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Synthesis and Catalytic Testing of a Proline Functionalized Amphiphilic Block Copolymer

by

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Thesis

Submitted to the Department of Chemistry

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in partial fulfillment of the requirements for the degree of

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in

Chemistry

Thesis Committee:

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Abstract

Catalysts are reagents used to reduce the amount of energy that a reaction needs to execute, allowing it to proceed at a higher rate while not being consumed. The use of catalyst functionalized amphiphilic copolymer allows easier recovery of the catalyst at the end of the synthesis and allows for the reaction. In water, under appropriate conditions, the amphiphilic block copolymers will form micelles and allow the reaction to occur on the interior of the micelle. The synthesis of amphiphilic copolymer with a hydrophobic *O*-methacryloyl-*trans*-4-hydroxy-L-proline and methyl methacrylate end and a hydrophilic acrylic acid end was characterized. The polymer was tested as an asymmetric catalyst for an aldol reaction in aqueous conditions. The polymer was able to successfully stereoselectively catalyze the reaction with a preference for the anti-addition.

Table of Contents

List of Figures

List of Schemes

List of Abbreviations

AIBN: azobisisobutyronitrile

Boc-MAP: *N*-Boc-O-methacryloyl-*trans*-4-hydroxy-L-proline

Boc: *tert*-Butyloxycarbonyl

CTA-8: 2-(dodecylthiocarbonothioylthio)-2- methylpropanoic acid

^{1}H-NMR: Proton Nuclear Magnetic Resonance

MAP: 4-(methacryloyloxy)-proline [equivlant to O-methacryloyl-*trans*-4-hydroxy-L-proline]

P[MMA:MAP]: Poly(methylmethacrylate-co-*N*-boc-O-methacryloyl-*trans*-4-hydroxy-L-proline)

P[MMA:MAP:B:AA]: Poly(methylmethacrylate-co-*N*-boc-*O*-methacryloyl-*trans*-4-hydroxy-L-proline-block-acrylic acid)

RAFT: Reversible Addition-Fragmentation chain Transfer

Chapter 1: Introduction

1.1 Polymer Introduction

Polymers are large molecules that are made up of long chains of repeating units of monomers. The properties of polymers differ greatly from their monomers. For example, vinyl chloride is known to cause steatohepatitis and liver cancer[1]; however, polyvinyl chloride is safe enough to use as piping for water systems.

1.2 RAFT Polymerization

One of the most common polymerization techniques is known as reversible addition-fragmentation chain transfer (RAFT) polymerization. RAFT polymerizations are popular due to their nature as living polymers. A living polymerization is defined as "a chain polymerization from which irreversible chain transfer and irreversible chain termination are absent."[2] This means that after the polymerization has been completed and all the monomer has been consumed, the polymer does not terminate and can instead be reinitiated with the addition of further monomer.

RAFT polymerization is able to achieve its living status through the use of the thiocarbonylthio group. The thiocarbonylthio group is capable of transferring from the various actively growing polymer chains. Whenever the thiocarbonylthio is bound to a polymer chain, it prevents that chain from continuing to grow. This provides all the growing chains with an equal probability to increase the chain length. Due to the fact that the growth of all of the chains is slowed equally, it allows all of the chains to grow equally. This means that the polymers formed using RAFT polymerization have a narrow dispersity, allowing them to be easily controlled.[2-4]

1.3 Copolymers

Due to the living nature of RAFT polymers, they can easily be grown into copolymers. Copolymers are polymers that are made of two or more monomers. Copolymers can be produced by either simultaneous or sequential reaction of the monomer. If the monomers are reacted simultaneously, the resulting structure can range from an alternating copolymer, where monomer A is followed by monomer B then monomer A again until all the monomer is used up, to a truly random copolymer where either monomer can be equally likely to follow the previous monomer.

A polymerization where the monomers are added sequentially can result in a block copolymer. Block copolymers are formed by fully polymerizing monomer A then following that by fully polymerizing polymer B. This makes it so there are two completely different blocks of monomers with completely different properties bound together. It is possible to then construct an amphiphilic copolymer, allowing one end of them to dissolve in an aqueous solution and the other in organic solvents.

1.4 Self Assembly of Block Copolymers

Due to the amphiphilic nature of block copolymers, they are able to form micelles when placed in various solutions.[5,6] A micelle in aqueous solution is formed when the hydrophobic block of the copolymer folds inside the hydrophilic block, making it so that only the hydrophilic monomer is exposed to water, protecting the hydrophobic monomer.[7] The formation of micelles is similar to that of surfactants of smaller molecules, such as soaps. The primary difference between small molecule micellization and polymer micellization is due to the large size of the molecule, which lowers the critical association concentrations of the polymers, making them more stable and, thus, potentially preferable.[8-10] The critical association concentration is defined

as the concentration required for a surfactant, or a polymer, to form a micelle. Polymers have significantly lower critical association concentrations than smaller surfactants due to a combination of electrostatic intermolecular forces, dispersion, and the hydrogen bonding associated with the hydrophilic block.[11,12] When the polymer achieves the critical association concentration, aggregates begin to form, and eventually the aggregates form micelles as the local concentration of the polymer increases.[13,14]

Another factor that controls micellization is the temperature of the system. Temperature affects micelles in various ways. As the temperature increases, it can cause a stable micelle to destabilize due to the increased mobility of the chains due to the added energy, which causes the micelle to disassociate.[15] For some polymers, however, the increase in temperature can also take a fully disassociated polymer and cause the polymer to initiate micellization.[16,17]

The ability of the polymer to ionize due to a change in the pH of the solution is yet another cause of the micellization of a polymer. For some polymers that are completely disassociated when ionized in acidic conditions, as the pH increases the polymer will begin to aggregate and micellize.[18] It has also been found that polymer chains may disassociate at higher pH as the carboxylic acids in the polymer are deprotonated and made more water soluble.[19]

1.5 Organocatalysis

In the modern era, catalysis has become an essential tool for chemists. Catalysts have the ability to reduce the requirements for a reaction, such as allowing the reaction to run at a lower temperature, run at a higher level of efficiency, or run with control of the stereochemistry of the reaction.[20] Historically, organometallic catalysts have been the primary catalyst for most reactions; however, they can be quite expensive due to the fact that each organometallic catalyst

is tailor made to a specific reaction.[20] With the increasing importance of green chemistry, having a component of a reaction that can be recovered at the end of the reaction has become vital to chemists worldwide.

