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Polyurethane research for applications in the field of dentistry: Limiting side reactions in monomer development and synthesizing N-capped polymenthide

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Polyurethane research for applications in the field of dentistry: Limiting side reactions in monomer development and synthesizing N-capped polymenthide

An Honors Thesis

College of St. Benedict/St. John's University

In Partial Fulfillment
of the Requirements for All College Honors

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Advisor: Dr. Chris Schaller
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Abstract

Modern dentistry has found uses for polyurethanes in both dental arch models and removable dental appliances. In an attempt to make polyurethanes from renewable resources, both naturally derived menthone and dihydrocarvone were oxidized in order to form menthide and dihydrocarvide, respectively. The resulting ester, if copolymerized could be modified to form a polyuria; however, dihydrocarvide synthesis was complicated by epoxidation. Different reaction environments with varying salts showed no positive effect on limiting epoxide products. A homopolymerization of menthide resulted in a polymenthide chain that was reacted in the presence of N,N'-Dicyclohexylcarbodiimide (DCC) in order to form an N-capped polymenthide chain. This N-capped polymenthide can then be reacted with diisocyanate in order to form a PU.

Introduction

Polyurethanes (PUs) were discovered in the year 1937 by Otto Bayer's laboratory as they were seeking out an alternative source to rubber.[1] Now, in 2015, PUs have been incorporated into consumer goods. They are in toys, mattresses, biomedical equipment, hoses, shoes, etc.[2,3,4,5] PUs have a wide array of applications because of their strong, yet flexible qualities.[4]

PUs consist of both hard and soft segments. The hard segment is due to the functional groups that have the ability to hydrogen bond (Fig. 1.1). The hydrogen bonding makes the structure rigid and unable to undergo conformational changes. These functional groups can be an amide, urea, or ester-amide group.[5] The soft segment is due to the polymenthide chains. The repeating monomers are flexible and do have the ability to undergo conformational changes.

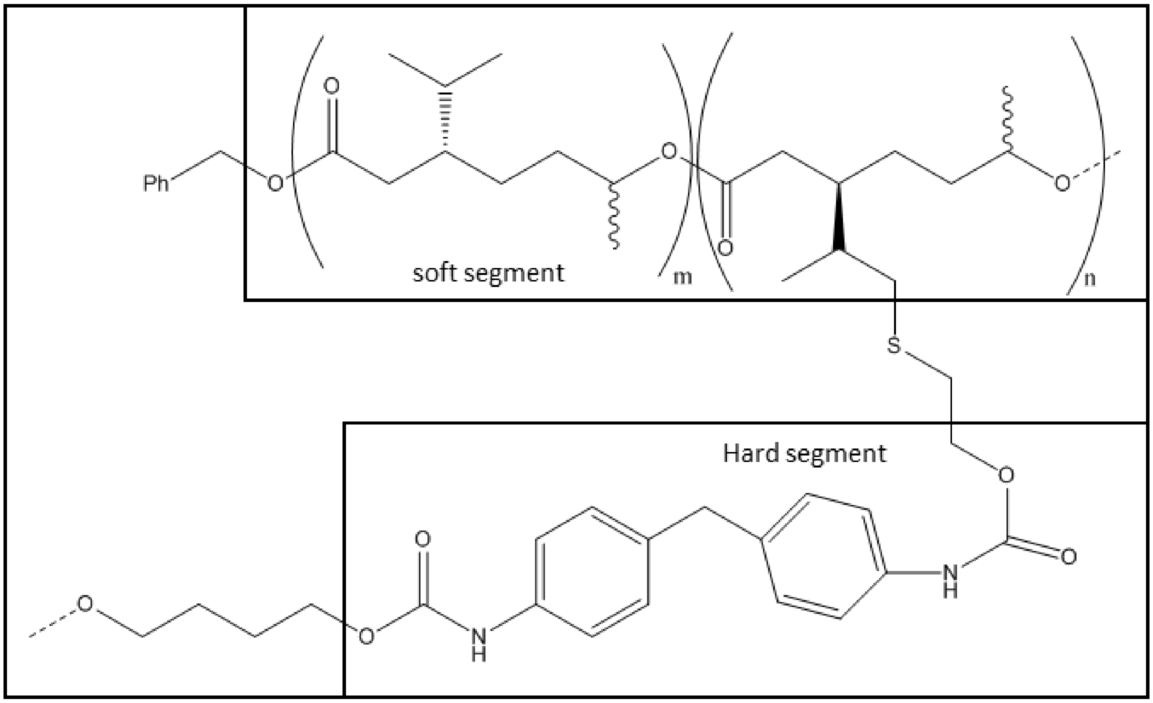

Fig. 1.1. Soft and hard segments of a PU.

PUs are rapidly making their way into the medical field and for good reasons. PUs show histocompatibility, low toxicity, blood compatibility, and better biodegradability.[6] Their ability to have different properties allows them to be used in medical applications that need both strength and flexibility. These important properties mimic body tissues. Similarly tissues are measured by their elasticity and PUs can be too.[7] Tissues and PUs both show cross-linking and force resistance which is beneficial for PUs biocompatibility. In diseases, tissues' properties are compromised and for restorative purposes PUs are being integrated into artificial hearts.[6,7] By manipulating the ratio of hard to soft segments numerous PUs with different properties can be achieved. Their ability to be molded also makes them extremely useful for biomedical equipment. In the field of dentistry PUs are being tested as replacements for previous gypsum-based arch models that are used to model the position of the teeth in a patient.[8] They are also the material used for removable dental aligner restorative treatments, a substitute for braces.[9]

Dental models are necessary for most restorative work, such as crowns and bridges.[10] Negative impressions are taken of a patient's mouth and then filled with some sort of casting material. A giant stride was made in 1995 when the impressions could be pinned together and the casting material could be poured in a single pour.[10] It was later suggested in 2007 that gypsum, calcium sulfate dihydrate, was the casting material of choice. Mixing gypsum with water would limit the inaccuracies of the casting pour.[11] However, gypsum is sensitive to degradation thus presenting issues with the gypsum models, also they have other downfalls of storage and mass.[8] PUs are tested as substitutes for these gypsum-based arch models. The strong yet flexible properties of PUs present them as an alternative dental arch model.[8]

PU dental arch models are made by 3D subtractive rapid prototyping, a technique that starts with more material than the final product and uses a digital scanner to make the impression. The precision and accuracy of the PU models was acceptable.[8,12] This improvement in dental arch models allows less plaster to be used and a more resilient dental arch model to be made.

