SYNTHESIS AND CHARACTERIZATION OF PENDANT-FUNCTIONALIZED POLYMERS FROM BAYLIS-HILLMAN ADDUCTS

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SYNTHESIS AND CHARACTERIZATION OF PENDANT-FUNCTIONALIZED POLYMERS FROM BAYLIS-HILLMAN ADDUCTS

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Thesis

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ABSTRACT

Over the past decades, chemists have explored various approaches to prepare functionalized polymers for improved properties. The combination of organic chemistry and polymer chemistry is a promising approach to build novel polymer structures, therefore synthetic organic chemistry has been employed to design novel monomers for polymer synthesis. Our group takes advantage of the Baylis-Hillman reaction, since it is a simple and convenient method to synthesize densely functionalized molecules. This feature makes Baylis-Hillman adducts good substrates for synthesizing functionalized polymers.

In this work, we synthesized two types of polymers by a bottom-up design of monomers using Baylis-Hillman (BH) reaction. We designed two types of monomers: a hydroxyl-functionalized acrylate and an unsaturated diol, which can undergo chain-growth polymerization and step-growth polymerization, respectively. Using the BH acrylate, we synthesized a hydroxyl-functionalized polyacrylate via reversible addition-fragmentation chain transfer (RAFT) polymerization. Using a BH diol, we were able to synthesize an unsaturated poly(ester-urethane). This unsaturated poly(ester-urethane) can undergo post-functionalization via thiol-ene click reaction. Thermal properties and potential applications of these polymers were investigated.
I would like to thank my advisor, Dr. Abraham Joy for his guidance during these two years. He offered me great help during my study, not only teaching me knowledge and experimental skills but also how to think. Also, for the perfection of my thesis, he gave me a lot of suggestion, such as grammar, the use of word as well as the organization of the thesis. Second, I would like to thank Dr. Coleen Pugh who takes the time off her busy schedule to be my committee member. Also, I would like to thank all the group members in our group for their help in my study. At last, I would like to thank my parents for their support on both my study and my life.
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CHAPTER I

INTRODUCTION

1.1 Motivation

Polymers are long chain molecules composed of repeating units. The long chain structure makes polymers have a range of unique properties different from small molecules. Therefore, polymers have been widely used in many fields, such as agriculture, manufacturing, aerospace as well as medicine. However, one of the disadvantages of traditional polymers, such as polystyrene (PS), polylactide (PLA) and polycaprolactone (PCL), is the lack of functionalities, which limits their applications in certain areas. Therefore, many research groups are working on the synthesis of pendant-functionalized polymers.

Our group is interested in using the Baylis-Hillman reaction, which is a simple and convenient method to synthesize functionalized molecules.\textsuperscript{[1]} This feature makes Baylis-Hillman adducts good substrates for synthesizing functional polymers. Although Baylis-Hillman adducts are promising substrates for polymer synthesis, there are only a few reports describing the polymerization of Baylis-Hillman adducts, and most of these are not detailed investigations of the reaction.

In this work, polymers based on Baylis-Hillman adducts were synthesized via both chain polymerization and condensation polymerization in order to expand the utility of the Baylis-Hillman reaction. For the chain polymerization part, a class of hydroxymethyl
substituted polyacrylates was synthesized by reversible addition-fragmentation transfer (RAFT) polymerization. Thermal properties, self-assembly properties as well as potential applications were studied. For the condensation polymerization part, a novel pendant-functionalized polyester was synthesized, which can easily incorporate two functionalities in one repeating unit. Thermal properties were studied.

1.2 Background
1.2.1 Pendant-functionalized polymers
1.2.1.1 Introduction

For traditional materials, such as polyethylene (PE), polystyrene (PS), polylactide (PLA) or polycaproactone (PCL), their lack of functionalities hinders the modification of the polymers and limits their applications. Therefore, pendant-functionalized polymers are designed to expand their applications. The main components of pendant-functionalized polymers are: backbone, side-chain functionalities.\(^2\) Side-chain functionalized polymers contain dense functionalities such as hydroxyl\(^3\), carboxyl\(^4\) and amine\(^5\) pendant group, which provide improved physiochemical properties such as hydrophobicity and biodegradability, and also facilitates conjugation and modification of the polymer.

Therefore side-chain functionalized polymers can be used in many fields, such as biomedical and industrial applications. For example, poly(N-(2-hydroxyethyl)acrylamide) (polyHEAA)\(^6\), which contains hydroxyl functionalities, shows good resistance to both protein adsorption and bacteria adhesion and therefore shows very promising antifouling properties. Another example is polymer-drug conjugates that are widely used in cancer
therapy, which incorporate drug, targeting and solubilizing moieties in the polymers.[7]
This can be achieved by using polymers with reactive functional groups which enable post-functionalization of the polymers.

1.2.1.2 Synthetic strategies towards pendant-functionalized polymers

1.2.1.2.1 Direct polymerization of functional monomers

I. Living Radical Polymerization

Several strategies have been employed to synthesize functionalized polymers. Synthesis of functional polymers can be achieved by polymerization of functional monomers by either conventional or living radical polymerization. However, because of the living nature and low polydispersity of the polymer, living radical polymerization techniques are usually chosen, such as ATRP (atom transfer radical polymerization), NMP (nitroxide-mediated polymerization), and RAFT (reversible addition-fragmentation transfer) polymerization.

Here is an example about the synthesis of polymers with azido-pendant groups. As illustrated in scheme 1,[8] an azido-functionalized methacrylate was first synthesized. Then the monomer was polymerized via ATRP to give a homopolymer with pendant azido functionalities which can be used for highly efficient click reactions. In this work, the good control of the polymerization was observed, which was indicated by linear consumption of the monomer over time and the linear increase in molecular weight with conversion. The Mn of the obtained polymer is 18400 g/mol and the PDI is 1.33. The azide group was then used to react with different alkynes using CuI catalyst. The conversion reached greater than 95 % in 2 hours at room temperature.
By living radical polymerizations, it is also easy to prepare block copolymers with two or more functionalities. Droumaguet\cite{9} reported hydrophilic triblock copolymers which were made from three functionalized methacrylate, a protected glycerol methacrylate, a protected propargyl methacrylate and a fluorescent methacrylate. The polymer was synthesized by ATRP and the obtained molecular weight of the obtained polymer is 11.5 kDa and the PDI is 1.15. Subsequent deprotection of the protected groups makes the polymers amphiphilic and provides a reactive propargyl group that can be used for click reactions. This triblock amphiphiles exhibit aggregation properties and are potential for biomedical and biotechnological applications.
Scheme 1.2 Synthesis of multifunctional polymers via ATRP

I. Ring-opening polymerization

In recent years, studies\textsuperscript{[10-13]} have shown the use of functionalized cyclic carbonates (Figure 1) as substrates for ring-opening polymerization to give pendant-functionalized polyesters.

Figure 1.1 Functionalized Cyclic Carbonate
For example, Jiang\textsuperscript{12} reported a propargyl-pendant polyester made by ring-opening polymerization of propargyl-functionalized lactide catalyzed by tin carboxylate. The reactive propargyl group facilitates the post-functionalization of the polymer. The insertion-coordination mechanism of the metal catalyzed ROP provides less transesterification side reactions than anionic or cationic catalysis. In this study, molecular weight range from 9000 to 60000 g/mol was prepared using different monomer-to-initiator ratios. Compared to polycondensation, the ROP provides relatively lower polydispersity, which is around 1.2.

![Scheme 1.3 Synthesis of functionalized PLA](image)

II. Condensation polymerization

Hahn\textsuperscript{14} reported a new method to prepare hydroxyl-pendant polyesters by polycondensation of diols and malic acid without protecting the secondary hydroxyl group of malic acid. When the reaction is catalyzed by scandium triflate at ambient temperatures, the primary hydroxyl group is much more reactive than secondary hydroxyl group. Therefore the polycondensation of diols and malic acid can be achieved without the reaction of secondary hydroxyl group of malic acid. The molecular weight of the obtained polymer is about 16 kDa and the PDI is 2.5.
1.2.1.2.2 Post-functionalization of polymers

Keul\textsuperscript{[14]} reported a method to prepare multifunctional polymers from polyamines and carbonate couplers. The functional carbonate coupler is a molecule that contains a functional site and a reactive site. A broad library of functional couplers has been reported in the above paper, such as hydrophobic, hydrophilic, fluorescence, and photoactive couplers. The functionalities can be connected to the polymer by the reaction between amine and cyclic carbonate, and the generated urethane group will act as the linkage.

Scheme 1.4 Synthesis of hydroxyl-functionalized polyesters based on malic acid.

Scheme 1.5 Post-functionalization of polymers using functional couplers
1.2.1.2.3 Generation of functionalities during the reaction

Although side-chain functionalized polyester can be made via ring-opening polymerization or polycondensation of side-chain protected monomers, some of them still need deprotection, which may cause polymer degradation or incomplete deprotection. In another example, You\textsuperscript{[15]} reported the synthesis of a hydroxyl-pendant polyester by the reaction of diacids with diglycidyl monomers. In this reaction, there is no need to use protected monomers and therefore simplified the procedure.

![Scheme 1.6 Synthesis of hydroxyl-pendant polyesters by ring-opening reaction](image)

1.2.2 Baylis-Hillman reaction

1.2.2.1 Introduction

The Baylis-Hillman reaction was originally reported in a German patent by A. B. Baylis and M. E. D. Hillman in 1972.\textsuperscript{[1]} The reaction involves the coupling of the α-position of activated alkenes with carbon electrophiles catalyzed by a tertiary amine, to give multifunctional molecules. The reaction is illustrated in Scheme 7.\textsuperscript{[16]}

![Scheme 1.7 Baylis-Hillman reaction](image)
A variety of activated alkenes can be used, such as alkyl vinyl ketones, alkyl (aryl) acrylates, acrylonitrile, vinyl sulfones, acrylamides, allenic esters, vinyl sulfonates, vinyl phosphonates and acrolen.\textsuperscript{[1]} For electrophiles, aldehydes have been widely used, other electrophiles such as $\alpha$-keto esters, nonenolizable 1,2-diketones, aldime derivatives and fluoroketones have also been employed.\textsuperscript{[1]}

1.2.2.2 Mechanism

The most generally accepted mechanism of Baylis-Hillman reaction proceeds through the Michael addition-initiated addition-elimination sequence catalyzed by a tertiary amine.\textsuperscript{[17]} As illustrated in Scheme 8, the model reaction is the reaction between methyl vinyl ketone and benzaldehyde catalyzed by DABCO. The first step of the reaction is the Michael-type nucleophilic addition of DABCO to methyl vinyl ketone to generate a zwitterionic enolate A which can attack the aldehyde to generate zwitterion B. Then proton migration and catalyst release provides the product, which contains several functionalities.

