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Synthesis of Polyelectrolytes for Biomedical Applications via Ring Opening Metathesis Polymerization of 7-Oxanorbornene Derivatives And Development of a Polymer Laboratory Course for Undergraduate Students

Mu Zheng

A Dissertation Presented to the
Graduate Faculty of Middle Tennessee State University
in Partial Fulfillment of the Requirements
for the Degree Doctor of Arts

December, 1997

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APPROVED

Graduate Committee

Andrienne C. Friedli

Major Professor

Dwight A. Gates

Committee Member

Nancy C. Kerr

Committee Member

James N. Hutchinson

Chairman of the Department of Chemistry

Donald L. Gump

Dean of the Graduate School

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ABSTRACT

Synthesis of Polyelectrolytes

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And

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Mu Zheng

A 7-oxanorbornene derivative, 2-*exo*-methoxymethyl-3-*exo*-2[2-(2-trimethylammoniumethoxy)ethoxy]ethoxymethyl-7-oxabicyclo[2.2.1]hept-5-ene chloride (**1**) was designed and synthesized as a monomer for biomedical applications. To arrive at **1**, a total of six synthetic steps were required of which the last two steps were original. Numerous precursors of this compound were synthesized and discussed. Model compounds were chosen and polymerized under ring opening metathesis polymerization(ROMP) conditions. Copolymers were made with a neutral monomer, *exo*-5,6-dimethoxymethyl-7-oxabicyclo[2.2.1]hept-2-ene(**4**). The polymers and copolymers had molecular weights ranging from 2.63×10^5 to 3.71×10^6 with narrow polydispersity. Thermal analysis as measured by

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Differential scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) showed the polymers to have T_d (decomposition temperature) > 274 °C and some had a T_g (glass transition temperature) around 190 °C. The target polymer, **poly-1**, made for the first time, had a thermal stability comparable to the other polymers.

Since the Doctor of Arts degree has a fundamental pedagogy component, a section entitled "Development of a Polymer Laboratory Course for Underdgraduate Students" was discussed in Part II. Specifically, the role of the Teaching Assistant was described, and a qualitative analysis of the success of the course was made.

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ACKNOWLEDGMENT

I would like to thank Dr. A. Friedli for her advice and guidance.

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A special thanks goes to my husband, my parents and other family members. Without their love and support, this project would never have been completed.

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PART I. SYNTHESIS OF POLYELECTROLYTES FOR BIOMEDICAL APPLICATIONS VIA RING OPENING METATHESIS POLYMERIZATION OF 7-OXANORBORNENE DERIVATIVES

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CHAPTER 1 INTRODUCTION

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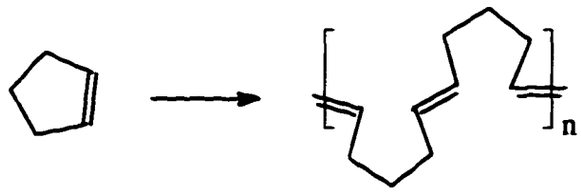
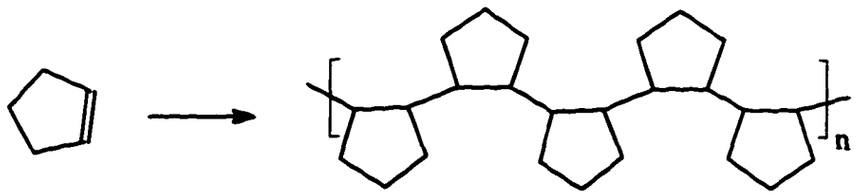
I. An Introduction to Aqueous Ring-Opening Metathesis Polymerization of 7-Oxanorbornene Derivatives

Ring-Opening Metathesis Polymerization (ROMP)

Ring-opening metathesis polymerization was discovered during the investigation of the Ziegler-Natta polymerization of strained cyclic olefins in the 1960's. A new type of polymer was formed from cyclic olefins (Equation 1) rather than the products expected from normal addition polymerization (Equation 2).[1]



(1)



(2)

Another unexpected result occurred when polymerization of the norbornene compound was investigated (Equation 3).[2] Instead of the fully saturated polymer, the product polymer still possessed carbon-carbon double bonds which indicated that some kind of ring-opening polymerization had occurred.

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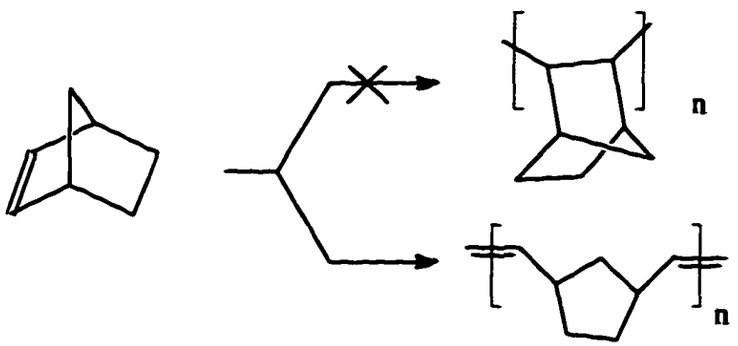
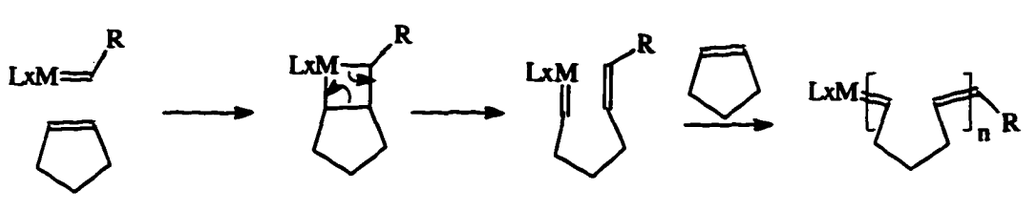


(3)

Ring-opening metathesis is unique in that all of the unsaturation present in the monomers is conserved in the polymeric product. This feature makes ROMP techniques very attractive for the preparation of highly unsaturated and fully conjugated materials.[1]

The mechanism of ROMP is shown in Equation 4.[3]



(4)

M - transition metal

L - ligand

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The ROMP technique has made an impact in the commercial market.[4-13] For instance, transparent recording sheets, heat and fire resistant materials with good anisotropy, moldability, adhesion properties, protecting layers for containers used for medical tubes and bottles, heat and moisture-resistant optical materials, and cold and ozone resistant materials have been made by using polynorbornene with different functional groups.

ROMP of 7-Oxanorbornene Derivatives

(i) Monomers

A range of 2,3-disubstituted 7-oxanorbornene derivatives (7-oxabicyclo[2.2.1]hept-5-ene derivatives) can be obtained by Diels-Alder reaction of furan with a functionalized dienophile followed by transformation of the functionalities (Figure 1).[14]

The *exo,exo* monomers were obtained by initially reacting furan with maleic anhydride to form the thermodynamically stable *exo,exo* anhydride.

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(ii) Catalysts

Although ROMP has been well-studied in systems that employ empirically derived Mo, W or Re catalysts, their sensitivity to air and protic media severely limits their application as living ROMP catalysts. Recent studies have

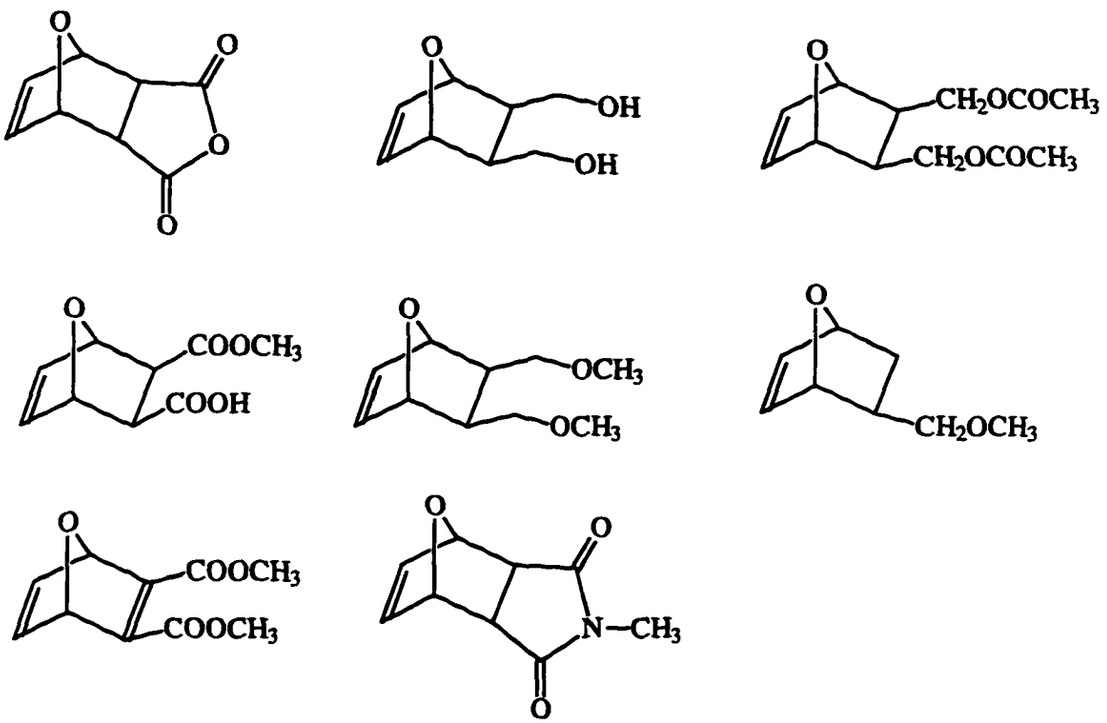

Figure 1: Some 7-oxanorbornene derivatives

shown that the ROMP of functionalized 7-oxanorbornenes has been achieved by using ruthenium, iridium, and osmium salts,

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such as $RuCl_3$, $OsCl_3$, $(NH_4)_2OsCl_6$, $[Ru(NH_3)_5Cl]Cl_2$, K_2RuCl_5, $Ru(H_2O)_6(tos)_2$.[14]

Aqueous ROMP using $RuCl_3$ as a catalyst in aqueous media was first reported by Grubbs' group.[16] When they investigated Group VIII (Ru, Os, Ir) metal catalysts, it was found that the polymerizations were actually cocatalyzed by water. The observation that a large excess of water in the reaction mixture does not inhibit polymerization ultimately led to the finding that the 7-oxanorbornene monomers can be polymerized in aqueous solution.[17]

It was also found that the most successful catalysts were $RuCl_3$ and $OsCl_3$.[14] During the initiation period, a small amount of reactive metal carbene is formed, which very rapidly polymerizes the cyclic olefin. The mechanism involves the disproportionation of an equilibrium amount of Ru^{3+}-olefin complex, if $RuCl_3$ is the catalyst, to provide a Ru^{2+}-olefin complex and a Ru^{4+} species which is trapped by additional Ru^{3+}.[14]

Used solutions of aqueous ruthenium ion are recyclable after an initial polymerization, giving an approximately 5000-fold increase in the initiation rate when reused.[17] The increased activity of the recycled catalyst solutions was

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attributed to the *in situ* formation of Ru^{2+} olefin complex. The choice of the catalyst can potentially allow significant synthetic control over polymer characteristics such as the *cis/trans* ratios of the metathesized double bonds and the ring diad tacticity.[17]

$RuCl_3$ is tolerant of a wide range of organic functionality. This functionality includes alcohols, ketones, thiols, and esters, which severely disable metathesis catalysts based on the early transition metals.[17,18] The tolerance for functional groups has allowed the preparation of polymers with different mechanical and chemical properties by varying the functionality along the polymer chain. In addition, this functional group tolerance should allow chain transfer reactions with acyclic olefins containing functional groups to produce oligomers and telomers with specific functionalized end groups.