PUs are also used as removable dental aligners, like the commonly known Invisalign, among others. Invisalign can be a replacement for fixed restorative treatment, such as braces and wires.[9] Fixed aligners have both hygienic and aesthetic downfalls. They provide a place for plaque to build up, and some patients needing orthodontic treatment prefer not to have bulky fixed aligners.[9,13] The biocompatibility of PUs is essential for an aligner, in order to not irritate tissues in the mouth.[14] Despite the advantages, there are disadvantages as well. Treatment can only start when all permanent teeth are present, and the success is up to the patient as far as commitment to wearing the aligners.[13]

By using both PU dental arch models and removable aligners, dentistry has already found uses for PUs. By synthesizing PUs from renewable resources, dentistry has the ability to become a more sustainable field.

Polyurethanes contribute to petroleum-based waste, a vital reason to develop a new synthesis for these valuable polymers.[15] The reaction of 1,4-butanediol, polyol, and diisocyanate yields a PU.

The goal of the first chapter of this research was to produce menthide and dihydrocarvide with minimal epoxide product in the dihydrocarvide reaction. Epoxide product is when the double bond of dihydrocarvide is involved in the reaction with oxone. Based on previous literature,[2] menthide is synthesized from menthone, while dihydrocarvide is synthesized from carvone. Both menthone and carvone are naturally occurring compounds making the synthesis of the polyol a greener reaction. The epoxidation would be limited by varying the salts added to the reaction. Salts have the ability to change the polarity within the reaction.

In the second chapter of this project, the telechelic polymenthide (PM) was synthesized from menthide in a homopolymerization.[16] PM was then reacted with lysine to convert PM into a polyol with one reactive nitrogen group on each end.[17] In further reactions, PM could react with an isocyanate in order to form a PU. Although that experiment was not reached in this research.

Results and Discussion

General: Renewable Polymers

Emphasis on synthesizing PUs from renewable resources has found its way into research. Vegetable oils, which are triacylglycerols, are naturally occurring materials that have been used to form polymers.[18] They have favorable qualities, such as their level of unsaturation. The degree of unsaturation, double bond availability, allows polymerization to occur when exposed to heat.[18] Research on synthesizing a polyol with hydroxyl end groups from vegetable oils has also been explored considering the high demand for PUs throughout the world.[18] Vegetable oil-derived diisocyanates have also been synthesized for PU coatings in an attempt to reduce the use of diisocyanates coming from petroleum.[18,19]

Different stages of PU synthesis are looked into to make the entire process of PU formation more sustainable. For synthesis of the soft segment, polyesters, usually formed using a metal catalyst, are being synthesized from organic catalysts[4]. Polylactides and polymenthide can be used as the soft segment of the PU.[2,16] The importance of the polyesters, soft segments, coming from renewable polymers is also researched.

Chapter 1: Monomer Development

One approach to having PUs derived from renewable resources is to synthesize the monomers from renewable resources. Previous literature shows research into making PUs from limonene, a major waste product of the citrus fruit industry.[20] Another natural product, menthone can be developed into menthide.[21] The success within these two monomer syntheses gives a foundation for the goal of this project.

In the conversion of dihydrocarvone to dihydrocarvide (Fig. 1.2) much epoxide product is accumulated with the use of oxone. The epoxide product has the potential to be useful for different polymer syntheses; however, this project was to limit the different products and identify the best reaction environment in which the Baeyer-Villiger reaction is the most favored. The Baeyer-Villiger reaction forms an ester. The product of the Baeyer-Villiger reaction maintains the double bond, which can be used in the thiol-ene reaction in PU synthesis.

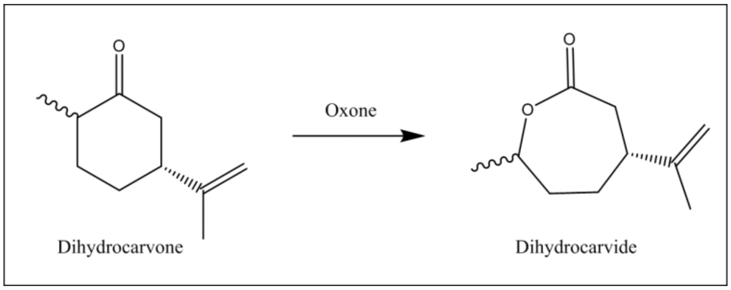

Fig. 1.2. Conversion of dihydrocarvone to dihydrocarvide.

Once dihydrocarvide could be synthesized successfully, a copolymerization between dihydrocarvide and menthide would form the polymer. The polymer could then participate in the thiol-ene reaction, or a similar reaction with an amide, in which the amide group would attach to the double bond. The reaction scheme is shown in Fig. 1.3.

