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Programmable Polymers Preparation Optimization and Applications On Solute Templates

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PROGRAMMABLE POLYMERS PREPARATION OPTIMIZATION AND
APPLICATIONS ON SOLUTE TEMPLATES

By

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Bachelor of Science
Jilin University, 2011

Submitted in Partial Fulfillment of the Requirements

For the Degree of Master of Science in

Chemistry

College of Arts and Sciences

University of South Carolina

2013

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DEDICATION

To Mom & Dad

ACKNOWLEDGEMENTS

I would like to express my deepest appreciation to my advisor, Prof. Ken D. Shimizu, who gave me great encouragement and inspiration in keeping my graduate life in this completely new environment. Without his guidance and persistent help this thesis would never be possible. I will never forget how you help me out from the situation that I felt great frustration for my language and research. You showed me step by step to find a creative and reasonable idea for the research. Also, you incorporated me to take the recitations for students, which helped me a lot in strengthening the public speaking skills and organic chemistry background.

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ABSTRACT

Programmable polymer is a type of stimuli-responsive polymer which can keep their induced properties after removal of the stimulus, as well as programmable polymers maintain the general properties as stimuli-responsive polymers, such as recognize and respond to the stimulus. The previous reported solvent $C_{\text{aryl}}-N_{\text{imide}}$ bonds based programmable polymers (SPP-1) can freely rotate and change the carboxylic acid recognition group orientation in response to templates. Solvent templates were used in the SPP-1. One potential application for SPPs is using their recognition and memory properties for the identification and separation of mixture solutions of various analytes. In my first project, I wanted to develop a series of new SPPs with improved recognition and memory properties. There are several ways to optimize SPPs, such as changing the crosslinking degree, crosslinker length, crosslinker percentage, changing the recognition groups or modifying the ring opening metathesis polymerization (ROMP) catalyst to prepare the SPPs. Development of new SPPs through free radical polymerization (FRP) instead of ROMP were meaningful to obtain various programmable polymers with varying applications. To obtain an optimized programmable polymer with higher amount of recognition groups, the second generation SPP (SPP-2) was prepared by the third generation Grubbs catalysts (Grubbs III) instead of the second generation (Grubbs II).

In conclusion, the SPP-2 showed similar recognition and memory properties with SPP-1, however, the wet-processed SPP showed higher recognition and lower memory capability than the wet-processed SPP.

The other aspect of optimization on programmable polymers is applying them on recognizing and remembering solute templates instead of solvents. In another word, we want to develop new programmable polymers in the separation of solute templates, especially for the chiral templates. The new amide programmable polymers were designed and the SPP-1 was used as blank groups. The recognition and memory properties of the new programmable polymers were measured and compared with the SPP-1. Also three solute templates (lactic acid, 2-hydroxy-3-pinane and camphor) were found to make significant induced change on both amide and carboxylic acid programmable polymers.

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CHAPTER I
OPTIMIZED SOLVENT PROGRAMMABLE POLYMERS BASED ON
RESTRICTED ROTATION

1.1 ABSTRACT

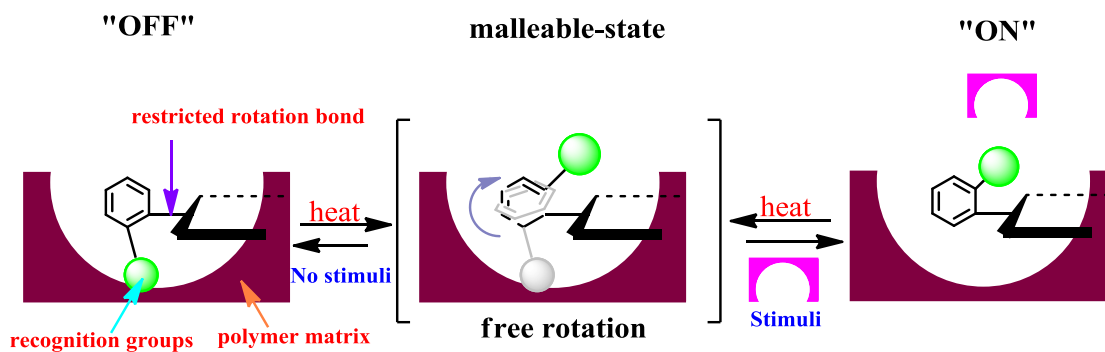
In the first project, our goal was to develop a series of new programmable polymers that have improved recognition and memory properties.¹ The first aim was the optimization of the 1st generation solvent programmable polymers (SPP-1) made through ring opening metathesis polymerization (ROMP) by using a new ROMP catalyst,² therefore, more rigid polymer with better memory properties were expected to obtain.³ The second aim was to develop programmable polymers using free radical polymerization (FRP) instead of ROMP, which greatly limited the choice of monomer, crosslinker and morphologies of polymers. Therefore, FRP based programmable polymer would have multiple morphologies, which could potentially use in chiral separation.

1.2 INTRODUCTION

Stimuli-responsive polymers are polymers which show a significant change in their structures and properties in response to changes in environments, such as temperature,⁴ light,¹ metal ion concentration,⁵ and pH.⁶ The dynamic properties make them capable of many applications including drug delivery,⁷ biomedical application in tissue engineering

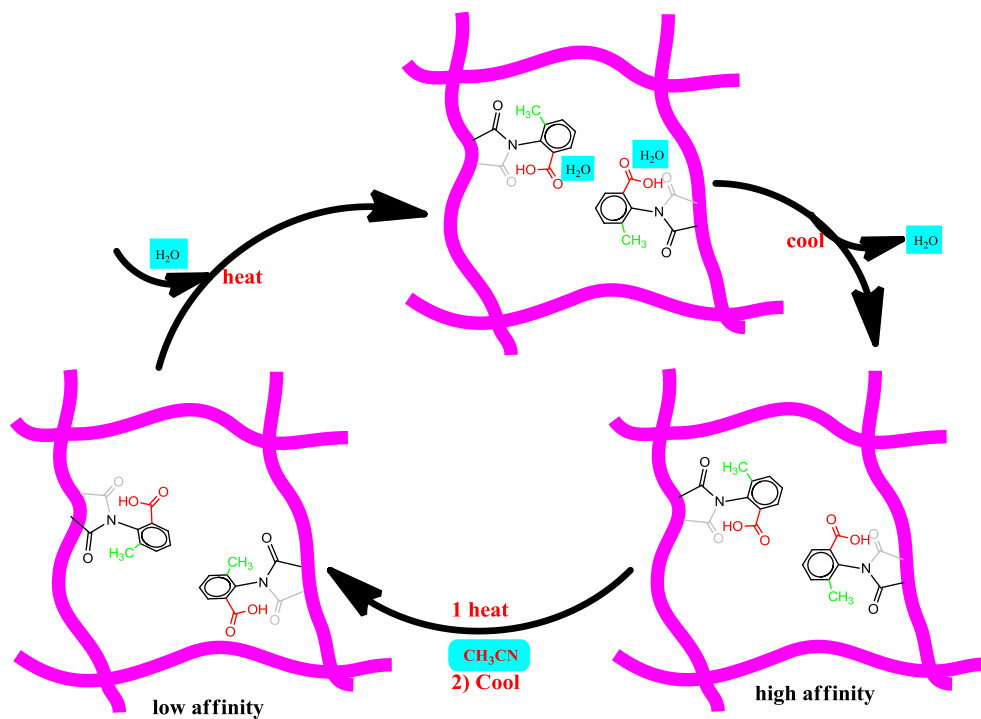
surface patterning, sensing and mechanical actuation.¹ However, a major limitation of most stimuli-responsive polymers is that the stimuli induced changes are typically not maintained after the removal of the stimuli.⁸ Therefore, developing a new class of stimuli-responsive polymers which can remember their stimuli-induced properties is needed. These new programmable polymers have two major properties and advantages. They can be used in different environments without stimulus, and the programming process is reversible. Thus, their properties can be repeatedly optimized and reoptimized.

Our strategy is based on monomers with restricted rotation around a $C_{\text{aryl}}-N_{\text{imide}}$ single bond (Scheme 1.1). Incorporation of monomers into a rigid polymer matrix leads to the formation of distinct “ON” and “OFF” states, which are stable at rt due to restricted rotation. When the polymer solutions were heated with a template guest, the $C_{\text{aryl}}-N_{\text{imide}}$ bond freely rotated, the addition of a guest could act as a stimulus to induce a change in conformation to the “ON” state. When the polymer solutions were heated without a guest, there would be no conformational preference. On cooling to rt, these solvent-induced conformations are maintained due to the reestablishment of $C_{\text{aryl}}-N_{\text{imide}}$ restricted rotation.



Scheme 1.1. Schematic representation of the programmable polymers based on restricted rotation of the $C_{aryl}-N_{imide}$ single bond. Rotation around the bond can switch the orientation of the recognition groups to point either toward the matrix ("OFF" state) or away from the matrix ("ON" state).

SPP-1 can switch the orientation of their carboxylic acid recognition groups by heating in different polarity solvents (Scheme 1.2).² When heated in a polar solvent, such as water, the carboxylic acid recognition groups will rotate to form hydrogen bonds with solvent. After cooling to rt and removal of the solvent stimuli, the induced changes are maintained. The carboxylic acid groups will rotate to point away from the solvent when heated in a less polar solvent, such as acetonitrile. Based on the study of the 1st generation SPPs, we are working on optimizing the preparation of SPPs through a better understanding of the switching and memory processes. By synthesizing new monomers and changing the crosslinking degree, our first aim was to develop a 2nd generation of ROMP SPPs (SPP-2) with better recognition and memory properties.



Scheme 1.2. Scheme shows the 1st generation solvent programmable polymers (SPP-1) which can modulate its recognition and memory properties when heated in solvents with different polarities.

The studies on the 1st generation SPPs showed that the crosslinking degree greatly influenced the magnitude of the SPP-1's memory effect, which was indicated by the binding capacity difference between SPPs heated in polar and a non-polar solvent. Higher degrees of crosslinking favored the maintenance of the guest-induced changes. Therefore, our first aim was to prepare new SPPs⁹ with higher crosslinking degrees, which will make the framework of SPPs more rigid. Secondly, the use of ring opening metathesis polymerization (ROMP) greatly limited the choice of monomer and crosslinker and the control of the polymer morphology. Therefore, our second aim was to develop free radical polymerization (FRP) programmable polymers by using a pair of programmable

atropisomers with polymerizable vinyl groups.¹⁰ These atropisomers were used as monomers to be copolymerized with ethylene glycol dimethacrylate (EGDMA).¹¹ Hence these atropisomeric monomers based polymers can be potentially used in chiral separation.