To investigate whether the ROMP system was living in aqueous media, two well-defined ruthenium carbene complexes $(Cy_3P)_2Cl_2Ru=CHCH=CPh_2$ and $(Cy_3P)_2Cl_2Ru=CHPh$ (Cy=cyclohexyl) were used to catalyze functionalized 7-oxanorbornene.[19] The linear relationship between molecular weight and

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monomer/catalyst ratios and the absence of chain transfer and termination processes indicated that these systems were indeed living. Furthermore, it was shown that ROMP technique was an efficient method for the preparation of well-defined block copolymers.

Microstructure of poly(7-oxanorbornene) derivatives was found to vary with catalyst and was not dependant on molecular weight. [22] For instance, when $RuCl_3$ was used as catalyst, the highly *trans* structure was observed.[17]

(iii) Kinetics of ROMP in Aqueous Solution

The rate of polymerization (Rp) was followed by ^{13}C NMR as a function of monomer, catalyst,and water concentration.[20] The results showed the second-order dependence of Rp on the monomer concentration and the unusual dependence of Rp on the catalyst concentration. The molecular weight and polydispersity of the products were independent of the catalyst and monomer concentrations.

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(iv) Molecular Weights

The molecular weights of poly(7-oxanorbornene) derivatives polymerized in H_2O or H_2O/EtOH solution were reported to the range from 1.33×10^5 to 1.34×10^6 daltons.[14,20] When 3-buten-1-ol and methyl acrylate were used as chain transfer agents, lower molecular weight oligomers in low yields were formed.[21] Molecular weights of the polymers varied between 155×10^3 and 1×10^3 daltons when 2-butene-1,4-diol was used as a chain transfer agent.[2]

(v) Solvent Effects

When $RuCl_3$ is used as the catalyst for ROMP, benzene, chlorobenzene, chloroform, ethanol, methanol, water or the mixture of two of the solvents could serve as solvent. For example, 1 M solution of *exo*-5,6-dimethoxymethyl-7-oxabicyclo[2.2.1]hept-2-ene in C_6H_6/EtOH (5/1) at 50 °C, requires an initiation period between 22 and 24 hours. In contrast, the reaction only takes 30 minutes to initiate in water and the yield is almost quantitative. The molecular weight of polymer formed from water was about four times higher than that from organic solvents. Polydispersity was

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nearly 1 if water was used as the solvent, while it was about 2 in organic solvents.[17]

(vi) Special Properties: Charge Transport

Molecular modeling studies indicated that poly(7-oxanorbornene) has the ability to form helical structures with all of the tetrahydrofuran oxygens facing into the interior of the helix.[15] This unique helical conformation may allow these polymers, when in solution, to act as acyclic ionophores so that they can be made into ion-permeable synthetic membranes. In the long run, environmental uses and industrial processing could benefit from polymerizations performed in aqueous media.

Ion complexation by poly(exo-5,6-dimethoxymethyl-7-oxabicyclo[2.2.1]hept-2-ene was reported. It was found that this polymer coordinated Na^+ and Cs^+(but not K^+) and complexed large polyaromatic cationic dyes such as methylene blue and rhodamine 6G. This polymer demonstrated high selectivity by complexing only dyes comprised of large organic cations and small anions (Cl^-). Dyes comprised of Na^+ and large aromatic anions were not complexed. The

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selectivity was exactly opposite to that observed for ion complexation by using 18-crown-6. In addition to binding ions in solution, these polymers acted as ion permeable membranes. From the measured membrane potentials, action transport numbers for K^+, Na^+ and Li^+ were 0.84, 0.73 and 0.73.[16]

(vii) Applications of Polyoxanorbornene

ROMP of 7-oxabornornene derivatives in aqueous solution to form carboximide-functionalized oxanorbornenes[23] and siloxane-functionalized oxanorbornenes for inorganic-organic network nonshrinking composites (Figure 2) have been investigated.[24]

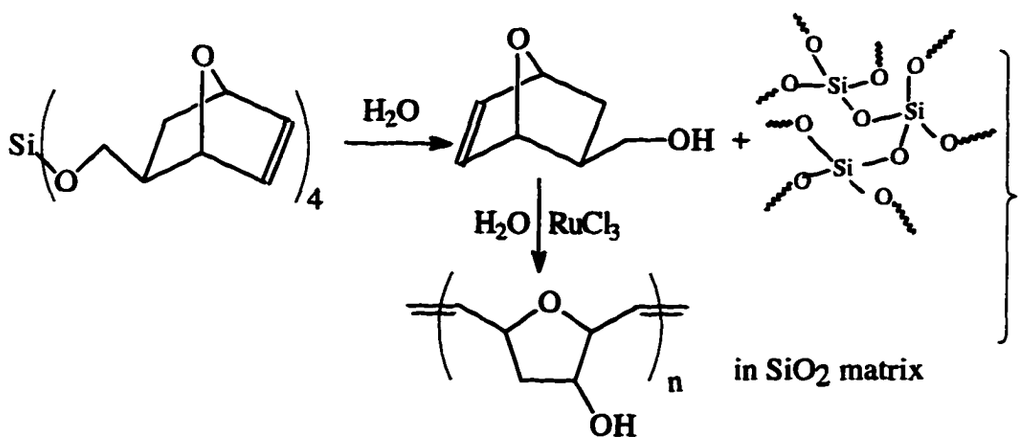

Figure 2: Inorganic-organic network formed by 7-oxanorbornene derivatives.

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Homo-and copolymers of oxanorbornene carboximide esters were synthesized and the molecular weights were controlled with 2-butene-1,4-diol as chain transfer agent. These polymers (Figure 3) can be used to formulate very sensitive positive tone high resolution microresists. They are the first positive working photoresists based on a metathesis polymer backbone.[26]

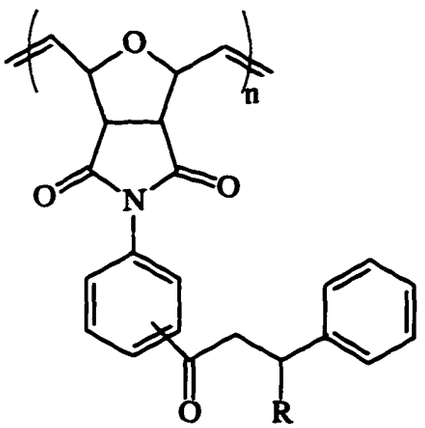

Figure 3: Polyoxanorbornene derivatives used as photoresists.

Polyoxanorbornene derivatives also have found applications in the biomedical field. A new class of polyvalent carbohydrate ligands (Figure 4) were prepared by ROMP. Such saccharide-substituted polymers act as

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polyvalent ligands for the mannose/glucose-binding protein concanavalin A. The polymers exhibit both high affinity and selectivity.[27]

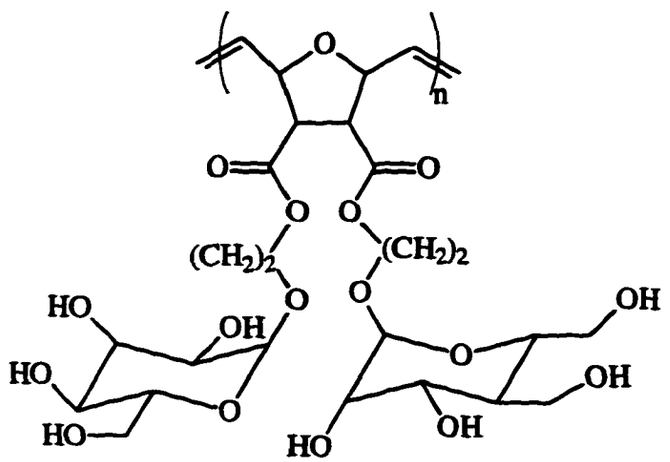

Figure 4: Polyvalent carbohydrate formed from ROMP of 7-oxanorbornene derivatives

Another 7-oxanorbornene derivative, poly(*exo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride), is of potential importance as a biologically active anionic polymer due to its structural similarity to the copolymer formed by the free radical polymerization of a mixture of maleic anhydride and divinyl ether.[28] Its derivatives (Figure 5) may also find use as hydrogels,[29] ionophoric

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materials or as selective ion permeable membranes[15] for encapsulation.

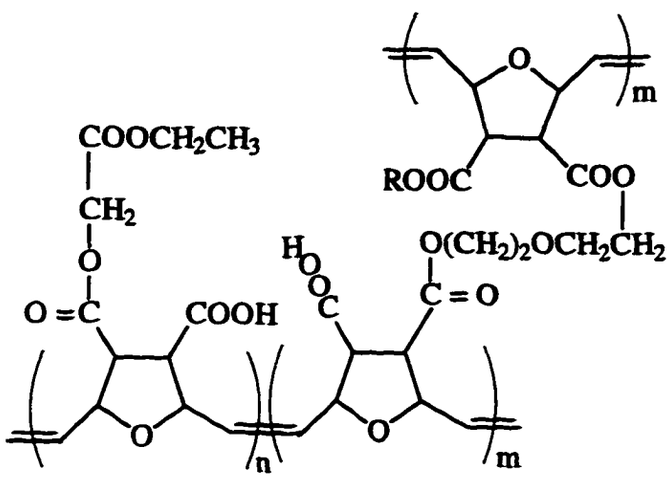

Figure 5: Poly(7-oxanorbornene) derivative used as hydrogel

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II. Biomedical Applications of Microencapsulation

Microencapsulation is the envelopment of small solid particles, liquid droplets, or gas bubbles with a coating. The coating material used to form the capsule is called a carrier, coating, membrane, shell or wall. It may be an organic polymer, hydrocolloid, sugar, wax, fat, metal or inorganic oxide.[30]

In recent years, there has been broad interest in microencapsulation in the biomedical community. Many studies on drug delivery,[31-37] encapsulation of enzymes[38,39] and living cells[40-53] have been published.

Encapsulation in Drug Delivery

Antibacterial drugs, anti-inflammatory agents, anti-cancer drugs and vitamins, have been encapsulated in polymers or copolymers, such as poly(glycolic acid), poly(lactic acid), polycaprolactone; glycol-lactic acid copolymer, polydioxyalkyltetrahydrofuran, copolymer of poly(3,9 bis(methylene)-2,4,8,10-tetra-oxaspiro(5,5)undecane with 1,6-hexanediol), olefin-maleic anhydride copolymers, polyacrylates, polymethacrylates, poly(ethylene glycol monomethacrylate), dextran, poly(glutanic acid), glutamic

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acid-leucine copolymer, alkyleneaminotriazole copolymers and albumin cross-linked with glutaraldehyde.[36]

Polymeric materials generally release drugs by the following mechanisms: (1) diffusion through reservoirs or matrices; (2) chemical reaction, which is accomplished either by polymer degradation or chemical cleavage of the drug from a polymer; or (3) solvent activation, which involves either swelling of the polymer or osmotic effect. Generally, if the drug is placed in a polymeric material, optimal control of delivery rate can be afforded.

The advantages of polymeric drugs are that the polymers exhibit delayed action, prolongation of activity, and decreased rate of drug metabolism and drug excretion.

One of the future directions in the drug delivery area is the creation of polymer that could alter an orally-administered drug's destination. This could be particularly important for drugs that are absorbed only in certain segments of the gastrointestinal tract.[37]

Encapsulation of Living Cells

Successful microencapsulation of cells requires that the cells survive encapsulation and retain their normal

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function. It is also important that the microcapsules be biocompatible so as to resist a fibrous reaction by the host. The membrane formed for microcapsules should permit the passage of nutrients and oxygen, but not high molecular weight substances (host antibodies). Several polymers used as microcapsules have been studied and the results have been published. [31-39] Important approaches to encapsulation using polymers are summarized here.

