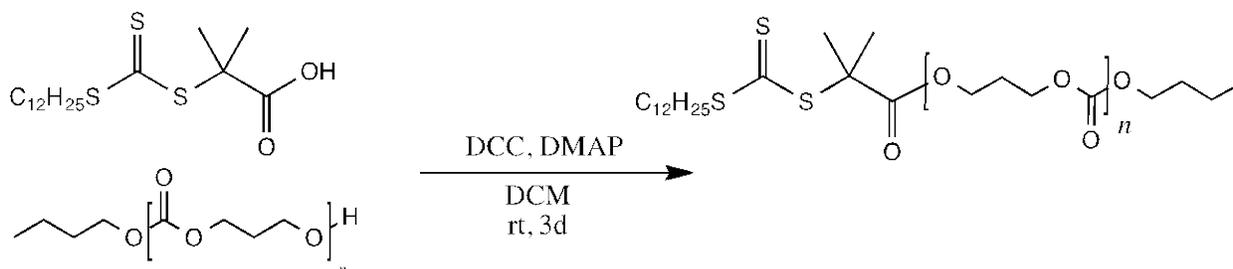
To a 25mL round bottom flask with small magnetic stir bar and septum was added pTMC (500mg, 0.087mmol), DMP (95mg, 0.261mmol), DCC (97mg, 0.261mmol), DMAP (11mg,

38

0.043mmol) and 5mL degassed DCM. The yellow solution was allowed to stir at room temperature for 3 days, after which it was concentrated in vacuo to give a yellow powder (0.788g). Yellow powder dissolved in 3mL $CHCl_3$ and precipitated with ice cold MeOH to give a light yellow powder, 0.414g.

^{1}H NMNR (500MHz, CDCl$_3$): δ 0.88 (t, J = 7 Hz, 3H), 1.26-1.31 (m, 23 H), 2.05 (q, J = 6 Hz, 57 H), 3.35 (t, J = 7 Hz, 1 H), 3.49 (t, J = 3.5 Hz, 1 H), 4.24 (t, J = 6 Hz, 112 H)

F. Synthesis of pDMAA
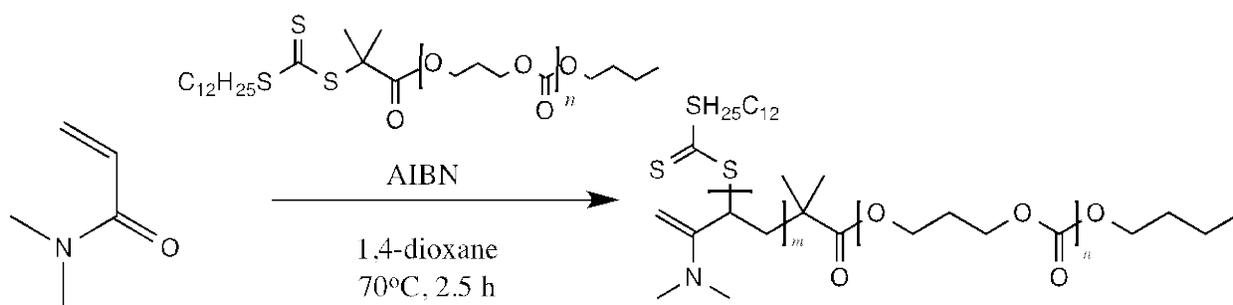
RAFT Agent (399mg, 0.069mmol) [product from E] and AIBN (1.1mg, 0.007mmol) were added to a 50mL rbf with a cylindrical magnetic stir bar and septum, followed by DMAAm (482mg, 4.86mmol) and 1,4-dioxane (14mL, 5mM RAFT Agent). The light yellow solution was degassed with Ar and then placed in preheated oil bath at 70°C. After 3 hours, reaction mixture was removed from the oil bath and concentrated in vacuo to give a yellow oil, 0.87g, after which a crude ^{1}H NMR was taken. The yellow oil was redissolved in $CHCl_3$ and precipitated with ice cold MeOH, filtered and dried under vacuum to give a white/tan powder.