1.3 RESULTS AND DISCUSSIONS

AIM 1: OPTIMIZATION OF ROMP PROGRAMMABLE POLYMERS BY USING A NEW ROMP CATALYST TO PREPARE MORE RIGID POLYMER FRAMEWORK

First, the crosslinking degree of the polymers was optimized, which influences the rigidity of the polymer matrix. There were two reasons: 1) Recognition groups on the monomer would be better in keeping their solvent-induced conformations. 2) The morphologies of the polymer matrix would not change significantly when heated in different solvents when the polymer matrix was more rigid. Since more active Grubbs III is supposed to be more active in the ROMP, therefore, higher crosslinking degree polymers were expected to obtain. We prepared SPP-2 using the Grubbs III catalyst, and we prepared SPP-1 as blank group. The monomer with restricted rotation and diimide crosslinker used in the preparation of the SPPs are shown in Figure 1.1. The prepared polymer gel was not soluble in water and organic solvents, but the interior parts were accessible to the solvent templates. To verify that SPP-2 was more rigid than SPP-1, swelling experiments were did to test the flexibility of these two SPPs when heated with

water (very polar) and acetonitrile (less polar) solvents. To verify that SPP-2 had better recognition and memory properties, the two SPPs were heated in cyclohexane (non-polar) and water (very polar). The solvent-induced changes were assessed by comparing their binding capacities for ethyl adenine-9-acetate (EA9A) in acetonitrile.

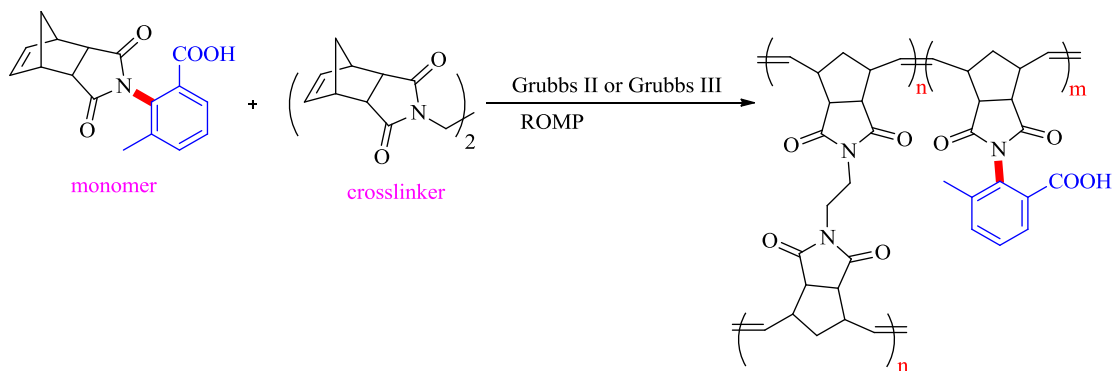


Figure 1.1. Functional monomer 1, crosslinker and solvent programmable polymers (SPP-1, SPP-2) and the preparation of SPPs through the second and the third generation Grubbs catalysts

1.4 POLYMER GEL SWELLING EXPERIMENTS

To test whether SPP-2 was more rigid than SPP-1, a series of swelling experiments were prepared. By heating the polymer with water and acetonitrile and comparing the swelling volume differences after soaking in a solvent, the ability of the polymer matrix to expand was measured. SPP-2 was expected to show lower swelling volumes due to their higher crosslinking degree.

Figure 1.2 showed significant differences for the abilities of SPP-1 and SPP-2 to absorb solvents. SPP-2 showed twice the swelling capacity as compared to SPP-1 in water and acetonitrile. These swelling differences demonstrated that SPP-2 was more

rigid as we expected.

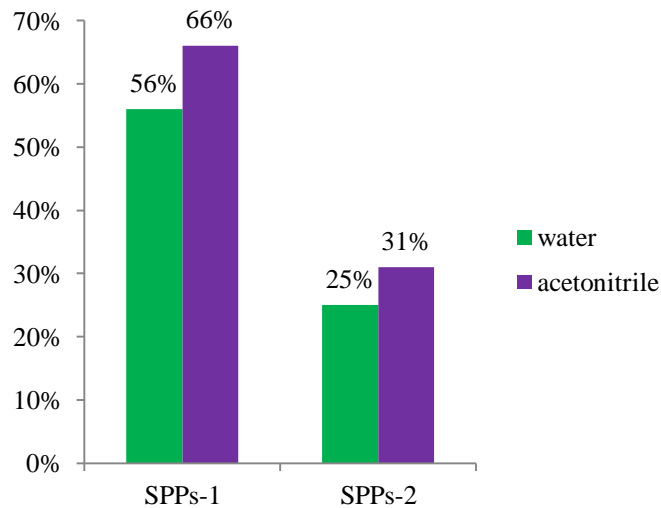


Figure 1.2. Measurement of the percent volume increase after heating SPP-1 and SPP-2 (160 mg) in water (2.5 mL) and acetonitrile (2.5 mL) for 26 h at 83 °C

Swelling experiments were used to compare the flexibility of SPP-1 and SPP-2, so as to verify that SPP-2 had higher crosslinking degree. SPP-1 increased 56% in water and SPP-2 increased only 25% in water, and the same trend showed for SPP-1 and SPP-2 heated in acetonitrile, therefore, these data verified that SPP-2 are more rigid than SPP-1.

1.5 BATCH BINDING STUDIES

To test whether SPP-2 had improved recognition or memory properties, the SPPs were bound with polar (water) and non-polar (cyclohexane) solvents to compare the binding capacities differences. The hydrogen bonding strength between EA9A and carboxylic acid recognition groups in the polymers was used to measure the quantity of solvent accessible recognition sites. Therefore, we can use it to test the recognition

properties of polymers. Also, by comparing the binding capacities differences between polar and non-polar solvent templates bound polymers (binding gap), we were able to verify that the ability of programmable polymers in keeping the induced changes (memory properties).

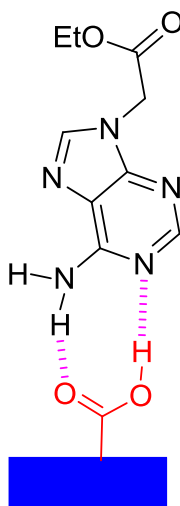


Figure 1.3. Hydrogen bonding between the ethyl adenine-9-acetate (EA9A) and solvent programmable polymers with carboxylic acid recognition groups

Both SPP-1 and SPP-2 showed higher binding capacities for the polymers heated in water versus cyclohexane, which was a characteristic of the solvent memory effect (Figure 1.4). The recognition groups of SPPs have higher binding capacities after heating with more polar solvents, since polar solvents have stronger hydrogen bonding strength with carboxylic acid recognition groups. SPP-2 showed higher binding capacities and slightly differences in water and cyclohexane binding capacities than SPP-1. The differences between SPP-2 and SPP-1 were within the error of the experiments, thus, these two types of SPPs showed similar recognition capacities. Also, the binding gap for

both SPP-2 and SPP-1 were similar, therefore, they showed similar memory properties as well.

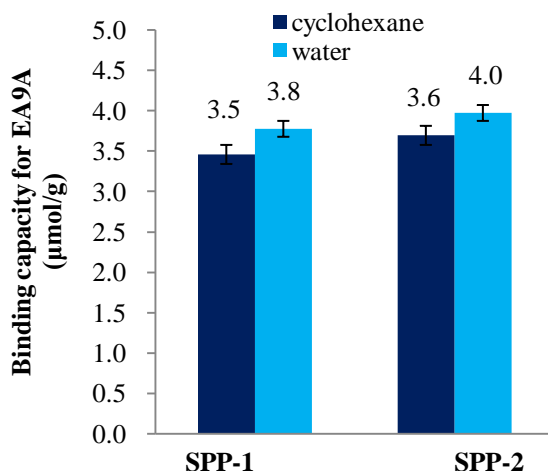


Figure 1.4. Measured binding capacities for EA9A of SPP-1 and SPPs-2 after heating (83 °C, 26 h) in cyclohexane and water

Interestingly, when comparing the binding capacity of the SPP-1 prepared in this study with the SPP-1 prepared in the original study, the new SPP-1 showed significantly higher binding capacity (Figure 1.4). We hypothesized that this might be due to differences in the procedure for quenching the ROMP reactions. The new SPP-1 was ground when they were still wet with the polymerization solution, but the old SPP-1 was ground after they were first dried. The wet processed polymers were probably quenched the ROMP reaction earlier than the dry processed polymer.

To test this hypothesis, a set of dry processed and wet processed SPP-1 were prepared. In Figure 1.4, the dry processed SPPs (SPP-1 dry) showed lower binding capacities than the wet processed SPPs (SPP-1 wet). Also, the dry processed SPPs

showed similar binding capacity with the previous dry processed SPP-1. Similarly, the wet processed SPPs showed around twice binding capacities than the dry processed SPPs, which means that the earlier quenched SPPs made more accessible recognition sites. However, the wet processed polymers showed lower binding gap between polar and non-polar templated SPPs than dry processed SPPs, therefore, the wet processed polymers have lower memory capability. We hypothesized that these wet processed polymers had lower crosslinking degree, which means the wet processed polymers were flexible. Therefore, wet processed polymers are more difficult in keeping the induced changes.

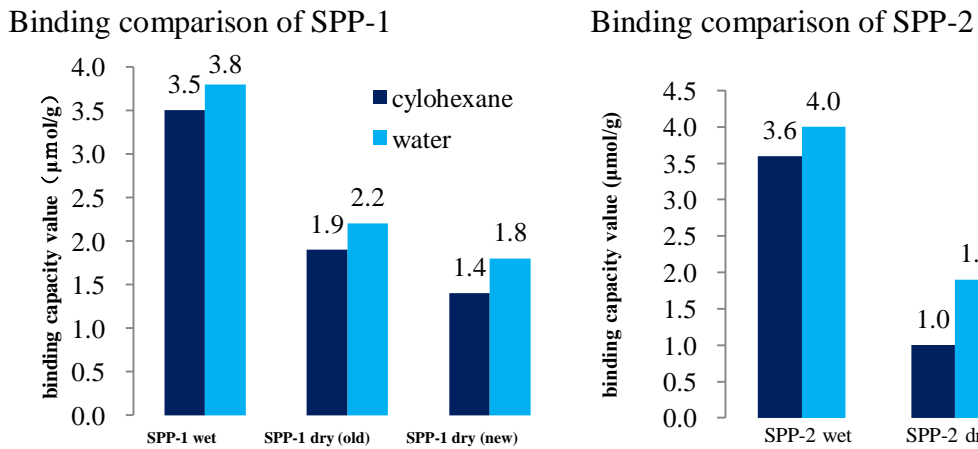


Figure 1.5. Binding comparison of wet processed SPPs with dry processed SPPs. Wet processed SPPs showed around two times binding capacities than the dry processed SPPs.

1.6 SWELLING EXPERIMENTS TO COMPARE OF THE “DRY” SPPs WITH “WET” SPPs

The above binding studies suggested that the “dry” SPPs might be more rigid than the “wet” SPPs due to a higher crosslinking degree, since the “dry” SPPs ROMP quenched later than the “wet” SPPs. To test this hypothesis, a set of swelling experiments were prepared to compare the rigidity of the frameworks for the “wet” SPPs and the “dry” SPPs.