Dupuy used a photochemical process to initiate the polymerization of acryamide and bisacrylamide for microencapsulating Pancreatic islet cells and pituitary cells. The membranes had pore size sufficient for diffusion of insulin and their *in vitro* biocompatibility was satisfactory.[40-42] Mosbach and Larrson prepared entrapped cells of *curvularia lunata* in polyacrylamide gels and successfully used the gel-cell granules for hydroxylation of a steroid.[43] Chibata immobilized *Escherichia coli* cells in polyacrylamide gels and autolyzed the immobilized cells to obtain a highly active form of aspartase. The enzyme was stable for more than 40 days in a continuous column reactor.[44]

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Motohiro Uo prepared porous silica with the sol-gel process to immobilize a large number of yeast cells. The porous silica gel was prepared from tetramethoxysilane (TMOS)-polyethylene glycol (PEG)-H_2O-methanol solution. Pore diameters of porous gels ranged from 0.1 μm to 10 μm. It was shown that some PEG still remained in the silica skeleton after leaching with water. Yeast cells were immobilized in porous silica gel. After incubation, yeast spores germinates and growth of the yeasts were confirmed.[45]

P. Aebischer encapsulated PC 12 cells, a potential therapy for Parkinson's Disease, in hollow fibers. The hollow fibers were fabricated from a 15 % weight-by-volume solution of poly(acrylonitrile vinyl chloride) in dimethylsulfoxide (DMSO). The capsules had a diameter of 560 μm and contains, on average, 300 to 500 cells per capsules. PC 12 cells loaded in hollow fibers maintained in vitro and transplanted in an experimental Parkinson model rat for four weeks. The conclusion is that the implantation of polymer-encapsulated cells may provide a means for long-term delivery of neurotransmitters providing adequate encapsulation technology.[46]

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Lacy encapsulated small numbers of rat islets in hollow fibers fabricated from an acrylic copolymer. The fibers were biocompatible, and prevented rejection, but hyperglycemia returned when the fibers were removed at 60 days. Normoglycemia was also maintained by subcutaneous implants that had an appropriately constructed outer surface on the fibers.[47]

Joung immobilized growing cells by using polyethyleneimine-modified alginate. When yeast beads prepared with the new carrier were applied to ethanol fermentation, the biocatalyst expanded to 1000 % of its original volume, permitting a high degree of retention of cells and carrier polymer.[48]

Pathak reported a synthesis of stable, biocompatible gels with permselectivity appropriate for immunoprotection via rapid photopolymerization of water-soluble poly(ethylene glycol)-based macromers in direct contact with cells and tissue without cytotoxicity.[49]

Crooks used 2-hydroxyethyl-methacrylate(HEMA)-methyl methacrylate (MMA) copolymer for encapsulation of mammalian cells.[50] Since HEMA can be easily polymerized, possesses a hydrophilic pendant group, and can form hydrogels, an

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increasing number of applications have been found in various biomedical fields.[51,52]

Microencapsulation by Polyelectrolyte Complex

One approach to microencapsulation of drugs and living cells is to use a polyelectrolyte complex to form a membrane. Polyelectrolyte complexes are formed when polymers of opposite charge are allowed to interact. The small particles formed by polyelectrolyte complexes usually have a narrow size distribution of 20-40 nm. [53]

The driving force for complex formation is the release of microions. In most systems, insoluble polyelectrolyte complexes exhibit 1:1 stoichiometry in charged groups, independent of the charge density on the polymer and the structure of their backbones. In some systems, non-stoichiometric precipitates are formed as a result of pH changes during complex formation or when very low or very high polymer concentrations are used. Poor accessibility of ionic groups and branching can also cause deviations from 1:1 stoichiometry.

Polyelectrolyte complexes form precipitates or gels in most cases, but they can also remain in solution. The

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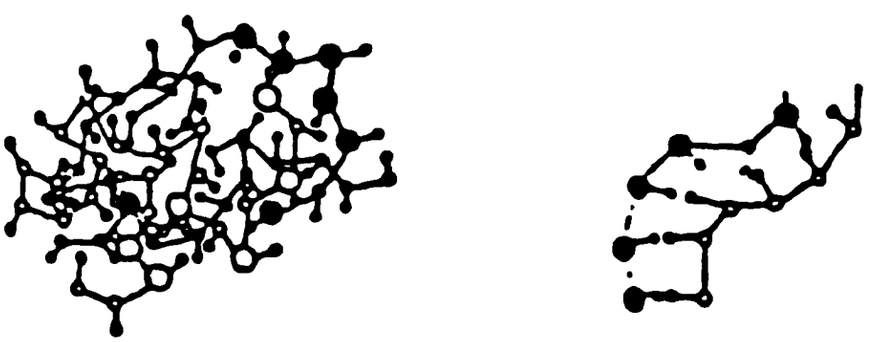
The ultimate structures of the membranes are determined by electrostatic interactions, hydrogen bonds, ion dipole forces, and hydrophilic/hydrophobic interactions.

The actual structure of the polyelectrolyte complex has been described as one between that of a "scrambled-egg" model and a ladderlike structure (Figure 6). The first model resembles a network structure of oppositely charged polymer chains in which charge neutralization is largely a random process. In ladderlike structures, two chains are compressed into one another and the ionic crosslinks are ordered in a regular fashion. This arrangement is likely to produce a more crystalline complex. The structures of most polyelectrolyte complexes fall in between these two extremes. [54]



"scrambled egg" model ladder model

Figure 6: Polyelectrolyte complexes models

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Polyelectrolyte complexes have already been used in the biomedical area.

Dautzenberg investigated cellulose sulfate-poly-diallyldimethylammonium chloride (DADMAC)] polyelectrolyte complex microcapsules, encapsulating enzymes such as lactate dehydrogenase or invertase, hepatic microsomes for extracorporal detoxification, pancreatic islets, cattle embryos, and different drugs.[55] The controlled release of a peptide hormone from microcapsules and the activity of urease in these capsules was also studied.[56,57]

Kokufuta used the polyelectrolyte complex formed between trimethylammonium glycolchitosan iodide and polyvinyl alcohol sulfate to entrap *Escherichia coli* cells. Two steps were observed, i.e., an aggregation of cells by the cationic component added first and a subsequent flocculation by complex formation between the excess of polycations and the polyanions added later. The glucose-oxidizing activity of *E. Coli* persisted even with the cells grown in the complex.[58]

Kawashima studied a polyelectrolye complex formed between Na-polyphosphate and chitosan. This complex was

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proposed as a release-controlling coating on theophylline granules.[59]

Davison reported a biocompatible drug delivery system which was formed by dextran sulfate and an ionene.[60]

Wang's group is studying the encapsulation of living mammalian cells in a biocompatible polymeric semipermeable membrane by dropping a polyelectrolyte with negatively charged groups (polyanion) into a polyelectrolyte with positively charged groups (polycation) (Figure 7).[61] The

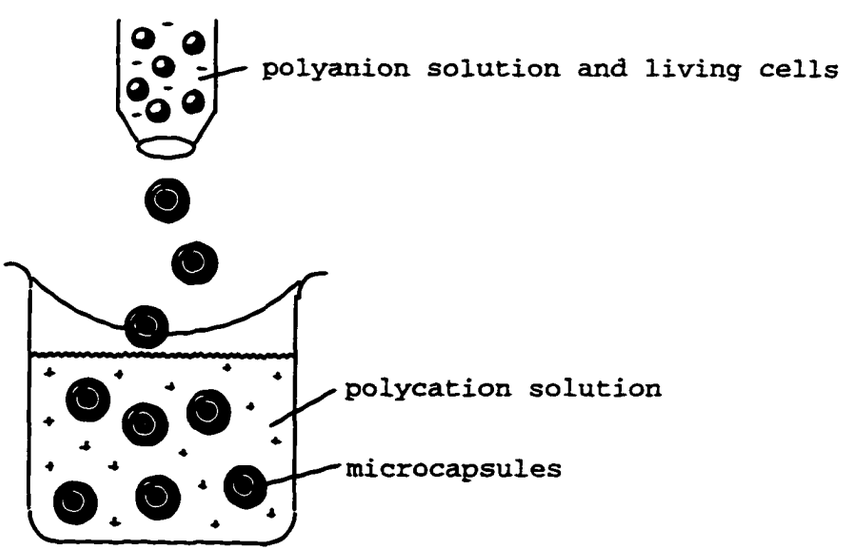

Figure 7: Microencapsulation by polyelectrolyte complex

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formation of polyelectrolyte complexes is usually independent of the order of mixing. However, the living cells to be encapsulated are preferentially incorporated in the solution of the anionic component because direct contact with the cationic polyelectrolyte solution can be detrimental to the living cells. After formation of the complex, the toxic effect of the cationic polyelectrolyte was not observed.

Three potential problems need to be considered when a polyelectrolyte complex is used for living tissue: 1) the toxicity of interaction of the polyelectrolyte complex with the cell membrane; 2) the compatibility of the polyelectrolyte complex with blood; 3) the interaction of the polyelectrolyte complex with the immune system. These biocompatibility issues must be overcome in order for encapsulation materials to be suitable for therapeutic use.

The structure and the composition of a polyelectrolyte complex and the interaction between the oppositely charged polyelectrolytes may lead to a diversity of physical and chemical properties of these complexes. By governing the structure and composition of main chain, degree of branching or crosslinking, molecular weight of polymer and charge

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density, the stability, biocompatibility and permeability (pore sizes) of the membranes could be controlled. At this point, it is of great interest to explore new materials.

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III Scope of the Research

Poly(7-oxanorbornene) derivatives were designed and obtained with ROMP for the purpose of microencapsulation for biomedical application.

The reason for choosing these polymers (Figure 8) was that they have semi-rigid structures on the main chain and were likely to have high glass transition temperatures. The side chain was designed to be flexible enough to promote ion migration, yet has diffuse charges to prevent trapping of the ions at a given site.

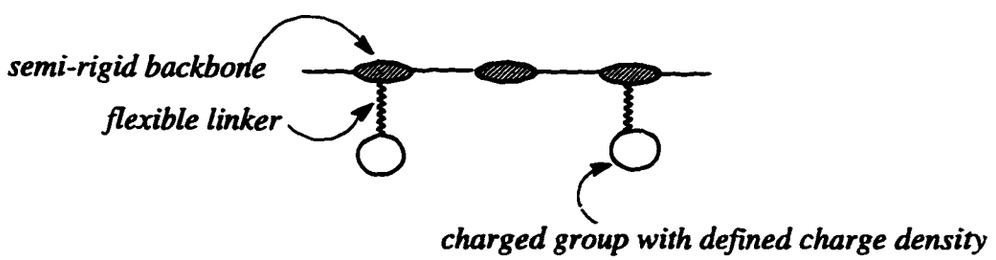

Figure 8: The model of designed polyelectrolyte.

The target polyelectrolyte (Figure 9) has a five-membered ring in the main chain, which comes from the ring opening polymerization of oxanorbornene. A side chain has ethylene oxide repeat units to promote flexibility and a charged group at the end to promote complexation.

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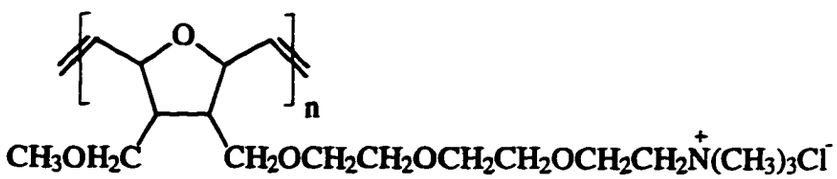

Figure 9: Target polyelectrolyte.

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CHAPTER 2 SYNTHESIS OF MONOMERS AND POLYMERS

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Monomer Synthesis

Several 7-oxanorbornene derivatives and other compounds were made in this work. They are listed in Figure 10. Each of them is discussed below:

*a. Exo-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic Anhydride (**2**)*

A common synthetic approach to oxanorbornene derivatives **2** is through the Diels-Alder reaction of furan and maleic anhydride.[62,63] This reaction proceeds under thermodynamic, rather than kinetic control,[62] and results in formation of nearly 100 % of the exo-isomer. The reaction went well and the yield of **2** was 61.3 %. However, the melting point (118 °C) was not as high as the literature report (125 °C).[63] The reason for this was that a trace of acid was present. By changing the solvent to benzene, it was found that the yield was enhanced to 78 % and the melting point increased to 119 °C.

