Synthesis of Stimuli-Responsive Programmable Polymers Through Ring-Opening–Metathesis Cross-Metathesis (ROM-CM)

[1]Courtney S. Dziewior, [1]Sharon M. S. Strickland, [2]Ping Li, [2]Ken D. Shimizu

[1]*Department of Biology, Chemistry, and Physics, Converse College, Spartanburg, S.C. 29203*
[2]*Department of Chemistry and Biochemistry, University of South Carolina, Columbia. SC 29208*

Stimuli-responsive polymers can change their physical and/or chemical properties in response to external stimuli. These polymers have found great success in a number of important areas including molecular gels and biomedical engineering, as well as success in applications such as targeted drug delivery and biosensors. We have been working toward the development of programmable polymers that remember the response after a stimulus is withdrawn. To this end, we set out to synthesize specific functional monomers. While different types of reactions could potentially result in the desired target monomer, we studied the ring-opening metathesis–cross-metathesis reaction (ROM-CM). Previous work of ours synthesized monomer **1a**, a *cis*-norbornene-2,3-dicarboxylic imide precursor to functional monomer **2a**. We report herein the attempts to prepare the target monomers **2a** and **3** via alternative ROM-CM routes that varied in starting materials, solvent systems, reaction temperatures, and catalyst amounts. We discovered that methanol based solvent systems resulted in a higher production of oligomers and other side products. In addition, one promising route using the new maleic acid starting material in place of ethyl acrylate was found to effectively undergo the ROM-CM reaction with monomer **1b**. This reaction appeared to produce the desired product **2b** which is currently being converted to the diester monomer **3** for further characterization. Future efforts will involve further examination of the ROM-CM reaction of maleic acid and other olefins with the norbornene-dicarboxylic imide precursor, dilute conditions in norbornene reactions, and alternative synthetic routes.

Introduction

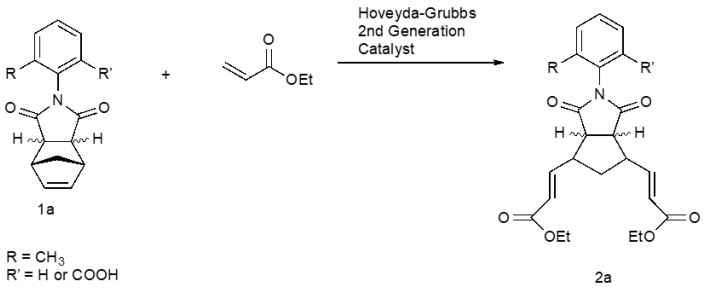
Polymers are macromolecules originating in nature or from chemical synthesis, and they are widely present in our everyday life manifesting in broad range of applications. Polymers have been shown to be essential to life. One type is biopolymers such as DNA and proteins. Another type of polymers is synthetic polymers which have greatly improved the quality of life through common everyday substances such as rubber, nylon, and plastics. Stimuli-responsive programmable polymers are the next step in polymer chemistry in order to discover a greater number of improved applications.

Stimuli-responsive polymers are an emerging type of smart material with adaptive recognition properties. These polymers respond to external stimuli such as solvent, temperature, light, or pH change.[1] Their chemical and/or physical properties change depending on the environment they are in. A diverse range of applications have been discovered including targeted drug delivery, biosensors, tissue engineering, and artificial muscles and actuators.[2,3]

A valuable feature of the stimuli-responsive polymers we have been studying is their ability to retain their response properties without the constant presence of the stimuli. These specialized molecules are called programmable polymers and can be programmed to maintain their response to stimuli even after the stimulus has been removed. These polymers can be heated in different, specifically chosen solvents to alter their binding and recognition properties, and upon cooling and removal of the solvent, the polymers will still maintain these altered properties.[8] In comparison, non-programmable polymers would lose their "responding" state upon removal of the stimuli which limits their applications in functional materials and molecular devices. This unique ability to maintain different response properties makes stimuli-responsive programmable polymers particularly valuable because this enables a greater ability for application if the stimulus does not need to be constantly present in order for the polymer to maintain their new properties.[4]

In order to 'write' and 'save' different recognition properties by heating and then cooling in the programmable polymers, we decided to implant a recognition group such as carboxylic acid that is kinetically restrained at room temperature. This is because the programmable capability relies on hindered bond rotation at room temperature that becomes sterically unrestrained when heated. For instance, after polymerization, the desired monomer **2a** with the carboxylic acid group could be heated in a polar solvent such as water. This would cause the carboxylic acid group to rotate outwards towards the solvent. Upon cooling the reaction, the outward position of the group would remain, even after removal of the solvent. The monomer can then be flushed at room temperature and return to its natural state. This can also be repeated with a nonpolar solvent for an inward turned COOH group.