Recently, organocatalysis, the use of organic molecules as catalysts, has become more common due primarily to their significantly lower price compared to that of typical organometallic catalysts. The lower price is due to a combination of how readily available the organocatalysts are, especially those based off of common amino acids, and the versatility of the catalysts. Proline, for example, is capable of catalyzing a variety of reactions such as aldol reactions, intramolecular α-alkylation reactions, the Mannich reaction, the Michael reaction, and many more.[20]

1.6 Polymers in Organocatalysis

Polymers have recently come to the forefront as organic catalysts.[21,22] By utilizing the amphipathic nature of a block copolymer, it may be possible to create mini hydrophobic environments, within which a reaction, such as the aldol reaction, can take place.[21] If a catalyst for the aldol reaction, such as proline, is built into the backbone of the polymer, when the polymer micellizes the substrates would be entrapped within the micelle in proximity to the reaction site, which would enable the catalysis of the reaction. Once the reaction is finished the micelle can be disassociated, which will cause the hydrophobic aldol product to precipitate out of solution, allowing the product to be isolated and collected. The polymer catalysts can then be reused for the next batch of reactions.

1.7 Proline as an Organocatalytic Building Block

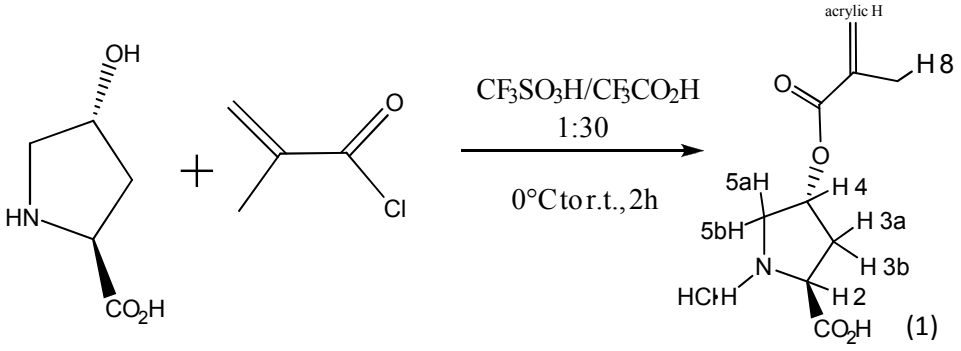
Proline has been used to make functionalized copolymers in prior studies. Evans et al. was able to successfully synthesize a variety of proline functionalized copolymer using a polystyrene backbone. These polymers were polymerized with a high degree of control and excellent enantioselectivity, and they were able to successfully incorporate various degrees of active monomer.[23]

Cotanda et al. utilized functionalized copolymers containing organocatalysts to form nanoreactors to catalyze aldol reactions. They were able to synthesize temperature sensitive amphiphilic block copolymers, through which they were able to form micelles at low temperatures and break up the micelles at high temperatures. The ability to control the micellization of the copolymers allowed them to recover the catalyst containing polymer and reuse it in further reactions. The catalyst was also able to increase the acylation rates of the aldol reaction up to 100 times greater than unsupported catalyst in organic solvents.[24]

Chapter 2: Results and Discussion

2.1 Synthesis of the Catalytic Monomer:

Scheme 1: Synthesis of *O*-Methacryloyl-*trans*-4-hydroxy-L-proline Hydrochloride

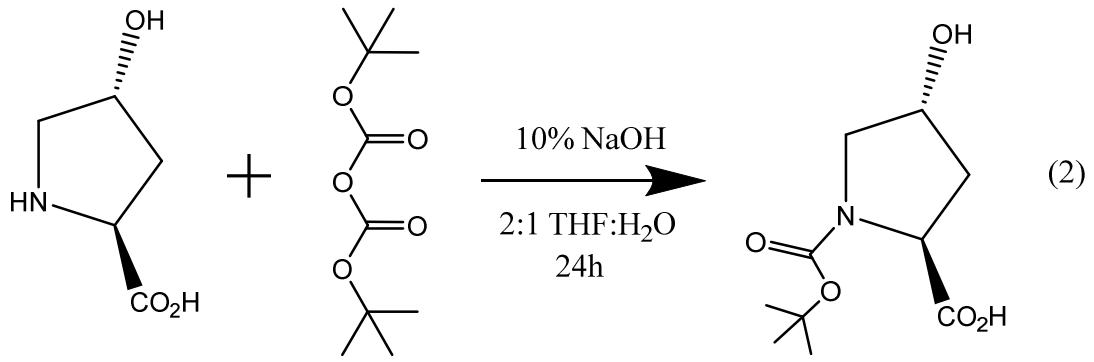


An initial attempt was made to form the ester of *trans*-4- hydroxyproline and methacrylate without the use of a protecting group. The product (1) was successfully synthesized at a 22.1% yield from *trans*-4-hydroxyproline and methacryloyl chloride (Scheme 1). The presence of the product was verified by ^{1}H-NMR; however, it was synthesized in its hydrochloride form. This caused issues with the next step in the reaction, due to the fact that no solvent was found which could dissolve all the necessary reagents for the polymerization. Also, it was discovered that any attempt to remove the hydrochloride from the product caused the MAP to degrade and become unusable.

After the unprotected HCl salt of the MAP failed to polymerize, it was then decided to synthesize the MAP using a protecting group (Scheme 2). *tert*-Butyloxycarbonyl (Boc) was chosen as the protecting group due to its known ability to protect amines. The Boc-protected

proline was successfully synthesized with a 50.4% yield and was verified via ^{1}H-NMR (Scheme 2). This is the product that was used in further experiments.

Scheme 2: Synthesis of *N*-boc-*trans*-4-hydroxyproline

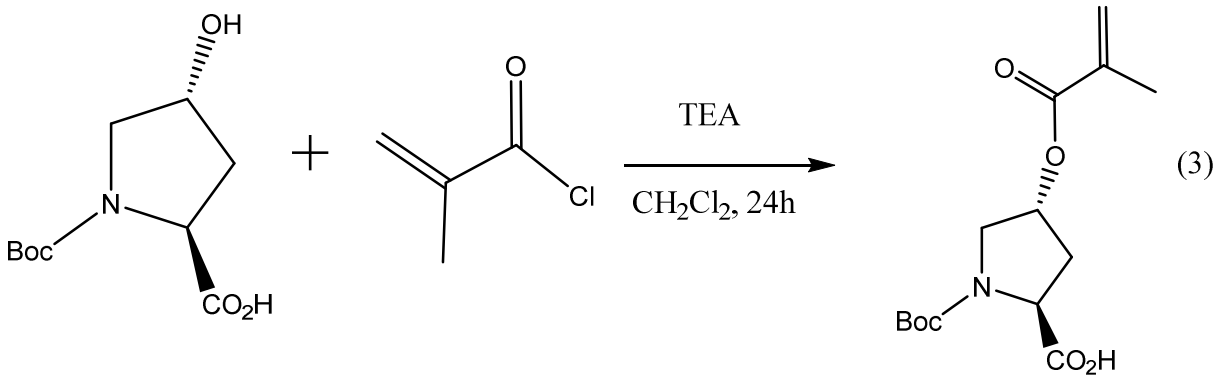


(2)