*b. Exo-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dicarbinol (**3**)*

A classical lithium aluminum hydride reduction of the Diels-Alder adduct gave diol **3**. To get pure diol was

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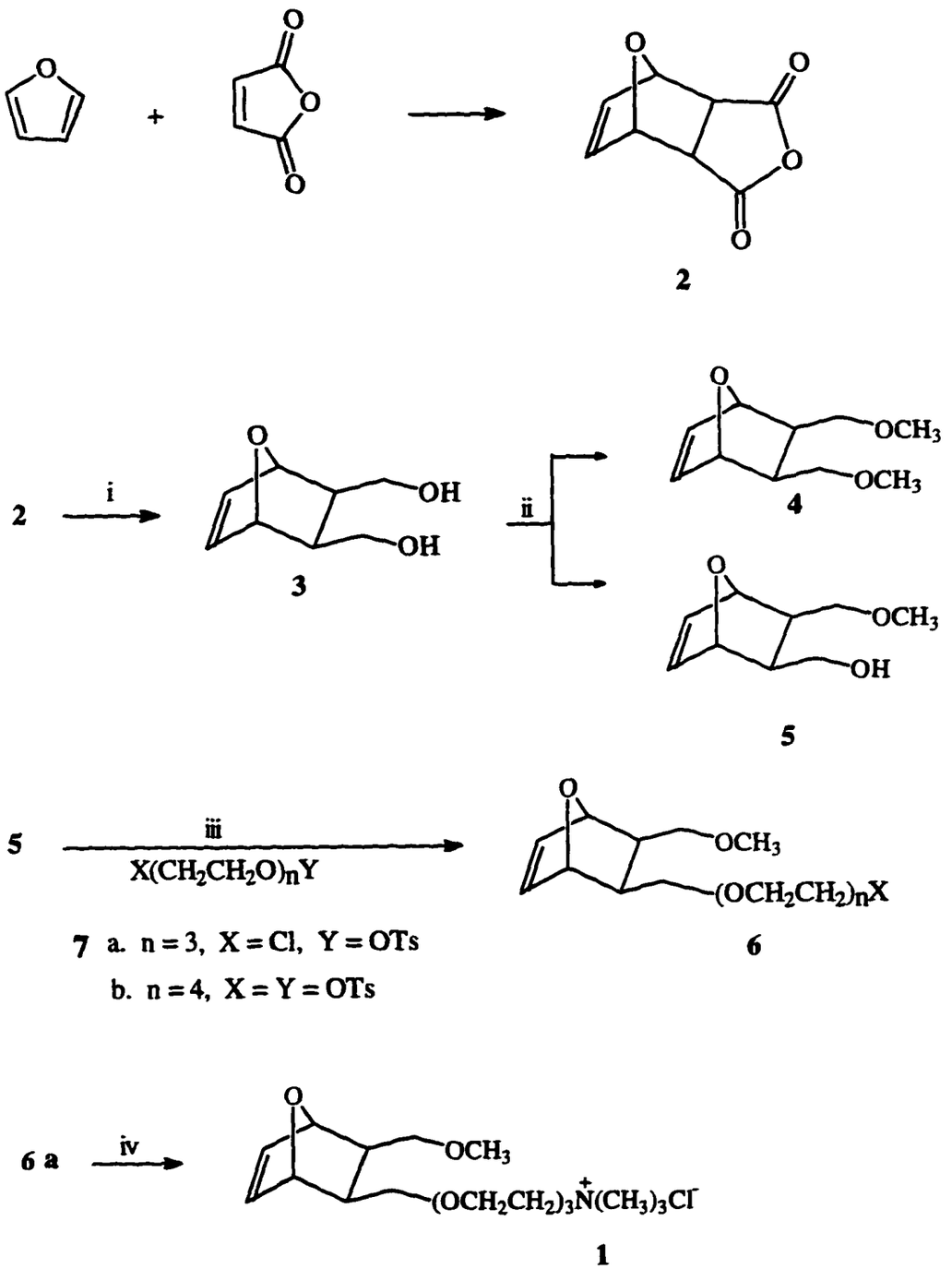

Figure 10. Synthesis route.

i. $LiAlH_4$; ii. NaH, MeI; iii. NaH; iv. NMe_3

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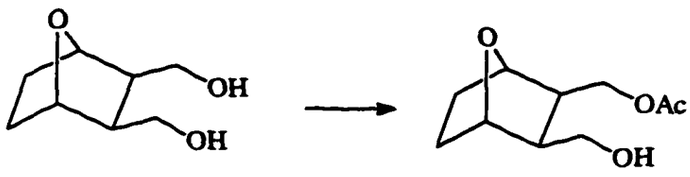
critical because the molar ratio of diol, sodium hydride, and iodomethane needs to be stoichiometric in the next steps in order to selectively convert the alcohol to an ether group. There was no purification procedure described in the literature for this compound.[20] The diol was extracted with CH_2Cl_2 by using a Soxhlet extractor,[17] and it was shown that this was a efficient purification method. Further purification can be accomplished using a Kugelrohr distillation.[17] However, it was found that the diol decomposed and bumped during distillation.

Selective monosubstitution of diol (**3**) was attempted. According to the literature,[64] cis-*exo*-2,3-bis(hydroxymethyl)-7-oxabicyclo[2.2.1]heptane can be partially esterified by using lipase to give a monoacetate (Equation 6). However, **3** was not successfully esterified in this research. The presence of the alkene may affect the selectivity of enzyme.



(6)

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*c. Exo-2,3-dimethoxymethyl-7-Oxabicyclo [2.2.1]hept-5-ene (**4**)*

The diether (**4**) was made using 4:1 molar ratio of NaH and diol, and the product showed a single spot on TLC. Purity of the crude product was confirmed by NMR and GC/MS.

*d. 2-exo-Hydroxymethyl-3-exo-methoxymethyl-7-oxabicyclo [2.2.1] hept-5-ene (**5**)*

To synthesize (**5**), the critical factor was the extensive drying of (**3**) and the exactly stoichiometric ratio of NaH, diol and MeI. Even when the reaction conditions were controlled, the product was always a mixture of compounds **3**, **4** and **5**. Column chromatography was found to be the best way to separate the product because the compounds decomposed and gave very poor separation when Kugelrohr distillation was used.

*e. 1-Chloro-2-[2-(2-tosylethoxy)ethoxy]ethane (**7a**)*

Compound **7a** was synthesized by Tomohiro, Avval and Okuno in 1992.[65] According to their study, the compound was made in CH_2Cl_2 by using $N(CH_2CH_3)_3$ and DMAP as reagents. No yield or characterization data were reported. The procedure

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was modified to make compound **7a** from 2-[2-(2-chloroethoxy)ethoxy]ethanol and *p*-toluenesulfonyl chloride in NaOH aqueous solution and a high yield was obtained(93%). Analysis of the ^{1}H NMR of **7a** was unclear due to the overlapping multiplets between 3 to 4 ppm. These peaks belong to two types of methylene groups: 3.39 to 3.63 ppm (4H), and 3.36-3.57 ppm (6H). 2D NMR showed that these two groups of peaks coupled to each other. However, assignment of the peaks to individual protons was not possible.

*f.2-exo-Methoxymethyl-3-exo-2-[2-(2-chloroethoxy)ethoxy]ethoxymethyl-7-oxabicyclo[2.2.1]hept-5-ene (**6a**)*

Compound **6a** was synthesized under classical Williamson conditions. Since a tosylate group is a better leaving group than chloride, the substitution reaction took place at the carbon attached to the tosylate. Separation was the most difficult step. The crude mixture had to be put through a chromatotron several times before a pure product was obtained. Distillation under reduced pressure was also tried, but resulted in less pure material. NMR analysis indicated that **6a** readily absorbs water, probably due to the

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hydrophilic oligoethylene glycol chain. Sodium fusion and ignition tests confirmed the presence of chlorine.

Synthesis of series of compounds similar to compound **6a** were proposed in order to get different numbers ethylene glycol repeat units and different leaving groups. However, none of these transformations except **6a** and **6e** were successfully completed.

5 + $X(CH_2CH_2O)_nCH_2CH_2Y$ → **6**

7a. X = Cl, Y = OTs; n = 3 — **6a.** X = Cl; n = 3

b. X = Y = Br; n = 4 — **b.** X = Br; n = 4

c. X = Br, Y = OTs; n = 4 — **c.** X = Br or OTs; n = 4

d. X = Br, Y = OTs; n = 2 — **d.** X = Br or OTs; n = 2

e. X = Y = OTs; n = 4 — **e.** X = OTs; n = 4

Figure 11. Synthetic approaches to **6**

Tetraethylene glycol ditosylate (**7e**) is commercially available. Compound **6e** was made and has been reported.[56] However, crude product contained unreacted starting material, product, and byproduct (**8**) (Figure 12), making it a worse key intermediate than **6a**.

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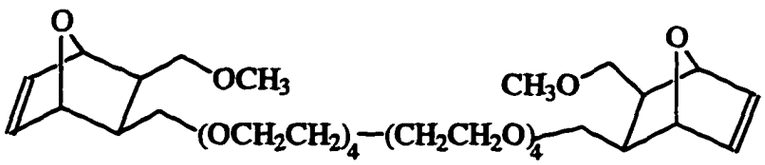
Purification was done by using silica gel, neutral aluminum oxide, acidic aluminum oxide and sephadex as absorbants combined with various solvents. It was found



(8)

Figure 12: Structure of byproduct.

that both silica gel and aluminum oxide could separate the crude product. However, using a chromatotron, 1 mm of aluminum oxide support and 2:1 ethyl acetate:hexane eluent was found to be the best combination to separate this mixture. TLC indicated that the separation was sucessful, but the baseline of ^{1}H NMR spectrum revealed that an impurity still existed. Low temperature crystallization from petroleum ether (80 mg **6a** in 2 mL solvent) improved the purity. Repeated low temperature crystallization followed by chromatotron separation gave a more pure product.

Due to the purification problems with **6b**, **7c** and **7d**, compound **6a** was the only one used for polymerization.

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*g. Bis [2-(2-bromoethoxy)ethyl]Ether (**7b**) and its series compounds*

Compound **7b** was synthesized using thionyl bromide and tetraethylene glycol according to literature.[67] The mixture was stirred at room temperature because decomposition occurred when the reaction was left at reflux temperature for 16 hours. The crude product was washed with 5 % NaOH and H_2O, followed by extraction with hexane. The pure product was acquired after distillation.

Two other compounds were also studied: 1-bromo-(2-tosylethoxy)ethane (**7c**) and 1-bromo-2{2-[2-(tosylethoxy) ethoxy]-ethoxy}ethane (**7d**). To make these two compounds, ethylene glycol and *p*-toluenesulfonyl chloride were used as starting materials. Both of the reactions required three steps and separation from byproducts was critical in each step. As a leaving group, bromide and tosylate have similar ability.[68] It was hard to control which group would react faster in the Williamson ether synthesis. No further study of these two compounds was attempted.

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*h. 2-exo-Methoxymethyl-3-exo-2[2-(2-trimethylammonium ethoxy)ethoxy]ethoxymethyl-7-oxabicyclo[2.2.1]hept-5-ene chloride (**1**)*

Trialkylamines were desirable to form soluble ammonium salts. Since trimethylamine was more likely to form a water soluble product, a procedure was developed to utilize it. Although it is a gas at room temperature (bp. 3 °C), it could be cooled in a dry ice-acetone solution before transferring as a liquid to a Schlenk tube. The reaction mixture was warmed to 50 °C in this sealed tube for 24 hours and a reasonable yield (67 %) of product was formed. Triethylamine was also used as a nucleophile. However, the yield was extremely low even after the anion was changed to I^- using the Finkelstein reaction.

i. Other compounds

Two asymmetric Diels-Alder reactions were explored to obtain pure stereoisomers: lactone (**9**)[69] and monoester (**10**)[70] (Figure 13). Compound **2** was reduced with $NaBH_4$ in DMF to **9**. Recrystallization gave pure product in 70% yield. Ester **10** was made from freshly distilled furan, methyl acrylate, and $BF_3.OEt_2$ catalyst. The resulting product contained a mixture

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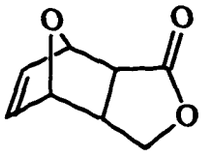
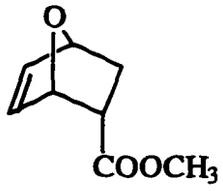
of *endo* and *exo* isomers, which was separated by silica gel column chromatography.