Scheme 1.8 Generally accepted mechanism of Baylis-Hillman reaction
Although DABCO is the most generally used catalyst for Baylis-Hillman reaction, there are also other choices for the tertiary amine, such as quinuclidine, 3-HQD, 3-quinuclidone and indolizine, which are shown in Figure 2.\[16\]

![Tertiary amine catalysts](image)

Figure 1.2 Tertiary amine catalysts (1) DABCO (2) quinuclidine (3) 3-HQD (4) 3-quinuclidone (5) indolizine

Complete conversion of monomers to the Baylis-Hillman product usually takes a few days or weeks. To accelerate the reaction, several ways have been tried, such as microwave irradiation, high pressure, excess catalyst or aqueous medium.\[1\] Recently, Hu\[18\] reported that Baylis-Hillman reaction can be accelerated by the use of a dioxane-water medium. The reaction between methyl acrylate and reactive aldehyde in presence of 100mol% DABCO provides the product in shorter time.

![Reaction scheme](image)

Scheme 1.9 Baylis-Hillman reaction in dioxane-water medium

1.2.2.3 Modification of Baylis-Hillman adduct

The Baylis-Hillman reaction is an efficient approach to synthesize densely functionalized molecules,\[1\] since the reaction can generate two functional groups: a
hydroxyl group and an alkene group. Functionalities can be also incorporated by choosing functionalized activated alkenes and electrophiles. For example, Man-Kin Wong\cite{19} synthesized bioconjugates by Baylis-Hillman reaction with subsequent modification. In this work, an oligosaccharide-functionalized aldehyde was reacted with a fluorescently labeled vinyl ketone, which gave a functionalized adduct. Subsequent modification was achieved by reaction between the generated alkene group and thiol-based peptides.

\begin{center}
\textbf{Scheme 1.10 Modification of Baylis-Hillman adduct}
\end{center}

1.2.3 Previous work on polymerization of Baylis-Hillman adducts

1.2.3.1 Radical polymerization of methyl α-hydroxymethyl acrylate

Kress\cite{20} synthesized methyl α-(hydroxymethyl)acrylates by the Baylis-Hillman reaction of formaldehyde and methyl acrylate. This adduct was then polymerized via radical polymerization. The polymers possess pendant hydroxyl moieties, which provides improved physical properties and have the potential for post-functionalization. The polymer shown in Figure 1.3 has a poor solubility in most common organic solvent, but hexafluoro-2-propanol (HFIP) which is a very polar solvent. Also, this work didn’t provide any molecular weight information of this polymer. This type of polymers that bearing other pendant groups were not studied.
1.2.3.2 Preparation of graft copolymers using Baylis-Hillman derivatives

Huang[21] synthesized well-defined graft copolymers using the grafting-from method with the use of reversible addition-fragmentation transfer (RAFT) polymerization and atom transfer radical polymerization (ATRP). The graft copolymers contain a poly(tert-butyl acrylate) backbone and a poly(methyl acrylate) side chains. The synthetic route is shown in scheme 11. First, Baylis-Hillman adduct was prepared by using formaldehyde and tert-butyl acrylate. This adduct was then modified by converting the hydroxyl group into an ATRP initiation group. The derivative was copolymerized with tert-butyl acrylate via RAFT polymerization. Then the ATRP initiation group was used to initiate the polymerization of methyl acrylate to give graft copolymers with molecular weight ranging from 9000 to 90000 g/mol and low PDI around 1.2.

![Scheme 1.11 Synthesis of graft copolymers](image-url)
1.2.3.3 Baylis-Hillman polymerization

![Chemical reaction diagram]

Scheme 1.12 Baylis-Hillman Polymerization

Ji[22] synthesized low molecular weight side-chain functionalized polyesters by Baylis-Hillman polymerization. The polymerization involved the condensation between diacrylate and dialdehyde catalyzed by base. The obtained polymer had two chemically orthogonal groups, hydroxyl and vinyl moieties, which are a handle for post-functionalization. Baylis-Hillman polymerization does not require the protection of the monomer, since the functionalities are generated during the reaction, which is an alternative approach to prepare side-chain functional polyesters. The polymers obtained by this method exhibit molecular weight ranging from 630 to 4200 g/mol. It was also demonstrated that the post-functionalization was achieved by reacting the side-chain hydroxyl and vinyl groups with phenyl isocyanate and methyl-3-mercaptopropionate, respectively.
Scheme 1.13 Post-functionalization of polymers from Baylis-Hillman polymerization
1.2.4 Synthetic techniques used in this work

1.2.4.1 Reversible addition-fragmentation chain transfer (RAFT) polymerization

RAFT polymerization is carried out with a conventional initiator such as AIBN and mediated by a chain-transfer agent. The RAFT agent, usually dithioester derivatives, which has a large chain-transfer constant, controls chain growth. Scheme 1.14 shows the mechanism of RAFT polymerization. The initiator decomposes and yields a primary radical which reacts with monomers to form a propagating radical. Addition of the propagating radical to the chain-transfer agent forms an intermediate radical which subsequently fragments into a new radical and a new chain-transfer agent. The transferred end group in the newly formed chain-transfer agent is as labile as that in the initial chain-transfer agent. The rapid equilibrium between the propagating radicals and dormant
polymer chains provides equal opportunities for all chains to grow, which results in a narrow polydispersity.

1.2.4.2 Thiol-ene Click Chemistry

The thiol-ene reaction consists of a few steps. i) The initiator dissociate to give a radical when treated with heat or UV light. ii) The radical captures a hydrogen from the mercapto group of the thiol to give a thyl radical. iii) The thyl radical add to the C=C bond to yield an intermediate carbon-centred radical followed by chain transfer to another thiol to give a thiol-ene product.[24]

Using this technique, quantitative conversion can be easily obtained in a short time. Due to the high efficiency of thiol-ene reaction, it has been widely used for functionalization of polymers. Currently, various functionalized thiol molecules are commercially available. Using these thiol molecules, it is easy to convert an alkene group into other functional groups, such as alcohol, amine or carboxylic acid. Also, it is convenient to attach biomolecules to the polymer using a thiol-based drug or peptide.
1.3 Importance of this work

Although there has been a few reports about the polymerization of Baylis-Hillman adducts, there are still several aspects of this reaction need to be investigated. For example, Kress\textsuperscript{[20]} reported the simplest hydroxymethyl substituted polyacrylates: poly(methyl α-(hydroxymethyl)acrylates. However, this work didn’t provide any information about the molecular weight and polydispersity of this polymer. Also, the thermal properties such as glass transition temperature and decomposition temperature that provided in this paper are dubious, which do not accord with our experimental data about this polymer. Another example is the Baylis-Hillman polymerization\textsuperscript{[22]} which provided functionalized polyesters. The problems of Baylis-Hillman polymerization are the low molecular weight and limited variety of functional groups. These disadvantages would limit their applications in certain areas.

In order to solve these problems, in this work, we synthesized polymers based on Baylis-Hillman adducts via both chain-growth polymerization and step-growth polymerization. In the chain-growth polymerization part, we synthesized a series of hydroxymethyl α-substituted polyacrylates with different alkyl pendant groups by both conventional radical polymerization and RAFT polymerization. We studied the thermal properties and self-assembly properties of these polymers. In the step-growth polymerization part, we synthesized unsaturated diols by the Baylis-Hillman reaction. Using these unsaturated diols, we synthesized unsaturated poly(ester-urethane)s. The unsaturated polymers can be modified by thiol-ene click chemistry. By this approach, we achieved higher molecular weight and expanded the variety of functional groups of the polymers.
The advantage of the polymers synthesized from Baylis-Hillman adducts is that it is easy to incorporate two functional groups in one repeating unit. In the chain-growth polymerization part, one functional group is the hydroxyl group and another is from the acrylate used for the monomer synthesis. In the step-growth polymerization part, one functional group is the alkene group and another is from the aldehyde used for the monomers synthesis. These highly functionalized polymers would be useful in many applications.
CHAPTER II

SYNTHESES OF α-SUBSTITUTED POLYACRYLATE: EXPERIMENTAL

2.1 Materials

2-2’-Azobis(2-methylpropionitrile) (Aldrich, 98 %) was purified by recrystallization in methanol for three times.

Acetone-d$_6$ (Cambridge Isotope Laboratories, 99.9 %) for NMR analysis was used as received.

Chloroform-d (Cambridge Isotope Laboratories, 99.8 %) for NMR analysis was used as received.

Methanol-d$_4$ (Cambridge Isotope Laboratories, 99.8 %) for NMR analysis was used as received.

1,4-Dioxane (Acros Organics, 99.5 % extra dry) for free radical polymerization was used as received.

1,4-Dioxane (Aldrich, 99 %) was used as received.

Formaldehyde (Alfa Aesar, 37 % w/w aq. Soln.) was used as received.

1,4-Diazabicyclo[2.2.2]octane (Alfa Aesar, 98%) was used as received.

Ethyl acrylate (Alfa Aesar, 99 %) was used as received.

tert-Butyl acrylate (Alfa Aesar, 99 %) was used as received.

n-Hexyl acrylate (Alfa Aesar, 95 %) was used as received. n-Butyl acrylate (Aldrich, 99 %) was used as received.
Ethyl acetate (Certified ACS Reagent Grade) was used as received.

Hexane (Certified ACS Reagent Grade) was used as received.

2.2 Instrumentation and characterization

2.2.1 $^1$H and $^{13}$C NMR spectroscopy

The chemical structure of small molecules was confirmed by $^1$H NMR and $^{13}$C NMR spectroscopy using Varian NMRS 300 and Varian NMRS 500. The NMR spectra were processed by ACD NMR Processor.

2.2.2 Size exclusion chromatography (SEC)

The molecular weight and polydispersity of the polymers was determined using HLC-8320 GPC from TOSOH with DMF as the eluent. The molecular weight was calculated using PMMA as the standard.

2.2.3 Thermal gravimetric analysis (TGA)

The decomposition temperature of the polymers was determined by TA thermal gravimetric analysis instrument Q500. The sample was heated at a heating rate of 10 $^\circ$C/min to 600 $^\circ$C.

2.2.4 Differential scanning calorimetry (DSC)

The glass transition temperature of the polymers was determined by TA differential scanning calorimetry instrument Q2000. The sample was heated and cooled at a rate of 10 $^\circ$C/min.
2.2.5 Scanning electron microscope (SEM)

The SEM images were taken using JEOL-JSM-7401F with operating voltage as 4kV. Before SEM analysis, one drop of the nanoparticle aqueous suspension was added onto a SEM holder and dried in vacuum oven.

2.2.6 Dynamic light scattering (DLS)

The size and size distribution of the nanoparticles were measured by a Zetasizer Nano ZS (Malvern Instruments). The nanoparticle solution was passed through to a 0.45\(\mu\)m pore size nylon filter prior to measurements.