After the proline was protected, the next step was to couple it with a polymerizable group by a reaction with methacryloyl chloride (Scheme 3). This reaction was run under milder conditions and successfully produced the Boc-protected MAP (2). While the Boc-protected MAP was synthesized, the reaction needed to be purified via column chromatography using 1:1

hexanes:diethyl ether, which drastically reduced the isolated yield to 8%, while the yield was low it was extremely pure as verified by ^{1}H-NMR.

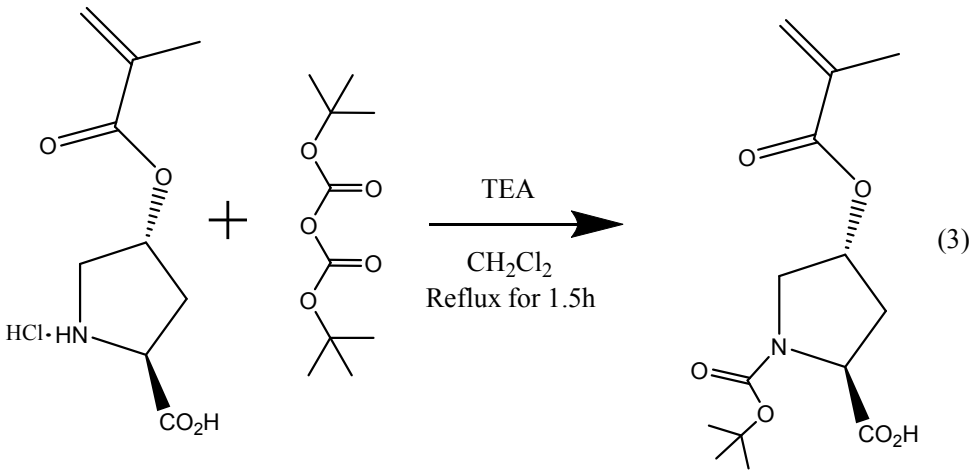
Scheme 3: Synthesis of *N*-boc-*O*-methacryloyl-*trans*-4-hydroxy-L-proline



(3)

Due to the low yield of this pathway, it was determined that it was not efficient enough to be utilized for the synthesis of the Boc-protected monomer. After some literature research, a new pathway (Scheme 4) was found that expanded upon the original technique of Scheme 1.[25] This pathway was chosen due to the fact that the first attempt had an acceptable yield, and by protecting the hydrochloride monomer with Boc, it would overcome the inability of the reagents to dissolve in a single solvent.

Scheme 4: Synthesis of *N*-boc-*O*-methacryloyl-*trans*-4-hydroxy-L-proline

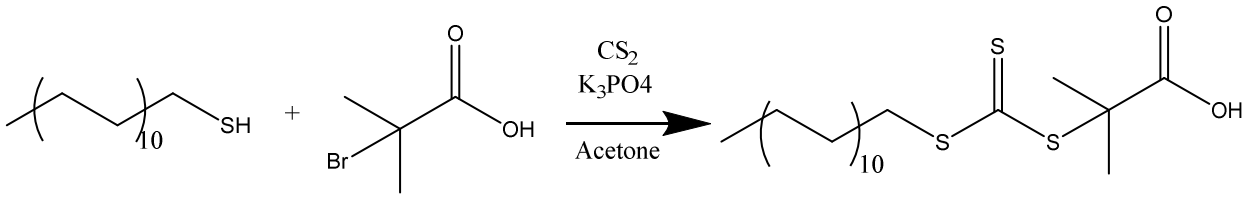


(3)

By utilizing the reaction shown in scheme 4, *N*-boc-*O*-methacryloyl-*trans*-4-hydroxy-L-proline (Boc-MAP) was successfully synthesized with an overall yield of 89.9%. Due to the overwhelming success of this reaction, the catalytic monomer was efficiently synthesized, and the project was able to move on to the synthesis of the amphiphilic block copolymer.

2.2 Synthesis of the Amphiphilic Block Copolymer

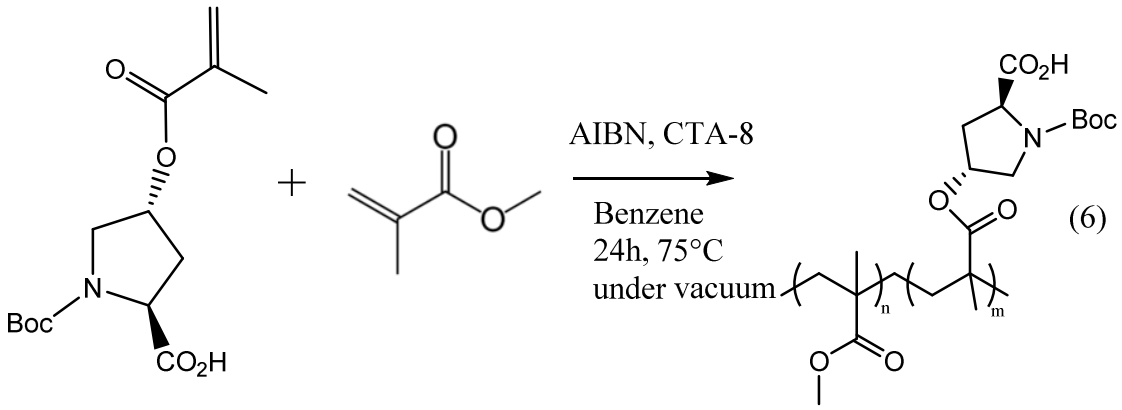
Scheme 5: Synthesis of CTA-8



In order to synthesize the block copolymer, a hydrophobic random copolymer containing both methyl methacrylate and the Boc-MAP was first required. To form the polymer, RAFT polymerization was used using azobisisobutyronitrile (AIBN) as the initiator and 2-

(dodecylthiocarbonothioylthio)-2-methylpropanoic acid (CTA-8) as the chain transfer agent. Before the polymerizations could be performed, it was necessary to synthesize CTA-8. The procedure of Skey et al.[26] was followed for the synthesis of CTA-8 (Scheme 5) and resulted in a 74.9% yield.