^{1}H NMR (500MHz, CDCl$_3$): δ 2.04 (t, 1H), 2.90-3.08 (m, 0.44 H), 4.23 (t, 2H)

Second Route

G. Synthesis of RAFT Agent with ROP functionality[11]
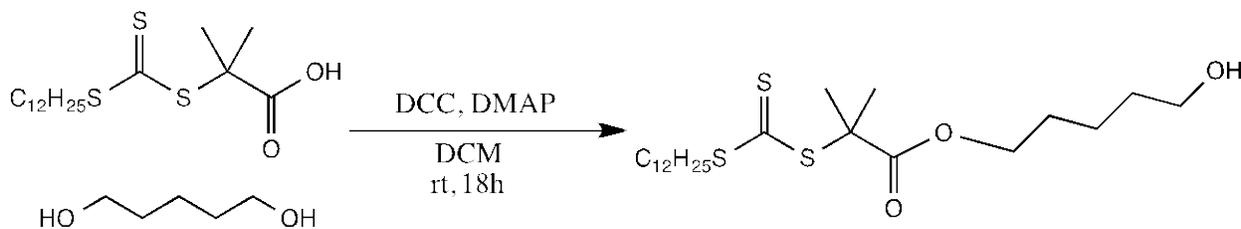
To a 50mL round bottom flask with small magnetic stir bar and septum was added DMP (75mg, 0.206mmol), DMAP (10.1mg, 0.041mmol), 1,5-pentanediol (107mg, 1.029mmol), and THF (3mL) to give yellow/orange solution. A solution of DCC (8.5mg, 0.041mmol) in THF (2mL) was added dropwise to reaction mixture over 5 minutes. The yellow/orange solution was allowed to stir at room temperature overnight. Vacuum filtration the following day afforded a yellow filtrate, which was concentrated in vacuo to give yellow oil, 0.496g. Yellow solid (product) was obtained via flash column chromatography with ethyl acetate/hexanes eluent (2:1) (visualized with $KMnO_4$ stain).

R_f value = 0.69

^{1}H NMR (500MHz, CDCl$_3$): δ 0.88 (t, J = 6.5 Hz, 3 H), 1.26 (s, 26 H), 1.43-2.27 (m, 11 H), 3.28 (t, J = 7.5 Hz, 1 H), 3.36 (t, J = 7.5 Hz, 1 H)

[11] Li, A.; Leuhmann, H.; Sun, G.; Samarajeewa, S.; Zou, J.; Zhang, S.; Zhang, F.; Welch, M.; Liu, Y.; Wooley, K. "Synthesis and *In Vivo* Pharmacokinetic Evaluation of Degradable Shell Cross-Linked Polymer Nanoparticles with Poly(carboxybetaine) *versus* Poly-(ethylene glycol) Surface-Grafted Coatings" *ACS Nano*. **2012**; 6(10). 8970-8982.

H. Simultaneous ROP/RAFT
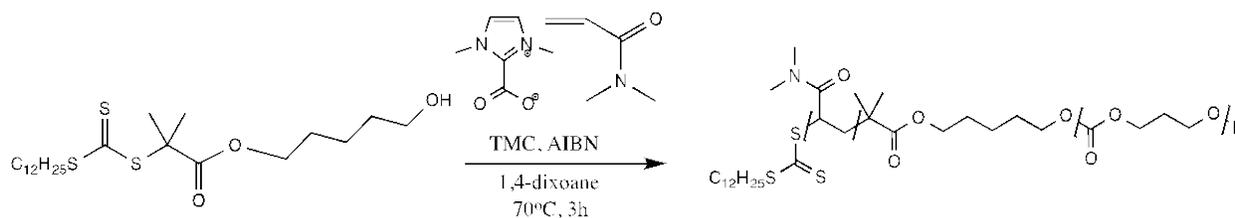
To a 100 mL round bottom flask with stir bar and septum was added TMC (1.3g, 13.1mmol), AIBN (2.1mg, 0.013mmol), and ROP catalyst (18mg, 0.131mmol). A solution of RAFT Agent with ROP functionality [product from G] (59mg, 0.131mmol) in 1,4-dioxane (10mL) was prepared and added to the reaction mixture, followed by DMAA (909mg, 9.17mmol) and 3mL dioxane. The light yellow solution was submerged in preheated oil bath at 70°C. After 3 hours, the yellow solution with white precipitate was allowed to cool to room temperature and concentrated in vacuo to give yellow oil, 2.840g, after which a crude ^{1}H NMR in CDCl$_3$ was taken. The yellow oil dissolved in 3mL CHCl$_3$ and precipitated in ice cold MeOH, affording tan powder (product) after removal of MeOH.