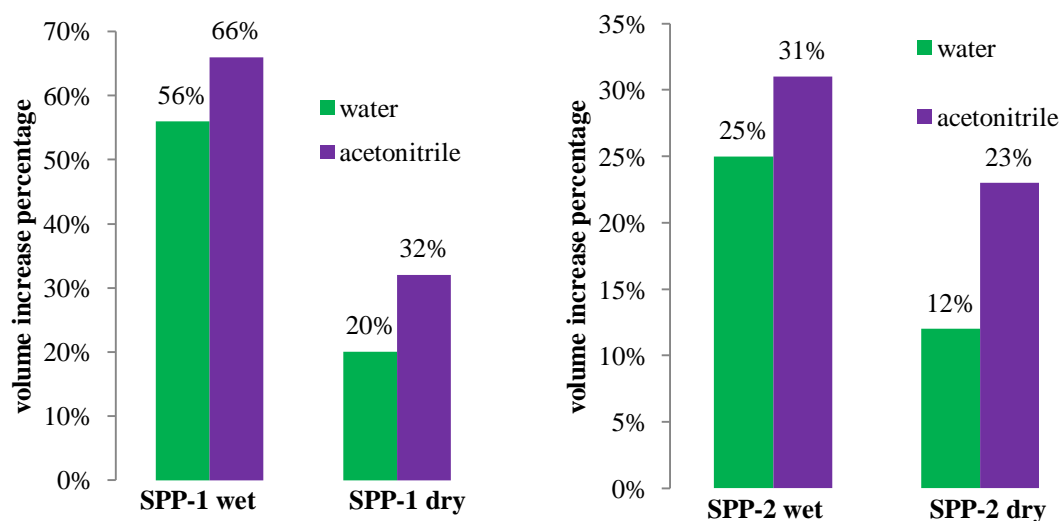


Figure 1.6. Swelling experiments to compare the rigidity of the “wet” SPPs and the “dry” SPPs

As shown in Figure 1.6, “wet” SPP-1 showed much higher swelling volume increase than “dry” SPP-1, which means that “wet” SPP-1 were less rigid than “dry” SPP-1, as well as “wet” SPP-2 and “dry” SPP-2 showed the same effect. Therefore, wet processed SPPs having higher recognition capacities are more flexible in the frameworks.

1.7 CONCLUSIONS FOR AIM 1

In summary, SPP-2 formed with the Grubbs III catalyst was more rigid than SPP-1 formed with the Grubbs II catalyst. Initially, SPP-2 showed similar recognition capacities and similar memory effects with SPP-1, which means that the new ROMP catalyst increased the crosslinked degree of SPPs. However, the increasing crosslinking degree made very less effective in increasing the recognition properties, since the rigid framework only allowed very rare accessible recognition groups to bind with the solvent templates. We found that the work up procedure for the polymerization also influenced the recognition and memory properties of the SPPs. The dry processed polymer was more rigid and low recognition capacities. However, the higher crosslinking degree of the dry processed polymers gave them higher ability in keeping induced changes, therefore, higher binding gap were obtained.

AIM 2: FREE RADICAL POLYMERIZED PROGRAMMABLE POLYMERS

Our second aim was to use FRP instead of ROMP to prepare a series of new programmable polymers. Free radical polymerization can be used to prepare various programmable polymers with varying morphologies and there are more choices for the functional monomers. Also, ROMP-based programmable polymers usually have limited choices of crosslinkers and needs expensive Grubbs catalyst. Programmable polymers prepared using FRP would have multiple morphologies, thus they would have various applications. The major application of the FRP programmable polymers is using in chiral

separation. We used atropisomers as functional monomers in preparing programmable polymers, which were able to keep their induced changes after removal of templates. Since these atropisomers had preference in inducing one specific isomer in chiral mixtures, also, the atropisomer-based programmable polymers are able to keep their induced changes after removal of templates. Therefore, atropisomers-based programmable polymers had potential application in chiral separation.

A pair of atropisomeric monomers (Figure 1.7.a), which are stable rotamers at rt but isomerizable on heating, were designed. The atropisomers contain two polymerizable acrylate groups which allow them to be efficiently copolymerized with EGDMA via FRP.¹³ Based on their similarity to the previously reported atropisomeric diimides,¹³ the rotation barrier of these diimide atropisomers would be 29.4 kcal/mol. Hence these atropisomers are stable at rt (Figure 1.7.b) but can rotate on heating (>100 °C). In addition, these atropisomers were expected to have distinct recognition properties, which would allow them to be rapidly screened against a library of guests.¹⁴

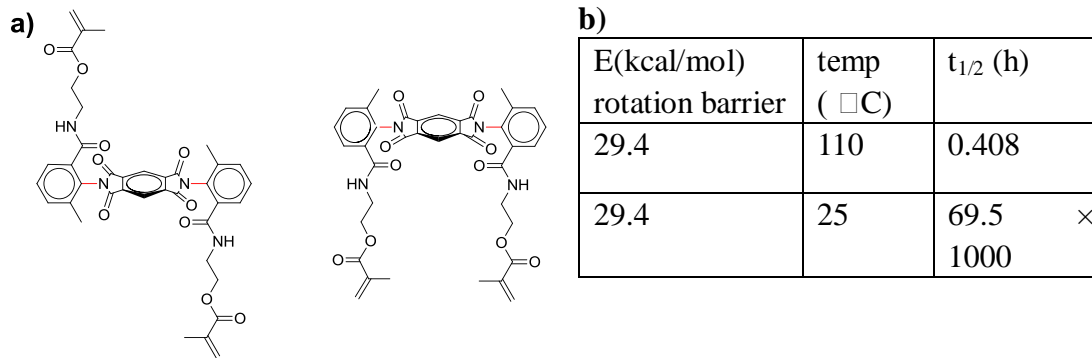
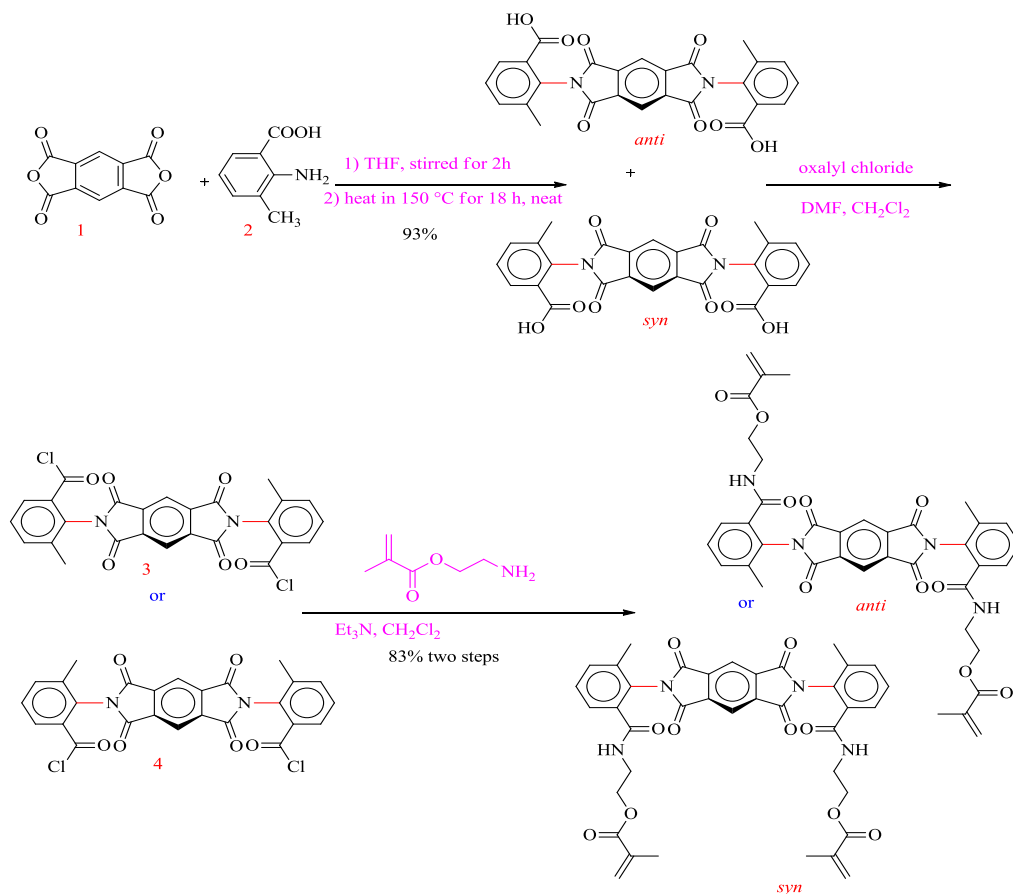


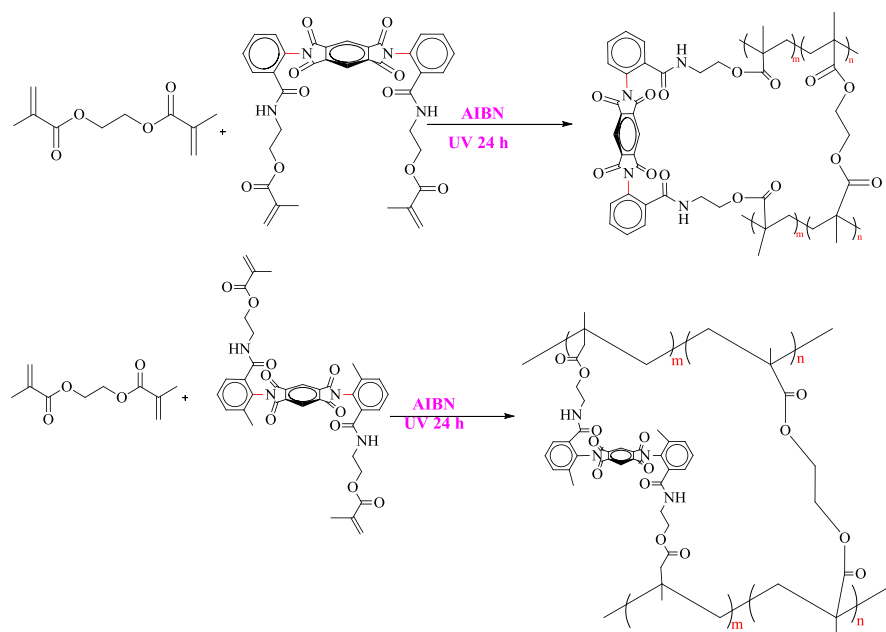
Figure 1.7. *Syn* and *anti*-diimide structures and half-life data table

First, the atropisomeric diacid platforms were synthesized (as shown in scheme 1.3), the *anti* and *syn* isomers were separated using column chromatography. The individual diacid isomers were used to prepare *anti* or *syn* diimide monomers. To avoid isomerization, the *syn* and *anti* diimide transformation were conducted without heating. The new monomers were copolymerized with the crosslinker ethylene glycol dimethacrylate (EGDMA) through FRP.



Scheme 1.3. Synthesis of *anti* and *syn* diimide atropisomer monomers

Since EGDMA are easy to copolymerize and can be highly crosslinked with imide based monomers, therefore, EGDMA is a great crosslinker for imide based functional monomer to prepare atropisomeric programmable polymers.¹² EGDMA and *anti* or *syn* diimide monomers were copolymerized through FRP. The polymerization reaction was initiated with AIBN and with UV-light at rt. for 24 hours.