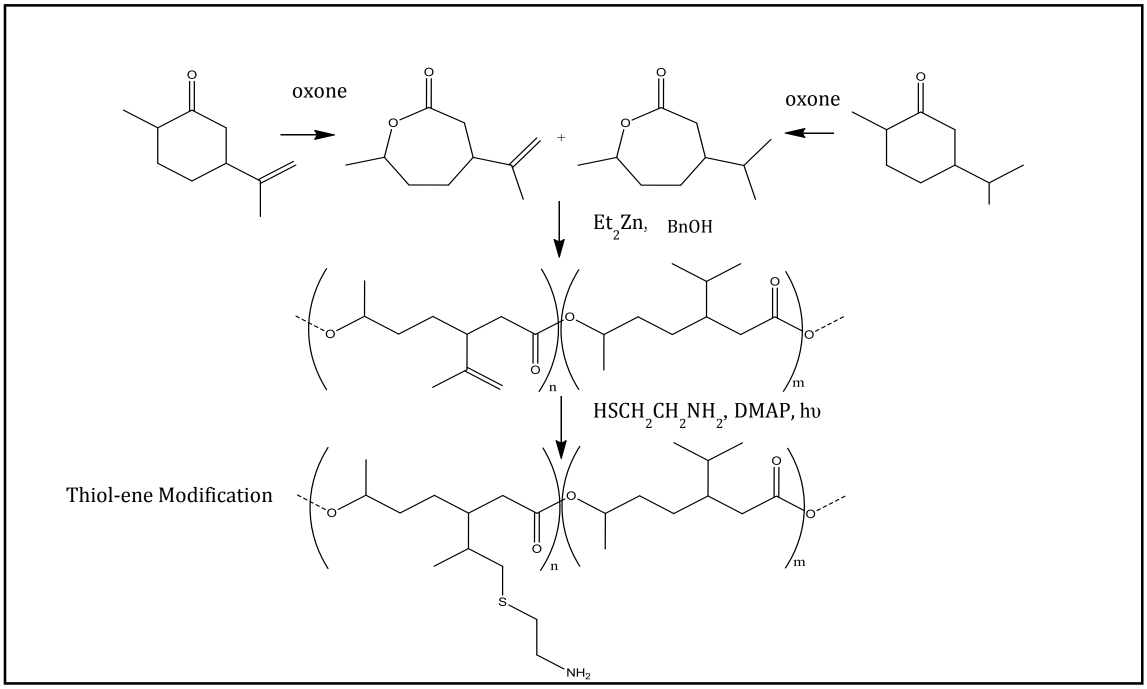

Fig. 1.3. Overall goal of the project.

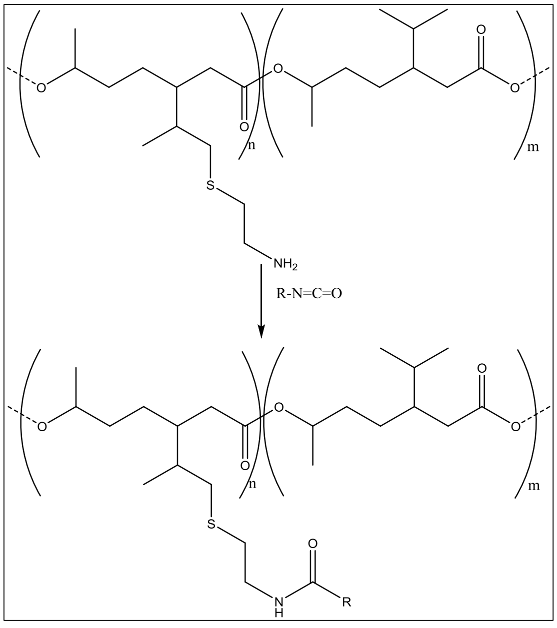

Fig. 1.4. Polyamine to Polyurea formation.

Following previous literature[2,22], the Baeyer-Villiger reaction converting dihydrocarvone to dihydrocarvide was catalyzed by oxone ($KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) (Fig. 1.3 and 1.4). Three potential products resulted from this reaction, as well as the unreacted dihydrocarvone (Fig. 1.5). Epoxide dihydrocarvone and epoxide dihydrocarvide can be used for other reactions. Dihydrocarvide was the desired product to preserve the double bond that would assist in cross-linking. A thiol-ene reaction could contribute to the strength of the PU by assisting in cross-linking.

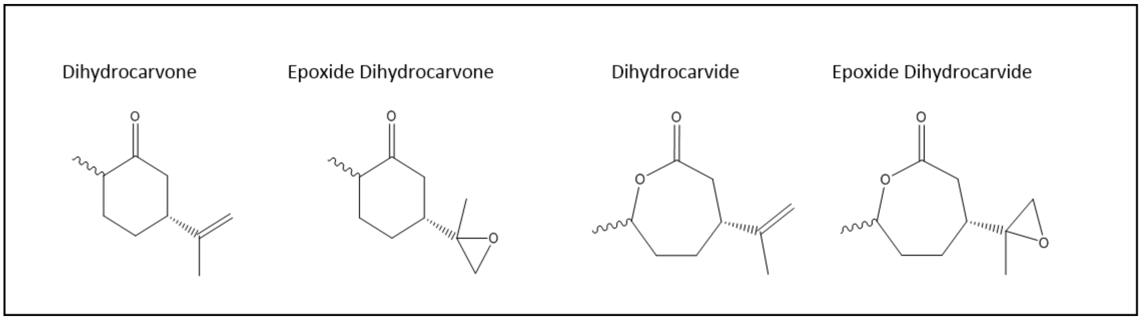

Fig. 1.5. Possible products of dihydrocarvone synthesis to dihydrocarvide.

In an attempt to limit the epoxidation product of the reaction, different salts were introduced. E. pure and two times the mole ratio of oxone reactions were also tested to alter the reaction environment (Table 1).

Table 1. Different salts added to the oxidation reaction.