^{1}H NMR (500MHz, CDCl$_3$): δ 2.05 (quintet, 1H), 3.05 (d, 0.12H), 4.22-4.25 (m, 2.01H)

Results and Discussion

From Experimental, part A, poly-N-isopropylacrylamide was synthesized from the monomer N-isopropylacrylamide by a RAFT reaction, in which DMP was used as the RAFT Agent and AIBN was used as a radical initiator. The reaction took place in 1,4-dioxane at 70°C for 2.5 hours under Ar. These conditions had been optimized previously. These conditions worked reasonably well as a 98% conversion was obtained. This conversion was determined from a crude ^{1}H NMR spectrum, comparing proton peaks found in the monomer to those found in the polymer. Specifically the peaks for the vinylic protons in the monomer at 6.2ppm, 6.0ppm,

and 5.6ppm were used to quantify how much of the monomer was left in the reaction mixture, and the peak at 4.0ppm was used to quantify how much of the polymer was formed. Conversion was calculated as follows

$$Conversion = \frac{Polymer}{Polymer + Monomer} \times 100 \qquad [2]$$

where Polymer denotes the integration for a specific polymer peak in the crude ^{1}H NMR and Monomer denotes the integration for a specific monomer peak in the crude ^{1}H NMR. The notebook code for this reaction was AAB001. A molecular weight and polydispersity were not obtained for the product of this reaction as it was a trial run.

First Route

  From Experimental, part B, DMP was synthesized from dodecanthiol, aliquot 336, chloroform, NaOH, carbon disulfide, and acetone. Aliquot 336 was used as an oxidizing agent for carbon disulfide, to form a trithiocarbonate complex with two end groups. The first end group was attributed to dodecanthiol, forming a twelve carbon chain terminating at one of the sulfur atoms in the triothicarbonate complex. The other end group is a methyl propionic acid formed from acetone. Chloroform allowed a ketoform reaction to take place and prepare the trithiocarbonate. No yield can be reported because the reaction was done twice and the remaining contents of each were taken onto recrystallization. The first time this reaction was performed, the reaction exploded in the hood overnight, leaving some reaction mixture left behind in the flask. The second time this reaction was performed, a balloon was attached to the reaction flask for the overnight portion of this experiment. This prevented an explosion from occurring. Therefore it was decided that the reaction mixtures from both attempts would be worked up together to avoid repeating the time-consuming and costly workup, not allowing a yield to be recorded. The proton

peaks provided in Experimental, part B, appropriately account for protons found in DMP as described in literature.[9] The notebook codes for these two reactions were AAB003 and AAB004.

From Experimental, part C, TMC was synthesized from 1,3-propanediol, ethylchloroformate, and triethylamine in THF under Ar. The column chromatography required to purify the product proved difficult because of its large scale. This reaction was carried out twice, scaling up the reaction the second time. The results are listed below in Table 1.

Table 1. Reagents listed for the synthesis of TMC, with Diol representing 1,3-propandiol, ECF representing ethyl chloroformate, and TEA representing triethylamine, with their corresponding molar quantities provided in mmol for the two attempts of this reaction, in the molar ratio of diol:ECF:TEA = 1:2:2. Each trial provided a yield, listed appropriately.

	Code	Diol	ECF	TEA	Yield
Trial 1	AAB005	44.1mmol	88.2mmol	88.2mmol	45%
Trial 2	AAB008	88.2mmol	176mmol	176mmol	48%

Considering that the reported yield for this reaction was 60%, the yields reported in Table 1 are acceptable. The proton peaks provided in Experimental, part C, appropriately account for protons found in TMC as determined in literature.