Scheme 1.4. Preparation of crosslinked programmable polymer by EGDMA and *syn*- or *anti*-diimide monomer and the structures of diimide and EGDMA copolymers

1.8 MOLECULAR SWITCHING STUDY

To test what kinds of templates were appropriate for these new programmable polymers, first, we picked several templates (Figure 1.8) based on molecular modeling. These templates had the potential to form two hydrogen bonding interactions with the *syn*-diimide, since they had been effective templates to bind with the atropisomeric diacid precursors.¹⁵ Good templates could be identified by their ability to shift the conformational ratio of the atropisomeric monomers.^{10, 16}

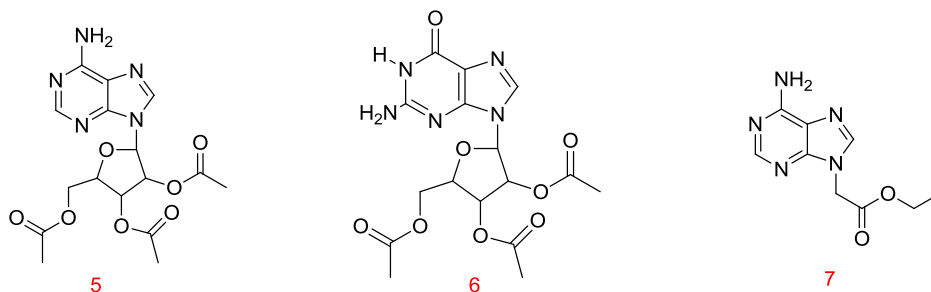


Figure 1.8. Templates used molecular switching study in inducing the conformation change of the atropisomeric diimide monomers.

As shown in Figure 1.9, each template was heated with the atropisomeric diimide monomers and resulting *syn* and *anti* ratios were measured. The reason for doing the molecular switching study with the monomers instead of the polymers was because measurement the guest-induced changes in the monomer using ^1H NMR is much easier.¹⁴⁻¹⁵ Unfortunately, similar conformational ratios were obtained after heating the *syn/anti* diimides with various templates.

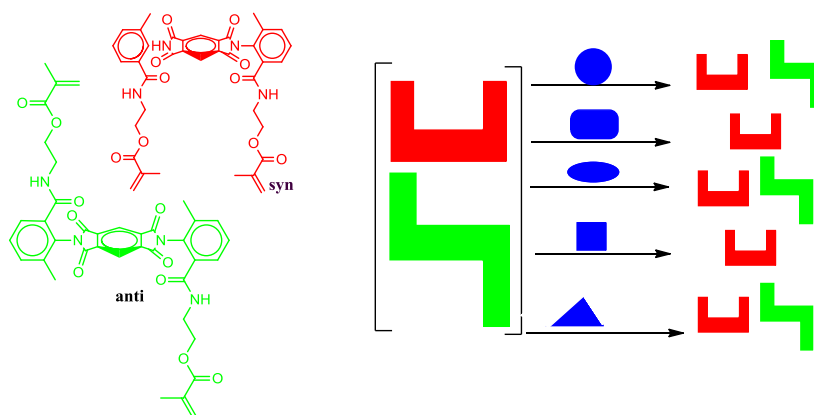


Figure 1.9. Schematic representation of our rapid screening method is used to identify good templates. By adding various stimuli into the diimide mixtures, certain *syn/anti*-diimide atropisomers were obtained. Such as the circle template could not change the ratio, but the rectangle and square templates are possible to induce the *anti*-diimide into *syn*-diimide.

1.9 CHARACTERIZATION OF THE FREE RADICAL POLYMERIZATION POLYMERS

To test whether the *anti* and *syn* diimide atropisomeric monomers were successfully incorporated into the EGDMA polymer matrix, blank polymers synthesized from pure EGDMA. By comparing the binding capacity of these polymers for EA9A, the EGDMA-diimide copolymer had twice binding capacity than the blank polymer, which suggested that diimide monomer had been successfully incorporated into the EGDMA crosslinker based polymer (Figure 1.10).

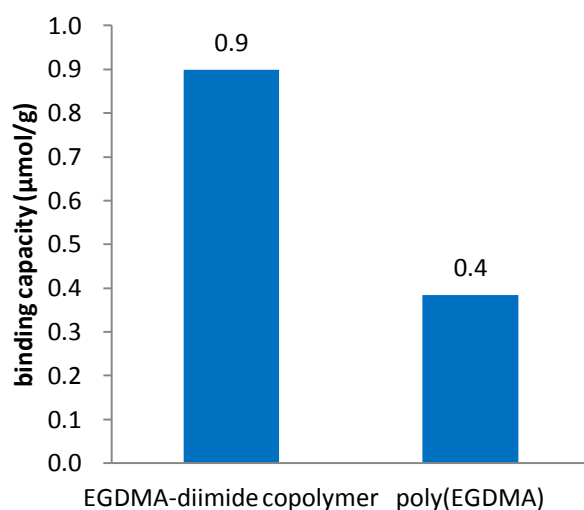


Figure 1.10. Binding study comparison of EGDMA-diimide copolymer and poly(EGDMA) with 0.1 N EA9A in acetonitrile (2.5 mL)

1.10 CONCLUSIONS FOR AIM 2

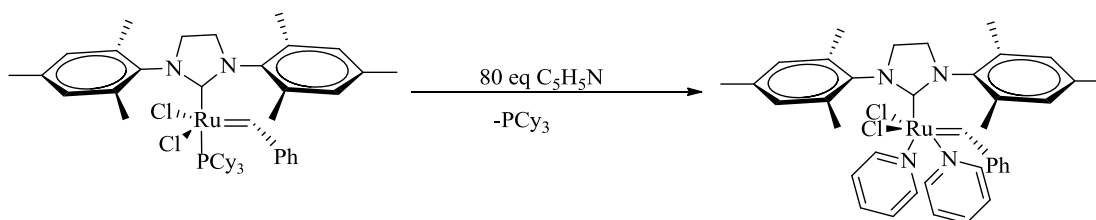
Thus far, a new atropisomeric functional monomer and a programmable polymer were prepared by FRP. Since the diimide atropisomeric monomers had little separation

properties for various templates, therefore, we thought these diimide atropisomeric monomer based polymers are very less likely able to separate chiral mixtures.

1.11 EXPERIMENTAL AND SUPPLEMENTAL SECTION

SYNTHESIS AND SUPPORTIVE INFORMATION IN AIM 1

1.12 PREPARATION OF GRUBBS III CATALYST



Scheme 1.5. Preparation of Grubbs III catalyst from Grubbs II.¹⁷

Grubbs II catalyst (0.153 g, 0.179 mmol) was dissolved in toluene (1 mL). Pyridine (1.15 mL) was added and stirred for 20 min. When the brown solid was totally dissolved and changed into a bright green solution, the solution was transferred into 4 mL cold pentane (-20 °C, cooled by dry ice) through injection to isolate from air. A green solid precipitates was obtained after 2 hours. The precipitate was filtered and washed with 2 mL pentane for five times. The solid was dried by vacuum to obtain Grubbs III catalyst (0.121 g, 92% yield). ¹H NMR (C₆D₆): 8.70 (s, 2 H, pyridine), 8.13 (s, 2 H, pyridine), 6.97 (d, 2 H, ortho CH, *J*_{HH} = 8 Hz), 7.09 (t, 1 H, para CH, *J*_{HH} = 7 Hz), 6.73 (multiple peaks, 9 H, pyridine, Mes CH), 3.51 (d, 4 H, CH₂CH₂), 2.94 (s, 6 H, Mes CH₃), 2.52 (s, 6 H, Mes CH₃), 2.23 (s, 6 H, Mes CH₃).

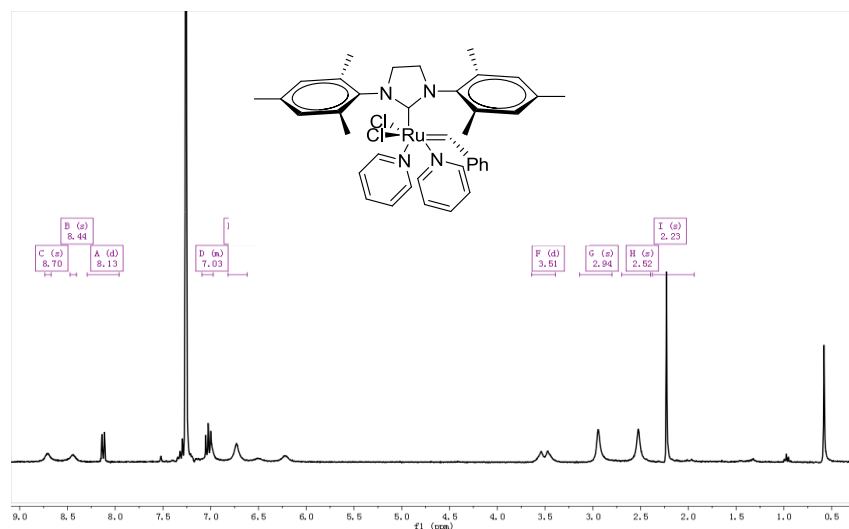


Figure 1.11. ^1H NMR (C_6D_6 , 300 MHz) of Grubbs III catalyst

1.13 PREPARATION OF MONOMER 1

Announcement: preparations of monomer 1 and crosslinker 1 followed the procedures used in the preparation of the first generation of SPPs.

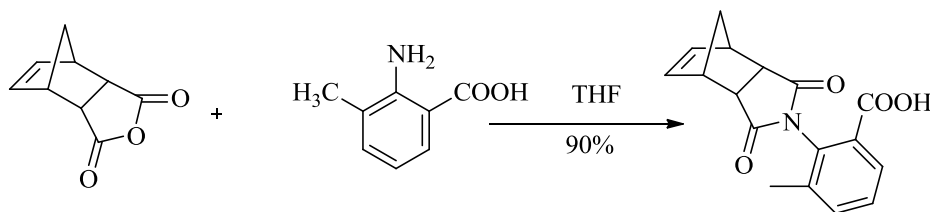


Figure 1.1. Synthesis of functional monomer 1^{2b}

Cis-norbornene-*endo*-2,3-dicarboxylic anhydride (1.50 g, 9 mmol) and 2-amino-3-methyl benzoic acid (1.25 g, 0.0080 mol) were mixed and dissolved in tetrahydrofuran (20 mL). The solution was shaken for 2 h, and solvent was removed under vacuum. The solid was heated at 110 °C in an oven for 16 h. *Bis*(norbornene-ethylenediimide) was obtained as a light grey solid (96% yield). ^1H NMR

(acetone-D₆, 300 MHz) δ ppm: 8.01 (d, $J = 7.8$ Hz, 1H), 7.52 (d, $J = 7.8$ Hz, 1 H), 7.40(dd, $J = 7.6$ Hz, $J = 7.8$ Hz, 1 H), 6.33 (dd, $J = 2.1$ Hz, $J = 1.9$ Hz, 2 H), 3.52 (d, $J = 1.5$ Hz, 2 H), 2.13 (s, 3 H), 1.66 (dd, $J = 1.6$ Hz, $J = 1.5$ Hz, 2 H).