2.3 Synthetic procedures of alkyl \(\alpha\)-(hydroxymethyl)acrylate

2.3.1 Synthesis of ethyl \(\alpha\)-(hydroxymethyl)acrylate

In a round-bottom flask equipped with a magnetic stir bar, 1,4-diazabicyclo[2.2.2]octane (4.1 g, 0.036 mol), ethyl acrylate (10.9 g, 0.109 mol), 1,4-dioxane (10.0 mL) and water (7.3 mL) were added and incubated for 2 minutes. Then formaldehyde aqueous solution (2.7 mL, 0.036 mol) was added. The mixture was stirred for 12 hours. The compound was extracted by ethyl acetate. The organic layer was washed by brine and followed by drying over anhydrous Na\(_2\)SO\(_4\). The filtrate was then concentrated under reduced pressure and purified by column chromatography (30 % ethyl acetate and 70 % hexane, \(R_f = 0.3\)) to give a colorless liquid (2.4 g, 50.4 %).
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.33 (t, \(J = 7.50\) Hz, 3H), 2.23 (t, \(J = 6.00\) Hz, 1H), 4.26 (q, \(J = 7.00\) Hz, 2H), 4.35 (d, \(J = 3.00\) Hz, 2H), 5.83 (s, 1H), 6.27 (s, 1H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 14.09 (s), 60.80 (s), 62.36 (s), 125.37 (s), 139.59 (s), 166.29 (s).

2.3.2 Synthesis of n-butyl \(\alpha\)-(hydroxymethyl)acrylate

In a round-bottom flask equipped with a magnetic stir bar, 1,4-diazabicyclo[2.2.2]octane (4.1 g, 0.036 mol), n-butyl acrylate (14.0 g, 0.109 mol), 1,4-dioxane (10.0 mL) and water (7.3 mL) were added and incubated for 2 minutes. Then formaldehyde aqueous solution (2.7 mL, 0.036 mol) was added. The mixture was stirred for 12 hours. The compound was extracted by ethyl acetate. The organic layer was washed by brine and followed by drying over anhydrous Na\(_2\)SO\(_4\). The filtrate was then concentrated under reduced pressure and purified by column chromatography (30 % ethyl acetate and 70 % hexane, \(R_f = 0.5\)) to give a colorless liquid. (2.9 g, 51.1 %)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.96 (t, \(J = 7.50\) Hz, 3H), 1.36 - 1.49 (m, 2H), 1.64 - 1.73 (m, 2H), 2.25 (t, \(J = 6.00\) Hz, 1H), 4.20 (t, \(J = 7.50\) Hz, 2H), 4.35 (d, \(J = 3.00\) Hz, 2H), 5.84 (s, 1H), 6.27 (s, 1H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 13.62 (s), 19.13 (s), 30.56 (s), 62.41 (s), 64.69 (s), 125.34 (s), 139.61 (s), 166.36 (s).

2.3.3 Synthesis of tert-butyl \(\alpha\)-(hydroxymethyl)acrylate

In a round-bottom flask equipped with a magnetic stir bar, 1,4-diazabicyclo[2.2.2]octane (3.8 g, 0.034 mol), tert-butyl acrylate (14.0 g, 0.109 mol), 1,4-dioxane (10.0 mL) and water (7.3 mL) was added and incubated for 2 minutes. Then formaldehyde aqueous solution (2.7 mL, 0.036 mol) was added. The mixture was stirred for 12 hours. The compound was extracted by ethyl acetate. The organic layer was washed by brine and followed by drying over anhydrous Na\(_2\)SO\(_4\). The filtrate was then...
concentrated under reduced pressure and purified by column chromatography (30% ethyl acetate and 70% hexane, $R_f = 0.5$) to give a colorless liquid (2.4 g, 42.5%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.52 (s, 9H), 2.32 (t, $J = 6.00$ Hz, 1H), 4.30 (d, $J = 6.00$ Hz, 2H), 5.75 (s, 1H), 6.16 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) 28.03 (s), 62.61 (s), 81.31 (s), 124.62 (s), 140.88 (s), 165.65 (s).

2.3.4 Synthesis of n-hexyl $\alpha$-(hydroxymethyl)acrylate

In a round-bottom flask equipped with a magnetic stir bar, 1,4-diazabicyclo[2.2.2]octane (3.8 g, 0.034 mol), n-hexyl acrylate (15.6 g, 0.109 mol), 1,4-dioxane (10.0 mL) and water (7.5 mL) was added and incubated for 2 minutes. Then formaldehyde aqueous solution (2.5 mL, 0.034 mol) was added. The mixture was stirred for 12 hours. The compound was extracted by ethyl acetate. The organic layer was washed by brine and followed by drying over anhydrous Na$_2$SO$_4$. The filtrate was then concentrated under reduced pressure and purified by column chromatography (20% ethyl acetate and 80% hexane, $R_f = 0.4$) to give a colorless liquid (2.9 g, 46.9%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.90 (t, $J = 7.50$ Hz, 3H), 1.32 - 1.43 (m, 6H), 1.65 - 1.74 (m, 2H), 2.26 (s, 1H), 4.19 (t, $J = 6.00$ Hz, 2H), 4.34 (s, 2H), 5.84 (s, 1H), 6.27 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) 13.90 (s), 22.46 (s), 25.57 (s), 28.48 (s), 31.35 (s), 62.46 (s), 65.01 (s), 125.37 (s), 139.61 (s), 166.34 (s).
2.4 Synthetic procedures of poly(alkyl α-(hydroxymethyl)acrylate) by conventional radical polymerization

2.4.1 Synthesis of poly(ethyl α-(hydroxymethyl)acrylate) by conventional radical polymerization

Ethyl α-(hydroxymethyl)acrylate (260.3 mg, 2.0 mmol), AIBN (0.33 mg, 0.002 mmol) and 1,4-dioxane (1.0 mL) were added to a round-bottom flask equipped with a magnetic stir bar and sealed with a rubber septum. The flask was purged with N$_2$ for 30 minutes. Then the reaction was carried out at 70 °C for 24 hours. The polymer was purified by precipitation in diethyl ether for 3 times, centrifuged and dried in vacuum oven to give a white solid.

$^1$H NMR (300 MHz, Methanol-d$_4$) δ (ppm) = 1.31 (m, 3H), 2.00 (m, 2H), 3.83 (m, 2H), 4.10 (m, 2H).

2.4.2 Synthesis of poly(n-butyl α-(hydroxymethyl)acrylate) by conventional radical polymerization

n-Butyl α-(hydroxymethyl)acrylate (316.4 mg, 2.0 mmol), AIBN (0.33 mg, 0.002 mmol) and 1,4-dioxane (1.0 mL) were added to a round-bottom flask equipped with a magnetic stir bar and sealed with a rubber septum. The flask was purged with N$_2$ for 30 minutes. Then the reaction was carried out at 70°C for 24 hours. The polymer was purified by precipitation in hexane for 3 times, centrifuged and dried in vacuum oven to give a white solid.

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 0.97 (m, 3H), 1.42 (m, 2H), 1.64 (m, 2H), 1.92 (m, 2H), 3.59 – 4.07 (m, 4H).
2.4.3 Synthesis of poly(tert-butyl α-(hydroxymethyl)acrylate) by conventional radical polymerization

tert-Butyl α-(hydroxymethyl)acrylate (316.4 mg, 2.0 mmol), AIBN (0.33 mg, 0.002 mmol) and 1,4-dioxane (1.0 mL) were added to a round-bottom flask equipped with a magnetic stir bar and sealed with a rubber septum. The flask was purged with N₂ for 30 minutes. Then the reaction was carried out at 70°C for 24 hours. The polymer was purified by precipitation in hexane for 3 times, centrifuged and dried in vacuum oven to give a white solid.

\(^1\)H NMR (300 MHz, Acetone-d₆) \(\delta\) (ppm) = 1.56 (m, 9H), 2.00 (m, 2H), 3.79 (m, 2H).

2.4.4 Synthesis of poly(n-hexyl α-(hydroxymethyl)acrylate) by conventional radical polymerization

n-Hexyl α-(hydroxymethyl)acrylate (372.5 mg, 2.0 mmol), AIBN (0.33 mg, 0.002 mmol) and 1,4-dioxane (1.0 mL) were added to a round-bottom flask equipped with a magnetic stir bar and sealed with a rubber septum. The flask was purged with N₂ for 30 minutes. Then the reaction was carried out at 70°C for 24 hours. The polymer was purified by precipitation in hexane for 3 times, centrifuged and dried in vacuum oven to give a white solid.

\(^1\)H NMR (300 MHz, Acetone-d₆) \(\delta\) (ppm) = 0.96 (m, 3H), 1.40 (m, 6H), 1.71 (m, 2H), 2.00 (m, 2H), 3.73 – 4.07 (m, 4H).
2.5 Synthetic procedures of poly(alkyl α-(hydroxymethyl)acrylate) by RAFT polymerization

2.5.1 Synthesis of poly(ethyl α-(hydroxymethyl)acrylate) by RAFT polymerization

Batch 1:

In a Schlenk tube, ethyl α-(hydroxymethyl)acrylate (260.3 mg, 2.0 mmol), 4-cyano-4-(phenylcarbonothioylthio) pentanoic acid (9.3 mg, 0.033 mmol), AIBN (1.8 mg, 0.011 mmol) and 1,4-dioxane (1.0 mL) were added. The Schlenk tube was subjected to freeze-pump-thaw cycles for three times. Then the tube was sealed and placed in heated oil bath (70 °C) for 24 hours. The product was precipitated in diethyl ether and dried in vacuum oven.

Batch 2:

In a Schlenk tube, ethyl α-(hydroxymethyl)acrylate (286.3 mg, 2.2 mmol), 4-cyano-4-(phenylcarbonothioylthio) pentanoic acid (2.8 mg, 0.01 mmol), AIBN (0.33 mg, 0.002 mmol) and 1,4-dioxane (1.1 mL) were added. The Schlenk tube was subjected to freeze-pump-thaw cycles for three times. Then the tube was sealed and placed in heated oil bath (70 °C) for 24 hours. The product was precipitated in diethyl ether and dried in vacuum oven.

$^1$H NMR (300 MHz, Acetone-$d_6$) δ (ppm) = 1.30 (m, 3H), 1.95 (m, 2H), 3.74 – 4.13 (m, 4H), 7.48 (m, end group), 7.62 (m, end group), 7.92 (m, end group).

