Spring 2016

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Recommended Citation

Fitch, Brian N., "The Synthesis of Poly(Propylene Fumarate)" (2016). *Honors Research Projects*. 259.
http://ideaexchange.uakron.edu/honors_research_projects/259

The Synthesis of Poly(Propylene Fumarate)

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April 2016

Submitted to: The University of Akron Honors College

Introduction

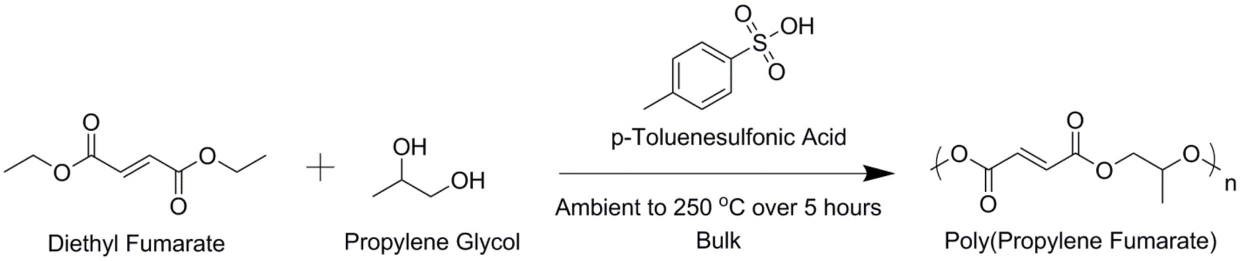
Background. There are numerous clinical applications for bone tissue regeneration scaffolds. These applications include treating significant injuries such as skeletal traumas, total joint arthroplasties, and trabecular voids.[1] The three kinds of bone grafts currently in use are natural bone grafts in the form of autographs (from the patient themselves) or allographs (from a donor) and synthetic bone grafts.[2,3] Autografts are preferred because they do not induce adverse immune system responses, but they are limited in quantity and collecting it creates a secondary wound site.[2,4] In contrast, allografts have the possibility of immune rejection by the patient and they can transfer diseases. Autografts and allografts are both constrained in their applicability as a consequence of the amount of available tissue and fabrication limitiations.[2] Synthetic bone grafts come in a variety of different materials including metals, polymers, and ceramics that each have their own advantages and disadvantages.[5] The current interest for many researchers is biodegradable synthetic materials. These materials are of interest because of their wide range of fabrication methods, as well as their tunable mechanical and degradation properties.[6,7]

Scaffold materials for tissue engineering must be non-toxic and cause minimal systemic inflammation in orthopedic applications.[8] The materials must also possess similar mechanical properties to human bone. Lastly, the material must maintain its strength and integrity through the sterilization and fabrication procedures.[1,8] Poly(propylene fumarate) (PPF) is a promising material for use as a bone tissue engineering material.[9,10] PPF is an unsaturated linear polyester. The main advantage of this polymer is the release of biodegradable byproducts including fumaric acid and propylene glycol through hydrolysis of the ester bonds. Fumaric acid is consumed during the Krebs cycle and propylene glycol is easily resorbed and excreted by the human body.[11] When implanted in rats, PPF and the degradation byproducts have not shown any long-term inflammatory responses.[6] These properties make PPF a good candidate for bone scaffolds. The double bond in PPF also allows the material to be thermally or chemically-crosslinked.[12,13] Additionally, PPF oligomers are viscous liquids at room temperature.[14] Both properties make PPF a promising material for applications preparing scaffolding using three-dimensional (3-D) printing techniques.[12, 13]

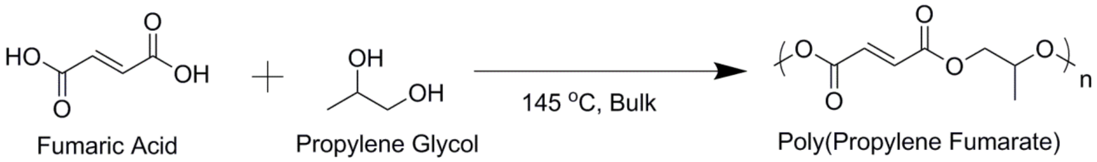
Synthesis and characterization.

The traditional synthetic method for the production of PPF utilizes a step growth polymerization. The PPF synthesis method designed by Sandarson involved the transesterification of diethyl fumarate and propylene glycol with *p*-toluenesulfonic acid as the catalyst at 250 ^{o}C (Scheme 1). This method showed relatively low yields of approximately 35%.[15] The PPF synthesis method developed by Gerhart and Hayes used a condensation reaction of propylene glycol and fumaric acid (Scheme 2).[16,17] This method produced poly(propylene fumarate) diol with M_n values ranging from 500 Da to 1200 Da and molecular mass distribution between 3 and 4.[6,11] These pathways require high energy inputs, long reaction times, and result in low yields. The reaction is also plagued by low molecular masses, unwanted side reactions, and uncontrolled cross-linking.[18]

Scheme 1. Poly(propylene fumarate) synthesis using a step-growth polymerization of diethyl fumarate and propylene glycol.[15]



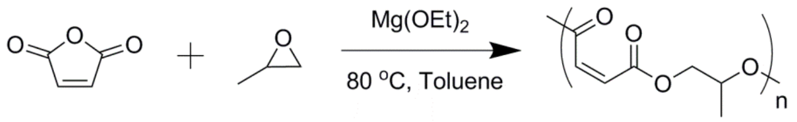
Scheme 2: Poly(propylene fumarate) synthesis using a step-growth polymerization of fumaric acid and propylene glycol.[16]



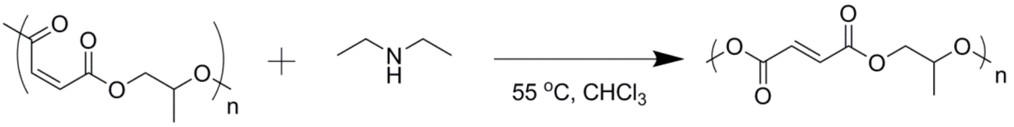
A recently described method of synthesizing PPF uses a chain-growth pathway that involves milder reaction conditions has been developed by DiCiccio and Coates (Scheme 3).[18] The pathway involves the ring-opening copolymerization of maleic anhydride with propylene oxide to yield poly(propylene maleate) (PPM). The PPM is then isomerized using diethyl amine to produce PPF.[18] This pathway is more atom economical then the step growth polymerization. The chain-growth mechanism has successfully achieved M_n values over 17 kDa and molecular mass distributions around 1.6.[18] The smaller mass distribution allows for more control over the chemical and physical properties. Overall, this method is better suited for large-scale production over previous methods because of the milder reaction conditions and improved control over the physical properties.

Scheme 3. Two step chain-growth polymerization of PPF using a ring-opening copolymerization of maleic anhydride and propylene oxide to form poly(propylene maleate). The poly(propylene maleate) is then isomerized using diethyl amine to yield PPF.[18]

Step 1. Ring-opening copolymerization



Step 2. Isomerization



The goal of this thesis was to improve the reaction and purification procedure of the chain-growth pathway. The work focused on reducing the amount of time and labor required for the synthesis and purification steps. The goal was to effectively use the chain-growth procedure in a 20L batch reactor.