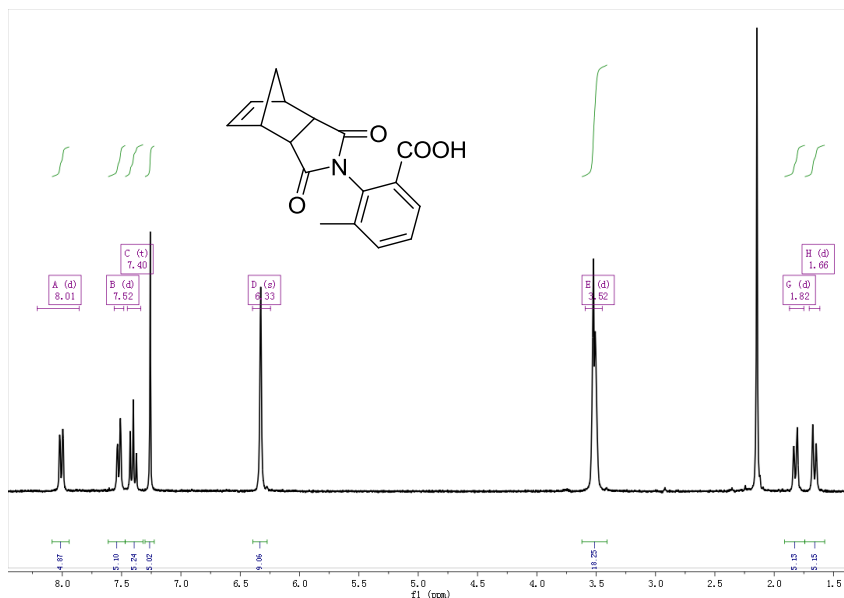


Figure 1.2. ¹H NMR (acetone-D₆, 300 MHz) of Monomer 1

1.14 PREPARATION OF CROSSLINKER

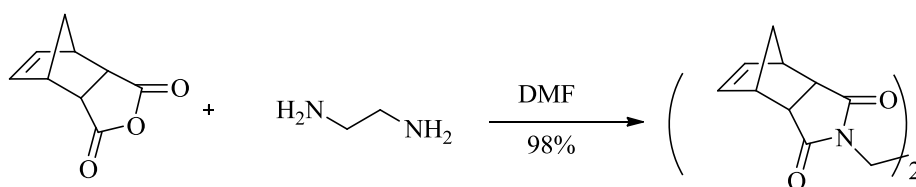


Figure 1.14. Synthesis of bis(norbornene-ethylenediimide) crosslinker

Cis-norbornene-*endo*-2,3-dicarboxylic anhydride (7.37 g, 0.0435 mol) and ethylene diamine (1.40 mL, 0.0207 mol) were dissolved in 10 mL DMF, and stirred at 110 °C in an oil bath for 22 h. After cooling the reaction to rt, by adding ice cold water, a white solid was obtained collected by suction filter and drying under vacuum (93% yield). ¹H NMR

(CDCl₃, 300 MHz) δ ppm: 6.05 (s, 4 H), 3.47 (s, 4 H), 3.32-3.34 (m, 4 H), 3.22-3.24 (d, 4 H), 1.71 (d, $J = 8.7$ Hz, 2 H), 1.51 (d, $J = 8.7$ Hz, 2 H).

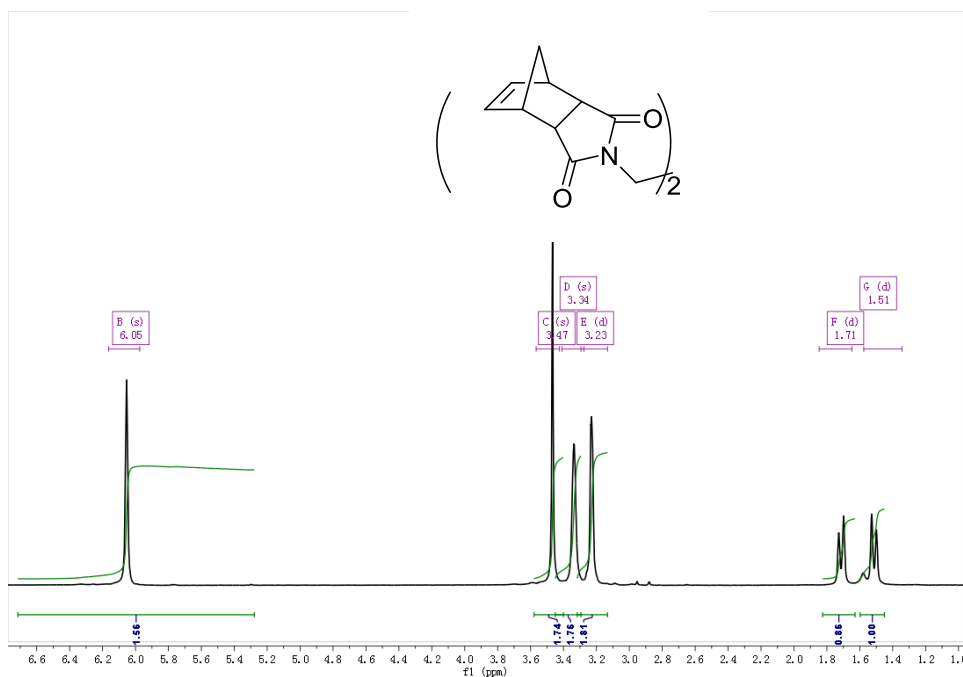


Figure 1.15. ¹H NMR (CDCl₃, 300 MHz) *bis*(norbornene-ethylenediimide) crosslinker

1.15 PREPARATION OF SOLVENT PROGRAMMABLE POLYMERS

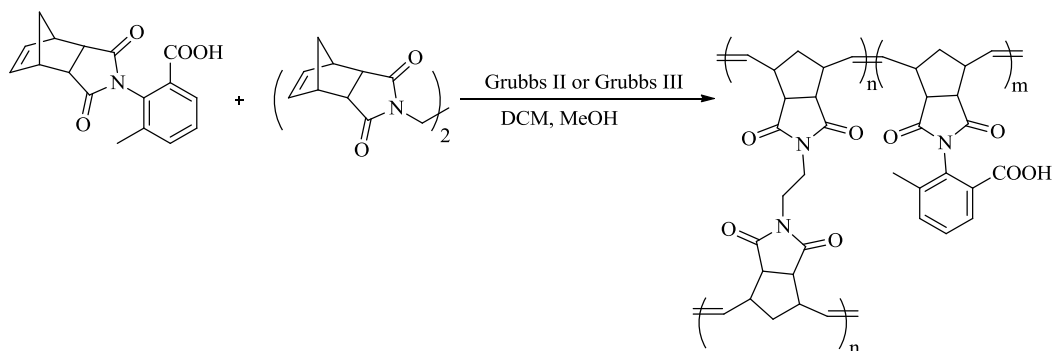


Figure 1.16. Synthesis of SPP-1 and SPP-2

Preparation of SPP-1(Based on the preparation of the previous reported SPP-1)^{2b}

Crosslinker *bis*(norbornene-ethylenediimide) (2.38 g, 6.74 mmol) and functional monomer norbornene-*endo*-diimidebenzoic acid (0.51 g, 1.69 mmol) were added to a 10 mL scintillation vial. These solid mixtures were dissolved using 10 mL dichloromethane and 4 mL methanol, and 0.049 g (1 mol%) of Grubbs II catalyst was added. The solutions were stirred for 25 min, the mixture turned into dark red cloudy suspension. Polymerization continued for 10 h at rt. Then, the reaction vial was put into a 60 °C water bath for 4 h. The reaction was cooled into rt. The polymers were ground by using a mortar and pestle while still wet and were dried under vacuum. The polymers were washed twice by soxhlet extraction. First with methanol for 24 h, and then with acetonitrile for 24 h. The polymers were dried under vacuum overnight to yield a dark red solid powder (1.93 g, 67% yield).

Preparation of SPP-2

Crosslinker *bis*(norbornene-ethylenediimide) (2.38 g, 6.74 mmol) and functional monomer norbornene-*endo*-diimidebenzoic acid (0.51 g, 1.69 mmol) were added to a 10 mL scintillation vial. These solid mixtures were dissolved using 10 mL dichloromethane and 4 mL methanol, and 0.042 g (1 mol%) of Grubbs II catalyst was added. The solutions were stirred for 25 min, the mixture turned into dark red cloudy suspension. Polymerization continued for 10 h at rt. Then, the reaction vial was put into a 60 °C water bath for 4 h. The reaction was cooled into rt. The polymers were ground by using a mortar and pestle while still wet and were dried under vacuum. The polymers were

washed twice by soxhlet extraction. First with methanol for 24 h, and then with acetonitrile for 24 h. The polymers were dried under vacuum overnight to yield a grey red solid powder (2.89 g, ~100% yield).

1.16 SWELLING EXPERIMENT

Equal weights of SPPs (160 mg) were placed into six NMR tubes, and the initial heights of the polymer packed in the tubes were the same. Water or acetonitrile were added to the polymer and heated for 26 hours at 83 °C. The changes in volume were measured from the differences with the control group.

1.17 ENVIRONMENTAL SCANNING ELECTRON MICROSCOPE STUDYING THE MORPHOLOGY OF SPPs

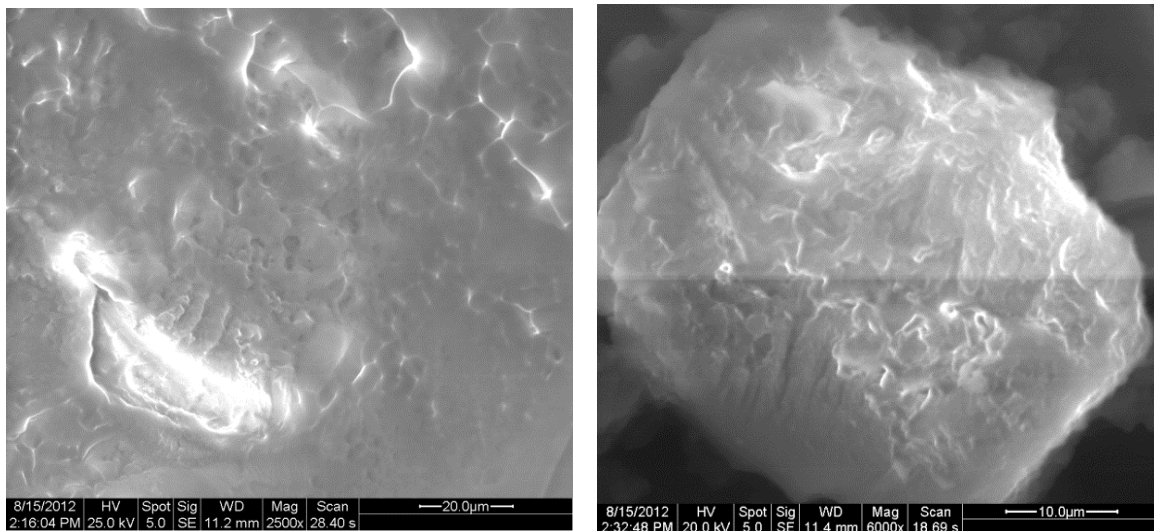


Figure 1.17. SEM images of SPP-1 (left) and SPP-2 (right)

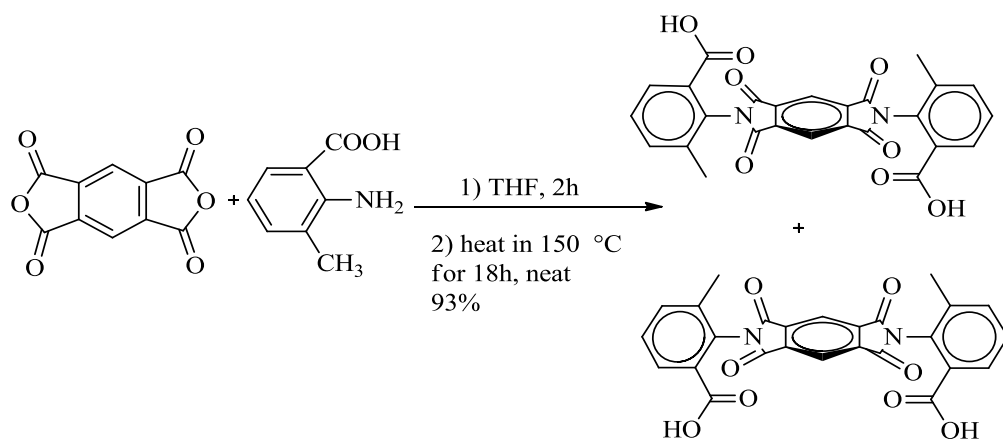
The morphology of SPP-1 was expected to be smoother than SPP-2 based on lower

crosslinking percentage. However, the SEM figures showed that SPP-1 and SPP-2 had very similar morphologies, which was resulted from gel-like polymers are always smooth.