2.5.2 Synthesis of poly(n-butyl α-(hydroxymethyl)acrylate) by RAFT polymerization

Batch 1:

In a Schlenk tube, n-butyl α-(hydroxymethyl)acrylate (316.4 mg, 2.0 mmol), 4-cyano-4-(phenylcarbonothioylthio) pentanoic acid (9.3 mg, 0.033 mmol), AIBN (1.8 mg, 0.011 mmol) and 1,4-dioxane (1.1 mL) were added. The Schlenk tube was subjected to freeze-pump-thaw cycles for three times. Then the tube was sealed and placed in heated oil bath (70 °C) for 24 hours. The product was precipitated in diethyl ether and dried in vacuum oven.

$^1$H NMR (300 MHz, Acetone-$d_6$) δ (ppm) = 1.30 (m, 3H), 1.95 (m, 2H), 3.74 – 4.13 (m, 4H), 7.48 (m, end group), 7.62 (m, end group), 7.92 (m, end group).
mmol) and 1,4-dioxane (1.0 mL) were added. The Schlenk tube was subjected to freeze-pump-thaw cycles for three times. Then the tube was sealed and placed in heated oil bath (70 °C) for 24 hours. The product was precipitated in hexane and dried in vacuum oven.

**Batch 2:**

In a Schlenk tube, n-butyl α-(hydroxymethyl)acrylate (653.4 mg, 4.12 mmol), 4-cyano-4-(phenylcarbonothioylthio) pentanoic acid (5.2 mg, 0.0186 mmol), AIBN (0.66 mg, 0.004 mmol) and 1,4-dioxane (2.0 mL) were added. The Schlenk tube was subjected to freeze-pump-thaw cycles for three times. Then the tube was sealed and placed in heated oil bath (70 °C) for 24 hours. The product was precipitated in hexane and dried in vacuum oven.

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \] \( \delta \) (ppm) = 0.97 (m, 3H), 1.42 (m, 2H), 1.64 (m, 2H), 1.92 (m, 2H), 3.59 – 4.07 (m, 4H), 7.36 (m, end group), 7.52 (m, end group), 7.88 (m, end group).

2.5.3 Synthesis of poly(t-butyl α-(hydroxymethyl)acrylate) by RAFT polymerization

**Batch 1:**

In a Schlenk tube, t-butyl α-(hydroxymethyl)acrylate (330.0 mg, 2.09 mmol), 4-cyano-4-(phenylcarbonothioylthio) pentanoic acid (9.3 mg, 0.033 mmol), AIBN (1.8 mg, 0.011 mmol) and 1,4-dioxane (1.0 mL) were added. The Schlenk tube was subjected to freeze-pump-thaw cycles for three times. Then the tube was sealed and placed in heated oil bath (70 °C) for 24 hours. The product was precipitated in hexane and dried in vacuum oven.
Batch 2:

In a Schlenk tube, t-butyl α-(hydroxymethyl)acrylate (481.3 mg, 3.04 mmol), 4-cyano-4-(phenylcarbonothioylthio) pentanoic acid (3.9 mg, 0.0138 mmol), AIBN (0.46 mg, 0.0028 mmol) and 1,4-dioxane (1.5 mL) were added. The Schlenk tube was subjected to freeze-pump-thaw cycles for three times. Then the tube was sealed and placed in heated oil bath (70 °C) for 24 hours. The product was precipitated in hexane and dried in vacuum oven.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 1.53 (m, 9H), 1.95 (m, 2H), 3.67 (m, 2H), 7.36 (m, end group), 7.51 (m, end group), 7.90 (m, end group).

2.5.4 Synthesis of poly(n-hexyl α-(hydroxymethyl)acrylate) by RAFT polymerization

Batch 1:

In a Schlenk tube, n-hexyl α-(hydroxymethyl)acrylate (372.5 mg, 2.0 mmol), 4-cyano-4-(phenylcarbonothioylthio) pentanoic acid (9.3 mg, 0.033 mmol), AIBN (1.8 mg, 0.011 mmol) and 1,4-dioxane (1.0 mL) were added. The Schlenk tube was subjected to freeze-pump-thaw cycles for three times. Then the tube was sealed and placed in heated oil bath (70 °C) for 24 hours. The product was precipitated in hexane and dried in vacuum oven.

Batch 2:

In a Schlenk tube, n-hexyl α-(hydroxymethyl)acrylate (409.8 mg, 2.2 mmol), 4-cyano-4-(phenylcarbonothioylthio) pentanoic acid (2.9 mg, 0.01 mmol), AIBN (0.33 mg, 0.002 mmol) and 1,4-dioxane (1.1 mL) were added. The Schlenk tube was subjected to freeze-pump-thaw cycles for three times. Then the tube was sealed and placed in heated oil bath (70 °C) for 24 hours. The product was precipitated in hexane and dried in vacuum oven.
1H NMR (300 MHz, CDCl₃) δ (ppm) = 1.53 (m, 9H), 1.95 (m, 2H), 3.67 (m, 2H), 7.36 (m, end group), 7.51 (m, end group), 7.90 (m, end group).

2.6 Preparation of nanoparticles.

To prepare the nanoparticles, poly(n-butyl α-(hydroxymethyl)acrylate) was used as a model polymer. The number-average molecular weight of the polymer is 8.0 kDa and the polydispersity is 1.16, which is determined by GPC.

2.6.1 Nanoparticle preparation by dialysis method

In general, the polymer sample was dissolved in DMF at a concentration of 1.0 mg/mL and dialyzed against distilled water for 24 hours. The water was exchanged every six hours. The morphology was observed by scanning electron microscope (SEM) and the size was determined by dynamic light scattering (DLS).

2.6.2 Nanoparticle preparation by the dropping technique

In general, the polymer sample was dissolved in acetone at a concentration of 1.0 mg/mL, and distilled water was added dropwise to the polymer solution under vigorous stirring. The morphology evolution of the nanoparticles was monitored by scanning electron microscope (SEM) after adding 15 wt%, 30 wt%, 40 wt% and 50 wt% water.
CHAPTER III

SYNTHESIS OF α-SUBSTITUTED POLYACRYLATE: RESULTS AND DISCUSSION

3.1 Synthesis of alkyl α-(hydroxymethyl)acrylate

In this work, a hydroxyl-functionalized α-substituted acrylate was synthesized by the coupling reaction of formaldehyde and alkyl acrylate catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO) in a dioxane/water medium. The synthetic scheme is shown in Scheme 3.1. Four examples were shown here, in which different pendant groups were attached to the ester bond, such as ethyl, n-butyl, t-butyl or n-hexyl group.

Scheme 3.1 Synthesis of alkyl α-(hydroxymethyl)acrylate

3.1.1 Conditions for the Baylis-Hillman reaction

In the past, the Baylis-Hillman reaction was carried out in neat solution with small amount of catalyst, and it usually takes several days or weeks to get a good conversion. In order to increase the efficiency of the reaction, a new method reported by Hu[18] was applied in this work. In brief, 1 equivalent of aldehyde, 3 equivalents of acrylate and 100 mol% DABCO were used. The reaction was carried out in a dioxane/water (1:1, v/v) medium. Following this reaction condition, about 50% conversion can be obtained in 12 hours, which is more efficient compared to the traditional way.
3.1.2 NMR analysis

The structure of the monomers was characterized by $^1$H NMR and $^{13}$C NMR, which are shown in Figure 3.1-3.8. Monomers with different alkyl groups were prepared, such as ethyl, n-butyl, t-butyl and n-hexyl, and their NMR spectra look similar. The two peaks around 5.83 and 6.27 ppm whose integration are one correspond to the two protons on the alkene group. The two peaks around 4.25 and 4.35 ppm correspond to the methylene groups that attached to the hydroxyl group and the ester bond. Also, the signal for the hydroxyl group can also be observed around 2.23 ppm, whose integration is one. In these $^1$H NMR and $^{13}$C NMR shown below, each peak was assigned by letters and all the integrations were in agreement with the correct structures. These NMR spectra confirmed the high purity of the monomers.

Figure 3.1 $^1$H NMR spectrum of ethyl α-(hydroxymethyl)acrylate
Figure 3.2 $^{13}$C NMR spectrum of ethyl α-(hydroxymethyl)acrylate

Figure 3.3 $^1$H NMR spectrum of n-butyl α-(hydroxymethyl)acrylate
Figure 3.4 $^{13}$C NMR spectrum of n-butyl α-(hydroxymethyl)acrylate

Figure 3.5 $^1$H NMR spectrum of t-butyl α-(hydroxymethyl)acrylate
Figure 3.6 $^{13}$C NMR spectrum of t-butyl α-(hydroxymethyl)acrylate

Figure 3.7 $^1$H NMR spectrum of n-hexyl α-(hydroxymethyl)acrylate
Figure 3.8 $^{13}$C NMR spectrum of n-hexyl α-(hydroxymethyl)acrylate

3.2 Synthesis of poly(alkyl α-(hydroxymethyl)acrylate) by conventional radical polymerization

These monomers were first polymerized by conventional free-radical polymerization, using AIBN as initiator. The reaction was carried out in dioxane at 70 °C for 24 hours. The synthetic scheme is shown in Scheme 3.2.

Scheme 3.2 Conventional Radical Polymerization of alkyl α-(hydroxymethyl)acrylates
3.2.1 Conditions for the polymerization

1,4-Dioxane was used as the solvent because it is a good solvent for both monomer and polymer. The reaction was carried out at 70 °C for 24 hours to achieve a high conversion. Thermal initiator azobisisobutyronitrile (AIBN) was used to initiate the polymerization. The initiator/monomer ratio was 1/1000. And the concentration of monomer was 2 mmol/mL.

3.2.2 NMR analysis of the polymers

The $^1$H NMR spectra of the polymers synthesized from conventional radical polymerization are shown in Figure 3.10 - 3.13. From the $^1$H NMR, it was observed that all the signals for the protons in the repeating unit of the polymer became broad compared to the $^1$H NMR spectra of the monomer. Around 2.0 ppm, a broad peak corresponding to the polymer backbone was observed, which indicated the polymerization of the monomers. The integration of all the peaks was in agreement with the structures.
Figure 3.9 $^1H$ NMR spectrum of poly(ethyl α-(hydroxymethyl)acrylate)

Figure 3.10 $^1H$ NMR spectrum of poly(n-butyl α-(hydroxymethyl)acrylate)
Figure 3.11 $^1$H NMR spectrum of poly(t-butyl α-(hydroxymethyl)acrylate)

Figure 3.12 $^1$H NMR spectrum of poly(n-hexyl α-(hydroxymethyl)acrylate)
After quenching the polymerization, the aliquot of the reaction solution was analyzed by $^1$H NMR to determine the monomer conversion. The conversion of the reaction was determined by the ratio of the integration of the $–$CH2 from the polymer backbone to the integration of the CH2= from the unreacted monomer by the following equation:

$$x(t) = \frac{I(–CH_2^b)^{polymer}(t)}{I(CH_2^b)^{polymer}(t) + I(=CH_2^a)^{monomer}(t)} \times 100\%$$

Monomer conversion of each polymerization was calculated using this equation. All the $^1$H NMR spectra of the reaction solution were attached in Appendix.

$$conversion(Ethyl) = \frac{11039.8}{11039.8 + 100.6 + 95.4} \times 100\% = 98.3\%$$

$$conversion(nButyl) = \frac{\frac{1}{3}(5865.7 - 301.7)}{\frac{1}{3}(5865.7 - 301.7) + 100.6} \times 100\% = 94.9\%$$

$$conversion(tButyl) = \frac{1179.5}{101.1 + 101.4 + 1179.5} \times 100\% = 85.4\%$$

$$conversion(nHexyl) = \frac{729.5}{100.5 + 101.4 + 729.5} \times 100\% = 78.3\%$$

The calculated results showed the high efficiency of the polymerization. In 24 hours, the obtained conversion was from 78 % to 98 %.