Experimental

Table 1. Materials and reagents.

Name	**Formula**	**Purity**	**Source**
Maleic Anhydride	$C_4H_2O_3$	99%	Fluka
Propylene Oxide	C_3H_6O	99.5%	Aldrich
Magnesium Ethoxide	$Mg(OEt)_2$	98%	Aldrich
Diethylamine	$C_4H_{10}N$	99%	Sigma-Aldrich
Toluene	C_7H_8	Anhydrous, 99.8%	Sigma-Aldrich
Tetrahydrofuran (THF)	C_4H_8O	GR ACS	Sigma-Aldrich
Chloroform	$CHCl_3$	GR ACS	Sigma-Aldrich
Hexane	C_6H_{12}	98.5%	Sigma-Aldrich
Sodium Phosphate Dibasic	Na_2HPO_4	BioXtra, ≥99.0%	Sigma-Aldrich
Sodium Phosphate Monobasic	NaH_2PO_4	BioXtra, ≥99.0%	Sigma-Aldrich
Hydrochloric Acid	HCl	ACS, 37%	Sigma-Aldrich
Sodium Phosphate Anhydrate	Na_2SO_4	Granular, 99%	EMD Millipore Corporation
Diethyl Ether	$O(C_2H_5)_2$	Anhydrous, 99%	EMD Millipore Corporation

Original Method

Step 1. Synthesis of poly(propylene maleate)

Maleic anhydride (70.1 g, 714 mmol) and propylene oxide (50.0 mL, 714 mmol) were dissolved in toluene (100 mL) in a 500 mL round-bottom flask at room temperature with the assistance of magnetic stirring. During the stirring, the flask was placed under a nitrogen atmosphere. Once the maleic anhydride and propylene oxide were completely dissolved, $Mg(OEt)_2$ (0.433g, 3.57 mmol) (molar ratio of maleic anhydride/$Mg(OEt)_2$ = 200:1) was added to the reaction flask. The flask was then placed in a pre-heated silicone oil bath set to 80 ^{o}C. A reflux condenser was added to the flask and the polymerization continued. After 42 hours, the flask was removed from the oil bath and cooled to room temperature under nitrogen.

Step 2: Work up of poly(propylene maleate)

The solvent and other volatiles from the reaction mixture were removed using a rotary evaporator under reduced pressure conditions. The residue remaining in the flask was diluted in chloroform ($CHCl_3$), transferred to a separatory funnel, and washed with water mixed with a trace amount of hydrochloric acid (HCl) to remove the $Mg(OEt)_2$. After separation, the organic layer was collected and the aqueous layer was discarded. The organic layer was placed back into the separatory funnel and washed with deionized water at a 1:1 ratio of organic layer to aqueous layer. This sequence was repeated until the aqueous layer had a neutral pH. The organic layer was washed with saturated solutions of NaCl (brine) three times (1:1 ratio of organic layer to aqueous layer) to remove water from the organic layer by the osmotic effect. The water was further removed from the organic layer by addition of anhydrous sodium sulfate to aliquots of the organic layer. The organic aliquots were then filtered using a Buchner funnel to remove the drying agent. The aliquots were combined and concentrated using rotary evaporation. The residue was dried overnight under vacuum in order to determine the mass of poly(propylene maleate) recovered.

Step 3: Isomerization of poly(propylene maleate)

The PPM was dissolved in $CHCl_3$ (1 mol PPM/1 L $CHCl_3$) in a round bottom flask. Diethylamine was added to the reaction solution at a 0.1 mole equivalent concentration to the double bond of the PPM. The flask was then placed in a pre-heated silicon oil bath (55 ^{o}C). A reflux condenser was added to the flask and the isomerization proceeded under nitrogen for 24 hours.

Step 4: Work up of poly(propylene fumarate)

The reaction mixture was concentrated by rotary evaporation to remove the unreacted diethyl amine. The solution was then diluted with $CHCl_3$ before washing with a phosphate buffered saline solution (1 M, pH = 4.0) in a separatory funnel. Like the water washes in Step 2, the method was repeated until the solution had a neutral pH (approximately three times). Water was removed from the organic layer by washing with brine three times. Aliquots of the organic layer were then dried by addition of sodium phosphate anhydrate. The drying agent was removed by filtering the solution using a Buchner funnel. The organic layer aliquots were combined and concentrated using rotary evaporation. The concentrated mixture was slowly precipitated into hexane. A minimal amount of $CHCl_3$ was added to the mixture and the solution was concentrated using rotary evaporation. The poly(propylene fumarate) was then dried under vacuum at room temperature overnight to remove any remaining solvent. The PPF was transferred from the round bottom flask to another container by freezing the flask and PPF in liquid nitrogen. The hardened PPF was carefully chipped off of the flask walls and into the other container for long term storage.

Batch Information

Table 2. Information on monomer, initiator, and solvent for the batches

Batch Number	Maleic Anhydride	Propylene Oxide	Toluene	$Mg(EtO)_2$	Maleic Anhydride/$Mg(OEt)_2$
Batch 1	0.714 mol 70.1 g	0.714 mol 41.5 g	100 mL	0.0036 mol 0.433 g	200:1
Batch 2	2.856 mol 280.6 g	2.856 mol 165.9 g	400 mL	0.079 mol 9.648 g	36:1
Batch 3	2.856 mol 280.6 g	2.856 mol 165.9 g	400 mL	0.079 mol 9.648 g	36:1

Characterization

The samples were examined with proton nuclear magnetic resonance spectroscopy (^{1}H NMR) and matrix assisted laser desorption/ionization time-of-flight (MALDI-TOF) spectroscopy to determine the chemical structures of the products. The ^{1}H NMR spectra were collected using 300 MHz Varian NMRS instrument. The solvent used for the analysis was deuterated chloroform or deuterated dimethyl sulfoxide (DMSO-d_6). The MALDI-TOF used was a Bruker Ultraflex III MALDI-Tof/ToF Mass Spectrometer. For this analysis, samples were dissolved in $CHCl_3$ at a concentration of 10 mg/mL. The MALDI analysis was done using the sandwich method with *trans*-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene] malonnitrile (DCTB) as a matrix and NaTFA (10:1) as a salt. The molecular mass and molecular mass distribution of the polymer samples were determined by Size Exclusion Chromatography (SEC). The SEC analysis was performed on a Viscotek GPCmax VE 2011 Solvent Sample Module with a Waters 2414 Reflective Index Detector. The analysis was completed in THF at 35 ^oC. Standard Series 1 (with M_w (g/mol): 580, 2940, 10440, 28770, 60450, 152800, 327300, 841700, 2348000) and Standard Series 2 (with M_w (g/mol): 580, 1280, 3180, 4910, 10440, 21810, 51150, 96000, 230900) were created using polystyrene standards of narrow molecular mass distribution. A summary of the different analytical methods and the instrumentation used is given in Table 2.

Table 2: Analytical methods and equipment.