SYNTHESIS AND SUPPORTIVE INFORMATION IN AIM 2

1.18 PREPARATION OF *BIS*(METHYLBENZOIC ACID)

Announcement: Preparation of *anti* and *syn*-diimide followed the procedure reported previously¹²



Scheme 1.6. Preparation of *anti* and *syn* bis(methyl benzoic acid)

1,2,4,5-Bezenetetracarboxylic acid dianhydride (0.823 g) and 2-amino-3-methylbenzoic acid 1.14 g) were dissolved in THF (100 mL). The solution was stirred at rt for 2 h, and the solvent was removed in vacuum. After that, these obtained solids were heated at 150 °C for 18 h, and these solids were purified by column chromatography (silica gel, 2.5-5.0% acetic acid/DCM).

1.19 PURIFICATION OF ANTI AND SYN DIACID BY COLUMN CHROMATOGRAPHY

Since the polarity difference of these atropisomeric diacids is small, therefore, it is a great challenge to isolate them separately. First of all, it can easily verify that the *anti/syn* isomers were obtained by using two dimensional TLC. By using a square TLC plate and running through the vertical and horizontal side each by once, we could obtain spots which showed as the right picture in Figure 1.18.

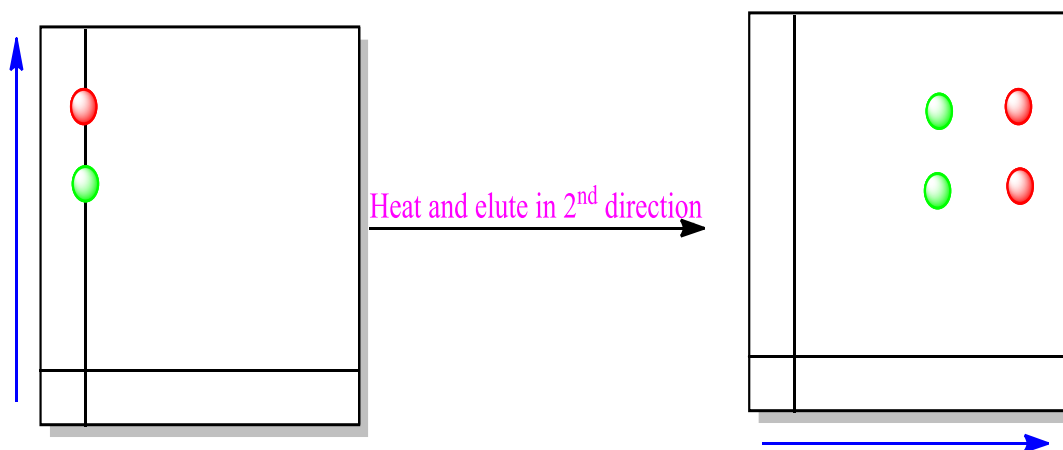


Figure 1.18. Two dimensional TLC to demonstrate that the diacid mixture are atropisomers, and also by calculating the R_f can instruct the solvent system used in column.

By trying different solvent systems, 4% acetic acid/DCM system is an ideal solvent system to separate *anti/syn* diimide efficiently. Purified *anti* and *syn*-diacid isolated isomers were obtained through chromatography column.

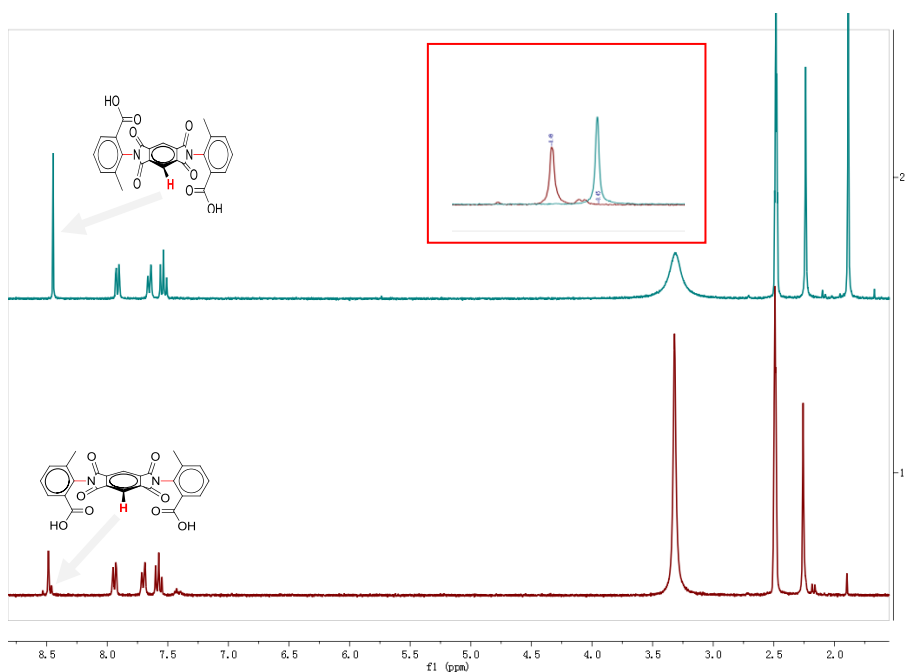
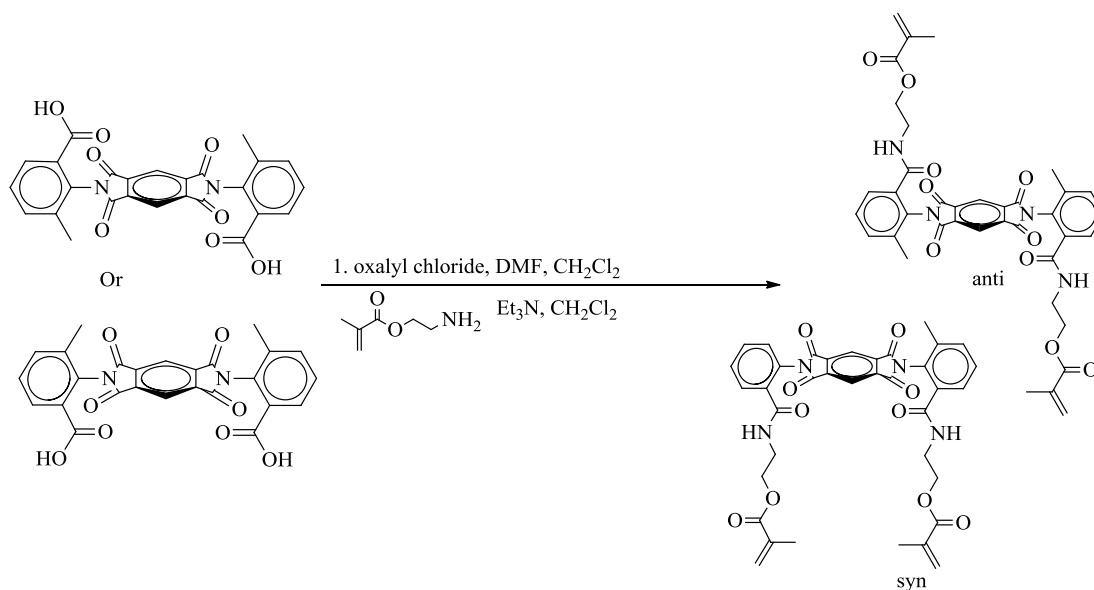


Figure 1.19. ^1H NMR of *anti* diacid (green) and *syn*-diacid (red) (DMSO- d_6 , 300Mz).

1.20 SYNTHESIS OF ANTI AND SYN-DIIMIDE



Scheme 1.7. Preparation of *anti* and *syn* diimide from *anti* and *syn* diacid¹²

Anti-diimide: To a refluxing suspension of *anti*-diacid (0.102 g, 0.206 mmol) in DCM (20 mL) and DMF (2 drops) was added with oxalyl chloride (0.5 mL, 5.7 mmol). The reaction was heated at reflux for 1.5 h and the solvent was removed under vacuum. Next, 2-aminoethyl methylacrylate (0.154 g, 0.927 mmol) and triethylamine (0.5 mL) in DCM (20 mL) was added. The reaction was poured into cold water and washed six times with 1 N HCl (50 mL). The solid was dried under vacuum to obtain a yellow solid (0.113 g, 89.6% yield). The same procedure used in preparing syn-diimide.

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CHAPTER II

SOLUTE PROGRAMMABLE POLYMERS

2.1 ABSTRACT

In the second project, our goal was to develop a series of new programmable polymers which can be used to recognize solute rather than solvent templates. These new programmable polymers have potential applications in the design of custom materials for the separation of mixtures. First, a 2nd generation programmable polymer was developed containing recognition groups, which have weaker affinity for the templates. The 1st generation SPPs containing carboxylic acid recognition groups have stronger hydrogen bonding strength than the amide groups when bound with hydrogen bonding based templates. Amide groups were picked as the recognition group for the 2nd generation programmable polymers, and several chiral natural products were selected as solute templates. The recognition and memory properties of the 2nd generation programmable polymer were measured. The new programmable polymers showed significant recognition and memory capabilities with solute templates, therefore, the 2nd generation programmable polymer is able to use in separation of mixtures.

2.2 INTRODUCTION

Stimuli-responsive polymers can be induced into various morphologies and functions using external stimuli, such as temperature, light, solvent, pH, magnetic and electric fields.¹⁸ However, there was very few reports on stimuli-responsive polymers applied to chiral analyte separations.¹ Chirality is a particularly important factor in living systems,^{18c} since living organisms are constructed from chiral molecules and macromolecules. A pair of enantiomers will usually show different biological activity.¹⁹ Hence, the development of programmable polymers capable of chiral separation are significant meaningful and valuable.¹⁹ As we emphasized in the first chapter, programmable polymers can maintain the template induced changes after the removal of templates.²⁰ Therefore, programmable polymers formed using chiral templates could be versatile in separating chiral mixtures. The polymer could quantitatively measure chiral mixtures and efficiently separate them.