3.2.3 SEC analysis of the polymers

All the polymers were analyzed by GPC using DMF as the eluent. It was observed that most of them can obtain a good molecular weight but the monomer with a tert-butyl group, whose molecular weight was lower than 20 kDa. For other polymers, they can get molecular weight from 35 kDa to 57 kDa, which are much higher. This is probably due to the steric hindrance of the monomer that prevents the reaction obtaining a high molecular
weight since the tert-butyl is a bulky pendant group. The polydispersity of the polymers was around 1.5.

The number-average molecular weight and polydispersity of the polymers are summarized in Table 3.1. The GPC spectra of the polymers are shown in Figure 3.9.

Table 3.1 Molecular weight data

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>R</th>
<th>[I]₀/[M]₀</th>
<th>[M]₀ (mol L&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>Time (h)</th>
<th>M&lt;sub&gt;n,GPC&lt;/sub&gt; (kDa)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>PDI (M&lt;sub&gt;w&lt;/sub&gt;/M&lt;sub&gt;n&lt;/sub&gt;)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Conversion (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethyl</td>
<td>1/1000</td>
<td>2</td>
<td>24</td>
<td>49.4</td>
<td>1.56</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>n-Butyl</td>
<td>1/1000</td>
<td>2</td>
<td>24</td>
<td>57.8</td>
<td>1.52</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>t-Butyl</td>
<td>1/1000</td>
<td>2</td>
<td>24</td>
<td>18.7</td>
<td>1.68</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>n-Hexyl</td>
<td>1/1000</td>
<td>2</td>
<td>24</td>
<td>35.1</td>
<td>1.51</td>
<td>78</td>
</tr>
</tbody>
</table>

<sup>a</sup>All the experiments (entry 1–4) used AIBN as initiator and 1,4-dioxane as solvent. The reaction temperature was kept at 70°C. <sup>b</sup>Determined by GPC using DMF as the eluent and PMMA as the standard. <sup>c</sup>Monomer conversion determined by <sup>1</sup>H NMR.

Figure 3.13 Gel permeation chromatography traces (measured in DMF) of the polymers synthesized by conventional free radical polymerization.
3.2.4 TGA, DSC analysis of the polymers

The thermal properties including decomposition temperature \( (T_d) \) and glass transition temperature \( (T_g) \) were measured by thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC). It was observed that the polymers started to decompose before 200 °C. Their glass transition temperature was from 55 °C to 139 °C. With different alkyl groups, the polymers exhibited different glass transition temperature. With more flexible side group, the glass transition temperature decreases. With a bulky pendant group such as tert-butyl group, the glass transition temperature is much higher, which is about 139 °C. The glass transition temperature decreases with the trend shown below:

\[
T_g (t\text{-Bu}) > T_g (Et) > T_g (n\text{-Bu}) > T_g (n\text{-Hex})
\]

Table 3.2 Thermal Characteristics of Poly(alkyl \( \alpha \)-hydroxymethyl acrylate)

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>( T_{5%} ) (°C(^a))</th>
<th>( T_{d1} ) (°C(^b))</th>
<th>( T_{d2} ) (°C(^b))</th>
<th>( T_g ) (°C(^c))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethyl</td>
<td>186.7</td>
<td>175.7</td>
<td>286.3</td>
<td>109.7</td>
</tr>
<tr>
<td>2</td>
<td>n-Butyl</td>
<td>152.6</td>
<td>144.9</td>
<td>324.7</td>
<td>83.9</td>
</tr>
<tr>
<td>3</td>
<td>t-Butyl</td>
<td>168.3</td>
<td>163.9</td>
<td>304.7</td>
<td>139.6</td>
</tr>
<tr>
<td>4</td>
<td>n-Hexyl</td>
<td>150.7</td>
<td>146.9</td>
<td>293.5</td>
<td>55.6</td>
</tr>
</tbody>
</table>

\(^a\)T_{5\%}=temperature of 5% mass loss. \(^b\)T_d=decomposition temperature. \(^c\)T_g=glass transition temperature.

3.3 Synthesis of poly(alkyl \( \alpha \)-(hydroxymethyl)acrylate) by RAFT polymerization

Scheme 3.3 RAFT polymerization of alkyl \( \alpha \)-(hydroxymethyl)acrylate
In order to achieve controlled molecular weight and low polydispersity, living radical polymerization was used to synthesize the polymers. Among different kinds of living radical polymerization, reversible addition-fragmentation chain transfer (RAFT) polymerization is compatible to most kinds of vinyl monomers, such as acrylate, acrylamide or vinyl esters. Therefore, RAFT polymerization was first tried to control the polymerization of alkyl α-(hydroxymethyl)acrylate. The reaction was shown in Scheme 3.3.

3.3.1 Conditions for the RAFT polymerization

4-cyano-4-(phenylcarbonothioylthio)pentanoic acid was selected as the chain transfer agent and it was found to be compatible with the hydroxyl-functionalized α-substituted monomers. The reaction was carried out in 1,4-dioxane at 70 °C for 24 hours. Different \([\text{M}]_0/\text{[CTA]}_0\) ratios were used to tailor different molecular weight, such as 60:1, 200:1 or 220:1. With higher \([\text{M}]_0/\text{[CTA]}_0\) ratio, higher molecular weight can be obtained.

3.3.2 NMR analysis of the polymers

The structures of the polymers were confirmed by \(^1\text{H}\) NMR, which is shown in Figure 3.15-3.18. Around 2.0 ppm, we can observe a broad peak which corresponds to the polymer backbone. The integration of each peak was in agreement with the polymer structure.

As shown in Figure 3.14, the signals of the RAFT end group were detected by \(^1\text{H}\) NMR and they were around 7.38 ppm, 7.54 ppm and 7.98 ppm, which indicated the successful addition of the RAFT agent to the polymers.
Figure 3.14 $^1$H NMR spectrum of poly(ethyl α-(hydroxymethyl)acrylate) from RAFT polymerization

Figure 3.15 $^1$H NMR spectrum of poly(n-butyl α-(hydroxymethyl)acrylate) from RAFT polymerization
Figure 3.16 $^1$H NMR spectrum of poly(t-butyl $\alpha$-(hydroxymethyl)acrylate) from RAFT polymerization

Figure 3.17 $^1$H NMR spectrum of poly(n-hexyl $\alpha$-(hydroxymethyl)acrylate) from RAFT polymerization
After quenching the polymerization, the aliquot of the reaction solution was analyzed by $^1$H NMR to determine the monomer conversion. The conversion of the reaction was determined by the ratio of the integration of the $\text{–CH2}$ from the polymer backbone to the integration of the $\text{CH2=}$ from the unreacted monomer by the following equation:

$$ x(t) = \frac{I(\text{–CH}_2^b)^\text{polymer}(t)}{I(\text{–CH}_2^b)^\text{polymer}(t) + I(=\text{CH}_2^a)^\text{monomer}(t)} \times 100\% $$

Monomer conversion of each polymerization was calculated using this equation. All the $^1$H NMR spectra of the reaction solution were attached in Appendix. The calculation of the conversions for Entry 1-8 is shown below.

Entry 1:

$$ conversion = \frac{\frac{1}{3}(4031.2 - 310.2)}{\frac{1}{3}(4031.2 - 310.2) + 103.38} \times 100\% = 92.3\% $$

Entry 2:

$$ conversion = \frac{805.7}{100.2 + 100.1 + 805.7} \times 100\% = 80.1\% $$

Entry 3:

$$ conversion = \frac{188.8}{188.8 + 102.4 + 105.3} \times 100\% = 47.6\% $$

Entry 4:

$$ conversion = \frac{537.0}{537.0 + 100.9 + 101.4} \times 100\% = 72.6\% $$

Entry 5:

$$ conversion = \frac{\frac{2}{3}(807.8 - 307.0)}{\frac{2}{3}(807.8 - 307.0) + 102.2 + 102.5} \times 100\% = 62.0\% $$
Entry 6:

\[
\text{conversion} = \frac{\frac{2}{3}(707.8 - 298.7)}{\frac{2}{3}(707.8 - 298.7) + 100.2 + 99.0} \times 100\% = 57.8\%
\]

Entry 7:

\[
\text{conversion} = \frac{139.9}{139.9 + 101.9 + 101.1} \times 100\% = 40.8\%
\]

Entry 8:

\[
\text{conversion} = \frac{350.2}{103.3 + 101.2 + 350.2} \times 100\% = 63.1\%
\]

From the calculated data, it was found that the conversion of the t-butyl monomer was apparently lower than other monomers at both high and low \([M]_0/[\text{CTA}]_0\) ratio, which was only about 40%. This is probably because of the steric hindrance of the monomer which makes it not very reactive.

3.3.3 SEC analysis of the polymers

The molecular weight was characterized by GPC and summarized in Table 3.3. As we can see, the polydispersity of the obtained polymers ranges from 1.15 to 1.28, which indicates good living character. The GPC traces are shown in Figure 3.18 and 3.19, which look apparently narrower compared to that of the polymer synthesized by conventional radical polymerization.

The theoretical molecular weight was calculated based on the monomer conversion using the following equation:

\[
M_n^{\text{calc}} = \frac{[M]_0 \times MW_m \times \text{Conversion}}{[\text{CTA}]_0} + MW_{\text{CTA}}
\]
The calculation of the theoretical molecular weight for Entry 1-8 was shown below.