One limitation of previous work is that the polymers were synthesized using ring-opening metathesis polymerization (ROMP).[4-5] This limited the types of monomers and their applications. Our research focused on creating the monomers through ring-opening metathesis cross -metathesis (ROM-CM), and then polymerizing them through free radical polymerization. The information presented will focus on the initial efforts to synthesize functional monomers **2a** and **3**. Additionally, after previous unsuccessful efforts to produce monomer **2a**, a methodology study using norbornene in place of monomer **1a** (Scheme 1) was conducted. Further work was also completed on an additional synthesis path (Scheme 2) using maleic acid as the olefin instead of ethyl acrylate.[2] The different reactions, altered conditions, and their outcome for scheme 1, 2, and the norbornene methodology study are reported herein.

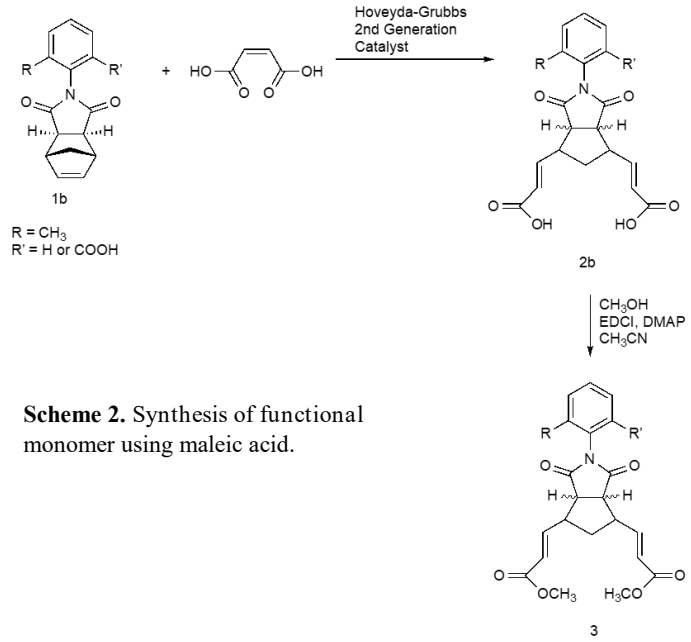


Scheme 1. Synthesis of functional monomer using ethyl acrylate.

Methods

General procedure for synthesis of scheme 1

Monomer 1 (0.2304 g, 0.9095 mmol) and 7 mL dichloromethane (DCM) were added to a 25-mL round bottom flask equipped with a magnetic stir bar. Ethyl acrylate (0.5643 g, 5.636 mmol, 6.2 equiv.) and Hoveyda-Grubbs 2nd Gen. catalyst (0.0148 g, 0.0236 mmol, 2.5 mol% equiv.) were added to the round bottom flask. The round bottom flask was placed on top of a stirrer plate with a nitrogen balloon and stirred for 24 hours. After 24 hours, Hoveyda-Grubbs 2nd Gen. catalyst (0.0143 g, 0.0228 mmol, 2.5 mol% equiv.) was added to the round bottom flask. After another 24 hours, stirring was stopped and the round bottom flask was removed.



Scheme 2. Synthesis of functional monomer using maleic acid.

General procedure for synthesis of scheme 2

Monomer 1 (0.2659 g, 1.102 mmol), 1 mL methanol and 4 ml dichloromethane (DCM) were added to a 20-mL scintillation vial equipped with a magnetic stir bar. Maleic acid (0.7676 g, 6.612 mmol, 6 equiv.) and Hoveyda-Grubbs 2nd Gen. catalyst (0.01920 g, 0.03064 mmol, 2.8 mol% equiv.) were added to the scintillation vial. The vial was placed on top of a stirrer plate and stirred for 24 hours. After 24 hours, Hoveyda-Grubbs 2nd Gen. catalyst (0.02891 g, 0.04614 mmol, 4.2 mol% equiv.) was added. The resulting mixture was then connected to a rotary evaporator to remove the solvent, producing monomer 3 and residual methanol mixture. The mixture was transferred to a dry 25-mL round bottom flask equipped with a magnetic stir bar and flushed with nitrogen. Methanol (0.1050 g, 0.003306 mol, 3 equiv.), 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (.6141 g, 0.003203 mol, 2.9 equiv.), and 4-Dimethylaminopyridine (DMAP) (0.07919 g, 0.6482 mmol) were added to the round bottom flask. 5 mL acetonitrile and 0.19 mL glacial acetic acid were added through a syringe. The mixture was stirred at room temperature overnight under nitrogen.

Results and Discussion

Scheme 1

Initial efforts to produce monomer **2a** (scheme 1) involved altering the reaction temperature, run time, presence/absence of air, catalyst amount, and catalyst addition rate. All reactions were monitored through thin layer chromatography (TLC) (EtOAc/hexane = 1/5 v/v).