Analytical Methods	Type/Equipment
^{1}H NMR Spectroscopy	Varian Mercury 300 Spectrometer
MALDI-TOF (Matrix Assisted Laser Desorption/Ionization Time-of-flight)	Bruker UltraFlex III MALDI Tandem Time-of-Flight (TOF/TOF) Mass Spectrometer (Bruker Daltonics, Billerica, MA, USA) equipped with a Nd: YAG laser emitting at 355 nm
SEC (Size Exclusion Chromatography)	Viscotek GPC max VE 2011 Solvent Sample Module equipped with a Waters 2414 Reflective Index Detector

Results and Discussion

Following the synthesis and purification of PPM, a small amount of the reaction mixture was collected and analyzed with ^{1}H NMR. The resulting spectrum was used to confirm the structure and purity of the PPM (Figure 1). The chemical shift at 6.24-6.27 corresponds to the vinylic protons of the *cis*-double bond of PPM. The tertiary proton ($\mathrm{OCH_2C}\mathit{H}\mathrm{(CH_3)}$) signal is observed at a shift of 5.22-5.27 ppm. The chemical shift at 4.22-4.26 ppm corresponds to the two protons at position c in Figure 1. The duplet at 1.30-1.32 ppm are representative of the three protons on the methyl-group of PPM. The remaining chemical shift at 7.26 ppm is from the solvent (chloroform-*d*). The ^{1}H NMR spectrum confirmed the synthesis of the PPM.

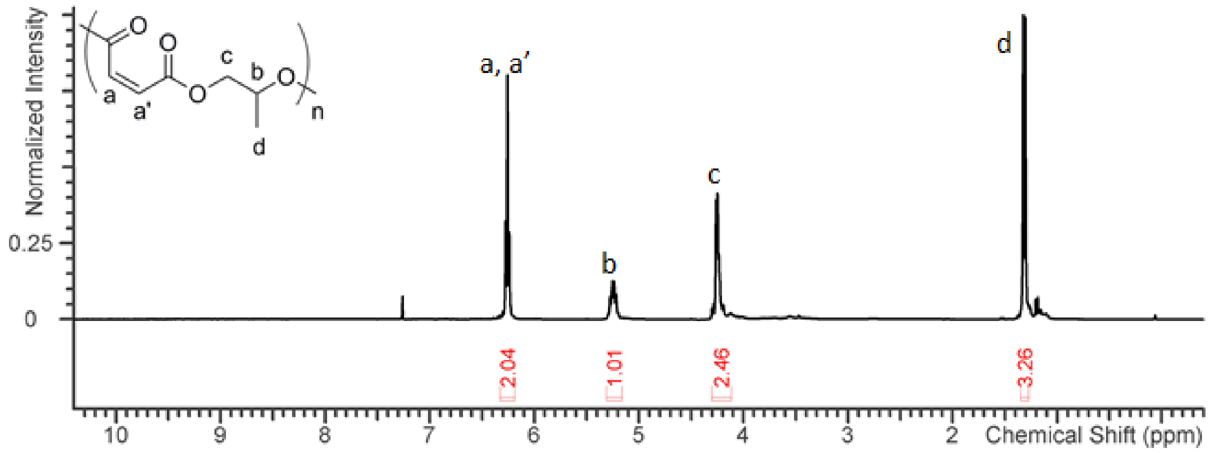


Figure 1: ^{1}H NMR spectrum of Batch 1 poly(propylene maleate). (300 MHz, chloroform-*d*) δ ppm 1.30-1.32 (d, 3H, $\mathrm{OCH_2CH(C}\mathit{H}_3\mathrm{)O}$), 4.22-4.26 (m, 2H, $\mathrm{OC}\mathit{H}_2\mathrm{CH(CH_3)O}$), 5.22-5.27 (m, 1H, $\mathrm{OCH_2C}\mathit{H}\mathrm{(CH_3)O}$), 6.24-6.27 (m, 2H, CH=CH (*cis*-configuration), 7.27 (s, 1H, $\mathrm{C}\mathit{H}\mathrm{Cl_3}$).

The structure of the product was further analyzed by MALDI-TOF MS. The mass spectrum in Figure 2 shows three distributions which correspond to different end groups on the PPM. The structures related to each of the distributions as well as expanded view of the mass spectrum are shown in Figure 3.

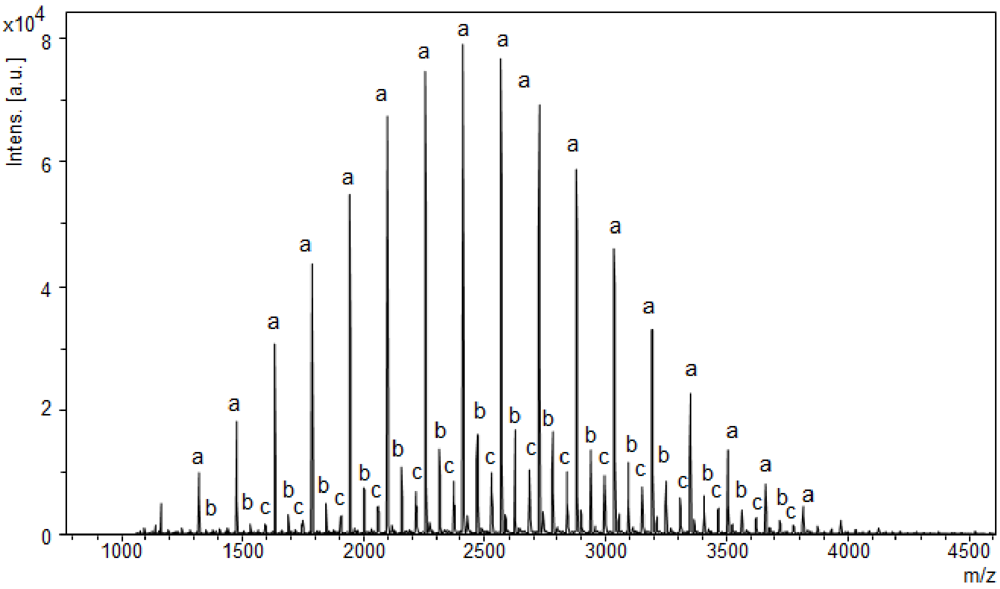


Figure 2: MALDI-TOF mass spectrum Batch 1 poly(propylene maleate) showing overall mass spectrum. The letters a, b, and c correspond to the three mass distributions of the sample. The end groups for the distributions are shown at the top of Figure 3.