Entry 1:

\[ M_{n}^{\text{calc}} = \frac{2.0 \times 10^{-3} \times 130.1 \times 0.923}{3.3 \times 10^{-5}} + 279.4 = 7560 \]

Entry 2:

\[ M_{n}^{\text{calc}} = \frac{2.0 \times 10^{-3} \times 158.2 \times 0.801}{3.3 \times 10^{-5}} + 279.4 = 7958 \]

Entry 3:

\[ M_{n}^{\text{calc}} = \frac{2.1 \times 10^{-3} \times 158.2 \times 0.476}{3.3 \times 10^{-5}} + 279.4 = 5049 \]

Entry 4:

\[ M_{n}^{\text{calc}} = \frac{2.0 \times 10^{-3} \times 186.2 \times 0.726}{3.3 \times 10^{-5}} + 279.4 = 8479 \]

Entry 5:

\[ M_{n}^{\text{calc}} = \frac{3.9 \times 10^{-3} \times 130.1 \times 0.620}{2.0 \times 10^{-5}} + 279.4 = 15852 \]

Entry 6:

\[ M_{n}^{\text{calc}} = \frac{4.1 \times 10^{-3} \times 158.2 \times 0.578}{1.9 \times 10^{-5}} + 279.4 = 20532 \]

Entry 7:

\[ M_{n}^{\text{calc}} = \frac{2.0 \times 10^{-3} \times 158.2 \times 0.408}{1.0 \times 10^{-5}} + 279.4 = 13191 \]

Entry 8:

\[ M_{n}^{\text{calc}} = \frac{2.2 \times 10^{-3} \times 186.2 \times 0.531}{1.0 \times 10^{-5}} + 279.4 = 26147 \]
It was found that the molecular weight determined by GPC is in agreement with the theoretical molecular weight calculated from $^1$H NMR. However, the polymerization of the monomer bearing a tert-butyl group didn’t show good effectiveness as other monomers. Using the same reaction condition, the polydispersity determined by GPC was slightly higher than others.

Table 3.3 Molecular weight data of the polymers synthesized by RAFT polymerization

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>[M]₀/[CTA]₀/[I]₀</th>
<th>$M_{n,\text{GPC}}$ (kDa)$^b$</th>
<th>PDI (Mₘ/Mₙ)$^b$</th>
<th>Conversion (%)$^c$</th>
<th>$M_{n,\text{theory}}$ (kDa)$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethyl</td>
<td>180/3/1</td>
<td>7.64</td>
<td>1.15</td>
<td>92.3</td>
<td>7.56</td>
</tr>
<tr>
<td>2</td>
<td>n-Butyl</td>
<td>180/3/1</td>
<td>7.95</td>
<td>1.16</td>
<td>80.1</td>
<td>7.96</td>
</tr>
<tr>
<td>3</td>
<td>t-Butyl</td>
<td>180/3/1</td>
<td>5.41</td>
<td>1.21</td>
<td>47.6</td>
<td>5.05</td>
</tr>
<tr>
<td>4</td>
<td>n-Hexyl</td>
<td>180/3/1</td>
<td>9.60</td>
<td>1.16</td>
<td>72.6</td>
<td>8.48</td>
</tr>
<tr>
<td>5</td>
<td>Ethyl</td>
<td>200/1/0.2</td>
<td>19.8</td>
<td>1.18</td>
<td>62.0</td>
<td>15.8</td>
</tr>
<tr>
<td>6</td>
<td>n-Butyl</td>
<td>220/1/0.2</td>
<td>25.4</td>
<td>1.19</td>
<td>57.8</td>
<td>20.5</td>
</tr>
<tr>
<td>7</td>
<td>t-Butyl</td>
<td>200/1/0.2</td>
<td>11.7</td>
<td>1.28</td>
<td>40.8</td>
<td>13.2</td>
</tr>
<tr>
<td>8</td>
<td>n-Hexyl</td>
<td>220/1/0.2</td>
<td>29.6</td>
<td>1.17</td>
<td>63.1</td>
<td>26.1</td>
</tr>
</tbody>
</table>

$^a$All the experiments (entry 1-6) used AIBN as initiator and 1,4-dioxane as solvent. The monomer concentration was 2 mol/L. The reaction temperature was kept at 70°C for 24 hours. $^b$Determined by GPC using DMF as the eluent and PMMA as the standard. $^c$Monomer conversion determined by $^1$H NMR.

Figure 3.18 Gel permeation chromatography traces (measured in DMF) of the polymers synthesized by RAFT polymerization (Entry 1-4)
3.4 Preparation of nanoparticles

3.4.1 Preparation of nanoparticles by dialysis

It is found that this type of hydroxyl-functionalized polymers can be used to prepare spherical nanoparticles easily. The first method applied is dialysis. The polymer sample was dissolved in a water-miscible solvent dimethylformamide (DMF) prior to dialysis. At a low concentration, the molecules in the solution are well-dispersed and able to separate into nanodomains. Therefore, 1.0 mg/mL was used for the polymer concentration. Then the solution was placed in a dialysis bag. It was observed that the solution inside the dialysis bag became light blue from transparent after 15 minutes. The dialysis was allowed to go for 24 hours in order to remove the organic solvent completely. The nanoparticle solution was then taken out from the dialysis bag and analyzed by scanning electron microscope (SEM) and dynamic light scattering (DLS).
Figure 3.20 SEM pictures of nanoparticles prepared by dialysis

From the SEM picture shown in Figure 3.20, the spherical structure was observed. The average diameter of the nanoparticles calculated from the SEM picture is 283.3 nm.

The size and the size distribution of the nanoparticles were also determined by dynamic light scattering (DLS). The size distribution was shown below in Figure 3.21. The average diameter obtained from DLS was 322.8 nm and the polydispersity of the nanoparticles was 0.177. Compared the results from these two techniques, it was found that the size from SEM was about 40 nm smaller than that from DLS. This is probably because the sample for SEM was dried prior to analysis. During this period, the nanoparticles would shrink, which leads to the smaller size.
Compared to other polymers, the nanoparticles prepared from the described polymers were found to have better stability. It has been reported that polystyrene can be used to prepare nanoparticles by dialysis. However, our experimental results for polystyrene nanoparticles showed that they didn’t have a good stability, since they were very easy to aggregate due to the hydrophobic nature of the polymer. When the polystyrene solution was placed in the dialysis bag and immersed in water, polymer precipitate can be observed after a few minutes. Also, the amount of precipitate increased over time. At the end, there found to be some flocculent aggregate in the dialysis bag. On the contrary, the nanoparticles prepared from the hydroxyl-functionalized polymer were very stable in aqueous solution. No precipitate was observed during dialysis. The stability probably comes from the hydroxyl group in each repeating units which provide hydrophilicity to the polymer that prevent them from aggregating.
3.4.2 Preparation of nanoparticles by the dropping technique

Nanoparticles can also be prepared using the dropping technique. Compared with dialysis method, it requires less time. In this work, the influence of the amount of water added to the solution on the morphology of the nanoparticles was studied. Acetone was used as the solvent because it is a volatile solvent, which makes it easy to remove. A low concentration of 1.0 mg/mL was also used in this experiment. The SEM pictures were taken after adding different amount of water to monitor the morphology evolution.

![SEM picture of the nanoparticles after adding 15 wt% of water](image)

Figure 3.22 SEM picture of the nanoparticles after adding 15 wt% of water

It was found that the nanoparticles have already formed after adding 15 wt% of water to the polymer solution, which is shown in Figure 3.22. The size calculated from SEM picture was 203 nm.
Figure 3.23 SEM picture of the nanoparticles after adding 30 wt% of water

The nanoparticles were found to grow with increasing amount of water. Shown in Figure 3.23, when the water content increased to 30 wt%, the size of the nanoparticles increased to 767 nm rapidly. After that the size increased slowly. When the water content increased to 40 wt%, the size was 920 nm (Figure 3.24). When the water content increased to 50 wt%, the size was 991 nm (Figure 3.25).
Figure 3.24 SEM picture of the nanoparticles after adding 40 wt% of water

Figure 3.25 SEM picture of the nanoparticles after adding 50 wt% of water
Figure 3.26 Summary of the size evolution

Figure 3.27 summarized the size of the nanoparticles at different water content. It was found that the size of the nanoparticle depends on the amount of water that added to the solution. By using the dropping technique, it would be able for us to prepare stable nanoparticles with controlled size, which would be useful for drug delivery applications.
CHAPTER IV

SYNTHESIS OF POLY(ESTER-URETHANE)S: EXPERIMENTAL

4.1 Materials

1,4-Dioxane (AcroSeal, 99.5%)

Butyraldehyde (Alfa Aesar, 98%)

3-Phenylpropionaldehyde (Alfa Aesar, 95%)

1,4-Diazabicyclo[2.2.2]octane (Alfa Aesar, 98%)

2-Hydroxyethyl acrylate (Alfa Aesar, 97%)

3-Mercaptopropionic acid (Alfa Aesar, 99%)

2-Mercaptoethanol (TCI, 98%)

2-Aminoethanethiol (TCI, 95%)

2-Hydroxy-4’-(2-hydroxyethoxy)-2-methylpropiophenone (Aldrich, 98%)

Tin(II) 2-ethylhexanoate (Aldrich, 95%)

4.2 Instrumentation and characterization

4.2.1 $^1$H and $^{13}$C NMR spectroscopy

The structure of small molecules was confirmed by $^1$H NMR and $^{13}$C NMR spectroscopy using Varian NMRS 300 and Varian NMRS 500. The NMR spectra were analyzed by ACD NMR Processor.
4.2.2 Size exclusion chromatography (SEC)

The molecular weight and polydispersity of the polymers was determined using HLC-8320 GPC from TOSOH with DMF as the eluent. The molecular weight was calculated using polystyrene standard.

4.2.3 Thermal gravimetric analysis (TGA)

The decomposition temperature of the polymers was determined by TA thermal gravimetric analysis instrument Q500. The sample was heated to 600 °C at a heating rate of 10 °C/min.

4.2.4 Differential scanning calorimetry (DSC)

The glass transition temperature of the polymers was determined by TA differential scanning calorimetry instrument Q2000. The sample was heated and cooled at a rate of 10 °C/min.

4.3 Synthetic procedures of unsaturated diols (UD)

4.3.1 Synthesis of UD1

2-Hydroxyethyl acrylate (6.0 g, 0.052 mol), DABCO (5.8 g, 0.052 mol) were added into a round-bottom flask equipped with a magnetic stir bar. 1,4-Dioxane (8.0 mL) and distilled water (8.0 mL) were added to the flask and the solution was incubated for 2 minutes. Then butyraldehyde (1.2 g, 0.017 mol) was added. The solution was stirred at
room temperature for 24 hours. The compound was extracted by ethyl acetate. The organic layer was washed by brine and followed by drying over anhydrous Na$_2$SO$_4$. The filtrate was then concentrated under reduced pressure and purified by column chromatography (50 % ethyl acetate and 50 % hexane, $R_f = 0.3$) to give a colorless liquid (1.3 g, 40.8 %).