The asymmetric compounds were intended to reduce the difficulty of separations experienced in this work. However, these compounds were not water soluble. Furthermore, ester linkages due to hydrolysis can be unstable under physiological conditions.



9



10

Figure 13: Other 7-oxanorbornenes made in this work.

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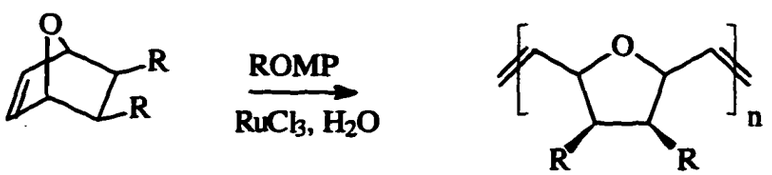
Polymer Synthesis

Polymerization

The polymerization of the 7-oxanorbornene monomer, proceeds rapidly and efficiently in water to produce the desired ROMP polymer (Equation 7). The initiation time is about 30 minutes. The yields of polymers are high: 100 % for **poly-4**, 88 % for **poly-6a** and 56 % for **poly-1**.



(7)

The presence of oxygen affects polymerization. No high molecular weight polymer was obtained from a nondegassed solution. Instead, a sticky substance formed and the solution changed in color from yellow to dark green. This might be due to the formation of an inactive oxidation state of ruthenium.[17] When water that had been sparged with oxygen was used in the polymerization, no polymer formed. The exact role that oxygen plays in the polymerization mechanism is still not fully known.

The resulting polymer can have many isomers: trans,

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cis, isotactic, syndiotactic, head-to-tail, and head-to head (Figure 14).

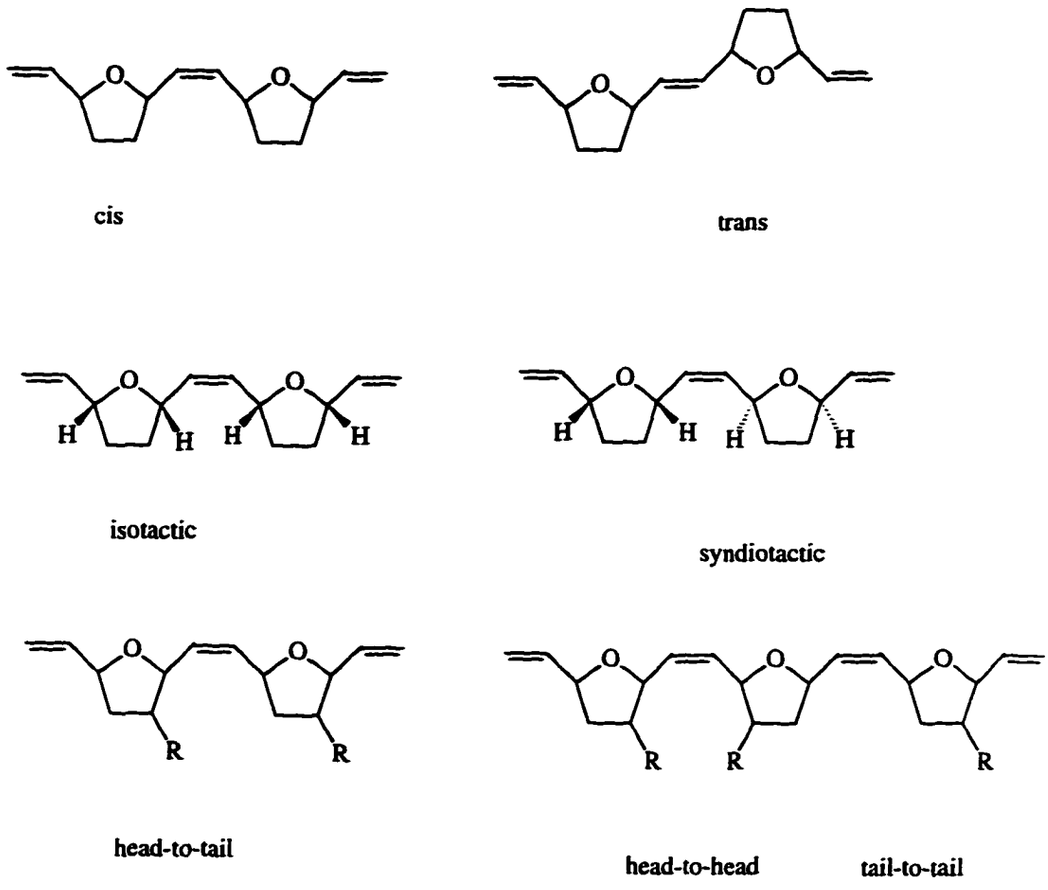

Figure 14. Isomers of the polymers

Most of the polymers described here have a slightly grey color. Purification of the polymers has been a problem due to the insolubility. Elemental analysis of **4** polymerized from water was off by 2.3 % for C and off by 0.5 % for H.

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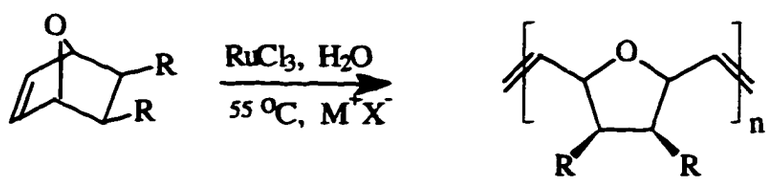
The poor analysis could be due to the fact that ~~It could contribute to~~ the not dried polymer or that catalyst ~~the residue of~~ remained ~~catalyst~~. In order to decrease the amount of residual catalyst in the polymers, instead of using fresh $RuCl_3$ solutions, the catalyst solution from mixing the oxanorbornene substrate and $RuCl_3$ in water can be used.[27]

Model Polymers

Compounds **2** and **4** were chosen as model compounds to test whether 7-oxanorbornene derivatives could undergo ring opening metathesis polymerization when ions were present (Equation 8).



(8)

$R = COOH,\ CH_2OCH_3$

$MX = NaCl,\ CH_3COOH,\ LiCl,\ (CH_3)_4N^+Cl^-,\ Na_2B_{12}H_{12}$

It was found that the polymerization was fairly tolerant of ionic additives including NaCl, LiCl, Me_4NCl, CH_3COOH and $Na_2B_{12}H_{12}$. The results are listed in Table 1.

There was no effect on the yield of polymers even when

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M^+X^- (mmol)	Monomer (**2**) (mmol)	Yield (%)	Monomer (**4**) (mmol)	Yield (%)
None	0.6	90-100	2.7	96
NaCl (0.043)	n/a	n/a	0.54	54
CH_3COOH (0.040)	0.6	80	0.54	80
LiCl (0.181)	0.6	100	*n/a*	*n/a*
$Me_4N^+Cl^-$ (0.068) (0.27) (0.54)	0.6	100 100 100	0.54	100 100 100
$Na_2B_{12}H_{12}$ (0.135) (0.54)	*n/a*	*n/a*	0.54	86 84

Table 1: Percentage yields of poly-**2** and poly-**4** in the presence of various ions. Notes: a) All the polymerizations were performed in degassed water (0.6 mL) and were initiated by $RuCl_3$ (0.0078 mmol). b) The polymers were purified by washing with distilled water several times.

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the concentration of salt was raised to 0.9 M, a molar ratio of 1:1 salt to monomer. The polymerization proceeded with a normal initiation time and the yield of polymer was still nearly quantitative. No monomer "salting out" of the aqueous solution at this high ionic strength was observed. Based on the model studies, we predicted that charged monomers should undergo ROMP.

The successful polymerization of **1** supported this prediction, at least in the case of cationic monomers.

ROMP worked in the presence of CH_3COOH, but not in the presence of $NaHCO_3$ or NH_4HCO_3.

Since we originally proposed to connect a boron cluster to the 7-oxanorbornene monomer to produce a polyanion, $Na_2B_{12}H_{12}$ was added during ROMP of model compounds. A normal initiation time and a reasonable yield (85%) of product was observed.

Copolymers

Several copolymers from 7-oxanorbornene derivatives have already been made.[17,19] Copolymers from **2** and **3** were made as an alternative to the copolymer from free-radical polymerization of maleic anhydride and divinyl ether, which

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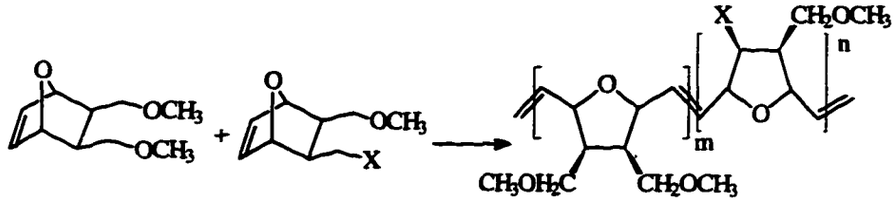
is used as an antitumor agent.[17] A block copolymer from a 7-oxanorbornene derivative and a norbornene derivative was made in order to probe the mechanism of ROMP.[19]

In this research, copolymers **poly-4-*co*-6a** and **poly-4-*co*-1** were made (Equation 9). **Poly-4-*co*-6a** was made at different molar ratios of monomers **4** and **6a**. Presumably, **poly 4-*co*-6a** can be converted to **poly 4-*co*-1** by reaction with trimethyl amine. Monomer **4** was included to dilute the charge density of the copolymer. The yields are listed in Table 2.



(9)

X = $(OCH_2CH_2)_3Cl$, $(OCH_2CH_2)_3N^+Me_3Cl^-$

All the copolymerizations had the same initiation times as homopolymerizations. However, the yields were lower than those of the homopolymers.

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Monomer Ratio	Monomer(**4**) (mmol)	Monomer(**6a**) (mmol)	Yield (%)
1:1	0.32	0.32	56.0
2:1	0.42	0.21	58.7
1:2	0.21	0.42	47.3
4:1	0.48	0.16	66.9
10:1	0.58	0.058	72.1

Table 2: Percentage Yield of **Poly-4-co-6a**.
Note: Polymerization was performed in degassed water (0.6 mL) and was initiated by $RuCl_3$ (8.7×10^{-3} mmol). The polymers were purified by washing with distilled water several times.

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Conclusions

Numerous 7-oxanorbornene derivatives and linking groups were synthesized as precursors to cationic monomer **1**. The target monomer (**1**) was synthesized in five steps from commercial starting materials in an overall yield of 16%.

ROMP of some of the 7-oxanorbornene derivatives, including **1**, in aqueous solution produced polymers in medium to high yields.

Model polymerizations in the presence of ionic materials were successful but proceeded in slightly lower yields .

Copolymers were synthesized from **4** and **6a** with a range of charge densities in 47 to 72 % yields.

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Experimental

General Procedures

Argon was dried by passage through anhydrous $CaCl_2$. Weighing of moisture-sensitive compounds was performed in a glove bag under nitrogen.

^1H NMR spectra at 200 MHz and ^{13}C NMR spectra at 50 MHz were recorded on Bruker AM 200 instrument in $CDCl_3$ unless otherwise indicated. Chemical shifts were referenced to TMS or to residual protons on the deuterated solvents.

IR spectra were measured on Nicolet Impact 410 as neat samples. IR spectra of polymers were measured as films cast from THF solutions.

GC/MS was performed on a Hewlett Packard 5890 Series II gas chromatograph interfaced to a Hewlett Packard mass-selective detector.