Conditions	Percent Reactant	Percent Epoxide	Percent Ester	Percent Epoxy Ester
LiCl	40	12	48	-
NaCl	42	5	54	-
KI	98	2	-	-
NaF	35	16	48	-
NaBr	25	71	-	4
KCl	40	33	27	-
LiBr	28	67	-	3
E. Pure	49	6	45	-
Double Oxone	15	3	47	35
DI Water	42	12	39	7

The results in Table 1 were measured using GC-MS. By comparing retention times of the four possible products at 12.0, 14.6, 15.2, 17.5 minutes. By analyzing the mass spectrum of the dihydrocarvide peak (15.2) and confirming the product was dihydrocarvide, comparison between the retention times allowed the calculation of the percent of each product. Salts interact with the ketone of dihydrocarvone in order to favor the Baeyer-Villiger reaction over the epoxide product. The Baeyer-Villiger intermediate has a negative oxygen and this negative charge could also be stabilized by the salt. As the results show, salts were not an effective solution to limiting either epoxide product. In one case, KI inhibited the majority of any reaction occurring at all. Salts, such as NaBr, KCl, and LiBr, produced a large percentage (33%-71%) of epoxidized dihydrocarvone and had small amounts of dihydrocarvide product. Epoxide dihydrocarvone and dihydrocarvide have similar boiling points making separation difficult. Whereas epoxidized dihydrocarvide has a much higher boiling point than dihydrocarvide, this property allows epoxidized dihydrocarvide and dihydrocarvide to be separated by distillation.

The double Oxone®, E. Pure, and DI water reactions had similar percentages (39%-47%) of dihydrocarvide at the end of the reaction.

The ineffectiveness of the salts to change the polarity of the reaction environment and favor the Baeyer-Villiger reaction caused the DI water reaction environment to be maintained for the synthesis of dihydrocarvide from dihydrocarvone. Since the ester yield was not improved, this was not a good reaction to pursue. The salts would no longer be used in the reaction. The focus shifted to creating polymenthide, which would be reacted with lysine monohydrochloride in order to have N-capped polymenthide, a precursor for a PU.

Chapter 2: N-capped Polymenthide

As discussed previously, polyesters are a component of PUs. A number of vegetable oil-derived polyesters have been synthesized.[18] Polylactide, derived from naturally occurring lactic acid, has been synthesized as a polyester.[16] Also, PM has been synthesized.[16] In one project, PM was synthesized using diethylene glycol and tin(II) ethylhexanoate,[16] eliminating a metal catalyst is desired. In other literature, menthide was reacted with diethylene glycol and diethyl zinc to synthesize PM.[16] The formation of polyesters from renewable resources is necessary for the synthesis of PUs to become more sustainable.

In this project, by changing the protocol from diethylene glycol to 1,4-butanediol, the reaction was less toxic[23] (Fig. 2.1). Once the PM was synthesized, it would be reacted with lysine monohydrochloride in order to have an N-capped PM. Polymers, such as PM, are then reacted with diisocyanate to become a PU.

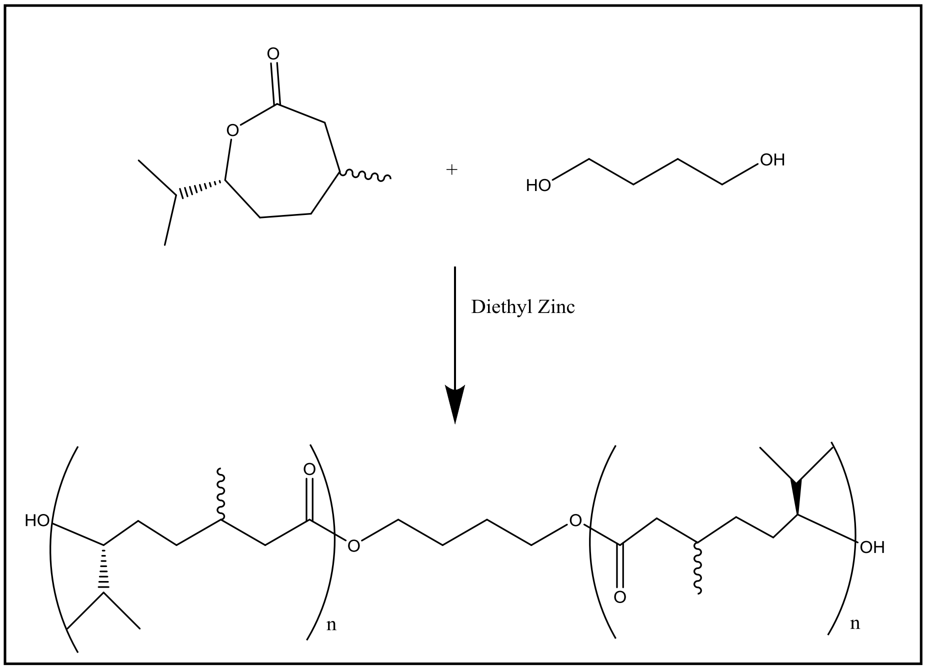

Fig. 2.1. Reaction scheme of menthide and 1,4-butanediol to make PM.

The target polymer ratio was 10:1:2 (menthide:butanediol). Polymers of different lengths were tested for the effects on properties. Four different polymers of varying ratios were reacted with lysine monohydrochloride (Table 2). The reaction between PM, N,N'-Dicyclohexylcarbodimide (DCC), and lysine monohydrochloride added a reactive nitrogen end group to each end of PM in order to convert the polymer to an N-capped PM[17] (Fig. 2.2). The N-capped PM could then participate in future reactions in which dihydrocarvide could be added to the end group.

The N-capped PM was synthesized by a procedure using hydroxybenzotriazole (HOBt) and N, N'-Dicyclohexylcarbodiimide (DCC). DCC is a coupling agent. Procedures using DCC have been widely studied. They are studied for drug carriers; by synthesizing polymer-peptide conjugates, the efficiency of drug delivery could be increased.[24,25] An advantage to using DCC is the insoluble precipitate (DCU) that is formed by the reaction.[26] The precipitate provides easier purification. The polymer needs active end groups to participate in the reaction producing the conjugate and these reactions have high yield in the presence of racemization limiting compounds, such as HOBt.[26,27]

Table 2. Four PM polymers that were selected to react with DCC.