Scheme 6: Random copolymerization of polymethylmethacrylate-co-*N*-boc-*O*-methacryloyl-*trans*-4-hydroxy-L-proline copolymer

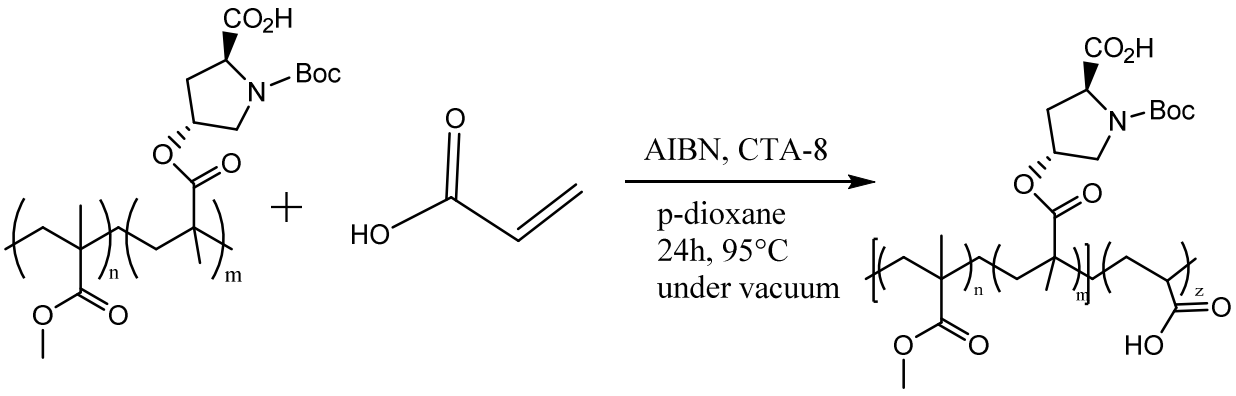


With all the reagents prepped, the synthesis of polymethylmethacrylate-co-*N*-boc-*O*-methacryloyl-*trans*-4-hydroxy-L-proline copolymer (PMMA:MAP) could begin (Scheme 6). For this copolymer, the aim was to have 100-unit long monomer chains at an 8:2 ratio of methyl methacrylate to the Boc-MAP. In order to achieve this, a 1000:10:1 molar ratio of monomer to CTA-8 to AIBN was used. After 24 hours, ^{1}H-NMR showed that the conversion was over 95% based on the ratio of unreacted methyl methacrylate monomer to methyl methacrylate monomer incorporated into the polymer. Comparison of the peaks at 5.557 ppm and 5.609 ppm in the ^{1}H-NMR spectrum showed that the polymer consisted of methyl methacrylate and the Boc-MAP in a roughly 8:1 ratio. This indicates that the random polymerization is slightly preferential to the

catalytic monomer of the Boc-MAP over the methyl methacrylate, which in turn means that there is a slightly higher catalyst content in the polymer than intended. After purification of the product via precipitation in hexanes, the mass recovery for this polymerization was 63.67%.

After the random copolymer was synthesized, the next step was to begin the polymerization of the block copolymer (Scheme 6). For the block copolymer, it was desired that the hydrophilic acrylic acid chain length be of equal chain length to the hydrophobic random copolymer.

Scheme 7: Synthesis of poly(methylmethacrylate-co-*N*-boc-*O*-methacryloyl-*trans*-4-hydroxy-L-proline-block-acrylic acid) (P[MMA:MAP:AA])



After the polymerization of the block copolymer, an accurate yield was unable to be determined. This was due to the fact that after 48 hours, prior to the product being utilized in the next step, the product had a 111% mass recovery. This indicates that solvent was still trapped within the polymer matrix. Also, due to technical difficulties, an adequate ^{1}H-NMR was unable to be taken of the product, thus making it impossible to determine the efficiency or purity of the reaction. A test was done to determine if any hydrophilic monomer was added to the product, by testing the micellization of the block copolymer, which will be discussed later.

After the polymerization of the block copolymer, it was necessary to deprotect the catalyst by removing the Boc group. The overall yield of this step was quite low, at 27.6%. This number is artificially low due to the fact that the starting block copolymer was still wet at the onset of this reaction.

2.3 Micellization Test

A series of ^{1}H-NMR spectra were obtained to determine whether the block copolymer was capable of micellization. Samples were made of the copolymer in solvent mixtures of 100% p-dioxane, 75% p-dioxane:25% H_2O, 50% p-dioxane:50% H_2O, 25% p-dioxane:75% H_2O, and 100% H_2O. ^{1}H-NMR spectra of each sample were obtained at a series of temperatures: 25□, 40□, 60□ and 80□. Micellization was determined by monitoring the change of the methyl group attached to the backbone of the polymer to monitor the qualitative difference of the peak at the various solvent concentrations. If the copolymer is not in a micelle, the shapes of the peaks in the NMR are sharp, similar to what the standard peaks look like during the verification of the product. As more D_2O is added to the system, the hydrophobic P[MMA:MAP] block becomes more insoluble, which causes the chains to begin aggregating, thus forming micelles. As this happens the hydrophobic polymer chains get packed together and begin to decrease their mobility, which in turn causes the corresponding peaks to broaden out.[27] The micelles began forming at the 50:50 ratio but formed best in the 100% H_2O solvent system (Figure 1). Using this technique, it was determined that the temperature at which the micellization breaks for this copolymer is at roughly 60□. Due to these results, it is possible to say that while the exact ratio of the hydrophobic block to the hydrophilic block is still undetermined, there is a significant enough hydrophilic block attached to initiate micellization.