Elemental analyses were performed at Atlantic Microlabs, Norcross, GA.

All the organic chemicals were obtained from the Aldrich Chemical Company and, if not specified, used without further purification. Al_2O_3 TLC plates and Al_2O_3 used for making Chromatotron plates were purchased from Fluka

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Chemical Company. Silica Gel TLC plates were purchased from Whatman and Silica Gel containing gypsum was purchased from EM Science. THF was distilled from sodium benzophenone ketyl before use.

Monomer Synthesis

Exo-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic Anhydride (2).[63] Furan (13.6 g, 0.20 mol) was added to maleic anhydride (19.3 g, 0.20 mol) suspended in diethyl ether (45 mL) at 0 °C. The reaction was accompanied by a mild and gradual evolution of heat. The reaction mixture was stirred overnight in order to complete the reaction. Hard, colorless crystals were produced. The crystals were isolated by filtration, washed with cold diethyl ether and dried to give the desired product (21.1 g). Yield: 63.6 %; mp 118 °C (Lit[31] 125 °C); ^{1}H NMR δ 6.56 (s, 2H), 5.45 (s, 2H), 3.19 (s, 2H); ^{13}C NMR δ 169.9, 137.0, 82.3, 48.7.

Exo-7-Oxabicyclo[2.2.1]hept-2-ene-5,6-dicarbinol (3).[17,20] A 250 mL, 3-neck oven dried flask was equipped with a pressure-equalizing dropping funnel and a reflux condenser.

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The reaction vessel was charged with $LiAlH_4$ (1.40 g, 38.0 mmol) in dry THF (10 mL). Anhydride **2** (3.15 g, 19.0 mmol) dissolved in dry THF (90 mL) was placed in the dropping funnel and added dropwise to the $LiAlH_4$ slurry. The solution was then allowed to stir overnight. Water (1 mL), NaOH (1 mL, 15 % solution) and water (1 mL) were then added slowly in sequence to destroy excess reagent and the mixture was filtered through Celite to remove inorganic solids. The filtrate was vacuum evaporated to yield a crude product. The crude product and the inorganic solids were combined in a Soxhlet extraction apparatus and extracted with methylene chloride for two days. The methylene chloride was removed and the remaining viscous oil was dried under vacuum to yield the product (1.63 g). Yield: 52 %. ^{1}H NMR δ 6.40(s, 2H), 4.70(s, 2H), 3.72(s,4H), 3.51(s, 2H), 1.94(m, 2H). ^{13}C NMR δ 135.6, 81.0, 62.2, 42.2.

Exo-5,6-Dimethoxymethyl-7-oxabicyclo [2.2.1]hept-2-ene (4).[17,18,20] A 100 mL, 3-neck flask which equipped with a pressure-equalizing dropping funnel, a water-cooled reflux condenser and a magnetic stir bar was charged with NaH (2.76 g, 60 % in mineral oil, 69.0 mmol) in dry THF (20 mL).

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Diol **3** (4.31 g, 27.6 mmol)was dissolved in dry THF (10 mL) and added dropwise through the dropping funnel. After complete addition of the diol, the solution was stirred for an additional 30 min to insure complete reaction. Methyl iodide (6.85 mL, 27.6 mmol) was then added slowly through the dropping funnel. After complete addition of the CH_3I, the solution was stirred for 30 min and water was added dropwise until no further bubbling occurred. The reaction solution was then poured into diethyl ether (50 mL) and filtered. The solvent was removed at reduced pressure to yield the desired product as a clear liquid (4.30 g). Yield: 84.6%. ^{1}H NMR δ 6.35 (s, 2H), 4.84 (s, 2H), 3.49-3.31(m, 10H), 1.94-1.85(m, 2H); ^{13}C NMR δ 135.2, 80.2, 71.8, 58.4, 39.6; EIMS, *m/z* 115(37), 85(14), 84(41), 71 (40), 69(37), 68($C_4H_4O^+$, 100), 55(16), 53(12).

2-Exo-Hydroxymethyl-3-exo-methoxymethyl-7-oxabicyclo [2.2.1] hept-5-ene (5).[18,20] Compound **3** (1.00 g, 6.4 mmol) in THF (10 mL) was added to NaH (0.15 g, 6.4 mmol) dispersed in THF (20 mL) at 0 °C under nitrogen. After 30 min, iodomethane (0.4 mL, 6.4 mmol) was added at 0 °C and the cold reaction mixture stirred for 30 min before warming to room

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temperature and stirring for 3 hours. After filtration, vacuum evaporation gave crude **5**. Purification by column chromatography (silica gel, ethyl acetate) gave pure product (0.51 g). Yield: 51 %; ^{1}H NMR δ 6.38 (m, 2H), 4.73 (s, 1H), 4.68 (s, 1H), 3.48-3.82 (m, 4H), 3.37 (s, 3H), 3.25(m, 1H), 1.80-2.10 (m, 2H); ^{13}C NMR δ 136.3, 135.7, 81.5, 81.2, 73.3, 62.7, 59.1, 42.9, 40.2; IR 3414, 1125, 1011 cm^{-1}.

1-Chloro-2-[2-(2-tosylethoxy)ethoxy]ethane (7a). 2-[2-(2-Chloroethoxy)ethoxy]ethanol (0.5 g, 2.9 mmol) and *p*-toluenesulfonyl chloride (0.31 g, 1.6 mmol) were introduced into a flask. The mixture was cooled in an ice bath and 5 N NaOH (0.46 mL, 2.3 mol) was added slowly. The mixture was stirred for 3 h. Another portion of *p*-toluenesulfonyl chloride (0.31 g, 1.6 mmol) was added. 5 N NaOH (0.31 g, 2.3 mmol) was again added slowly. The mixture was stirred in an ice bath for 4 h, then at room temperature overnight. A small amount of precipitate was produced. The solid was filtered and 50 mL petroleum ether (bp 60-70 °C) was added to the solution. The solution was washed thoroughly with distilled water and dried with Na_2SO_4 followed by filtration and distillation to give a yellow liquid. The product was

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purified by chromatotron (silica gel/EtOAc 3:1 hexane) to give a colorless liquid (0.89 g). Yield: 93 %; ^{1}H NMR δ 7.76 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 4.13 (t, J=8.0 Hz, 2H,), 3.69-3.57 (m, 10H), 2.41 (s, 3H); ^{13}C NMR δ 144.8, 133.0, 129.8, 71.4, 70.7, 70.6, 69.2, 68.7, 42.7, 21.6; IR 2890, 1601, 1116, 814, 753 cm^{-1}.

2-Exo-Methoxymethyl-3-exo-2-[2-(2-chloroethoxy) ethoxy]ethoxymethyl-7-oxabicyclo[2.2.1]hept-5-ene (6a).
A 50 mL 3-neck flask was flame dried under argon. Sodium hydride (57 mg, 2.18 mmol) was introduced followed by dry THF (1 mL). Monoether **5** (0.185 g, 1.09 mmol) in THF (5 mL) was then added at 0 °C. After mixing, compound **7a** (0.35 g, 1.09 mmol) in THF (5 mL) was added dropwise to the flask. The mixture was stirred for 3 h at 0 °C and stirred at room temperature for 12 h. The mixture was filtered through a silica pad. The solvent was then removed, yielding a yellow oil (0.5 g). The crude oil was then purified using a Chromatotron (silica gel/ethyl acetate 2:1 hexane) to give 0.16 g product. Yield: 46 %; ^{1}H NMR δ 6.32 (s, 2H), 4.81 (d, J=5.1 Hz, 2H), 3.77-3.27 (m, 19H), 1.94-1.85 (m, 2H);

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^{13}C NMR δ 135.5, 135.4, 80.6, 72.0, 71.4, 70.7, 70.6, 70.4, 58.8, 42.7, 39.8, 39.7; IR 2910, 1597, 1095, 667 cm^{-1}. A ^{13}C spectrum of the purified material is provided as Figure 15, since elemental analysis was not satisfactory.

Bis [2-(2-bromoethoxy)ethyl] Ether (7b).[67] To a refluxing solution of tetraethylene glycol (freshly distilled, 19.4 g, 0.10 mol) and distilled pyridine (18.2 g, 0.23 mol) was added thionyl bromide (47.0 g, 0.23 mol) over 3 hour. After stirring for 16 hours at room temperature, the mixture was cooled and treated with 5% NaOH, washed with H_2O, and extracted with hexane. The yellow solution was dried over with Na_2SO_4. After the solvent was evaporated, a brown oil remained. Distillation yields the product as a pale yellow oil (13.3 g). Yield: 41.1%; bp:160 °C / 3 mm Hg (Lit[67] 117 °C/0.05 mmHg); ^1H NMR δ 3.79 (m, 4H), 3.65 (d, J= 2.1 Hz, 8H), 3.45 (t, J= 6.0 Hz, 4H); ^{13}C NMR δ 69.4, 69.2, 68.3, 68.1.

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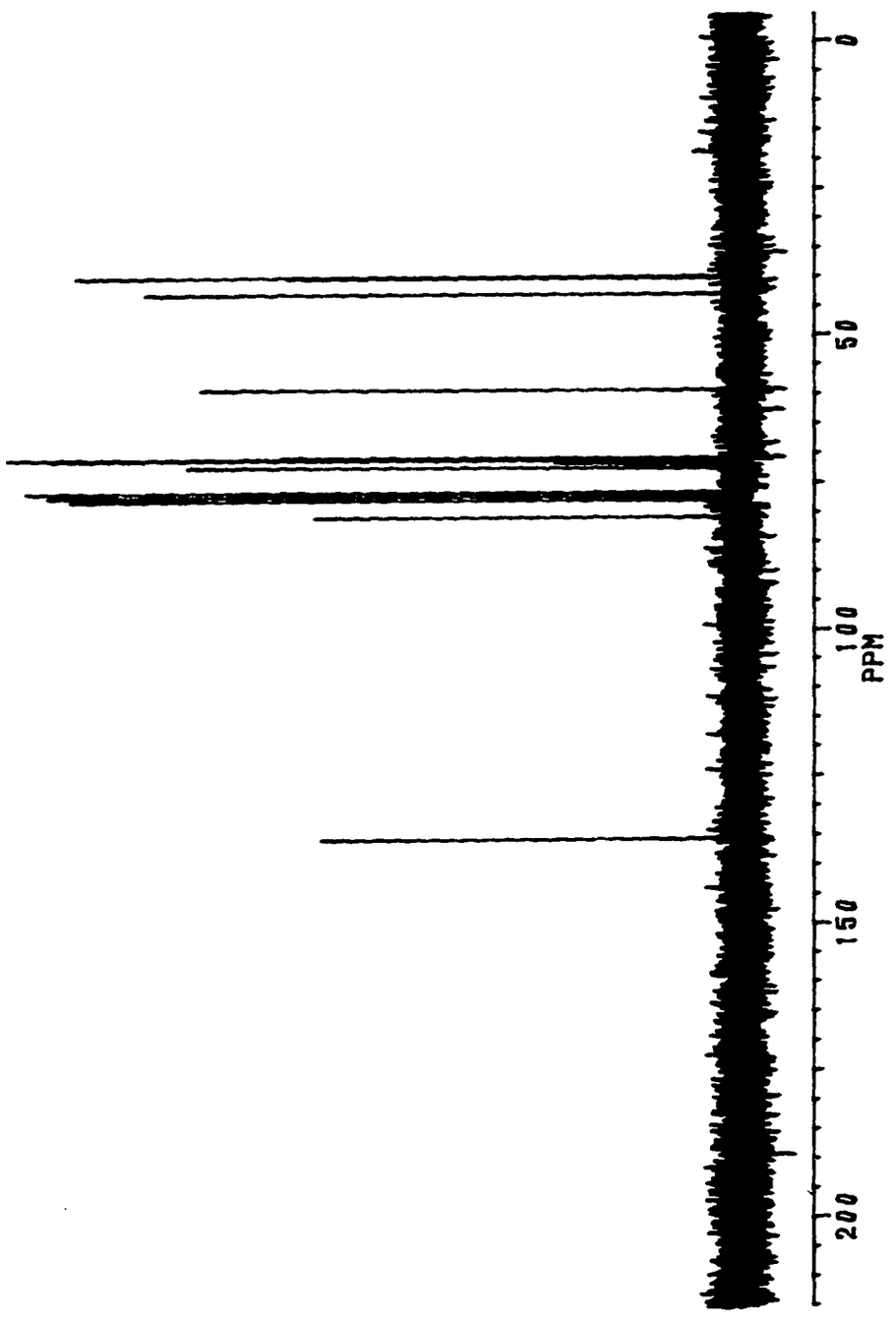

Figure 15: ^{13}C NMR spectra of 2-exo-methoxymethyl-3-exo-2-[2-(2-chloro-ethoxy)ethoxy]ethoxymethyl-7-oxabicyclo[2.2.1]hept-5-ene (**6a**).