Temperatures tested included room temperature, 45°C, 0°C, and -78°C. None of the temperature conditions yielded the desired product. Instead, various impurities such as oligomers and side products were produced. The reaction was also conducted with varying reaction times ranging from 24 hours to 7 days and monitored through TLC for changes. A closed system in nitrogen was also attempted but showed no change in the reaction results.[6]

We initially added 2.5 mol% Hoveyda-Grubbs 2nd Generation Catalyst at 0 hours and another 2.5 mol% at 24 hours. When this yielded no results, we added 2.5 mol% once at 0 hours. We also attempted this by adding 5 mol% once at 0 hours. No change was observed.

Norbornene

After lack of success with scheme 1, a norbornene methodology study was attempted due to norbornene's similar but simpler structure to monomer **1a**. Conditions studied were the effect of increasing amounts of ethyl acrylate and varying solvent conditions.

Solvents tested were methanol and dichloromethane (DCM). When conducted in only methanol, oligomers of norbornene were consistently produced and two other side products were discovered: an ethyl acrylate dimer and Hoveyda-Grubbs Catalyst–ethyl acrylate compound. Overall, solvents with a greater concentration of methanol yielded a larger amount of the norbornene oligomer.

Another variable that was adjusted was the amount of ethyl acrylate added, ranging from 6 to 12 to 88 equivalents. No change was visible. Surprisingly, an increase in amount of ethyl acrylate did not result in the ethyl acrylate dimer. The Hoveyda-Grubbs–ethyl acrylate side product was present in all variations of ethyl acrylate amounts.

We then followed another literature procedure to let the reaction run in dilute conditions in order to prevent oligomerization.[8] Initial results were similar to our previous findings, but further work will be conducted on this route.

Through the alteration of various different variables, and the norbornene methodology study, it was discovered that scheme 1, while stereochemically favorable, was unattainable. The presence of oligomer impurities suggests that the ring opening metathesis occurs at a high rate and polymerizes, preventing cross metathesis. The creation of the ethyl acrylate dimer and Hoveyda-Grubbs–ethyl acrylate side product further support this.

Scheme 2

An alternative reaction using a new olefin of maleic acid was attempted and appeared to produce the correct product. Due to the polarity of the carboxyl group, the monomer must first be esterified into monomer **3** before its identity can be assessed. Efforts are ongoing to esterify and analyze the product.

Conclusions

To date, the ROM-CM reaction for scheme 1 has been unsuccessful despite a variety of conditions examined. NMR spectra revealed that the ring opening metathesis successfully occurred but did not produce the desired product. The creation of oligomers and side products leads to the conclusion that a partial ring opening metathesis polymerization (ROMP) occurs before the cross metathesis of the ROM-CM reaction can take place. Despite efforts to slow down the reaction and facilitate the cross metathesis of monomer **1a** with ethyl acrylate through high equivalents levels, heat, and catalyst amount, no product was produced. Future work will study the effect of a more dilute reaction system. The alternative scheme using maleic acid shows potential, and efforts are ongoing to confirm whether the product can be produced.

Acknowledgements

Research reported in this publication was supported in part by the NSF and SC EPSCoR/IDeA Program under award number NSF Award # OIA -1655740 and SC EPSCoR/IDeA Grant #18-GC03. The views, perspective, and content do not necessarily represent the official views of the SC EPSCoR/IDeA Program nor those of the NSF.

Notes and References

**Corresponding author emails: sheri.strickland@converse.edu; CSDiewior001@converse.edu*

1. Stuart MA, Huck WTS, Genzer J, Muller M, Ober C, Stamm M, Sukhorukov GB, Szleifer I, Tsukruk VV, Urban M, et al. 2010. Emerging applications of stimuli-responsive polymer materials. Nat. Mater. 9(issue?):101-113.
2. Ferreira LA, Schrekker HS. 2016. Augmentation of productivity in olefin cross -metathesis: maleic acid does the trick! Catal. Sci. Technol. 6(issue?):8138-8147.
3. Wei M, Gao YG, Li X, Serpe MJ. 2017. Stimuli-responsive polymers and their applications. Polym. Chem. 8:127-143.
4. Zhang Y, Lavin JM, Shimizu KD. 2009. Solvent Programmable Polymers Based on Restricted Rotation. J. Am. Chem. Soc. 131:12062-12063.
5. Camm JD, Castro NM, Liu Y, Czechura P, Snelgrove JL, Fogg DE. 2007. Tandem ROMP-Hydrogenation with a Third-Generation Grubbs Catalyst. J.

Am. Chem. Soc. 129:4168-4169.
6. Randl S, Connon SJ, Blechert S. 2001. Ring opening-cross metathesis of unstrained cycloalkenes. Chem. Comm. 18:1796-1797.
7. Roe SJ, Legeay J, Robbins D, Aggarwal P, Stockman RA. 2009. Two-directional ring-opening cross metathesis. Chem. Comm. 29:4399-4401
8. Grubbs RH, O'Leary DJ. 2015. Handbook of Metathesis, Volume 2: Applications in Organic Synthesis. Weinheim, Germany: Wiley-VCH.