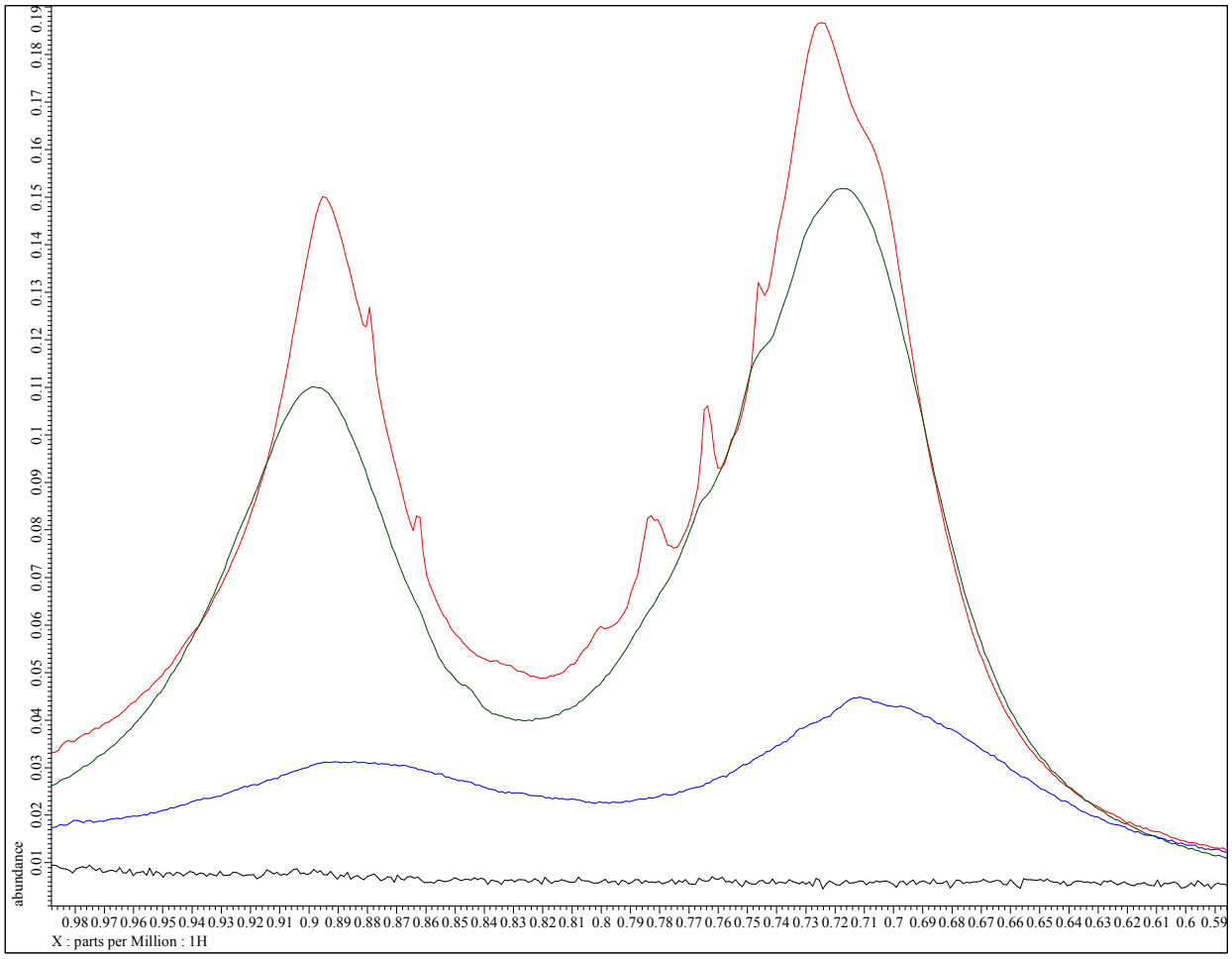


Figure 1. Data overlay of the ^{1}H-NMRs of the 100% D_2O solution of the block copolymer. Red is 100% p-dioxane, green is 75% p-dioxane: 25% D_2O, blue is 50% p-dioxane: 50% D_2O, and black is 100% D_2O. When the peak is very sharp it indicates that a micelle has not formed, and the broadening of the peaks as the percent of D_2O increases is due the micelle forming. This indicates that the block copolymer forms micelles in 100% water at room temperature.

2.4 Catalytic Testing

After verification of its ability to form micelles, the functionalized block copolymer was tested to see if it was able to asymmetrically catalyze the aldol reaction in an aqueous environment. Proline is a known organic catalyst for the aldol reaction. The test aldol reaction

for this catalyst was run using cyclohexanone and p-nitrobenzaldehyde, with water as its solvent. Four aldol reactions were run simultaneously with different catalysts; the block copolymer; P[MMA:MAP:B:AA], the random copolymer; P[MMA:MAP], *trans*-4-hydroxyproline, and no catalyst. It was expected that the block copolymer would catalyze the reaction the best, the random copolymer may catalyze the reaction a little but probably not much, and the *trans*-4-hydroxyproline and the sample with no catalyst were both chosen as negative controls due to the fact that the aldol reaction should not run with water as the solvent. The hydrophobic random copolymer was also tested alongside the block copolymer. The results of this test were quite interesting. The most efficient catalyst was the hydrophobic random copolymer, not the amphiphilic block copolymer, which remained true over all trials. There was a fivefold difference in the amount of product made between the random and the block copolymers, and both the reaction with the *trans*-4-hydroxyproline added catalyst and the reaction without an added catalyst did not make enough product to be within the detection limits of the ^{1}H-NMR. The fact that both the proline and the reaction with no catalyst made no product was understandable due to the fact that the reagents did not dissolve in the solution and would therefore have had a hard time interacting. The unusual thing was the fact that the random copolymer, which also was unable to dissolve in the solution, was a better catalyst than the micelle forming block copolymer.

As soon as the random copolymer was added to the water, it immediately settled to the bottom of the flask. When the other reagents were added, they also settled to the bottom of the flask, and within thirty minutes of the addition, a solid matrix was formed that was robust enough to prevent the stir bar from stirring. The random copolymer was the only catalyst that had this effect.

The preliminary hypothesis for this result was that the other reagents were absorbed into the solid matrix and proceeded to react within it, away from the solvent. This would have led to a similar state as the micelle; however, this solid matrix would have contained far more of the solid *p*-nitrobenzaldehyde. The *p*-nitrobenzaldehyde was unable to fully dissolve in any of the systems; even when the micelles formed for the block copolymer, a large percentage of the *p*-nitrobenzaldehyde still remained undissolved. Since the *p*-nitrobenzaldehyde was only in a fivefold excess compared to the cyclohexanone, if a large portion of the *p*-nitrobenzaldehyde remained undissolved, then the overall yield for the product would be significantly lowered.

While the yields for the catalysts were different than expected, both of the polymer catalysts were able to form a stereoselective product. The catalysts were heavily preferential for the anti-addition over the syn-addition. The diasteromeric ratio of *syn/anti* for the product with the highest crude yield was calculated to be 1:18 of *syn/anti* via ^{1}H-NMR (Figure 2). .