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2-*Exo*-methoxymethyl-3-*exo*-2[2-(2-trimethylammoniumethoxy) ethoxy]ethoxymethyl-7-oxabicyclo[2.2.1]hept-5-ene chloride (1). Compound **6a** (0.50 g, 1.56 mmol) dissolved in anhydrous methanol (5 mL) was introduced to a Schlenk reaction tube. Trimethylamine (0.73 mL, 7.8 mmol) was cooled in a dry ice-acetone bath and was added to the solution via a syringe under argon. The gas outlet was then closed. The solution was allowed to stir below 50 °C for 24 h. The mixture was cooled to room temperature before the excess amine and methanol were evaporated. To the mixture, $CHCl_3$ (2 mL) and H_2O (2 mL) were added. The solution was shaken to allow the amine salt to dissolve in aqueous layer. The two layers were separated. The aqueous layer was dried under vacuum to give product (0.34 g). Yield: 67 %; ^1H NMR (D_2O) δ 6.24 (s, 2H), 4.60(d, J=8.1 Hz, 2H), 3.61-3.17(m, 19H), 2.98 (s, 9H), 1.82 (m, 2H). ^{13}C NMR (D_2O, 3-(trimethylsilyl)-propanesulfonic acid as reference) δ 137.7, 136.6, 83.0, 74.3, 72.6, 71.7, 68.0, 66.9, 60.6, 56.3, 41.3. IR 2900, 1610, 1190, 1120 cm^{-1}. A ^{13}C NMR is provided as Figure 16, since elemental analysis was not satisfactory.

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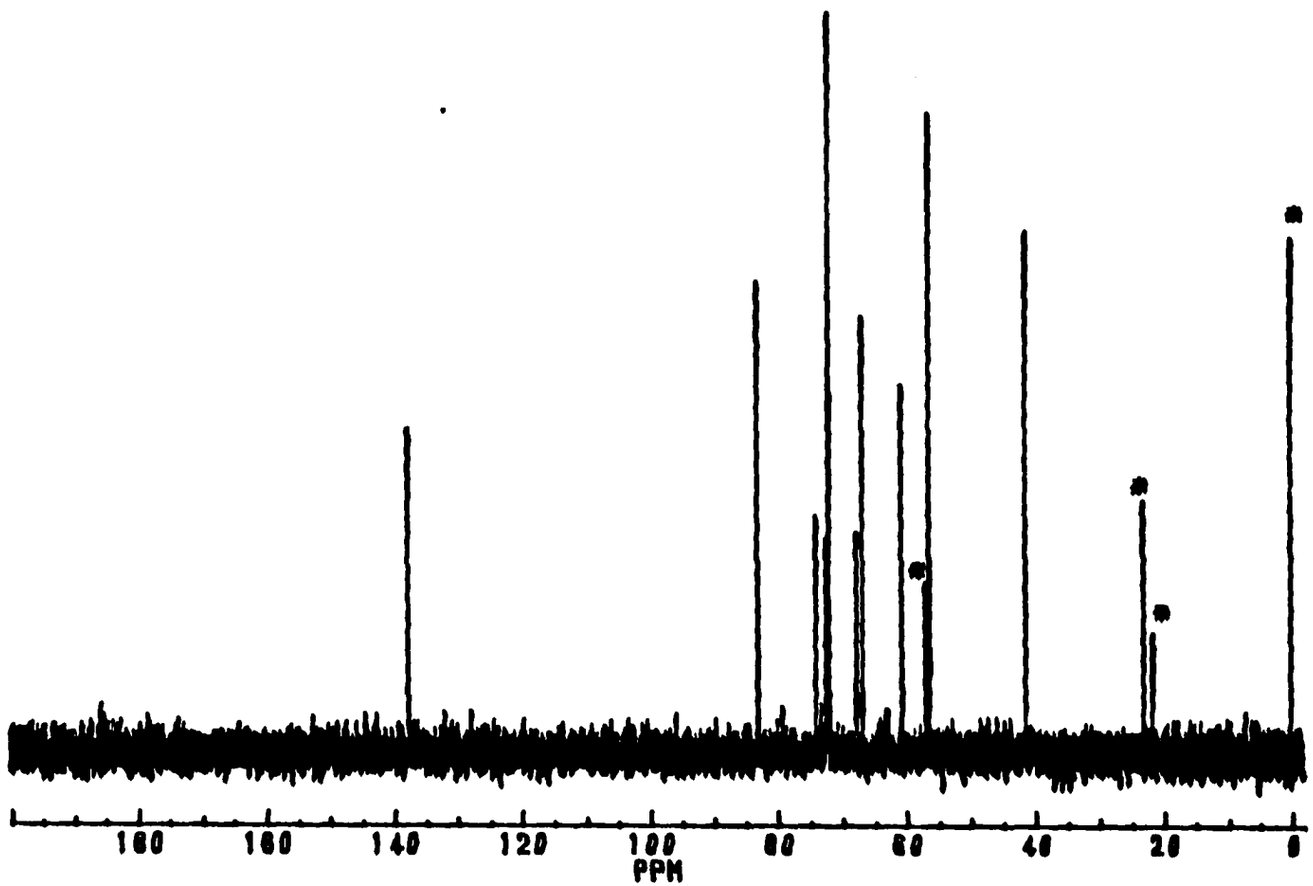

Figure 16: ^{13}C NMR spectra of 2-*exo*-methoxymethyl-3-*exo*-2-[2-(2-trimethylammoniumethoxy)ethoxy]ethoxymethyl-7-oxabicyclo [2.2.1]hept-5-ene chloride (**1**).
Note: * reference peak.

Polymer synthesis

Polymerization of exo-5,6-dimethoxymethyl-7-oxabicyclo[2.2.1]hept-2-ene (4).[17] The procedure presented here is typical of all of the aqueous $RuCl_3$ catalyzed reactions. A reaction tube was charged with $RuCl_3$ (1.34 mg, 6.46 mmol) and 0.6 mL distilled and degassed water. Monomer **4** (100 mg, 0.543 mmol) was added via syringe. Nitrogen was bubbled through the solution for 5 min and the solution was degassed under vacuum. The solution was then heated to 60 °C. After 30 min the first polymer precipitate appears. The reaction mixture was heated for 24 h. The catalyst solution was removed via syringe and the polymer was washed 7-8 times with 2 mL portions of water and dried under vacuum to yield 100 mg of **poly-4** (100 % yield). ^{1}H NMR δ 5.72, 5.51, 4.20, 3.45, 3.34, 2.26; ^{13}C NMR δ 132.9, 82.0, 70.5, 58.9, 47.0; IR 2900, 1724, 1191 cm^{-1}.

Poly(2). ^{1}H NMR (D_2O) δ 5.85, 5.56, 5.12, 3.01, ^{13}C NMR (D_2O, 3-(trimethylsilyl)-propanesulfonic acid as reference) δ 174.5, 129.4, 79.9, 75.2, 54.8; IR 3195, 2959, 1513 cm^{-1}.

Poly(6a). ^{1}H NMR δ 5.70, 5.50, 4.20, 3.80-3.20, 2.25; IR 2881, 1724, 1189, 667 cm^{-1}.

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Poly(1). ^{1}H NMR δ 5.71, 5.60, 5.50, 4.20, 3.93-3.18, 2.92, 2.23; IR 2916, 1754, 1185, 1122 cm^{-1}.

Polymerization of (4) in the Presence of Salts

The procedure presented here is typical of all of the aqueous $RuCl_3$ catalyzed reactions in the presence of various salts. A reaction tube was charged with $RuCl_3$ (1.34 mg, 6.46 mmol), salt (at a variety of concentrations) and 0.6 mL distilled and degassed water. Monomer **4** (100 mg, 0.543 mmol) was added via syringe. Nitrogen was bubbled through the solution for 5 min and the solution was degassed under vacuum for 30 min. The solution was then heated to 60 °C. After 30 min the first polymer precipitate was noticed. The reaction mixture was heated for 24 h. The catalyst solution was removed via a syringe and the polymer was washed with 7-8, 2 mL portions of water and dried under vacuum to yield **poly-4** (96 mg). Yields ranged from 54% to 100%. (See Table 1).

Copolymerization

A reaction tube was charged with $RuCl_3$ (1.59 mg, 7.66 mmol) and distilled and degassed water (0.6 mL). Monomers

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with different molar ratios were introduced via a syringe. Nitrogen was bubbled through the solution for 5 min and the solution was degassed under a weak vacuum for 30 min. The solution was then heated to 60 °C for 24 h. The catalyst solution was removed via a syringe. The copolymer was washed with water and dried under vacuum. Yields ranged from 47.3% to 66.9% when the molar ratio of **4** and **6a** changed from 1:2 to 3:1 (Table 2).

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CHAPTER 3 CHARACTERIZATION

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Although polymer molecules have the same repeat unit, these molecules have a range of molecular weights. Characterization of a polymer is important, especially when it is used as a material. Solubilities, structures, molecular weights, and thermal properties for the polymers synthesized in this work were studied. Biological testing of the polymers is still pending.

Solubilities of Polymers

The solubility of a polymer can be a deciding factor in its end use. In this work, the material is designed for biomedical applications, so the solubility in water is an important issue.

It was found that **poly-2** dissolved in hot water or dilute NaOH solution and that a transparent film formed after the polymer was completely dry. **Poly-2** was also slightly soluble in DMF, DMSO, and THF.

Poly-4 partially dissolved in $CHCl_3$. However, the solubility was not high. It could be cast into a film from a chloroform solution. **Poly-4** was slightly soluble in DMF, DMSO, and THF. It was previously reported that **Poly-4** could be purified by dissolution in chloroform and precipitation from a large excess of pentane.[22] This purification method

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did not work or **poly-4** because of its poor solubility in $CHCl_3$.

Poly-2-*co*-4 dissolved in THF. This was convenient for molecular weight measurements.

It was found that 0.04 g of **Poly-6a** dissolved in 5 mL of warm $CHCl_3$, or warm THF after three days and the solutions could be cast into films. Only swelling was observed in warm H_2O. Samples for GPC analysis were made in concentrations of 0.1-0.2 % by weight in THF.

Poly-1, the target polyelectrolyte, was designed to dissolve in water. Surprisingly, it only slightly dissolved in water. Instead, it acted more like a polyelectrolyte hydrogel. The polymer swelled with water to 70 times its dry weight. High molecular weight, hydrophobicity of the main chain, and crosslinking of the unsaturated portions could contribute to this gel effect.

Polymer Structure

The *cis/trans* double bond ratio in these unsaturated polymers can be determined directly from the ^1H NMR spectra.

The ^1H NMR spectrum of **Poly-2** and **Poly-4** are consistent with the unsaturated polymer backbone of ROMP polymers.

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Both *cis* and *trans* resonances are observed for the olefinic protons and the allylic protons. The backbone double bonds are predominately *trans* (67 %), as determined by integration of the olefin region of the ^{1}H NMR spectrum of **poly-4**, but are predominately cis (42 %) in **poly-2**. The ^{1}H NMR spectra of **poly-6a** and **poly-1** indicate about 50 % of the *trans* isomer in each of **poly-6a** and in **poly-1**.