From Experimental, part D, poly(trimethylenecarboante) was synthesized from TMC, 1,3-dimethylimidazolium-2-carboxylate, and 1-butanol in 1,4-dioxane at 70°C for 3 hours under Ar. These reaction conditions were previously optimized. It was critical to remove all water from this reaction, hence the reaction was carried out under Ar and the 1-butanol used needed to be dried. The reason water could not be present in this reaction was to avoid side reactions, taking

away from the yield and formation of the polymer, and to prevent premature hydrolysis. This reaction proceeded through a standard ring-opening polymerization. The product, generally a clear gel-like solid, was dissolved in chloroform and precipitated in ice cold MeOH. This mixture was allowed to sit overnight, and then the MeOH was pulled off the top, leaving the product at the bottom to be dried under vacuum. The molar equivalents and conversions of this reaction, repeated three times, are listed in Table 2 below.

Table 2. The reagents used to carry out the polymerization of trimethylene carbonate are listed as carbene representing 1,3-dimethylimidazolium-2-carboxylate, monomer representing trimethylenecarboante, and initiator representing 1-butanol, in a molar equivalent ratio of carbene:monomer:initiator = 1:100:1 for trials 1 and 2 and a ratio of 1:50:1 for trial 3. The conversions provided for each of the three trials are listed appropriately and were determined by ^{1}H NMR. Corresponding notebook codes are listed for each trial.

	Code	Carbene	Monomer	Initiator	Conversion
Trial 1	AAB002	3mmol	300mmol	3mmol	99%
Trial 2	AAB010	9.8mmol	980mmol	9.8mmol	95%
Trial 3	AAB012	4.9mmol	490mmol	4.9mmol	77%

The conversions were determined by ^{1}H NMR, and required analysis of peaks belonging to the polymer and those belonging to the monomer. Using [2], easily detectable peaks belonging to polymer protons were found at near 2.0ppm and 4.1ppm, where the protons at 2.0ppm represented the set of protons in the center of the three-carbon chain of the molecule and the protons at 4.1ppm represented two sets of protons per polymer unit, belonging to the two carbons

attached the oxygen atoms. These peaks were compared to peaks for the monomer found further downfield, at 2.3ppm and 4.4ppm, respectively. The integrations obtained for these peaks were used in [2] to determine conversion. It was convenient to have two different methods for determining the conversions as trace impurities may occur at different areas of the NMR spectrum, invalidating the conversions obtained. This did not ever prove to be the case for the three trials for which this reaction was performed.

As can be seen from Table 2, Trial 1 involved a molar scale at 3mmol of carbene/initiator and provided an excellent conversion of 99%. The data obtained from analysis by Size Exclusion Chromatography were a polydispersity of this polymer of 1.5 and a number-averaged molecular weight of 8000g/mol. Trial 2 involved a larger scale than Trial 1, at 9.8mmol of carbene/initiator, and provided a conversion of 95%, which is approximately the same conversion. The data obtained from analysis by Size Exclusion Chromatography provided a polydispersity of 1.2 and a number average molecular weight of 5800 g/mol. Trial 3 involved a change in the molar equivalents of reagents used, with the equivalents of monomer changed from 100 to 50, done at a 4.9mmol scale of carbene/initiator. This provided a conversion of 77%, significantly less than that of the previous two trials. This suggests that a molar equivalency of 100 instead of 50 is more effective under these reaction conditions. The polydispersity of the polymer obtained from the third trial was 1.5 with a number average molecular weight of 9400g/mol as obtained by Size Exclusion Chromatography analysis.

As can be evidenced from this data, this specific ring opening polymerization reaction affords a low polydispersity under the provided reaction conditions, which means the reaction conditions have been optimized effectively to obtain practically equivalent chain lengths of polymer. The conversions of this reaction stay constant at a 100 molar equivalent of monomer

but fell at a 50 molar equivalent of monomer. This suggests that the reaction itself works well in terms of consistent chain-formation, but that the rate at which this proceeds and the quantity at which those polymer chains form from the starting material is more dependent on molar equivalencies.