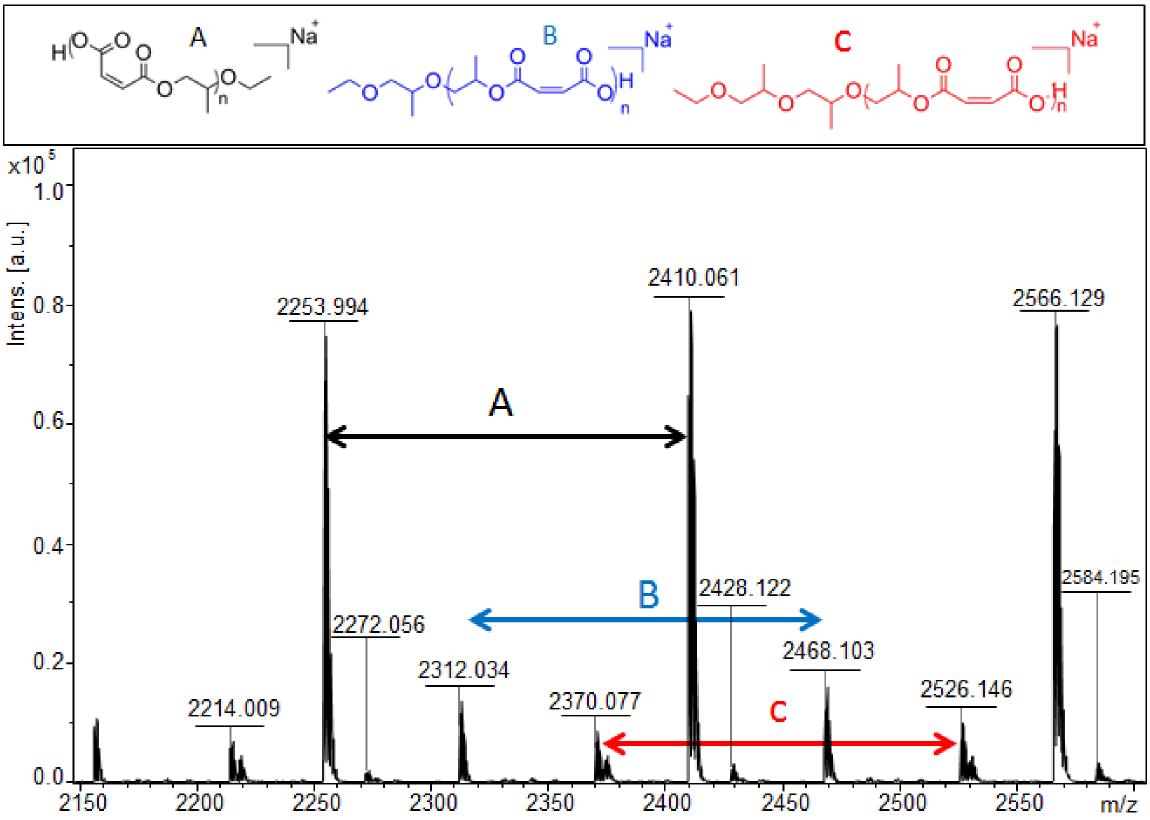


Figure 3: Expanded mass spectrum of Batch 1 poly(propylene maleate) from Figure 2 depicting the three mass distributions A, B, and C. The end groups of the mass distributions A, B, and C are displayed above the mass spectrum.

The isomerization of the *cis*-double bond in PPM was confirmed using ^{1}H NMR. The vinylic protons labeled a and a’ shifted downfield from 6.24-6.27 ppm to a chemical shift of 6.86 ppm. This occurred because vinylic protons in the *trans*-configuration have a larger coupling constant than vinylic protons in the *cis*-configuration. The remaining chemical shifts for the protons at position b, c, and d remained the same as before the isomerization. This confirmed the successful isomerization of PPM to PPF.

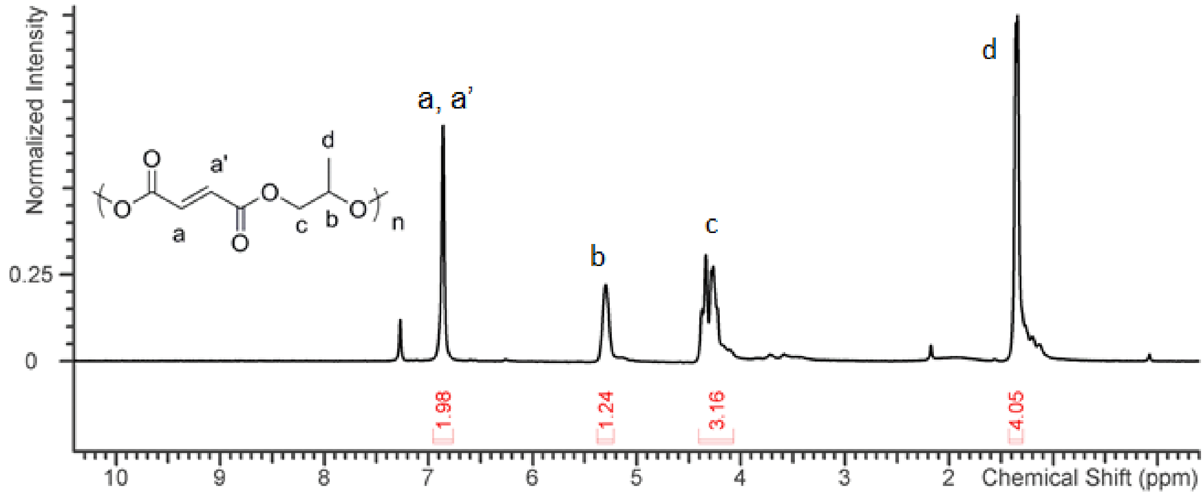


Figure 4: ^{1}H NMR spectrum of Batch 1 poly(propylene fumarate) (300 MHz, Chloroform-*d* ppm) δ ppm 1.34-1.36 (d, 3H, $OCH_2CH(C\textit{H}_3)O$), 4.23-4.37 (m, 2H, $OC\textit{H}_2CH(CH_3)O$), 5.30 (m, 1H, $OCH_2C\textit{H}(CH_3)O$), 6.86 (m, 2H, CH=CH (trans-configuration), 7.26 (s, 1H, $C\textit{H}Cl_3$).

The mass spectrum of the PPF sample was taken to determine the possible end groups. The mass spectrum was not able to confirm the conversion of the *cis*-double bond to a *trans*-double bond because the repeat units of the polymers have the same masses. The spectrum in Figure 5 shows three different distributions and the corresponding end groups are shown in Figure 6. These are the same end groups that were present on the PPM found in Figure 3. This indicated that the end groups of the polymer were conserved during isomerization.

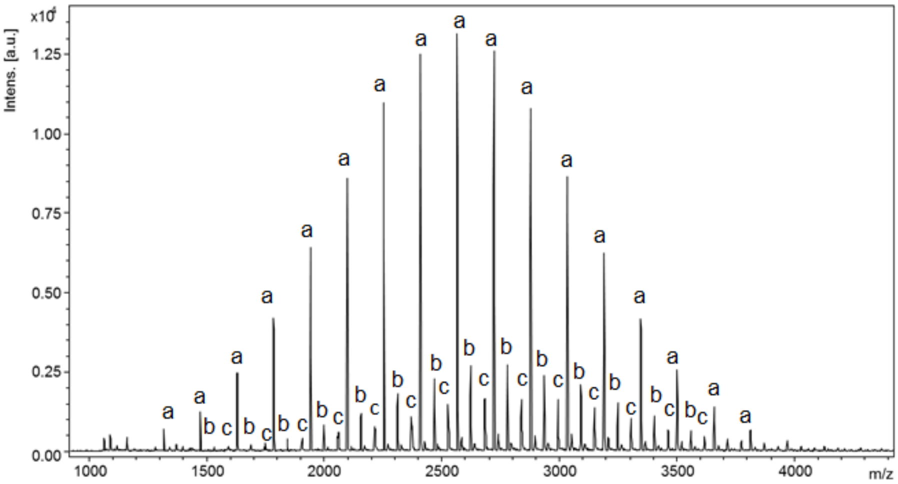


Figure 5: MALDI-TOF mass spectrum of Batch 1 poly(propylene fumarate) showing overall mass spectrum. The letters a, b, and c correspond to the three mass distributions of the sample. The end groups for the distributions are shown at the top of Figure 6.