The 2nd generation programmable polymers were designed with amide recognition groups that formed weaker hydrogen bonding interactions with templates. The 1st generation programmable polymers contained carboxylic acid groups that formed strong hydrogen bonding interactions, which made it possible to remove most templates without heating and erasing the templating effect. Only weak bound solvent molecules could be used as templates. Therefore, more weakly hydrogen bonding amide recognition groups were used in the 2nd generation programmable polymers. First, an amide monomer and programmable polymers were prepared. Carboxylic acid monomers and programmable polymers were prepared as controls. The recognition and memory properties were

compared by measuring the binding capacities of each polymer. The programmable polymers were templated with lactic acid, 2-hydroxy-3-pinanone and camphor (Figure 2.1).

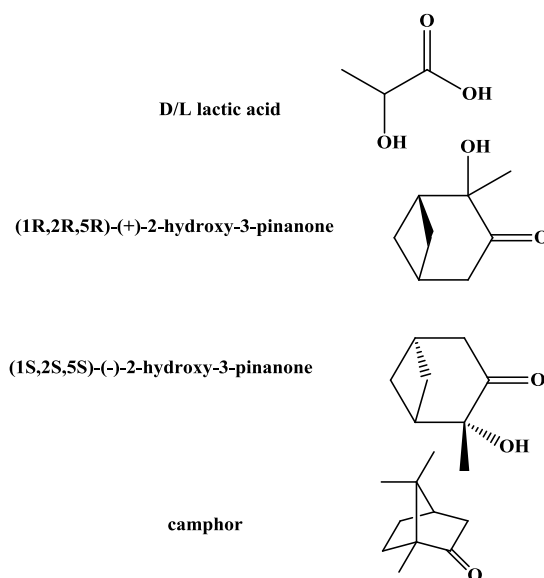


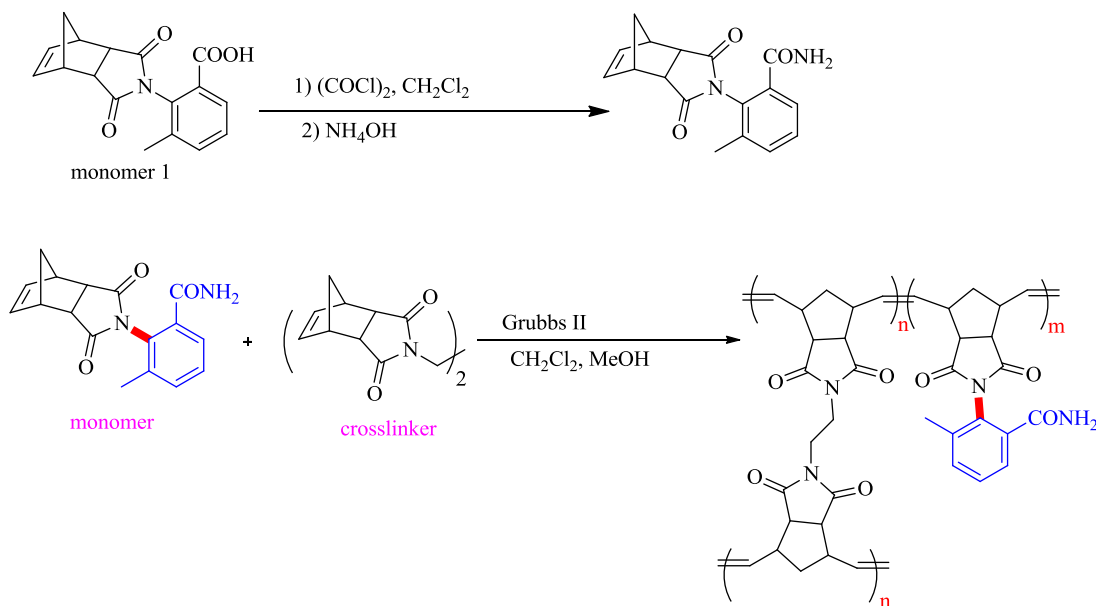
Figure 2.1. Small molecule templates used to test the recognition and memory properties with the amide and carboxylic acid programmable polymers.

Three small molecule templates were selected containing recognition groups of varying hydrogen bonding strength, such as carboxylic acid, alcohol and ketone. The lactic acid containing the carboxylic acid groups were expected to have the strongest hydrogen bonding interactions, and 2-hydroxy-3-pinanone containing ketone and alcohol groups have lower hydrogen bonding interactions. Finally, camphor containing only ketone groups have the weakest hydrogen binding interactions. Both carboxylic acid and amide programmable polymers were heated with the three solute templates in varying concentrations (0.001 to 1 M) to compare their templation efficiencies. After the polymers were cooled to rt, and the templates were removed by washing 5 times with

MeOH (5 mL, 20 min) and 5 times with acetonitrile (5 mL, 20 min). Finally, the templation effects were assessed by measuring binding capacities of the polymers with EA9A.

2.3 RESULTS AND DISCUSSIONS

First, the amide monomer was prepared based on the functional monomer **1**. The amide monomer was copolymerized with a crosslinker through ROMP using the 2nd generation Grubbs catalyst.



Scheme 2.1. Preparation of amide functional monomer 1, and amide programmable polymers

The amide and carboxylic acid programmable polymers were obtained through the procedures shown in Scheme 2.1 (details are described in the experimental part). First, 15×0.2 grams of carboxylic acid polymer were added into 15×10 mL vials (labeled as 1 M lactic acid, 0.5 M lactic acid, 0.1 M lactic acid, 0.01 M lactic acid, 0.001 lactic acid, 1

M hydroxy pinanone, 0.5 M hydroxy pinanone, 0.1 M hydroxy pinanone, 0.01 M pinanone, 1 M camphor, 0.5 M camphor, 0.1 M camphor and 0.01 M camphor, water and cyclohexane). Second, 2.5 mL of solid templates solution dissolving by cyclohexane were added into the corresponded vial. The vials were sealed very tightly and heated at 80 °C for 26 h. The templates were removed by using methanol and acetonitrile each for five times (shaken for 20 minutes each). The removal of the templates from the polymers was verified by monitoring the waste washing solvent using TLC. of the waste washing solvent. These polymers were dried at rt under N₂ environment. The binding capacities of the polymers for EA9A were measured following the same procedure as the batching binding studies we described in the first chapter.

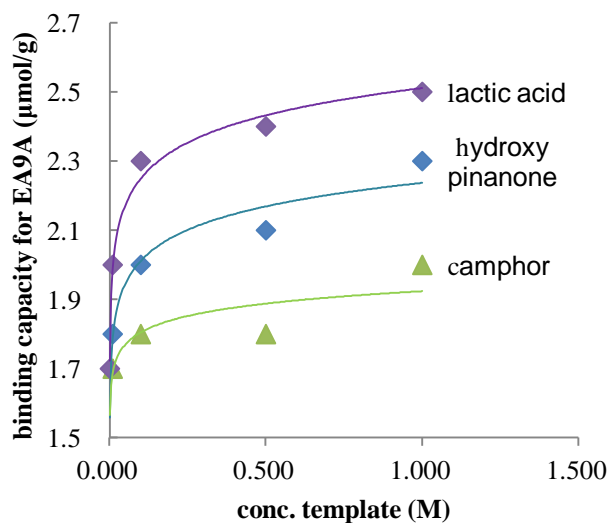


Figure 2.2. Measurement of binding capacity (0.1 mM EA9A in CH₃CN) of carboxylic acid programmable polymers after heating with various concentrations of the solute templates: lactic acid, hydroxy pinanone and camphor.

The binding capacities changed when heating the carboxylic acid polymers with

various concentrations of the three templates as shown in Figure 2.2. First, the binding capacities of the polymers increased with the concentration of the templates, configuring that each of these three solutes worked effectively as templates for the polymers. Second, polymers templated with lactic acid showed the largest increasing in binding capacities and polymers templated with camphor showed the lowest binding capacities. The trend was that the higher the polarity of the templates' recognition groups, the higher the binding capacities of the polymers.

The binding study for the new amide programmable polymers was conducted in the same way as the carboxylic acid programmable polymers. Amide programmable polymers were expected to be easier in removing templates after bonding with solute templates. Therefore, amide programmable polymers might show higher binding capacities than carboxylic acid programmable polymers.

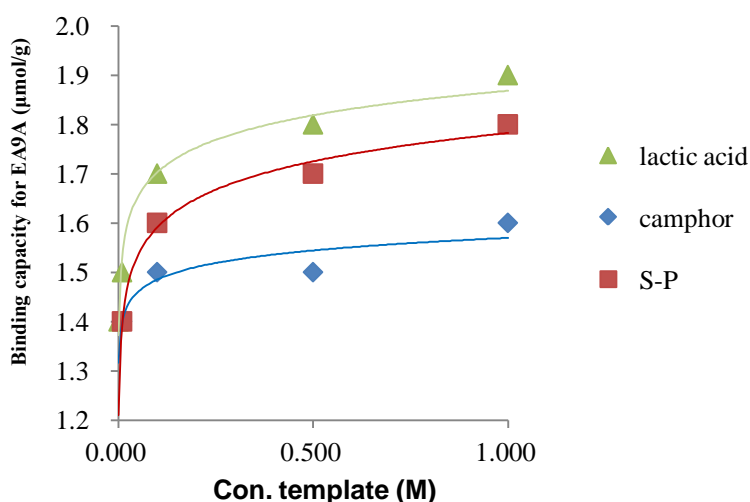


Figure 2.3. Measurement of binding capacity (0.1 mM EA9A in CH₃CN) of amide programmable polymers after heating with various concentrations of the solute templates: lactic acid, hydroxy pinanone, and camphor.

The binding capacities change when heating the amide polymer with the three solutes at various concentrations. Generally, the amide polymers followed the same trend as the carboxylic acid polymers. 1) Binding capacities increased with the concentration of the templates; 2) Binding capacities increased with the polarity of templates. In conclusion, the three solute templates made significant induced changes on both amide and carboxylic acid programmable polymers. The amide polymers showed lower binding capacities when compared with the corresponded carboxylic acid polymers.

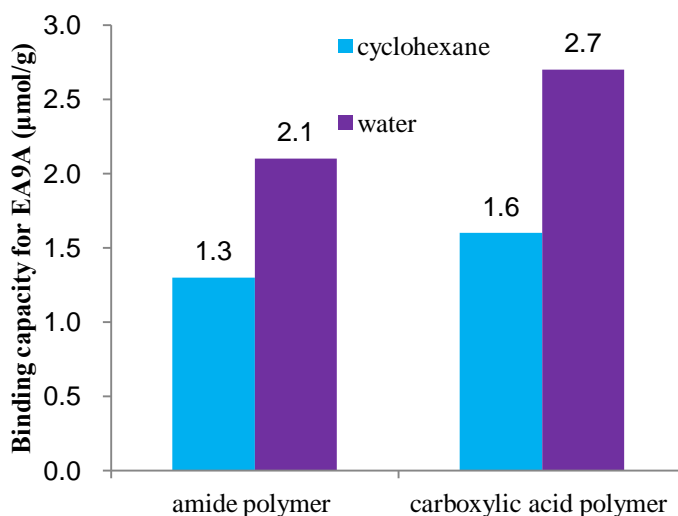


Figure 2.4. Comparison of the solvent memory effect for the carboxylic acid and amide polymers by their differences in binding capacity ($\mu\text{mol/g}$) after heating with cyclohexane and water

The memory properties of these two polymers can be measured by comparing the binding capacities differences between the high polarity water and low polarity cyclohexane. We found that these two polymers showed the similar binding gaps (0.9 ± 0.1), which means that the amide and carboxylic acid programmable polymers have

similar memory properties. Carboxylic acid polymers showed higher binding capacities compared with the corresponded amide polymers. Therefore, this result verified again that carboxylic acid programmable polymers had higher recognition capabilities compare with amide programmable polymers.