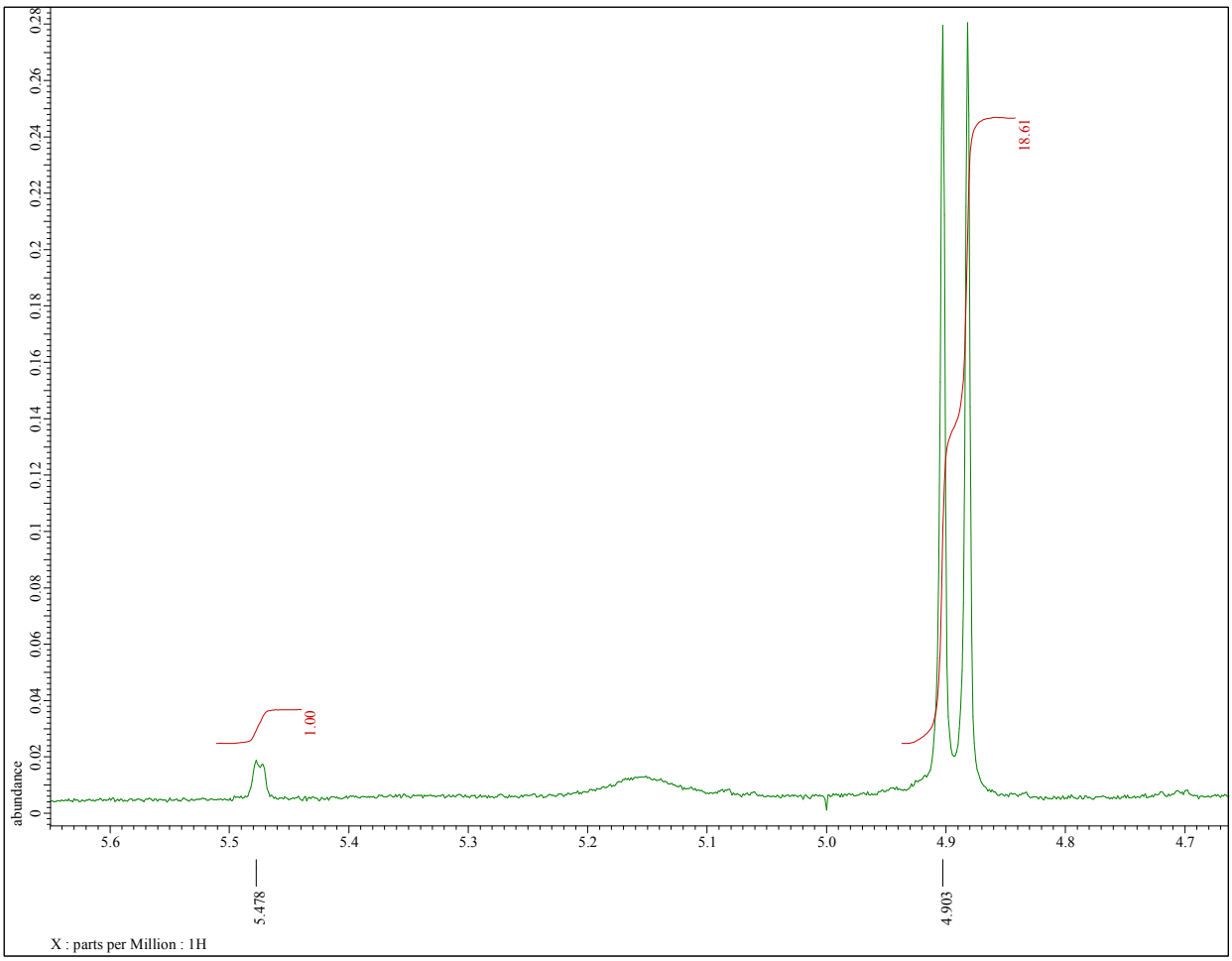


Figure 2. ^{1}H-NMR of the purest random copolymer catalyst test. The diastereomeric ratio of syn to anti for the product was calculated via ^{1}H-NMR, by comparing the relative peaks of the -C*H*OH peak in the product, which will show up at either 5.5 for syn-addtion or 4.9 for anti-addition. The diastereomeric ratio for this product was 1:19 syn:anti.

Chapter 3: Conclusions

After many hurdles, a successful procedure for the synthesis of polymethylmethacrylate-co-*O*-methacryloyl-*trans*-4-hydroxy-L-proline-block-acrylic acid was developed. Most of the steps of the synthesis had good yields and were relatively pure as determined via ^{1}H-NMR. The block copolymer was able to reliably micellize in aqueous conditions.

The catalyst testing gave many more questions than it answered, the most important of which is why the random copolymer is a more efficient catalyst than the block copolymer. However, it was determined that both of the polymer catalysts were able to selectively promote the formation of the anti-product over the syn.

Chapter 4: Future Work

The primary experiment that should follow this thesis is to determine why the random copolymer catalyzed the aldol reaction better than the block copolymer. After that is determined, how to purify the aldol reaction to determine the exact yields of each catalyst to have a more direct comparison should be investigated. It is also necessary to learn how to reliably recover the block copolymer from the aldol solution after the reaction has completed.

After these initial tasks have been completed for the aldol reaction, the next goal is to try to synthesize the MAP with different ratios of methyl methacrylate to the MAP to find the most efficient ratio to catalyze the aldol reaction. By better testing various ratios, we will be able to better understand how to optimize it. It is also recommended to test the MAP polymer on other reactions that proline is known to catalyze, such as the Mannich and Michael reactions.

Following that the next best direction for the research is to synthesize new polymers with different organocatalysts bound in the backbone of the polymer. Some potential organocatalysts would be α-diarylprolinol trimethylsilyl ether or piperidine.

While doing all of these different tests, it is also recommended to investigate how the change of the polymer backbone effects the micellization of the polymers. By understanding more on how to control polymer micellization, we will be able to investigate a variety of important subjects, such as using polymers as drug delivery systems.