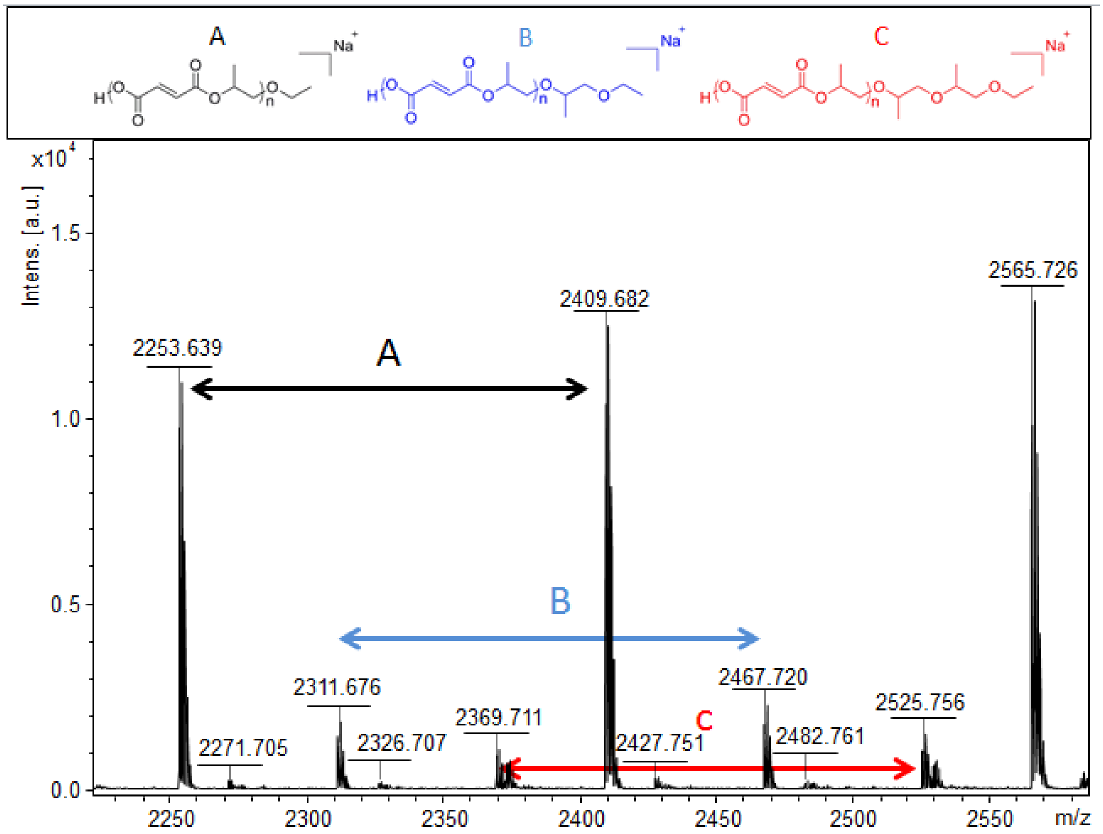


Figure 6: Expanded mass spectrum of Batch 1 poly(propylene fumarate) from Figure 5 depicting the three mass distributions A, B, and C. The end groups of the mass distributions A, B, and C are displayed above the mass spectrum.

The molecular mass of the polymer samples were determined from the MALDI-TOF MS. The peak with the highest intensity is reported as the peak molecular mass (M_p). The M_p is the mode of the molecular mass distribution and thus has the most chains at the given molecular mass. The M_p of Batch 1 PPM sample represented by the Figures in this work was 2410 Daltons (Da). The molecular mass of 2410 Da corresponds to a polymer chain containing 15 repeat units. The low number of repeat units means that the PPF produced should be considered an oligomer rather than a polymer. Following the isomerization, the M_p of Batch 1 PPF sample described in this work was 2566 Da. This corresponds to a polymer chain containing 16 repeat units. The small difference between the PPM and PPF samples suggests that the molecular mass of the polymer was conserved during isomerization and minimal chain scissions occurred.

The molecular mass of the polymer samples were also determined by SEC. The molecular weight of Batch 1 PPM was determined using Standard Series 1 calibration curve. Using the curve, Batch 1 PPM was determined to have an M_p of 3,357 Da and a molecular mass distribution of 2.213. The M_p determined using SEC is significantly higher than the M_p determined using MALDI-TOF MS and would suggest that the calibration curve is not ideal for the molecular mass range of the oligomers. To improve the analysis, Standard Series 2 calibration curve was created for the analysis of Batch 1 PPF. The SEC analysis resulted in an M_p of 2478 Da and a molecular mass distribution of 6.539. The large molecular mass distribution was due to a shoulder attached to the polymer peak. The shoulder is likely a result of an error in the injection as the mass spectrum in Figure 6 does not display a shoulder on the mass spectrum.

Modification to the work up of PPM: washes.

The purification steps for PPM in the original method were time consuming and labor intensive. These traits are not ideal for large scale production. For this reason, many of the modifications made in this study were done to improve or replace this portion of the procedure. The first change to the purification of the PPM was to remove the dilute acid wash step. The dilute HCl wash was used to remove the $Mg(OEt)_2$ initiator. The amount of acid used during the acid wash was based on the amount of initiator placed into the reaction vessel prior to the reaction. This value was only an estimate of the amount of initiator remaining in the solution after consumption during the reaction. The excess acid that was not used to quench the initiator most likely increased the acidity of the reaction mixture. In turn, the number of water washes needed to obtain a solution with a neutral pH was likely greater than necessary had the HCl not been used. To reduce the number of water washes, the addition of an acid wash step was removed completely.

The remaining acidity in the water washes was likely due to the unreacted maleic anhydride. The maleic anhydride is known to react with water to form maleic acid and fumaric acid.[19] The formation of these byproducts was likely the cause for the number of washes in purification of PPM. The acidity of the washes was assumed to be sufficient to quench the initiator, but further testing is required to confirm this.

The next change to the procedure was created to prevent the formation of emulsions during the water washes. An example of a typical emulsion can be seen in Figure 7. Emulsions are caused by the shaking of the separatory funnel. The shaking disperses the organic layer into the aqueous layer where the aqueous solution forms a layer around the small organic droplets. These droplets are called micelles. When many micelles form at the same time, the solution becomes an emulsion.[20] Emulsions are not thermodynamically stable, so they will separate over time.[21] However, the drawback to just allowing emulsions to separate on their own is that they can take hours or days to do so. Due to the number of washes required, waiting is not a practical method.

Figure 7: Example of the emulsion that forms during DI water/brine washes that can take hours or days to separate.