Polymenthide Synthesis	Menthide:Butanediol :Diethyl Zinc Feed Ratio vs. Outcome	Percent Recovery	Mol Ratio Hexanes: PM	Weight Ratio Hexanes:PM
PM1	18:1:2 7:1:2	43.0%	1.0:12.24	86.18:15667.2
PM2	18:1:2 25.5:1:2	60.3%	1.44:28.64	124.09:126732
PM3	10:1:2 9.3:1:2	43.2%	.74:34.53	64.29:5538.6
PM4	10:1:2 6.5:1:2	73.5%	.84:21.59	72.39:23964.9

*The polymers in this table were altered in order to test the effects on properties. The percent recovery was recovery by mass.

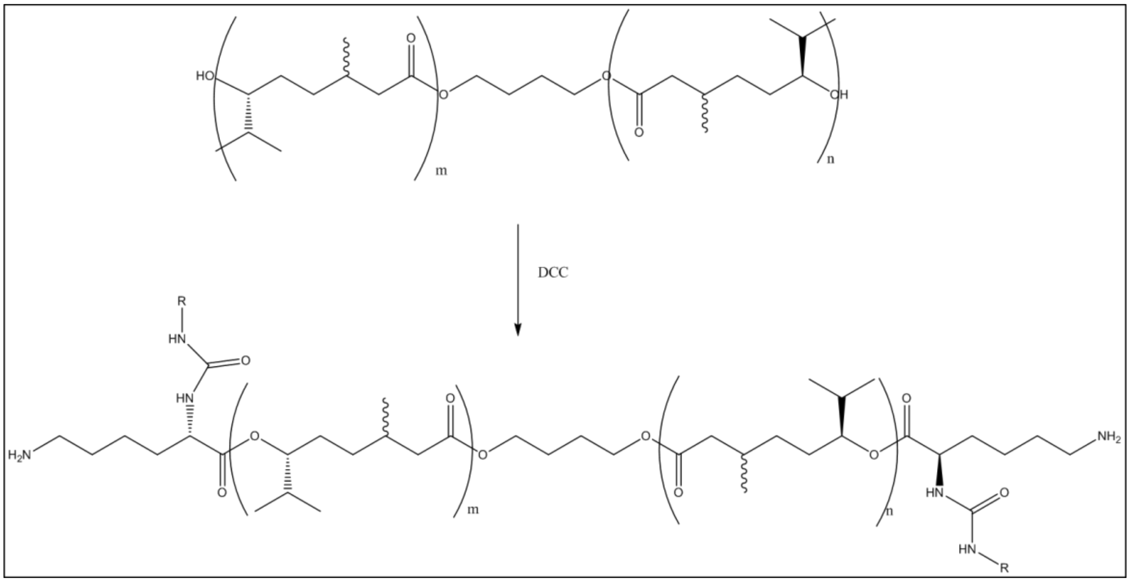

Fig. 2.2. PM reacts with DCC to make an N-capped PM.

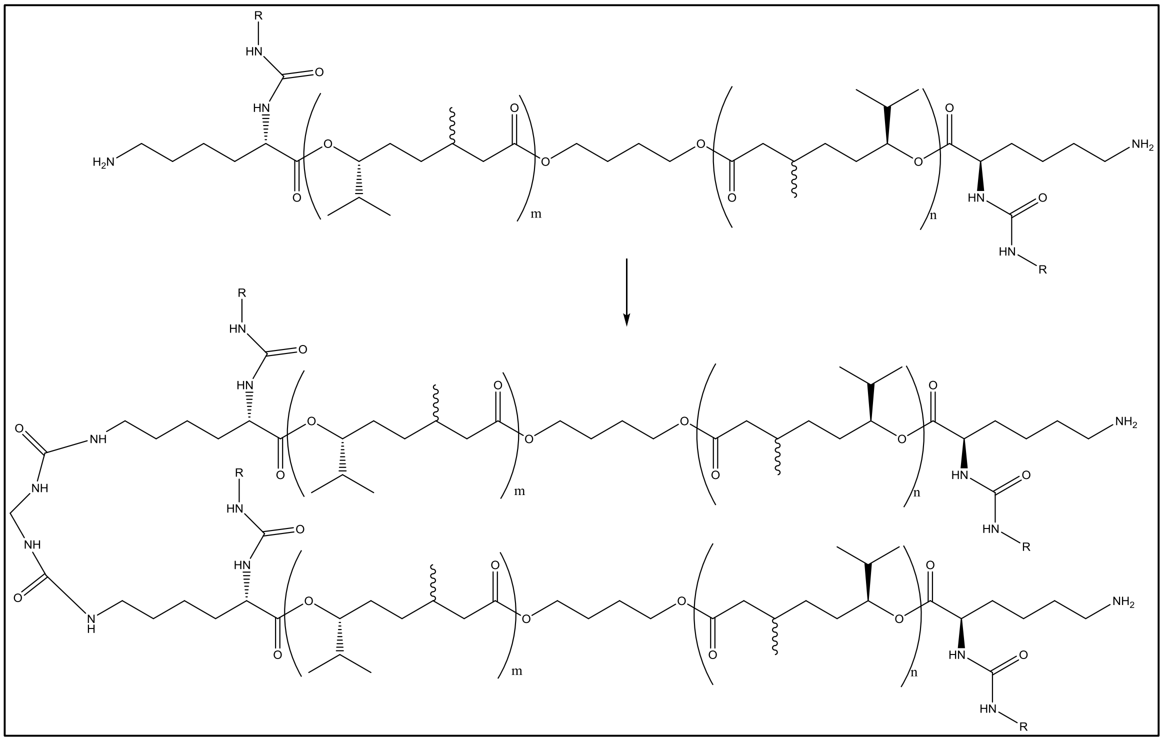

Fig. 2.3. Converting N-capped PM into a PU.