$^1$H NMR (300 MHz, CDCl$_3$) δ 0.96 (t, $J=7.50$ Hz, 3H), 1.32-1.54 (m, 2H), 1.62-1.70 (m, 2H), 2.00 (s, 1H), 2.51 (s, 1H), 3.90 (t, $J=4.50$ Hz, 2H), 4.34 (t, $J=4.50$ Hz, 2H), 4.44 (t, $J=6.00$ Hz, 1H), 5.84 (s, 1H), 6.28 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) 13.79 (s), 18.97 (s), 38.15 (s), 60.80 (s), 66.27 (s), 71.11 (s), 125.26 (s), 142.60 (s), 166.77 (s)

4.3.2 Synthesis of UD2

2-Hydroxyethyl acrylate (6.0 g, 0.052 mol), DABCO (5.8 g, 0.052 mol) were added to a round-bottom flask equipped with a magnetic stir bar. 1,4-Dioxane (8.0 mL) and distilled water (8.0 mL) were added to the flask and the solution was incubated for 2 minutes. Then 3-phenylpropionaldehyde (2.3 g, 0.017 mol) was added. The solution was stirred at room temperature for 24 hours. The compound was extracted by ethyl acetate. The organic layer was washed by brine and followed by drying over anhydrous Na$_2$SO$_4$. The filtrate was then concentrated under reduced pressure and purified by column chromatography (30 % ethyl acetate and 70 % hexane, $R_f = 0.3$) to give a colorless liquid (1.8 g, 43.0 %).
\[^1\text{H NMR (300 MHz, CDCl}_3\text{) }\delta 1.96\text{-}2.05 (m, 2H), 2.67\text{-}2.89 (m, 2H), 3.87 (t, J=6.00 Hz, 2H), 4.32 (t, J=4.50 Hz, 2H), 4.46 (t, J=7.50 Hz, 1H), 5.86 (s, 1H), 6.30 (s, 1H), 7.18\text{-}7.32 (m, 5H); \[^{13}\text{C NMR (125 MHz, CDCl}_3\text{) 31.95 (s), 37.47 (s), 60.69 (s), 66.25 (s), 70.50 (s), 125.58 (s), 125.83 (s), 128.32 (s), 128.38 (s), 141.53 (s), 142.39 (s), 166.64 (s).\]

4.4 Synthesis of poly(ester-urethane) derived from Baylis-Hillman adducts

4.4.1 Synthesis of PEU1

UD1 (0.7079 g, 0.00376 mol), 1,6-diisocyanatohexane (0.6326 g, 0.00376 mol) were added to a Schlenk tube. The tube was evacuated and backfilled with nitrogen for 3 times. Then anhydrous dichloromethane (3.0 mL) were added to the tube. After that 1 drop of Tin(II) 2-ethylhexanoate was added. The solution was purged with N\(_2\) and stirred at room temperature for 48 hours. The product was precipitated in diethyl ether, centrifuged and dried in vacuum oven.

\[^1\text{H NMR (300 MHz, CDCl}_3\text{) }\delta (ppm) = 0.92 (t, 3H, J = 7.5 Hz), 1.35 \text{-} 1.65 (m, 12H), 3.17 (m, 5H), 4.30 (m, 4H), 4.93 (br, 2H), 5.51 (s, 1H), 5.78 (s, 1H), 6.29 (s, 1H).\]

4.4.2 Synthesis of PEU2

UD2 (0.6554 g, 0.00262 mol), 1,6-diisocyanatohexane (0.4407 g, 0.00262 mol) were added to a Schlenk tube. The tube was evacuated and backfilled with nitrogen for 3 times. Then anhydrous dichloromethane (3.0 mL) were added. After that 1 drop of Tin(II) 2-ethylhexanoate was added. The solution was purged with N\(_2\) and stirred at room temperature for 48 hours. The product was precipitated in diethyl ether, centrifuged and dried in vacuum oven.
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 1.33 – 1.64 (m, 8H), 1.98 - 2.10 (m, 2H), 2.67 (m, 2H), 3.14 (m, 4H), 4.28 (m, 4H), 4.84 (br, 2H), 5.56 (s, 1H), 5.81 (s, 1H), 6.32 (s, 1H), 7.18 (m, 3H), 7.25 (m, 2H).

4.5 Post-functionalization of the unsaturated poly(ester-urethane) by thiol-ene reaction

4.5.1 Synthesis of PEU1-OH

PEU1 (0.1 g) and 2-mercaptoethanol (0.22 g), 2-hydroxy-4’-(2-hydroxyethoxy)-2-methylpropiophenone (31.4 mg) and chloroform (1.0 mL) were added to a quartz glass test tube. The solution was irradiated by 350 nm UV for 30 minutes. Then the product was precipitated in diethyl ether, centrifuged and dried in vacuum oven.

\(^1\)H NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) (ppm) = 0.85 (t, 3H, \(J = 7.5\) Hz), 1.22 – 1.50 (m, 12H), 2.54 – 2.82 (m, 6H), 2.94 (m, 5H), 3.50 (t, 1H, \(J = 7.5\) Hz), 4.14 – 4.21 (m, 4H), 4.88 (m, 1H), 6.99 – 7.12 (m, 2H).

4.5.2 Synthesis of PEU1-COOH

PEU1 (0.1 g) and 3-mercaptopropionic acid (0.30 g), 2-hydroxy-4’-(2-hydroxyethoxy)-2-methylpropiophenone (31.4 mg) and chloroform (1.0 mL) were added to a quartz glass test tube. The solution was irradiated by 350 nm UV for 30 minutes. Then the product was precipitated in diethyl ether, centrifuged and dried in vacuum oven.

\(^1\)H NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) (ppm) = 0.85 (t, 3H, \(J = 6.0\) Hz), 1.22 – 1.50 (m, 12H), 2.63 – 2.84 (m, 6H), 2.95 (m, 5H), 4.13 – 4.21 (m, 4H), 4.89 (m, 1H), 6.99 – 7.11 (m, 2H), 12.24 (s, 1H).
4.5.3 Synthesis of PEU2-OH

PEU2 (0.1 g) and 2-mercaptopethanol (0.16 g), 2-hydroxy-4’-(2-hydroxyethoxy)-2-methylpropiophenone (22.4 mg) and chloroform (1.0 mL) were added to a quartz glass test tube. The solution was irradiated by 350 nm UV for 30 minutes. Then the product was precipitated in diethyl ether, centrifuged and dried in vacuum oven.

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ (ppm) = 1.22 – 1.37 (m, 10H), 1.83 (m, 2H), 2.56 – 2.72 (m, 6H), 2.94 (m, 5H), 3.50 (t, 1H, J = 6.0 Hz), 4.12 – 4.19 (m, 4H), 4.89 (m, 1H), 7.09 (m, 2H), 7.17 (m, 3H), 7.26 (m, 2H).

4.5.4 Synthesis of PEU2-COOH

PEU2 (0.1 g) and 3-mercaptopropionic acid (0.21 g), 2-hydroxy-4’-(2-hydroxyethoxy)-2-methylpropiophenone (22.4 mg) and chloroform (1.0 mL) were added to a quartz glass test tube. The solution was irradiated by 350 nm UV for 30 minutes. Then the product was precipitated in diethyl ether, centrifuged and dried in vacuum oven.

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ (ppm) = 1.23 – 1.38 (m, 10H), 1.83 (m, 2H), 2.60 – 2.70 (m, 6H), 2.94 (m, 5H), 4.12 – 4.19 (m, 4H), 4.89 (m, 1H), 7.08 (m, 2H), 7.17 (m, 3H), 7.26 (m, 2H), 12.23 (s, 1H).
5.1 Synthesis of monomer

\[
\begin{align*}
R' \text{H} + \text{HO-CH}_{2}-\text{OH} & \xrightarrow{\text{DABCO}} \text{HO-CH}_{2}-\text{CH}-\text{OCOR'} \text{H} \\
\text{UD1: R=n-Pr} & \quad \text{UD2: R=(CH}_{2}\text{)}_{2}\text{Ph} \\
\text{Conditions:} & \quad \text{R.T. 24 hours} \\
\text{Medium:} & \quad \text{dioxane/water (1:1, v/v)}
\end{align*}
\]

Scheme 5.1 Synthesis of unsaturated diol (UD)

The unsaturated diols (UD) were synthesized by the coupling of aldehyde and 2-hydroxyethyl acrylate. This reaction can generate an alkene group and two hydroxyl groups. Two diols bearing two different pendant groups were synthesized, such as alkyl group and phenyl group.

5.1.1 Conditions for the reaction

A method reported by Hu\textsuperscript{[18]} was used in this work. Briefly, 1 equivalent of aldehyde, 3 equivalents of acrylate and 100 mol% DABCO were used. The reaction was carried out in a dioxane/water (1:1, v/v) medium. By following this reaction condition, about 40 % conversion was obtained after 24 hours.
5.1.2 NMR analysis of the monomers

The structure of the compound was confirmed by $^1$H NMR and $^{13}$C NMR. CDCl$_3$ was used as the solvent for NMR analysis. Each peak was assigned and the integration is in agreement with the correct structure. From $^1$H NMR, two peaks corresponding to the alkene group are around 5.84 and 6.28 ppm. For the diol bearing an alkyl pendant group, a peak at 0.95 ppm is observed, which corresponds to the methyl group of the alkyl group. For the diol bearing a phenyl group, there are two peaks between 7.0 ppm and 7.5 ppm, which correspond to the protons on the phenyl group. Except the difference, other part of the spectra looks similar. These $^1$H NMR and $^{13}$C NMR spectra show high purity of the monomers.

Figure 5.1 $^1$H NMR spectra of UD1
Figure 5.2 $^{13}$C NMR spectra of UD1

Figure 5.3 $^1$H NMR spectra of UD2
Figure 5.4 $^{13}$C NMR spectra of UD2

5.3 Synthesis of functionalized poly(ester urethane)

5.3.1 Reaction condition

In this study, the unsaturated diol was used to reacted with diisocynatohexane to make a poly(ester-urethane). The reaction was carried out in anhydrous dichloromethane at room temperature and catalyzed by Tin(II) octoate for 2 days. After that, the reaction
solution became very viscous. After precipitation in diethyl ether, a white polymer was obtained.

5.3.2 NMR analysis of the polymers

The structure of the polymers was confirmed by $^1$H NMR. The integration of each peak was in agreement with the expect structure. CDCl$_3$ was used as the solvent for NMR analysis. From the $^1$H NMR spectra shown in Figure 5.5 and 5.6, we can still see the signals of the alkene group, which appear around 5.78 and 6.29 ppm. Around 5.0 ppm, a broad peak corresponding to the urethane bond can be seen. For the polymer bearing an alkyl pendant group, the signal of the methyl group can be observed at 0.92 ppm. For the polymer bearing a phenyl group, the signals of the phenyl group can be observed between 7.0 and 7.5 ppm.