Chapter 5: Materials and Methods

5.1 Materials

Proline, methacryloyl cloride, methyl methacrylate (mma) (99%), 2,2′-azobis(2-methylpropionitrile) (AIBN) (98%), di-*tert*-butyl dicarbonate ($(Boc)_2O$) (97%), 2-methyl-2-popanethiol (99%), carbon disulfide (99.9%), potassium phosphate tribasic (98%), and 1-dodecanethiol (98%) were obtained from Sigma Aldrich. Triethylamine (TEA) (99%), benzene (99%), cyclohexanone (99%), and p-nitrobenzaldehyde (99%) were obtained from Alfa Aesar. Tetrahydrofuran (THF) (99.9%) was obtained from Fisher Scientific; p-dioxane (99%) was obtained from EMD. Chain transfer agent-7 (t-butyl dodecyl carbonotrithioate) was synthesized by a literature procedure.[28]

5.2 Methods

5.2.1 Synthesis of *O*-Methacryloyl-*trans*-4-hydroxy-L-proline Hydrochloride (1):

Trifluoroacetic acid (1.2 mL, 1.79 g, 16 mmol) was placed in an ice bath. t*rans*-4-Hyrdoxyproline (0.5160 g, 3.935 mmol) was added to the trifluoroacetic acid. After 5 minutes, 2 drops of trifluoromethanesulfonic acid (0.10 mL, 0.17 g, 1.1 mmol) was added to the solution, and after 5 more minutes, methacryloyl chloride (0.75 mL, 0.80 g, 7.7 mmol) was added to the solution, which was then removed from the ice bath. After 20 minutes 0.2 mL of CF_3CO_2H was added dropwise until the solution turned colorless and clear. Then 15 mL of Et_2O was added and stirred vigorously over 20 minutes. The solution was vacuum filtered and then washed with several portions of Et_2O. The product was left to dry for 24 hours. The product was then recrystallized from acetone. Mass of 0.203 g (22.1% yield) of *O*-methacryloyl-*trans*-4-hydroxy-L-proline hydrochloride was obtained. Product was verified via ^{1}H-NMR in methanol d-4 (EF-1-

1C): 6.175 (t, 1H, acrylic), 5.758 (dt, 1H, acrylic), 5.480 (t, 1H, 4), 4.599 (ddd, 1H, 2), 3.678-3.722 (dd, 1H, 5a), 3.501-3.538 (dt, 1H, 5b), 2.623 (ddt, 1H, 3b), 2.427 (ddd, 1H, 3a), 1.943 (dd, 3H, 8).

5.2.2 Polymer Synthesis

Prior to polymerization, MEHQ inhibitor in the methyl methacrylate was removed by running the monomer through a small filter of silica. AIBN (0.0037 g, 0.23 mmol) was dissolved in 10 mL of p-dioxane to make a stock solution. CTA-7 (0.0285 g, .231 mmol), methyl methacrylate (0.81 mL, 0.75 g, 0.76 mmol), 1.0 ml of AIBN solution (0.023 mmol) and *O*-methacryloyl-*trans*-4-hydroxy-L-proline hydrochloride (0.201 g, 0.853 mmol) were mixed together. The solution was degassed with three cycles, and the flask was filled with nitrogen. The reaction was run at 85°C for 24 hours, resulting in a mustard yellow solution. The solution was slowly poured into 20 mL of hexanes, washing with minimal p-dioxane, and stirred until cloudiness was gone (when stirring was stopped all particles settled). The solution was decanted. And 0.198 g of product was formed (20.6% mass recovery). Product was analyzed via ^{1}H-NMR in DMSO (EF-1-9C), but no target product appeared to have formed.

5.2.3 Formation of *N*-Boc-*trans*-4-hydroxy-L-proline (Boc-MAP) (2)

trans-4-Hydroxy-L-proline (6.02 g, 46.0 mmol) was added to 90 mL of 2:1 THF: H_2O. Then 19.2 mL of 10% (2.5 M) NaOH was added to the solution; solution became murky clear while stirring and formed two clear layers when not stirring. Solution was stirred vigorously for 20 minutes. Di-*tert*-butyl dicarbonate (14.404 g, 66.00 mmol) was slowly added to solution to form a murky pale-yellow solution. The solution was stirred for 1 week. The THF was removed via vacuum, then a 10% by mass solution of potassium bisulfate in water was added to the

solution until the pH was around 2 (about 55 mL). The solution was extracted 3 times with ethyl acetate. The combined organic layer was then washed twice with water then once with brine, then dried with magnesium sulfate. The solution was dried under vacuum, and the mass of the product was 0.536 g (23.2 mmol, 50.4% yield). Product was verified via ^{1}H-NMR in $CDCl_3$ (EF-1-15A): 5.917 (br, 1H, OH), 4.474 (m, 1H, 4), 4.362 (m, 1H, 2), 3.548 (m, 1H, 5a), 3.451 (m, 1H, 5b), 2.260 (m, 1H, 3a), 2.092 (m, 1H, 3b), 1.452 (d, 9H, Boc).

5.2.4 Formation of *N*-Boc-*O*-methacryloyl-*trans*-4-hydroxy-L-proline (3)

Boc-MAP (0.511 g, 21.0 mmol) was mixed with triethylamine (0.521 g, 5.15 mmol) and about 5 mL of dry THF. The reaction was then placed in an ice bath. Methacryloyl chlorine (1.43 mL, 1.53 g, 14.6 mmol) dissolved in 2 mL dry tetrahydrofuran was added dropwise to reaction solution. The solution was allowed to gradually warm to room temperature overnight. The white solid was filtered off and dried under vacuum for 30 minutes. The solid was then dissolved in minimal H_2O, and then extracted with dichloromethane three times and dried with magnesium sulfate. The organic layer was dried under vacuum. Extremely little product was formed in organic layer. Product was verified via ^{1}H-NMR in $CDCl_3$ (EF-1-19A): 6.085 (s, 1H, acrylic), 5.602 (s, 1H, acrylic), 5.313 (d, 1H, 4), 4.462 (d, 1H, 2), 3.618-3.736 (m, 2H, 5a-5b), 2.509 (m, 1H, 3a), 2.403 (m, 1H, 3b), 1.924 (s, 3H, 8), 1.471 (d, 9H, Boc).

5.2.5 Synthesis of *N*-Boc-*O*-methacryloyl-*trans*-4-hydroxy-L-proline (Boc-MAP) (4)

In a 250-mL round bottom flask, di-*tert*-butyl dicarbonate (3.770 g, 17.28 mmol), triethylamine (7.0 mL, 5.3 g, 50 mmol), and about 35 mL of dichloromethane were mixed, until the di-*tert*-butyl dicarbonate was fully dissolved. A few grains of hydroquinone were added to the mixture to inhibit any polymerization. Then methacryloyl-*trans*-4-hydroxy-L-proline

Hydrochloride (4.247 g, 18.04 mmol) was added gradually over 10 minutes, causing slight bubbling and cloudiness to occur. The solution was heated to reflux for 1 hour and 30 minutes. Then about 50 mL of a 15% by mass potassium bisulfate in water solution was added to the reaction, and was stirred for 5 minutes. The solution was extracted with 50 mL dichloromethane and washed with 50 mL brine. The organic layer was dried with magnesium sulfate, and the solvent was removed under vacuum. Reaction yielded 4.465 g (89.90% yield) of Boc-MAP. Ran ^{1}H-NMR of reaction solution in $CDCl_3$ (EF-1-44A): 6.082 (s, 1H, acrylic), 5.605 (s, 1H, acrylic), ~5.36 (1H, C*H*-O), 4.511 (1H, C*H*-COOH), 3.735 (2H, CH_2-N), 2.393-2.573 (2H, CH_2-CH), 1.923 (3H, CH_3), 1.479 (d, 9H, Boc).