This reaction would form a linear polyurethane. Lysine monohydrochloride reacted with DCC in order to make the ester a better electrophile. The PM hydroxyl group was the nucleophile. The reaction between the electrophile and nucleophile would result in an N-capped PM (Fig. 2.4).

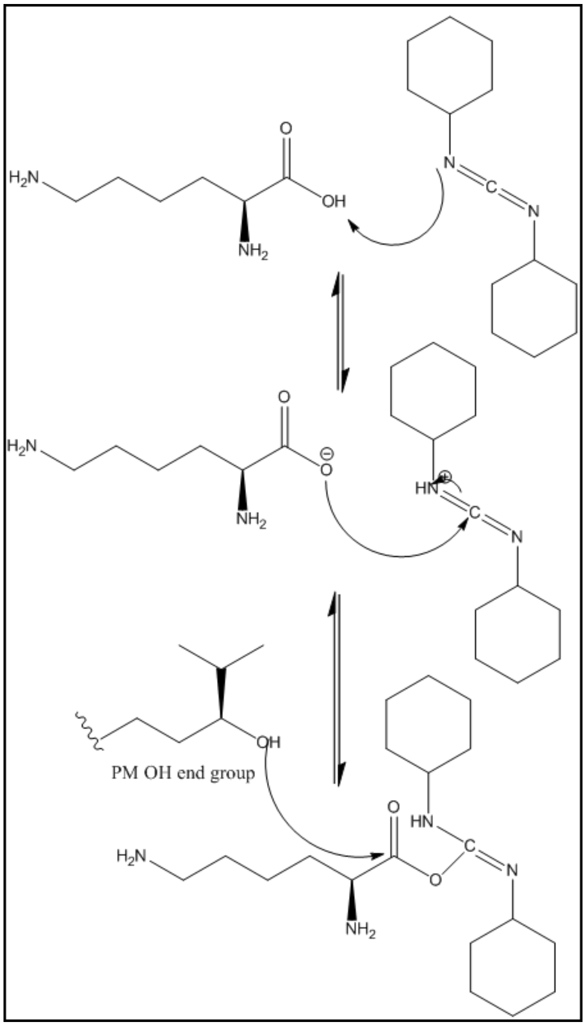

Fig. 2.4. Activated electrophile of lysine after reacting with DCC.

The literature for this procedure used an HCl wash in order to remove the precipitated dicyclohexylurea (DCU).[17] However, the percent recovery was too low to do further experimentation with. It was thought the positively charged nitrogen groups on each end of the PM would make the newly formed N-capped PM polar. This would cause the product to be taken up in the water layer rather than the organic layer with ethyl acetate.

PM4 was added to the same reaction in the next attempt with DCC, but rather washed with NaOH in order to have the product remain in the organic layer. The percent recovery was still unquantifiable. The product recovered was enough for a ^1H NMR, COSY, and IR analysis.

A polymer with a high ratios of menthide to 1,4-butanediol were too difficult to analyze after adding the lysine monohydrochloride as the end group. The IR spectrum showed the O-H peak at 3300 cm $^{-1}$ was now an N-H peak at 3300 cm^{-1}. A COSY spectrum comparison between both PM and N-capped PM indicatecd that the lysine monohydrochloride had added to the end of the polymer chain (Fig. 2.6). There were more proton-proton correlations from the hydrogens of the lysine (Table 3). There was also a shift in correlation between the hydrogen at 3.2 ppm. The shifted correlation was upfield, which would be caused by the replacement of the terminal oxygen with a less electronegative nitrogen.

Possible reasons the percent recovery was so low include loss of product through filtration, lysine monohydrochloride not adding, and the two solvents causing the reaction to bump easily in the rotary evaporation process.

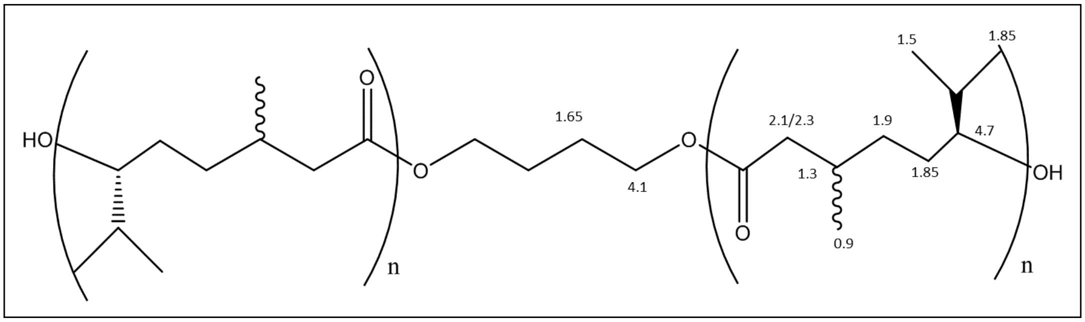

Fig. 2.5. ^{1}H NMR assignments for PM.

Table 3. COSY correlations of PM.

Shift	correlates to	Shift
0.9		1.9
1.3		1.5
1.3		3.3
1.5		4.7
1.65		4.1
1.85		4.7
1.9		2.3
2.1		2.3
3.2		4.7*

*Correlation missing in N-capped PM indicating that 3.2 is the H next to the hydroxyl end group; this hydrogen shifts when hydroxyl group is replaced with lysine. This table is used to show the relationships of the assignments in Fig. 2.4. Data from both NMR and COSY was used.