From Experimental, part E, esterification of the RAFT Agent, DMAP, containing a carboxylic acid group, with polytrimethylenecarbonate, containing an alcohol group, proceeded under conditions of standard esterification of carboxylic acids, that is in the presence of N,N'-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in dried dichloromethane. The reaction progressed for 3 days at room temperature. This reaction was attempted three times, with the corresponding molar amounts of pTMC used reported along with the yields in Table 3 below.

Table 3. The molar amounts of pTMC used in the esterification of the RAFT Agent, DMP, are reported in the table below for the three trials with corresponding yields. The molar ratio of these reactions was alcohol:DMP:DCC:DMAP = 1:3:3:0.5. Notebook codes are listed for their corresponding trials.

	Code	pTMC	Yield
Trial 1	AAB007	0.012mmol	18%
Trial 2	AAB011	0.087mmol	78%
Trial 3	AAB016	0.021 mmol	86%

As can be seen from the data presented in Table 3, the yields progressively improved as the reaction was repeated. This is partially owed to familiarity with the reaction conditions. For

trial 1, the solvent had completely evaporated twice during the 3 day period over which this reaction took place. This is likely owed to the small scale at which this reaction was performed, and it required constant attention to run effectively. For the second trial, the solvent had never evaporated despite the increased awareness of such occurring. This is likely due to the increase in quantity of reagents used, and thus the increase in solvent that afforded evaporation but never to the point of complete dryness over the 3 days. The solvent also evaporated completely for the third trial. The yields were obtained after removing the remaining DCM in the reaction by rotoevaporation, dissolving the obtained product (typically a yellow oil) in chloroform and precipitating it in ice cold MeOH. The product collected after this precipitation was dried under vacuum and the yield obtained appropriately. By ^{1}H NMR, these products appeared clean enough to consider this yield appropriate for the reaction, with trace impurities present.

Part F of Experimental is the final step of the first route toward the diblock copolymer, and this involved the RAFT polymerization of dimethylacrylamide (DMAA) with the product from part E, which was the RAFT Agent containing the polytrimethylenecarbonate group, and azobisisobutryonitrile (AIBN) in 1,4-dioxane for 2.5 hours under Ar. This reaction was repeated twice, as the third trial is still in progress and may not be finished by the time this report is completed because of complications with lab space and time. The molar equivalents with the corresponding conversion of the monomer to polymer are reported in Table 4.

Table 4. The molar quantity of dimethylacrylamide, represented as DMAA, in the RAFT polymerization of this compound with the RAFT Agent containing the pTMC moiety are reported below, with the corresponding conversions of DMAA to pDMAA or poly(dimethylacrylamide) as determined by ^{1}H NMR.

	Code	DMAA	Conversion
Trial 1	AAB009	0.001mmol	50%
Trial 2	AAB015	0.069mmol	77%

The conversions were calculated from [2] and using proton peaks known to belong to the

polymer, pDMAA, and the monomer, DMAA. For the polymer, peaks at approximately 2.9ppm

and 3.1ppm are expected to be present as reported in previous literature.[12] For the monomer, the

peaks belonging to the vinylic protons of the acrylic group are used for comparison as these

protons would not be present at the same locations in the proton NMR spectrum due to the loss

of the double bond that occurs during polymerization. These monomer peaks were found to

occur at 5.6ppm, 6.2ppm, and 6.5ppm in the crude ^{1}H NMR. The equation presented in [2] was

therefore used with the appropriate peak integrations to obtain the conversions listed in Table 4,

of 50% for trial 1 and 77% for trial 2.