5.2.6 Synthesis of 2-(dodecylthiocarbonothioylthio)-2-methylpropanoic acid (CTA-8) (5)

1-dodecanethiol (1.6 mL, 1.4 g, 6.7 mmol) and tripotassium phosphate (1.033 g, 4.87 mmol) were mixed together while stirring. The solution was stirred for 10 minutes. Carbon disulfide (1.1 mL, 1.4 g, 18 mmol) was added to the cloudy solution and allowed to stir for 10 minutes, turning the solution a deeper yellow over time. The 2-bromo-2-methylpropionic acid (1.085 g, 6.501 mmol) was added to the cloudy yellow solution and let stir for 24 hours. Solvent was removed via vacuum, and the residue was dissolved in about 100 mL 1 M HCl. The solution was extracted with two 100 mL portions of dichloromethane and washed with 100 mL of water. The organic layer was dried with magnesium sulfate. Air was blown over the solution to dry. Solid was dissolved in minimal boiling pentane and gravity filtered to remove an insoluble solid contaminate. Pentanes were removed via vacuum. Mass of product 0.273 g (0.751 mmol, 74.9% yield) of CTA-8. ^{1}H-NMR of reaction solution in $CDCl_3$ (EF-1-84B): 6.082 (s, 1H, acrylic), 5.605 (s, 1H, acrylic), ~5.36 (1H, C*H*-O), 4.511 (1H, C*H*-COOH), 3.735 (2H, CH_2-N), 2.393-2.573 (2H, CH_2-CH), 1.923 (3H, CH_3), 1.479 (d, 9H, Boc).

5.2.7 Synthesis of Poly(methylmethacrylate-co-*N*-boc-*O*-methacryloyl-*trans*-4-hydroxy-L-proline) copolymer (P[MMA:MAP]) (6)

Prior to polymerization, MEHQ inhibitor in the methyl methacrylate was removed by running the monomer through a small filter of silica, and AIBN was recrystallized from minimal methanol. Boc-MAP (2.723 g, 0.009116 mol) was dissolved in 10 mL of benzene. In a 25 mL Schlenk flask, methyl methacrylate (1.42 mL, 1.33 g, 0.0133 mol), CTA-8 (0.0603 g, 1.70×10^{-4} mol), 3.66 mL (0.00334 mol) of the Boc-MAP solution and AIBN (0.0028 g, 1.7×10^{-5} mol) were added and mixed. The solution was degassed via the freeze-pump-thaw method and was left stirring for 24 hours under vacuum at 80°C. The solution was slowly poured into 20 mL of hexanes, washing with minimal p-dioxane, and stirred until cloudiness was gone (when stirring was stopped all particles settled). The solution was decanted. The solid was then dissolved in approximately 20 mL of benzene and precipitated again in hexanes. Mass recovered was 1.529 g (63.67% recovery). ^{1}H-NMR was taken of the product in $CDCl_3$ (EF-1-89D).

5.2.8 Synthesis of Poly(methylmethacrylate-co-*N*-boc-*O*-methacryloyl-*trans*-4-hydroxy-L-proline-block-acrylic acid) (P[MMA:MAP:B:AA])

Prior to polymerization, MEHQ inhibitor in the acrylic acid was removed by running the monomer through a small filter of silica and AIBN was recrystallized from methanol. In a 25 mL Schlenk flask, P[MMA:MAP] (0.6654 g, 0.004621 mol), acrylic acid (0.31 mL, 0.32 g, 0.0046 mol), p-dioxane (5 mL), and AIBN (0.0038 g, 2.3×10^{-5} mol) were added and mixed. The solution was degassed via the freeze-pump-thaw method and was left stirring for 24 hours under vacuum at 96°C. The solution was precipitated in about 20 mL of hexanes and let stir for approximately 5 minutes and then the liquid was decanted off. The solid was then dissolved in approximately 20

mL of p-dioxane and the precipitation step was repeated. Mass recovered was 1.073 g (111.0% recovery: product was still wet).

5.2.9 Deprotection of P[MMA:MAP:B:AA]

Polymer was dissolved in approximately 20 mL of p-dioxane. Trifluoroacetic acid (8 mL) was added dropwise while stirring. The reaction was let stir for 4 hours. Mass of product was 0.495 g (percent yield 27.6%). ^{1}H-NMR was taken in $CDCl_3$ (EF-1-92B2).

5.2.10 Micellization Testing

P[MMA:MAP:B:AA] (0.0318 g) was dissolved in 1.2 mL of 1,4-dioxane-d_8. Polymer solution (0.4 mL) was added to 3 separate NMR tubes. Each tube had some combination of 1,4-dioxane-d_8 or D_2O added to make various ratios: 100% 1,4-dioxane-d_8 (EF-1-68A), 75% 1,4-dioxane-d_8:25% D_2O (EF-1-68B), 50% 1,4-dioxane-d_8:50% D_2O (EF-1-68C). This process was repeated for a 100% D_2O solution (EF-1-98A-D). Another sample was made up of a small amount of polymer solution in 25% 1,4-dioxane-d_8:75% D_2O (EF-1-92E). ^{1}H-NMR spectra were obtained at 25°C, 40°C, 60°C, and 80°C for each sample.

5.2.11 General Reaction for Catalytic Test of the Aldol Reaction

Four aldol reactions were run simultaneously with different catalysts; P[MMA:MAP:B:AA], P[MMA:MAP], *trans*-4-hydroxyproline, and no catalyst. Catalyst (0.05 mmol) was added to a 5 mL round bottom flask containing 1 mL H_2O and stirred for 10 minutes; the catalysts, aside from the P[MMA:MAP], fully dissolved in the solution. The 4-Nitrobenzaldehyde (0.5 mmol) and cyclohexanone (1 mmol) were added to the solution.

Reactions were left stirring for 24 hours. ^{1}H-NMR spectra were obtained of the solution in $CDCl_3$ prior to reacting and at 24 hours to determine a rough percent conversion.

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