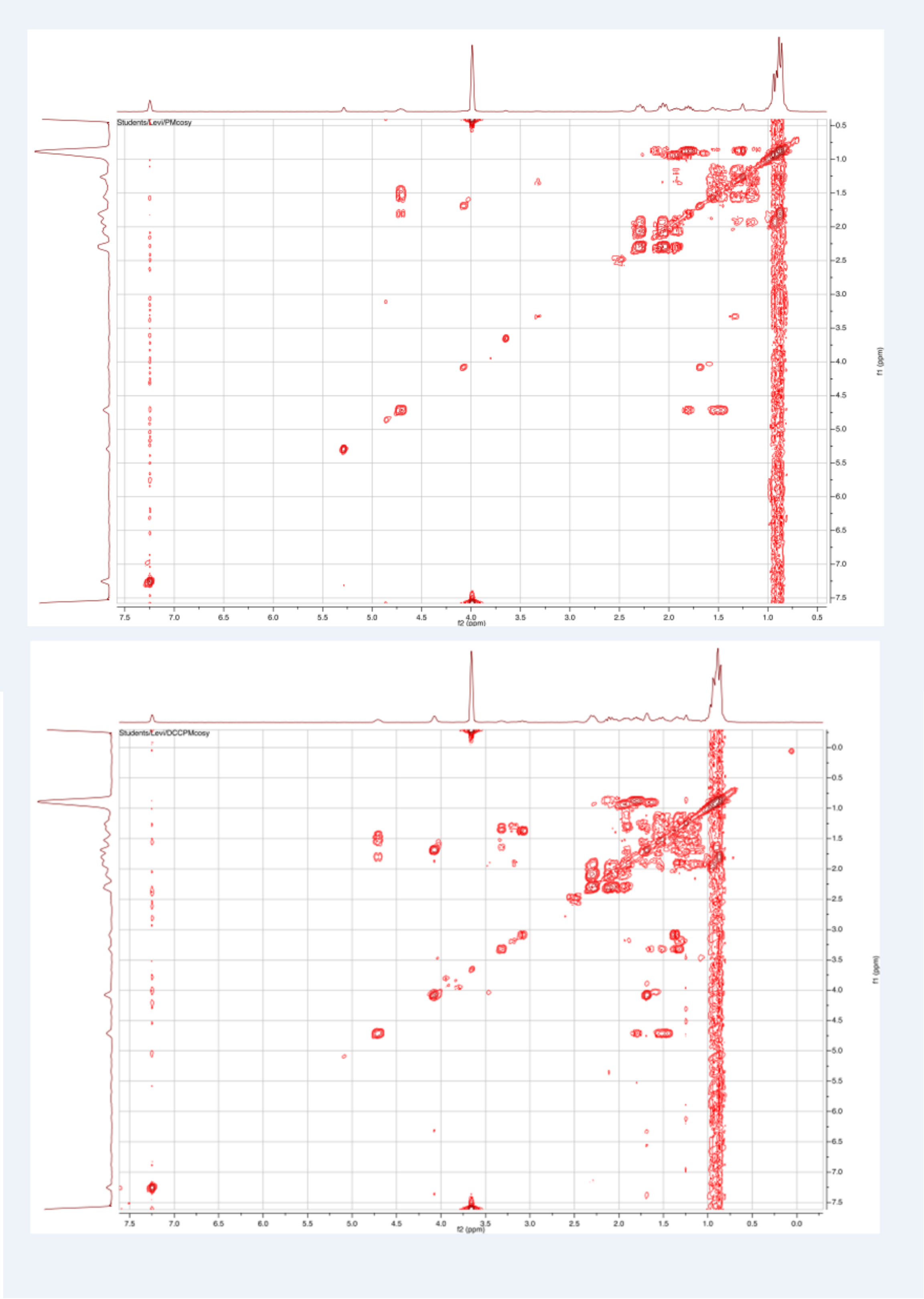

Fig. 2.6. COSY comparison of PM (top) and N-capped PM (bottom). Note the increased amount of hydrogen correlations around 1.0-2.0 ppm.

PM was synthesized seven times. In three of these attempts, the result was unreacted monomer. Impure menthide could have caused this. If methanol was still present in the menthide, the ratio of initiator would be too large causing many short chains to form rather than the desired 10:1:2 ratio of monomer to 1,4-butanediol.

The only DCC reaction with quantifiable percent recovery was the reaction using PM2 with the 25.5:1:2 ratio. The length of this chain made analysis difficult. It was too difficult to conclude whether the lysine had indeed attached to the PM or was just present in the sample, unattached.

The limited product from the PM-lysine monohydrochloride reaction presented limitations for both analysis and further experimentation. Calorimetry could have been a useful technique in identifying if the lysine addition had indeed occurred. Other limitations included polymerization of PM. Many attempts resulted in unreacted monomer, possibly from impure menthide.

The goal to synthesize an N-capped PM chain has little evidence marking its success. In future research, DCU precipitate could be removed from the reaction using different techniques. The polymer could be precipitated out in cold hexanes and DCU and hexanes would be decanted.

Experimental

Monomer synthesis

Microscale reactions for varying salt reactions for the synthesis of dihydrocarvide were set up. The amount of salt in each reaction was a 1:1 mole ratio of dihydrocarvone to salt. All of the monomer reactions were stirred at room temperature for 48 hrs. Throughout the 48 hrs, sodium bicarbonate and oxone were added twice a day. The amount of sodium bicarbonate (0.053 g, 0.0006 mol) and oxone (0.074 g, 0.0002 mol) added each time was the same amount as added to the initial reaction. Dihydrocarvone (0.11 mL, 0.0007 mol), E. pure water (2 mL), methanol (2 mL), oxone (0.074 g, 0.0002 mol), and sodium bicarbonate (0.053 g, 0.0006 mol) were all added to a vial. Salt was also added. Seven different salts were tested: LiCl (0.029 g), NaCl (0.039 g), KCl (0.050 g), NaBr (0.069 g), NaF (0.028 g), LiBr (0.058 g), and KI (0.115 g). A double oxone (0.150 g) reaction was also set up.