The reaction is believed to have run successfully because the diblock copolymer appears

to be present from analysis of the ^{1}H NMR spectra obtained for each of these products. The

RAFT Agent appears to be present from the proton groups found at 0.88ppm and the multiplets

found between 1.2ppm and 2.2ppm, although the complex peak structures in this region could

also be due to signals from protons in the long alkyl chains of the pTMC unit. Additionally the

presence of peaks near 3.3ppm suggests the presence of the RAFT Agent. The peaks from the

pTMC unit are easily found in the NMR of these products, where large peaks are found near

2.0ppm (multiplet) and 4.1ppm (triplet). Additionally the pDMAA peaks are found in the NMR

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[12] Gia, H.; McGrath, J. "High Resolution NMR Spectra of Poly N,N-Dimethylacrylamide in CDCl$_3$ Solution" *Polymer Bulletin*. **1980**; 2. 837-840.

spectra, as described for the conversion analysis. The monomer groups are found in significantly higher quantities in the crude ^{1}H NMR spectrum than in the spectrum taken after work up, however the monomer is still detectable as trace impurity in the spectrum after work up signifying that the monomer is not being removed successfully enough through the work up conditions. Repeating of the work up may ameliorate this problem. The presence of these groups by NMR analysis is sufficient to indicate only their presence, but does not necessarily preclude that these groups are all connected in one molecule and as one product. They could be separate impurities found in what is believed to be the product. Additional characterization would need to be conducted to conclude that this reaction worked successfully and the diblock copolymer was obtained.

Additional reasons to doubt the success of this reaction come from the data provided from Size Exclusion Chromatography analysis. For Trial 1 a polydispersity of 8.8 is reported with a number average molecular weight of 76000g/mol. While the molecular weight appears sufficient in size for a molecule containing two polymer groups, the polydispersity is so high as to suggest the polymer obtained is not even remotely close to ideal in chain length. For Trial 2, a polydispersity of 1.5 and a number average molecular weight of 6000g/mol is obtained. While the polydispersity appears to be sufficient in suggesting that the chain lengths of the polymer groups present in the sample tested are approximately the same in size, the molecular weight appears to be too low for a realistic representation of a diblock copolymer.

This analysis concludes the Results and Discussion section of the first synthesis route taken toward obtaining the diblock copolymer containing pTMCC and pDMAA blocks. The success of this reaction is unclear and certainly requires further analysis.

Second Route

From Experimental, part G, a RAFT Agent with a free alcohol group was synthesized from DMP, 1,5-pentanediol, N,N'-dicyclohexylcarbodiimide (DCC), and 4-dimethylaminopyridine (DMAP), as reported in Li and Leuhmann. These reaction conditions again represent standard esterification conditions of a carboxylic acid, the carboxylic acid being the RAFT Agent, DMP, with the alcohol chosen as 1,5-pentandiol to afford a free alcohol group after esterification. This reaction ran for 18 hours and required column chromatography to purify the product, which was a yellow solid. The yield for this reaction was 63% on a 0.206mmol scale, with the ratio of DMP:diol:DMAP:DCC = 5:25:1:1 at a concentration of 41 mM DMP in THF. By ^{1}H NMR it was believed that the product had been successfully synthesized, where the triplet at 0.88ppm, the singlet at 1.26ppm, and the triplets at 3.28ppm and 3.36ppm indicate the presence of the RAFT Agent, and the multiplet from 1.43ppm to 2.27ppm indicates the presence of both the RAFT Agent and the alkyl chain from the coupling with the diol.

When purifying, DMP was not found in the reaction mixture by TLC in $KMnO_4$ stain, which indicates the reaction went to completion. The column separation was needed to separate the RAFT Agent with the alcohol group from the diol starting material. By TLC analysis, the product and starting material were sufficiently far apart in the eluent system reported in Li and Leuhmann to afford easy separation. The notebook code for this reaction was AAB013.

From Experimental, part H, the product from G, the RAFT Agent containing the alcohol group, was taken through two simultaneous polymerizations, one being a ring opening polymerization of TMC with the alcohol group on the RAFT Agent in the presence of 1,3-dimethylimidazolium-2-carboxylate in 1,4-dioxane at 70°C, and the other being a RAFT polymerization of DMAA with the trithiocarbonate group in the presence of

azobisisobutyronitrile in the same solvent system and reaction temperature. This reaction was the combination of the two polymerizations done separately and repeatedly in the first route, although certain care was needed to perform this reaction under Ar environment given that a large amount of reagents were added to the flask and this proved difficult to do successfully under Ar. The time was chosen to be 3 hours for reaction completion. The molar equivalents used for this reaction were alcohol:DMAA:TMC:AIBN:carbene = 1:70:100:0.1:1, and were simply the molar equivalents used in the previous reactions of these polymerizations carried out separately.