![Figure 5.5 $^1$H NMR spectra of PEU1](image)

Figure 5.5 $^1$H NMR spectra of PEU1
Figure 5.6 $^1$H NMR spectra of PEU2

5.3.3 SEC analysis of the polymers

As shown in table 5.1, the molecular weight of the two polymers was about 5 kDa and 4 kDa, respectively. The PDI was about 1.5. The GPC traces are shown in Figure 5.7. The molecular weight was not high. From the monomer structure, one of the hydroxyl groups was not very reactive because there is a substitution next to it, which probably leads to the low molecular weight. Also, moisture can also lead to the low molecular weight.
Figure 5.7 Gel permeation traces of poly(ester-urethane)

Table 5.1 Molecular weight of poly(ester-urethane)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>$M_{n,GPC}$ (kDa)$^b$</th>
<th>PDI ($M_w/M_n$)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-(CH$_2$)$_2$-CH$_3$</td>
<td>CHCl$_3$</td>
<td>48</td>
<td>5.02</td>
<td>1.44</td>
</tr>
<tr>
<td>2</td>
<td>-(CH$_2$)$_2$-Ph</td>
<td>CHCl$_3$</td>
<td>48</td>
<td>4.17</td>
<td>1.43</td>
</tr>
</tbody>
</table>

$^a$All the experiments (entry 1-2) were carried out at room temperature. $^b$Determined by GPC using DMF as the eluent and polystyrene as the standard.

5.4 Post-functionalization of the polyesterurethane

One of the advantages of this type of poly(ester-urethane) is that it contains two functionalities in one repeating unit: one is the alkene group and another one is from the aldehyde used. Besides, the alkene pendant group can be used for post-modification of the polymer via thiol-ene click chemistry. Thiol-ene reaction is highly efficient. Complete conversion can be obtained in very short time. Commercially, there are many kinds of thiol compound bearing functional groups, such as hydroxyl group or carboxyl group.
5.4.1 Conditions for the thiol-ene reaction

![Scheme 5.3 Functionalization of poly(ester-urethane) via thiol-ene click chemistry](image)

Photo-initiated thiol-ene reaction was used in this work. Compared to thermally initiated thiol-ene reaction, it is much faster, which can easily get complete conversion in 30 minutes. As shown in Scheme 5.3, photoinitiator IRGACURE 2959 was used to initiate the reaction. In a typical procedure, 10 equivalents of thiol were used and very little solvent was used in order to keep the reaction solution concentrated. Chloroform is selected as the solvent because the polymer has a very good solubility in this solvent. The solution was then irradiated by 350 nm UV for 30 minutes.

5.4.2 NMR analysis of the structure of the functionalized polymers

The structure of the polymer was confirmed by $^1$H NMR, which are shown in Figure 5.10-5.13. However, for these functional groups, the hydrogen atoms attached to the oxygen and nitrogen atoms can exchange with each other. Their signal would disappear if deuterated methanol was used as the solvent for NMR. Therefore, deuterated DMSO was used to see those functional groups. The $^1$H NMR taken in deuterated DMSO was shown
below. As we can see, around 12 ppm, the peak for carboxyl group was detected. Around 3.5 ppm, the peak for hydroxyl group was detected. In deuterated DMSO, the signal of the amide bond is found around 7.0 ppm, which is different from that in CDCl₃.

Figure 5.8 †H NMR spectrum of (A) PEU1 (B) PEU1-OH (C) PEU1-COOH
Figure 5.9 $^1$H NMR spectrum of (A) PEU2 (B) PEU2-OH (C) PEU2-COOH

Also, shown in Figure 5.8 and 5.9, compared to the NMR spectra of the polymer before functionalization, the disappearance of the peaks for the alkene group indicated the complete conversion of the thiol-ene reaction. Except the difference, the rest part of the spectra looks similar to that of the polymer before functionalization.

Based on the molecular weight of the polymer before functionalization and the conversion of the thiol-ene reaction, the theoretical molecular weight of the functionalized polymer was calculated, which are summarized in Table 5.2.
Table 5.2 Reaction conditions of the poly(ester-urethane).

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>Solvent</th>
<th>Time (min)</th>
<th>Conversion (%)</th>
<th>$M_n$ (kDa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-(CH$_2$)$_2$-CH$_3$</td>
<td>-OH</td>
<td>CHCl$_3$</td>
<td>30</td>
<td>100</td>
<td>6.12</td>
</tr>
<tr>
<td>2</td>
<td>-(CH$_2$)$_2$-CH$_3$</td>
<td>-COOH</td>
<td>CHCl$_3$</td>
<td>30</td>
<td>100</td>
<td>6.51</td>
</tr>
<tr>
<td>3</td>
<td>-(CH$_2$)$_2$-Ph</td>
<td>-OH</td>
<td>CHCl$_3$</td>
<td>30</td>
<td>100</td>
<td>4.95</td>
</tr>
<tr>
<td>4</td>
<td>-(CH$_2$)$_2$-Ph</td>
<td>-COOH</td>
<td>CHCl$_3$</td>
<td>30</td>
<td>100</td>
<td>5.23</td>
</tr>
</tbody>
</table>

$^a$ Determined by $^1$H NMR. $^b$ Calculated based on the molecular weight before functionalization and conversion.

Figure 5.10 $^1$H NMR spectra of PEU1-OH
Figure 5.11 $^1$H NMR spectra of PEU1-COOH

Figure 5.12 $^1$H NMR spectra of PEU2-OH
5.5 Study of the thermal properties

The effect of chemical structure on thermal properties of the polymers such as decomposition temperature and glass transition temperature were studied by thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC). Post-modification of the polymer provides different glass transition temperature to the polymers. As shown in Table 5.3, for polymer PEU1 (with an alkyl side chain), when bearing a hydroxyl or a carboxyl group, the polymers exhibit apparent higher glass transition temperature (15.7 °C and 21.6 °C, respectively) with respect to the polymer before functionalization displaying a glass transition temperature of 4.5 °C. Similar result was also found for PEU2.
Table 5.3 Thermal characteristics of the poly(ester-urethane)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>T&lt;sub&gt;5%&lt;/sub&gt; (°C)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>T&lt;sub&gt;d&lt;/sub&gt; (°C)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>T&lt;sub&gt;g&lt;/sub&gt; (°C)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>N/A</td>
<td>146.6</td>
<td>141.5</td>
<td>4.5</td>
</tr>
<tr>
<td>2</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-OH</td>
<td>187.2</td>
<td>185.6</td>
<td>15.7</td>
</tr>
<tr>
<td>3</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-COOH</td>
<td>206.0</td>
<td>207.0</td>
<td>21.0</td>
</tr>
<tr>
<td>4</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-Ph</td>
<td>N/A</td>
<td>189.7</td>
<td>166.4</td>
<td>3.5</td>
</tr>
<tr>
<td>5</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-Ph</td>
<td>-OH</td>
<td>200.6</td>
<td>199.2</td>
<td>21.3</td>
</tr>
<tr>
<td>6</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-Ph</td>
<td>-COOH</td>
<td>204.6</td>
<td>210.1</td>
<td>22.1</td>
</tr>
</tbody>
</table>

<sup>a</sup>T<sub>5%</sub>=temperature of 5% mass loss.  <sup>b</sup>T<sub>d</sub>=decomposition temperature.  <sup>c</sup>T<sub>g</sub>=glass transition temperature.
CHAPTER VI

CONCLUSION

In this work, Baylis-Hillman reaction was utilized to synthesize functionalized monomers for polymer synthesis. Baylis-Hillman adduct can be used for polymerization via both chain-growth polymerization and step-growth polymerization.

Baylis-Hillman reaction was first used to synthesize a hydroxymethyl α-substituted acrylate with different alkyl groups attached to the ester bond. These monomers can be polymerized via conventional radical polymer with high yield and good molecular weight. This type of monomer can also undergo reversible addition-fragmentation chain transfer (RAFT) polymerization. Different [CTA]/[M]₀ ratio was used to tailor different molecular weight. The obtained molecular weight was quite consistent with the theoretical molecular weight. Also, the polydispersity was controlled successfully which was about 1.2. Thermal properties including decomposition temperature and glass transition temperature of this type of polymer were characterized by thermally gravimetric analysis (TGA) and differential scanning calorimetry (DSC). With more flexible pendant group, the polymer was found to exhibit lower glass transition.

The hydroxyl-functionalized polymers were used to prepare nanoparticles by dialysis method and the dropping technique. Spherical nanoparticles were obtained by both methods. These nanoparticles are observed to have good stability.
Besides, this type of polymer would also be useful to prepare other polymer architectures. There is hydroxyl group in each repeating unit. Therefore, the polymer can be used as a macro-initiator to prepare graft copolymers by the ring-opening polymerization of lactones. The preparation of graft copolymers will be studied in the future.

Baylis-Hillman reaction can also be used to prepare monomers for the synthesis of biodegradable polymers. Using 2-hydroxyethyl acrylate as the starting materials, the Baylis-Hillman adducts can be made into an unsaturated diol which can undergo step-growth polymerization. The unsaturated diol was used to react with diisocyanatohexane catalyzed by Tin(II) octoate to generate a poly(ester-urethane).

The unsaturated poly(ester-urethane) was modified by thiol-ene click reaction. Several kinds of thiol were used to functionalize the polymers. By click reaction, polymers bearing different functional groups were synthesized, such as alcohol or carboxylic acid. By differential scanning calorimetry (DSC) analysis, it was observed that bearing different functional groups, polymers have apparently different glass transition temperature compared to that of the polymer before functionalization.

The described poly(ester-urethane)s would fulfill needs in numerous biological applications. The polymers can be used to prepare hydrogels using a thiol-based cross-linker, such as poly(ethylene glycol) dithiol. The polymers can also be functionalized with bioactive ligands for applications such as angiogenesis, wound healing and drug delivery.
REFERENCES


APPENDIX

$^1$H NMR SPECTRA OF ALIQUOTS

$^1$H NMR spectra of aliquots of the reaction solution for the conventional radical polymerization:

Entry 1:
Entry 2:

Entry 3:
Entry 4:

1H NMR spectra of aliquots of the reaction solution for the RAFT polymerization

Entry 1:
Entry 4:

Entry 5:
Entry 6:

[Image of a graph showing a spectrum with labeled chemical shifts and normalized intensity values.]

Entry 7:

[Image of a graph showing another spectrum with labeled chemical shifts and normalized intensity values.]
Entry 8:

![NMR spectrum image with chemical shifts and normalized intensity values]

- Chemical Shift (ppm): 7.5, 7.0, 6.5, 6.0, 5.5, 5.0, 4.5, 4.0, 3.5, 3.0, 2.5, 2.0, 1.5, 1.0, 0.5
- Normalized Intensity: 350.18, 101.22, 103.33, 7.27, 6.24, 5.82, 1.90