Once the reactions were done stirring, they were washed with ethyl acetate (3X 1mL). The organic top layer was extracted using a syringe. The organic layer was washed with a 19g in 200 mL sodium bisulfite solution (1 mL). The organic layer was extracted and washed with DI water (2X 1mL) and brine (1 mL). The reaction was dried with $MgSO_4$ and then filtered to remove the $MgSO_4$. Rotary evaporation was used to remove any remaining methanol. GC/MS were obtained for each reaction to see the percent conversion and percent epoxidation. GC/MS (m/z) for dihydrocarvide: 38.8, 66.8, 124.5, 168. Retention times (min) reactant, epoxide, ester, epoxide ester: 12.0, 14.6, 15.2, 17.5.

Menthide was synthesized following previous literature.[2] Menthone (19 mL, 0.11 mol), methanol (300 mL), DI water (300 mL), oxone (12.4 g, 0.08 mol), and sodium bicarbonate (8.8 g, 0.105 mol) were added to a large Erlenmeyer flask. The reaction was set to stir at room temperature for 48 hrs. Sodium bicarbonate and oxone were added twice a day in the same amount as the initial reaction set up. The reaction was then filtered to remove the sodium bicarbonate and oxone. Methanol was removed by rotary evaporation. The solution was washed in the following order: ether (3X 100 mL), sodium bisulfite (19 g in 200 mL, 2X 100 mL), DI water (2X 100 mL), and brine (2X 200 mL). The solution was dried with $MgSO_4$, which was then filtered off. The solution was then rotary evaporated to yield an oil. Menthide was also distilled before use in the polymerization (65℃ -75℃). Menthide often crystallized after distillation, a visible indication of purity. GC/MS and ^{1}H NMR were taken. GC/MS (m/z): 39, 153, 170. ^{1}H NMR ($CDCl_3$): δ 0.9 (m, 6H), 1.0 (d, 3H), 1.3 (m, 1H), 1.6 (m, 1H), 1.8 (m, 2H), 1.9 (m, 2H), 2.4 (m, 2H), 4.0 (q, 1H).

Polymerization

Polymenthide was synthesized following previous literature.[16] The following procedure is for a polymer in a 10:1:2 ratio of menthide:butanediol:diethyl zinc. The bomb used for the polymerization was oven dried before use. The butanediol was dried with molecular sieves. In the glovebox, the bomb was loaded with menthide (2.00 g, 0.01 mol), butanediol (0.10 ml, 0.001 mol), and Et_2Zn (0.24 mL, 0.002 mol). The bomb was removed from the glovebox and placed in a 100℃ oil bath to stir for 22 hrs. After 22 hrs, the bomb was exposed to air and dichloromethane (0.25 mL) was added. The reaction product was then precipitated with addition of 50 mL of chilled hexanes. The hexanes were decanted from the yellow polymer. Rotary evaporation was then used to remove any remaining hexanes for a purer product. In successful polymerizations, the percent recovery varied from 43%-73.5%. ^1H NMR ($CDCl_3$): δ 0.9 (m, 3H), 1.3 (m, 1H), 1.5 (m, 3H), 1.65 (m, 2H), 1.85 (m, 5H), 1.9 (m, 2H), 2.1/2.3 (m, 2H), 3.2 (m, 1H), 4.1 (m, 2H), 4.7 (m, 1H).

N-Capped Polymenthide

Following a previous literature preparation[17], lysine was added to the ends of PM. The following procedure is calculated based on PM4 (6.5:1:2). A mixture of lysine monohydrochloride (0.166 g, 4.0 mmol), HOBt (0.139 g, 4.0 mmol), and ethyl acetate (20 mL) was chilled in an ice bath. DCC (0.21 g, 4.4 mmol) was added and the mixture was stirred for 30 min. After the 30 min passed, PM (1 g, 4.0 mmol) and triethylamine (0.13 mL, 4.0 mmol) were added to the reaction and stirred for 2 hrs at room temperature. The reaction was then poured into hexanes (10 mL) and stored in the freezer overnight.

DCU formed a white precipitate that was filtered off. The precipitates were washed with ethyl acetate (10 mL) followed by 1M NaOH (2X 10 mL), saturated $NaHCO_3$ (3X 10 mL), and finally brine (3X 10 mL). The solution was dried with $MgSO_4$ and filtered. Rotary evaporation was used to purify the product. Percent recovery was minimal. ^1H NMR ($CDCl_3$): δ 0.9 (m, 3H), 1.0 (m, 2H), 1.15 (m, 2H), 1.2 (m, 2H), 1.3 (m, 1H), 1.5 (m, 3H), 1.65 (m, 2H), 1.7 (m, 2H), 1.8 (m, 5H), 1.9 (m, 2H), 2.1/2.3 (m, 2H), 3.3 (m, 1H), 4.1 (m, 2H), 4.7 (m, 1H).

Conclusion

PUs derived from renewable resources is essential as the world's consumption is high and the supply resources are diminishing. Monomers derived from renewable resources were synthesized. In this experiment, the reaction converting dihydrocarvone to dihydrocarvide was not any more selective with the addition of salts, double oxone, or in an E. pure reaction than when conducted in DI water. Rather the epoxide dihydrocarvone product was increased. Improvement of selectivity/high dihydrocarvide yield was researched further and successful improvements were made.

In the synthesis of N-capped PM, no strong evidence indicated that the addition had been successful. Further development of both PM synthesis and lysine addition is necessary to increase the percent recovery of both products. By using different analysis techniques, the success of the reaction could be further analyzed.

The polymerization of PM was successful, but had its disadvantages. The feed ratio to the outcome ratio varied. There was no absolute prediction for the ratio of the obtained polymer. The reaction failed multiple times. The most likely reason for the failed attempts are due to the purity of the menthide. Even after distillation, any methanol remaining would act as additional initiator in the synthesis of the polymer.

Synthesis of N-capped PM has the potential to react in further experimentation with dihydrocarvide to form a linear PU. In the case of this successful reaction, PU synthesis becomes a greener reaction and has the potential to reduce the amount of the world's petroleum-based waste. It also has the ability to make the field of dentistry a greener profession as PUs have already been introduced for both arch models and removable dental appliances.

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