Another common method for breaking emulsions is to add salts to the solution. The salt in the aqueous layer disrupts the formation of the micelles and emulsions.[19] Using this principle, the water washes were changed to brine washes of saturated sodium chloride solutions. However, even with the brine washes, the emulsions could not be completely avoided. The variability in the emulsion formation and the additional time required to allow them to separate would not be ideal for large scale production. Additionally, the large number of washes required to remove all of the acidic impurities would involve a considerable amount of labor and time at the batch reactor scale. From this information, it was concluded that alternative purification methods would be needed for large scale batches.

Modification to the work up of PPM: distillation of maleic anhydride.

The most important components to remove during the PPM purification are the unreacted monomers. These needed to be removed in order to prevent side reactions during isomerization reaction. The propylene oxide monomer is easier to remove because of its low boiling point and can be separated by rotary evaporation. However, the maleic anhydride monomer is difficult to remove due to its high boiling point and low volatility. In the original procedure, the maleic anhydride was slowly removed by the washes. But, the combination of the numerous washings and emulsion formations added a significant amount of time to the purification step. With this in mind, another method of removing maleic anhydride was needed. The new technique used to remove the maleic anhydride was distillation. Maleic anhydride is a solid at room temperature but has a boiling point of 202 ^{o}C. At a low enough pressure (3-6 torr), the maleic anhydride could be distilled out of the reaction mixture at relatively low temperatures (50-60^{o}C).

The setup in Figure 8 was attached to a Schlenk line. The round bottom flask on the left side was filled with the reaction mixture of Step 1 and contained toluene (boiling point: 111 ^{o}C), propylene oxide (boiling point: 34 ^{o}C), maleic anhydride, and PPM. The system for cooling the trap was either liquid nitrogen or dry ice in isopropanol. The isopropanol bath was preferred over the liquid nitrogen because the liquid nitrogen would boil away quickly. The first three hours under vacuum was completed at room temperature. During this period, the propylene oxide and some of the toluene was removed from the reaction mixture. During the next three hour period, the oil bath was heated to 45 ^{o}C. The majority of the toluene distilled off during this period. Some maleic anhydride (white crystals) collected in the connector and cold trap. These white crystals can be seen in the connector shown in Figure 8. Finally, the oil bath was heated to 60 ^{o}C for nine more hours. During this period, the majority of the maleic anhydride was distilled off. The step-wise increase in temperature allowed for more efficient removal of the lower boiling point components before removal of the higher boiling point components. If the temperature was increased too quickly, the distillation mixture would bubble over into the connector and block the vacuum in the connector.

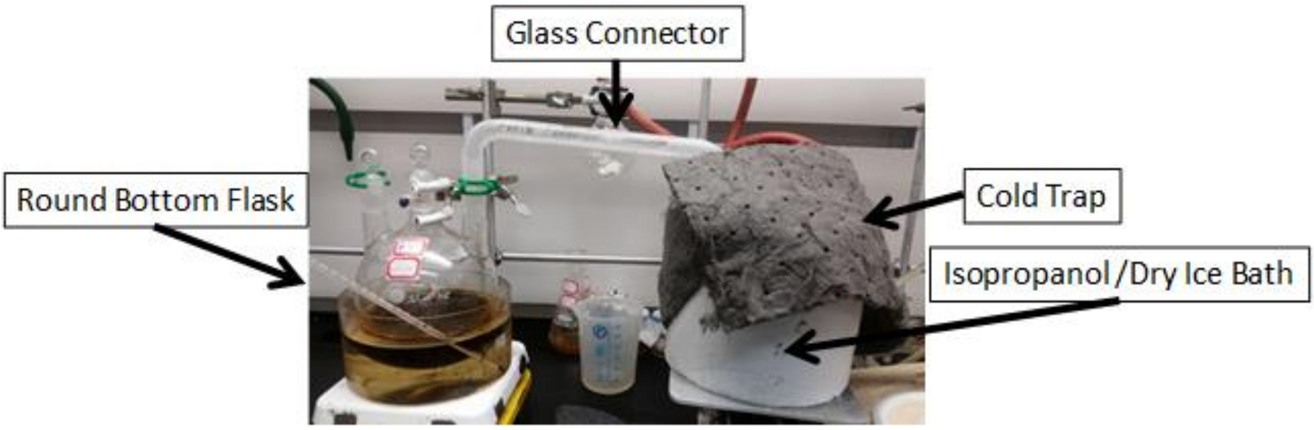


Figure 8: Representative vacuum distillation setup used in the distillation of Batch 2 poly(propylene maleate).

The crude ^{1}H NMR spectrum of Batch 2 PPM is shown in Figure 9. The chemical shift for the maleic anhydride occurs at 7.33 ppm and the chemical shifts for toluene are at 7.15-7.25 ppm and 2.30 ppm. The ^{1}H NMR spectrum of Batch 2 PPM following the distillation is shown in Figure 10. The signals for toluene have disappeared and the maleic anhydride peak significantly decreased. The presence of maleic anhydride even after the long distillation time was likely due to the viscosity of the PPM. By the time the temperature was increased to 60 ^{o}C, almost all of the solvent had been removed. This means, that PPM was the only major component left. The lack of a solvent was a problem as PPM has an intrinsic viscosity between 0.0288-0.0780 dL/g.[14] The thick nature of the mixture made it impossible for the magnetic stir bar to function properly. Without proper stirring, the maleic anhydride was difficult to remove from the solution. The problem could be seen visually, as large bubbles formed at the surface of the mixture when impurities tried to escape. This suggested that the maleic anhydride had difficulty escaping from the mixture.

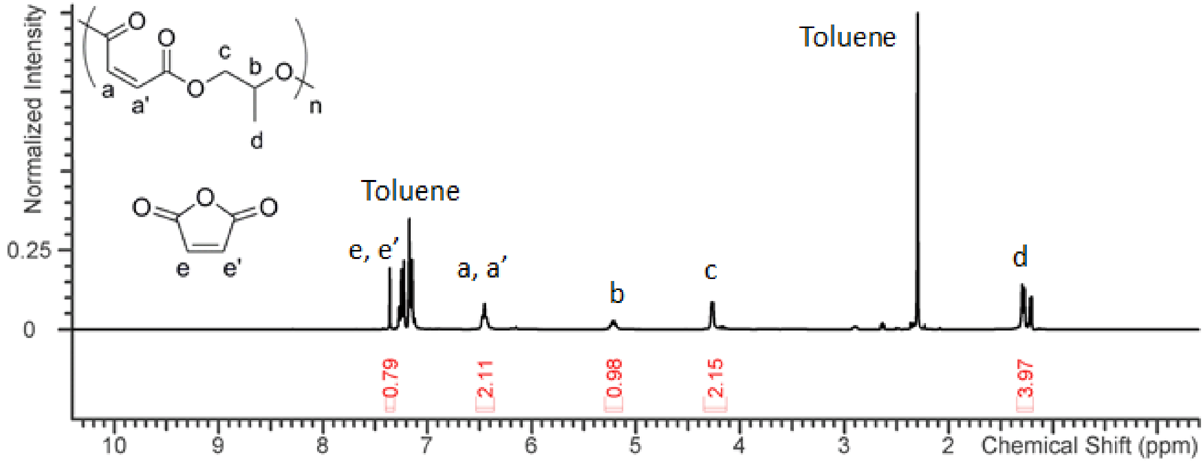


Figure 9: Crude ^{1}H NMR spectrum of Batch 2 poly(propylene maleate). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.27-1.29 (d, 3H, $OCH_2CH(C\mathit{H_3})O$), 2.30 (s, 3H, $C\mathit{H_3}(C_6H_6)$) 4.26-4.27 (m, 2H, $OC\mathit{H_2}CH(CH_3)O$), 5.17-5.25 (m, 1H, $OCH_2C\mathit{H}(CH_3)O$), 6.43-6.47 (m, 2H, CH=CH (*cis*-configuration), 7.12-7.27 (m, 6H, $CH_3(C_6\mathit{H_5})$), 7.36 (s, 2H, Maleic Anhydride).