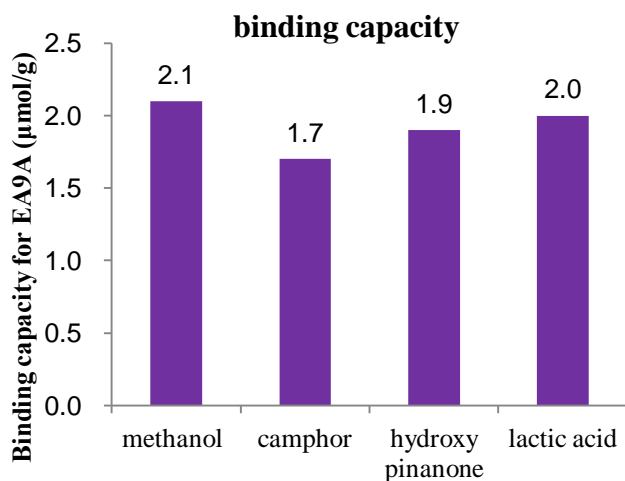


Figure 2.5. Comparison of the binding capacity for carboxylic acid polymers heated with 1 M methanol, 1 M camphor, 1 M hydroxy pinanone and 1 M lactic acid.

To figure out whether the polymer works on both non-polar and polar solvents, we tried polar solvent methanol instead of non-polar solvent cyclohexane using in dissolving solute templates. In Figure 2.5, the polymers showed induced changes when dissolved by polar methanol solvent. 2.5 mL of 1 M methanol, 1 M camphor, 1 M hydroxy pinanone and 1 M lactic acid were each reacted with carboxylic acid polymers (0.2 g). We selected carboxylic acid polymer based on their higher recognition properties than the amide polymers. The three templates made induced changes, since the binding capacities for the templated polymers were different with solvent templated polymers. Also, the higher of

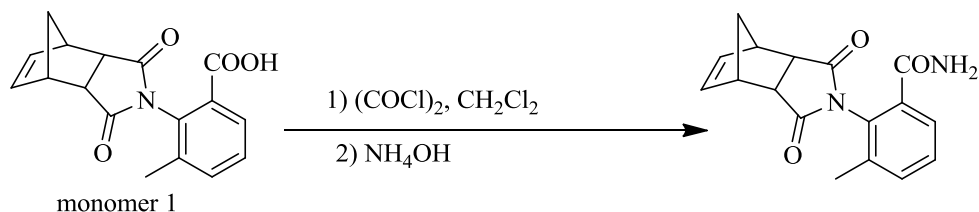
template polarity the higher of binding capacity effect existed again. Therefore, the three templates worked both on polar and non-polar solvents condition in inducing the carboxylic acid and amide programmable polymers.

2.4 CONCLUSIONS

Both the new amide programmable polymers and the previous carboxylic acid programmable polymers showed very effective recognition and memory properties when bound with solute templates. The carboxylic acid polymers showed higher recognition capabilities than the amide polymers. However, they both showed similar memory properties. Also the solute templates can induce changes of the amide and carboxylic programmable polymers on both non-polar and polar solvent systems.

EXPERIMENTAL

2.5 PREPARATION OF AMIDE FUNCTIONAL MONOMER



Scheme 2.2. Preparation of amide functional monomer 1

Functional monomer **1** (1 mmol) was dissolved into 5 mL CH_2Cl_2 and 2 M oxyl chloride (1 mL) dissolved in CH_2Cl_2 was added. The solution was stirred for 1 h and the

solvent was removed in vacuum, and the resulted acid chloride was suspended in 5 mL CH_2Cl_2 under N_2 at 0°C . The acid chloride was treated with 2.5 eq NH_4OH overnight. The aqueous were extracted by 3×10 mL CHCl_3 to separate the organic layer. Next, the organic layers were combined together. Finally, a grey solid was obtained after filtering and drying the organic layer solution (100% yield). ^1H NMR (acetone- d_6 , 300 MHz) δ ppm: 8.05 (d, $J = 7.9$ Hz, 1 H), 7.82 (d, $J = 7.6$ Hz, 1 H), 7.57 (dd, $J = 7.5$ Hz, $J = 7.1$ Hz, 1 H), 6.37 (dd, $J = 1.9$ Hz, $J = 1.5$ Hz, 2 H), 3.50-3.52 (m, $J = 1.5$ Hz, 2 H), 2.12 (s, 3 H), 1.71 (dd, $J = 1.6$ Hz, $J = 1.3$ Hz, 2 H).

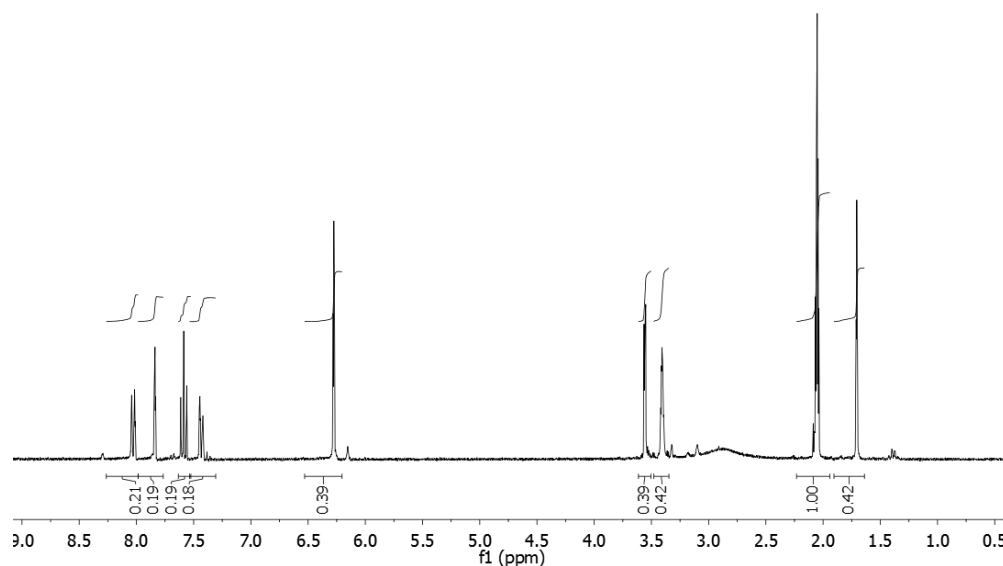
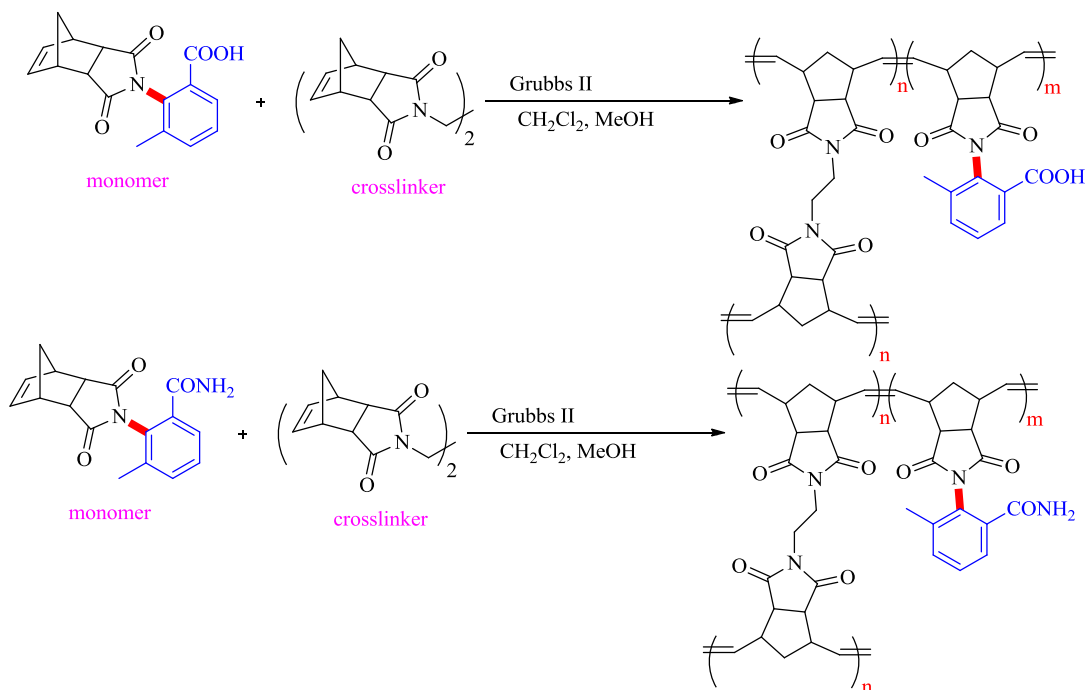


Figure 2.6. ^1H NMR (acetone- D_6 , 300 MHz) of amide functional monomer 1

2.6 PREPARATION OF AMIDE AND CARBOXYLIC ACID POLYMER



Scheme 2.3. Preparation of carboxylic acid and amide programmable polymer through ROMP

Preparation of carboxylic acid polymer followed the same procedure as preparing SPP-1. Amide programmable polymers were prepared through the following procedure: crosslinker *bis*(norbornene-ethylene)diimide (2.38 g, 6.74 mmol) and functional amide monomer norbornene-*endo*-diimidebenzyl amide (0.51 g, 1.69 mmol) were added to a 10 mL scintillation vial. These solid mixtures were dissolved using 10 mL dichloromethane and 4 mL methanol, and 0.049 g (1 mol%) of Grubbs II catalyst was added. The solutions were stirred for 25 min, the mixture turned into dark red cloudy suspension. Polymerization continued for 10 h at rt. Then, the reaction vial was put into a 60 °C water bath for 4 h. The reaction was cooled into rt. The polymers were ground by using a

mortar and pestle while still wet and were dried under vacuum. The polymers were washed twice by soxhlet extraction. First with methanol for 24 h, and then with acetonitrile for 24 h. The polymers were dried under vacuum overnight to yield a grey brown solid powder (2.13 g, 74% yield).

2.7 BATCH BINDING STUDY WITH UV-Vis

Carboxylic acid and amide programmable polymers (0.15 g) were heated with 2 mL template solution at 80 °C for 26 h. The templates were removed by shaking with acetonitrile and methanol for 5 times each. For the binding study in this chapter, 2.5 mL of 0.1 mM EA9A solution in acetonitrile was added to the vial within 60 mg polymers. The vial was shaken for 2 h. Next, 2.5 mL of acetonitrile was added to the vial within 60 mg polymers as blank groups. By comparing the absorbance value (257 nm) differences between polymer solutions with the stock solution (pure 0.1 mM EA9A solution), a relatively binding capacity value would be obtained. By comparing the binding capacities between the sample groups and blank groups, we can determine the accuracy of the data was obtained.

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