Conversions of each monomer were determined by crude ^{1}H NMR as done in the experiments discussed in the First Route. The peaks at 3.0ppm were used to represent the methyl protons present in the DMAA polymer and the peaks at 5.6ppm, 6.2ppm and 6.5ppm were used to represent the vinylic protons present in the DMAA monomer. Using the conversion equation provided in [2], the conversion of DMAA to pDMAA was calculated to be 83%.

The peak at 4.2ppm in the crude ^{1}H NMR was used to represent the protons of the ether-like linkages in the TMC polymer and the peak at 4.4ppm was used to represent the protons of the same carbon in the TMC monomer. With those integrations used in [2], the conversion of TMC to pTMC was calculated to be 96%. These conversions suggest that the reaction worked well under these conditions for TMC but not as well for DMAA. It should be noted that the amount of solvent used in the reaction was chosen to be 1M of TMC in 1,4-dioxane. Under such conditions, perhaps the reaction favored ROP and may explain the discrepancy in conversions between the two reactions. DMAA may also have been slower to react than TMC.

Analysis through Size Exclusion Chromatography provided a number average molecular weight of 1600g/mol and a polydispersity of 1.3. This analysis suggests that the diblock

copolymer may not have been obtained as product, as the number average molecular weight is too low to represent a diblock copolymer. The polydispersity obtained suggests that the oligomer that was obtained was synthesized in satisfactorily equivalent lengths. The notebook code for this reaction was AAB014.

Additional analysis through ^{1}H NMR of the product after work up indicates the presence of most functional groups. Peaks at 0.84ppm and 0.88ppm could belong to RAFT molecules either in a larger molecule or unreacted and remaining after workup. The peaks at 1.92ppm and 2.05ppm may be representative of alkyl chains or pTMC, respectively, found in the synthesized molecule. The peak at 3.74ppm and 3.78ppm may also belong to RAFT agent proton signals shifted downfield from where they are usually expected to appear. The peaks from 4.22-4.24ppm and 4.30ppm belong to pTMC. There is a notable lack of pDMAA peaks, except for broad peaks around 3.0ppm which could represent pDMAA but which are significantly smaller than those observed in the crude ^{1}H NMR.

Therefore it is likely that pDMAA did not form in great quantities or at all, or formed separately from the product due to the absence of its peaks after work up.

Thus for the second route, the synthesis of the diblock copolymer appears to have been unsuccessful but certainly warrants additional trials and attempts to more decidedly conclude this end result.

The data provided from ^{1}H NMR spectra and SEC of the diblock copolymer products obtained from the two routes described in this report suggest that the diblock copolymer may have been obtained because the functional groups can be found in the NMR spectra and the number average molecular weight increased from the first polymer (pTMC) to the synthesis of the diblock copolymer (pTMC and pDMAA). Data from these methods is inconclusive toward

the synthesis of the desired product, however, as NMR supports the presence of proper

functional groups but does not reveal their connectivity, and the number average molecular

weights provided by SEC of some of the synthesized material does not appear to have increased

substantially enough to have obtained the diblock copolymer. Additional testing, such as Mass

Spectrometry, is required to confirm the success of either route toward the synthesis of a diblock

copolymer containing pTMC and pDMAA groups.

Conclusion

The synthesis of a diblock copolymer containing pTMC and pDMAA blocks was

attempted in two different routes. The success of each route is inconclusive from the data

provided by analytical techniques such as ^{1}H NMR and SEC, allowing for neither a complete

confirmation nor rejection of the successful synthesis of the desired product. The synthesis of

pTMC was successfully scaled up to an approximate 10 mmol scale and provided a conversion

of 95% determined by ^{1}H NMR. For future experimentation, the simultaneous ROP/RAFT

polymerization should be repeated with 0.5 mM of DMAA in 1,4-dioxane, repeating the

conditions for RAFT polymerization, as the concentration for this reaction was only carried out

in conditions that were used for ROP.

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