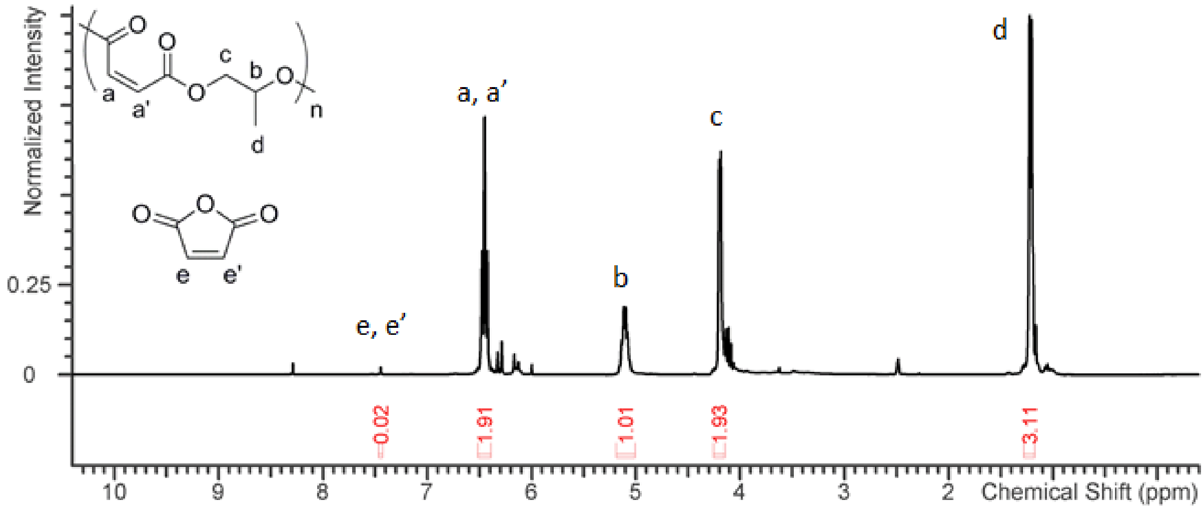


Figure 10: ^{1}H NMR spectrum of Batch 2 poly(propylene maleate) after vacuum distillation cycle. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.27-1.29 (d, 3H, $OCH_2CH(C\mathit{H_3})O$), 2.49 (m, DMSO-d_5) 4.16-4.20 (m, 2H, $OC\mathit{H_2}CH(CH_3)O$), 5.08-5.13 (m, 1H, $OCH_2C\mathit{H}(CH_3)O$), 6.42-6.48 (m, 2H, CH=CH (*cis*-configuration), 7.45 (s, 2H, Maleic Anhydride), 8.29 (s, H, $C\mathit{H}Cl_3$).

One way to improve the distillation method would have been to add a high boiling solvent prior to the distillation. The addition would have decreased the viscosity of the mixture and allowed the magnetic stirrer to operate effectively. Even if the procedure had been improved, the distillation would still not have been an effective method for removing acidic impurities from the mixture. In order to remove these, the mixture would still have needed to be washed in brine several times. The washes would have added more time and possibly caused emulsions. The long distillation and the requirement of some brine washes did not decrease the time or labor of the purification step significantly compared to that of the brine washes. The distillation also added additional equipment that would be required for a large scale production. These drawbacks made this method unfavorable for use in a batch reactor.

Modification to the work up of PPM: precipitation in ether.

One of the drawbacks to the distillation technique was that it required brine washes after distillation. This method of purification was unacceptable, so another purification technique was tested. Precipitation was chosen as a possible purification method because the polymer was not soluble in diethyl ether but maleic anhydride was. For the precipitation, the reaction mixture was concentrated using the rotary evaporator until the mixture became viscous. The mixture was then added dropwise into diethyl ether. The volume of ether used for the precipitation was approximately ten times the concentrated reaction mixture.

A ^{1}H NMR was taken before and after precipitation to determine its effectiveness. The pre-precipitation ^{1}H NMR spectrum is shown in Figure 11. The spectrum contains the four chemical shifts expected for PPM at 1.36-1.40 ppm, 4.31-4.34 ppm, 5.32-5.33 ppm, and 6.30-6.33 ppm. The signal at 2.41 corresponds to the methyl protons of toluene used as the solvent in Step 1. The signal at 7.22-7.43 ppm is likely due to the aromatic protons of the toluene. The remaining toluene in the sample was not a major concern as the solvent could have been removed by allowing the sample to dry overnight under vacuum. The main focus of the precipitation was to reduce or eliminate the signal at 6.94 ppm that corresponded to the maleic anhydride. To compare, the ^{1}H NMR spectrum of the post-precipitation PPM is shown in Figure 12. In Figure 12, the four chemical shifts expected for PPM are present but, the protons of the maleic anhydride at 7.02 ppm are much less prominent than in Figure 11. The results confirm that a significant amount of maleic anhydride was removed by precipitation.

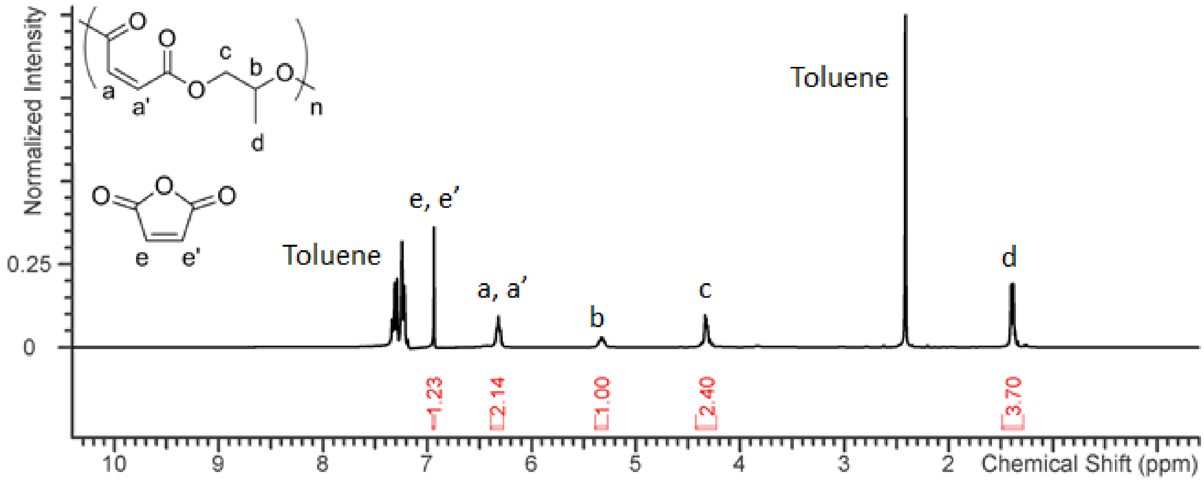


Figure 11: Crude ^{1}H NMR spectrum of Batch 3 poly(propylene maleate).^{1}H NMR (300 MHz, Chloroform-*d*) δ ppm 1.36-1.40 (d, 3H, $OCH_2CH(CH_3)O$), 2.41 (s, 3H, $CH_3(C_6H_6)$) 4.31-4.34 (m, 2H, $OCH_2CH(CH_3)O$), 5.32-5.33 (m, 1H, $OCH_2CH(CH_3)O$), 6.30-6.33 (m, 2H, CH=CH (*cis*-configuration), 6.94 (s, 2H, Maleic Anhydride), 7.22-7.34 (m, 6H, $CH_3(C_6H_6)$.

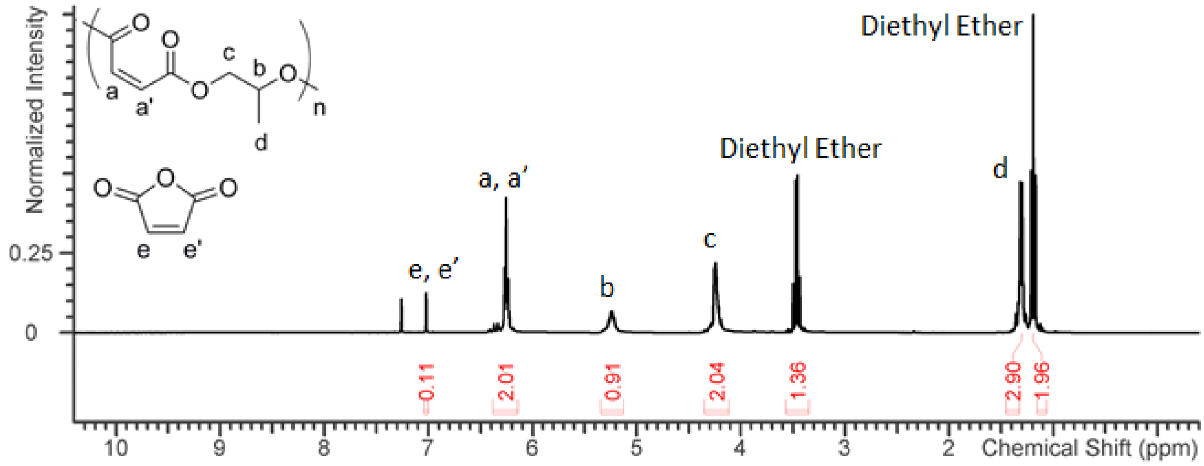


Figure 12: ^{1}H NMR spectrum of Batch 3 poly(propylene maleate) after precipitation in diethyl ether. ^{1}H NMR (300 MHz, Chloroform-*d*) δ ppm 1.17-1.21 (t, 6H, $O(CH_2CH_3)_2$), 1.30-1.42 (d, 3H, $OCH_2CH(CH_3)O$), 3.43-3.50 (m, 4H, $O(CH_2CH_3)_2$) 4.23-4.25 (m, 2H, $OCH_2CH(CH_3)O$), 5.21-5.27 (m, 1H, $OCH_2CH(CH_3)O$), 6.23-6.27 (m, 2H, CH=CH (*cis*-configuration), 7.02 (s, 2H, Maleic Anhydride), 7.26 (s, 1H, $CHCl_3$).

The precipitation method is a fairly quick and low labor technique that can be used to reduce the amount of maleic anhydride and remove the acidic impurities. This made it more advantageous than the brine washes and distillation as it was quicker and more efficient. The precipitation method did not require any brine washes so there was no chance for emulsions to form. The precipitation also removed the need for a high-boiling point solvent that would have been required in the distillation step. The main downside to the precipitation is the large amount of diethyl ether that is required. Diethyl ether is very volatile and evaporates into the surrounding air quickly, which meant that safety measures had to be taken to ensure that there was no possibility for sparks or heat sources.

Conclusion

Several methods were attempted to optimize the purification of PPM. The brine wash method was plagued by emulsions and required a significant amount of time and labor to work through. The distillation at reduced pressure method took a significant amount of time to remove the majority of the maleic anhydride due to the viscosity of PPM. The method also required brine washes to remove the acidic impurities. The best method for the purification of PPM was precipitation in diethyl ether. The precipitation method was significantly faster than the other methods and also removed the majority of the impurities in the PPM samples. The next step will be to attempt to improve the purification of PPF. When that is completed, the reaction will be ready for implementation at the batch reactor scale.

Future Work

During the end of the semester, some supplementary work will be done for this project. The first of which is a study aimed at optimizing Step 4: work up of PPF. This test will compare the effectiveness of PBS washes against precipitation into diethyl ether and hexanes. The study will also look into how many PBS washes is required to remove the impurities in the PPF. The aim of the study is to either decrease the number of washes or replace them with another more efficient method of purification. If successful, the reaction will likely be ready for batch reactor studies.

The next study will determine where in the purification of PPM the $Mg(OEt)_2$ is removed. The removal of the initiator will be determined by elemental analysis of samples from before and after precipitation in diethyl ether. If the precipitation is found to be ineffective at removing the initiator, the number of brine washes required for effective removal will be determined.

Acknowledgements

I would like to thank Dr. Matthew L. Becker for the opportunity to conduct undergraduate research in his laboratory. Next, I would like to thank Yuanyuan Lou and Alex Kleinfehn for their support, guidance, and teaching throughout the research. I would also like to thank the Becker Group for their kindness and openness to undergraduate researchers. I thank Dr. Claire A. Tessier and Dr. Matthew J. Panzner for taking the time to be my readers. Lastly, I would like to thank 3D BioResins for funding this work.

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Appendix 1

Safety Considerations

Laboratory safety training was required before laboratory work could begin. The main safety concern in the laboratory was exposure to the chemicals or solvents in the laboratory. To aid in preventing exposure, safety glasses, lab coats, and gloves were required at all times when in the laboratory. To reduce exposure to fumes, handling of chemicals and reactions was mainly completed in the hood. Solvent spills were absorbed with an inert dry material and then placed into the appropriate waste container. If any skin contact occurred, the area was flushed with water for 15 minutes. Finally, solvent waste was disposed of in the appropriate halogenated or non-halogenated waste container.

The use of pressurized glassware was another primary safety concern. Pressurized systems included Schlenk lines, vacuum pumps, and rotary evaporators using aspirators or vacuum pumps. A graduate student provided training before the use of each system. Glassware that used in pressurized systems was inspected for cracks, chips, or stars. If any of these defects were found, the glassware was not used. The glassware was then either sent for repair or discarded in the glass waste.

Special precautions were taken during the use of diethyl ether. During the use of ether, all sources of heat, sparks, or flame were either removed or turned off. To prevent backup of ether vapors in the chemical hoods, the containers of ether were covered with foil during the precipitation steps.