^{13}C NMR allowed identification of isomers. Four possible different isomeric diads (see Figure 14) exist in symmetrically substituted monomers. In non-symmetric monomers, 32 isomers are possible. Due to their low solubilities, the NMR spectra of these isomers could not be measured.

Gel Permeation Chromatography

The molecular weights were determined by gel permeation chromatography (GPC). The molecular weights and polydispersities of **poly-4**, **poly-6a**, **poly-4-*co*-6a** obtained under various conditions are listed in Table 3.

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Polymer[a]	Mn
Poly-6a[b]	5.62×10^5
Poly-4-co-6a[b]	
1:1	7.08×10^5
1:2	6.03×10^5
2:1	1.17×10^6
3:1	1.62×10^6
Poly-4[b]	2.63×10^6
Poly-4[c]	1.26×10^6
Poly-4[d]	1.05×10^6
Poly-4[e]	1.78×10^5
Poly-4[f]	5.13×10^5
Poly-4[g]	2.63×10^5
Poly-4[h]	3.71×10^6

Table 3: Molecular weights of some of the polymers.
Note:a) Molecular weights given relative to polystyrene standards. Polydispersities in the range of 1 to 1.2.
b) made from water.
c) made from NaCl solution, $[M]_{NaCl}$ =0.071M
d) made from CH_3COOH solution, $[M]_{CH_3COOH}$ =0.067 M
e) made from LiCl solution, $[M]_{LiCl}$ = 0.302 M
f) made from $Me_4N^+Cl^-$ solution, $[M]_{Me_4N^+Cl^-}$ = 0.113-0.9 M
g) made from $Na_2B_{12}H_{12}$ solution, $[M]_{Na_2B_{12}H_{12}}$ = 0.225-0.9 M
h) made from EtOH

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Classical ROMP systems typically display molecular weight distributions of 2.0 or greater.[62] Polymer with narrow molecular weight distributions are usually obtained from living polymerization systems.[63]

A narrow molecular weight distribution was found in this work. The polydispersity index of **poly-4** is close to 1. It has been reported to be about 2 by Lu[20] and about 2.5 by Feast and Harrison.[22]

High molecular weights were unexpected because the polymer tends to precipitate as it is formed. In most cases, low M_w materials are obtained if the polymer precipitates. One possible explanation for the high molecular weight might be the solubility of the 7-oxanorbornene polymers in their respective monomers. The accepted mechanism for formation of the polymers is the incorporation of monomers from the surrounding solution after the initial polymers precipitate. The reactive polymer end-groups then continue to propagate within the interior of monomer-swelled polymer.[17]

For biomedical applications, high molecular weights may not be desirable. Modest control over the molecular weight of the polymer could be achieved by adding chain transfer

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agents.[21] In metathesis polymerizations, acyclic olefins can act as chain transfer agents by end-capping the growing polymer chain and forming a new metal carbene. Another way to control molecular weights is to choose different catalysts.[17] A third option to control the molecular weight is the solvent. It was reported that the molecular weight increases and polydispersity decreases when water instead of water/ethanol was used as solvent.[18] Water was chosen as solvent in this work because a low PDI was desired. In the future, all of the factors above should be considered when the polymers are designed, in order to gain an understanding of the effect of molecular weight on membrane properties.

Although it is possible to use GPC to obtain information about the molecular weight of polyelectrolytes by using THF solution with up to 10 % water, this technique has been seldom used because of complications arising from charge and related effects. Assuming that **poly-1** should polymerize to a similar degree as **poly-4** in the presence of various charged groups, molecular weight in the 10^6 daltons range could be expected for **poly-1**.

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Thermal Properties

Thermal properties are important characterizing data for polymers if they are intended to be used as materials. Here, Differential Scanning Calorimetry (DSC), which shows phase changes and their enthalpies, and Thermogravimetric Analysis (TGA), which measures mass changes upon heating, are used.

DSC is the dominant technique for the thermal analytical investigation of polymeric materials. In DSC, the energy absorbed or evolved by the sample is compensated by adding or subtracting an equivalent amount of electrical energy to a heater located in the sample holder. In TGA, the mass of the sample is recorded continuously while the temperature is increased. Weight losses occur when volatiles absorbed by the polymer are driven off, or when degradation of the polymer occurs with the formation of volatile products.

DSC data for the polymers and copolymers were described here appear in Table 4.

The crystalline melting point, T_m, is the temperature at which the last trace of crystallinity disappears under equilibrium conditions. **Poly-2,** the only 7-oxanorbornene

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polymer which show signs of crystallinity, displays a T_m at *ca.* 200 °C, determined by differential scanning calorimetry (DSC) (Figure 15). A decomposition peak appeared at 286 °C. At this temperature, decarboxylation probably occurred.

Poly-4 began to decompose at 290 °C (Figure 16). A peak at 20 °C was observed with DSC. It was found that after cooling the polymer at 15 °C for 10 hours, the peak moved to a higher temperature, 34.2 °C. This peak was assigned to cold crystallinization.

As a result of the many possible isomeric forms of poly(7-oxanorbornene), these materials are, in general, highly amorphous. DSC results showed that **poly-6a** undergoes an exothermic reaction between 300 and 350 °C under nitrogen Glass transitions (T_g) were observed in **poly-6a** and **poly-1** with DSC. They appear at 191.8 °C (Figure 17) and 192.1 °C (Figure 18), respectively. No T_m was observed before the onset of the exotherm. Trace amounts of $RuCl_3$ may have catalyzed decomposition of the polymer sample prior to or around the melting point temperature. **Poly-1** began to decompose at 309 °C.

For the copolymers, when the molar ratio of monomer **4** and **6a** are 3:1, 2:1, 1:1 and 1:2, the T_d are 294, 278, 274

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and 290 °C. A T_m was observed at 195 °C for the **poly-4-*co*-6a** at the molar ratio 1:1 (Figure 19).

The onset temperatures for substantial mass loss (T_d) for the polymers under a nitrogen atmosphere were determined by TGA to fall in the range of 245 to 378 °C.

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Polymer	T_m (°C)	T_g(°C)[a]	T_d (°C)[b]
Poly-1		192	309
Poly-2	200		286
Poly-4			290
Poly-6a		192	
Poly-4-*co*-6a			
1:1	195		274
1:2			290
2:1			278
3:1			294

Table 4. DSC results

a. T_g is the same upon heating and cooling.
b. onset.

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Conclusion

All the polymers synthesized in this work contained both *cis* and *trans* isomers according to NMR. Molecular weight of the polymersand copolymer ranged from 1.17×10^5 to 3.71×10^6 as measured by GPC. Thermal properties of the polymers were measured by DSC and TGA. The results showed that the melting point of **poly-2** was 200 °C and **poly-4-*co*-6a** was 195 °C. **Poly-1** an **poly-6a** showed T_g at 192.1 and 191.8 °C. The polymer decomposition onset were between 274 to 309 °C. The thermal stabilities showed that they are stable enough to be used in microencapsulation development.

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Experimental

^{1}H NMR spectra at 200 MHz and ^{13}C NMR spectra at 50 MHz were recorded on Bruker AM 200 instrument in $CDCl_3$ unless indicated otherwise. Chemical shifts were referenced to TMS or to residual protons on the deuterated solvents.

IR spectra were recorded on a Nicolet Impact 410 spectrometer. Samples were prepared by casting films onto ATR crystal window (ZnSe).

Gel permeation chromatography (GPC) was performed connecting PLgel 5 μm 10^5A and PLgel 5 μm 10^4A column with THF as a solvent. The polymer was detected with a spectroflow variable wavelength, absorbance detector. The wavelength was set to 220 nm. Samples for analysis were prepared as 0.1-0.2 % by weight in THF. The molecular weights were referenced to narrow dispersity polystyrene samples ranging from M_n = 580 to 8,500,000.

Thermal analysis was performed on a Perkin Elmer DSC-7 and TGA-7 instruments under N_2. Indium and zinc were used to calibrate the DSC. Scan rates are provided in the figures.

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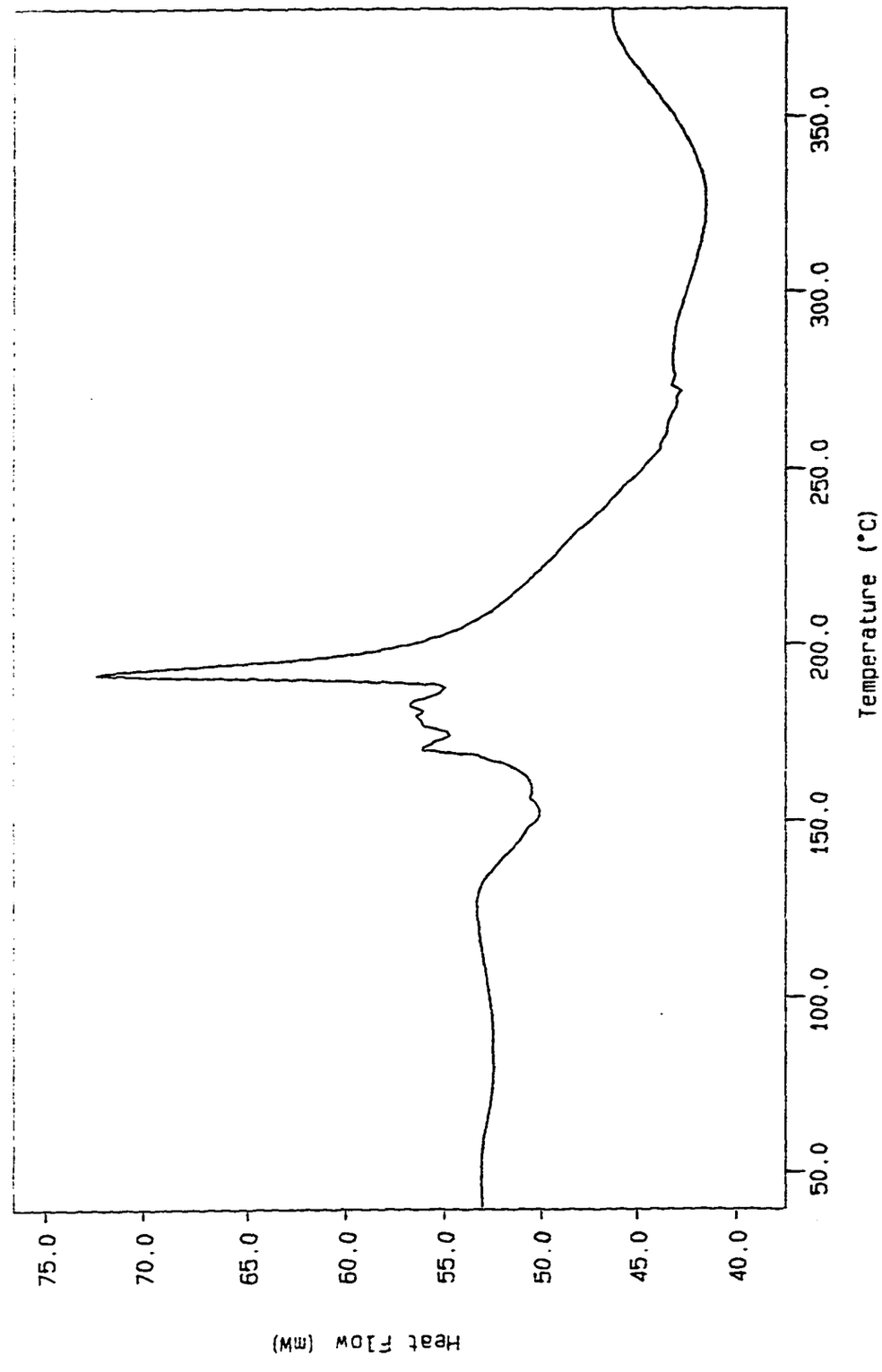

Figure 17. The DSC thermogram of **poly-2**, measured at a scan rate of 20 °C/minute.

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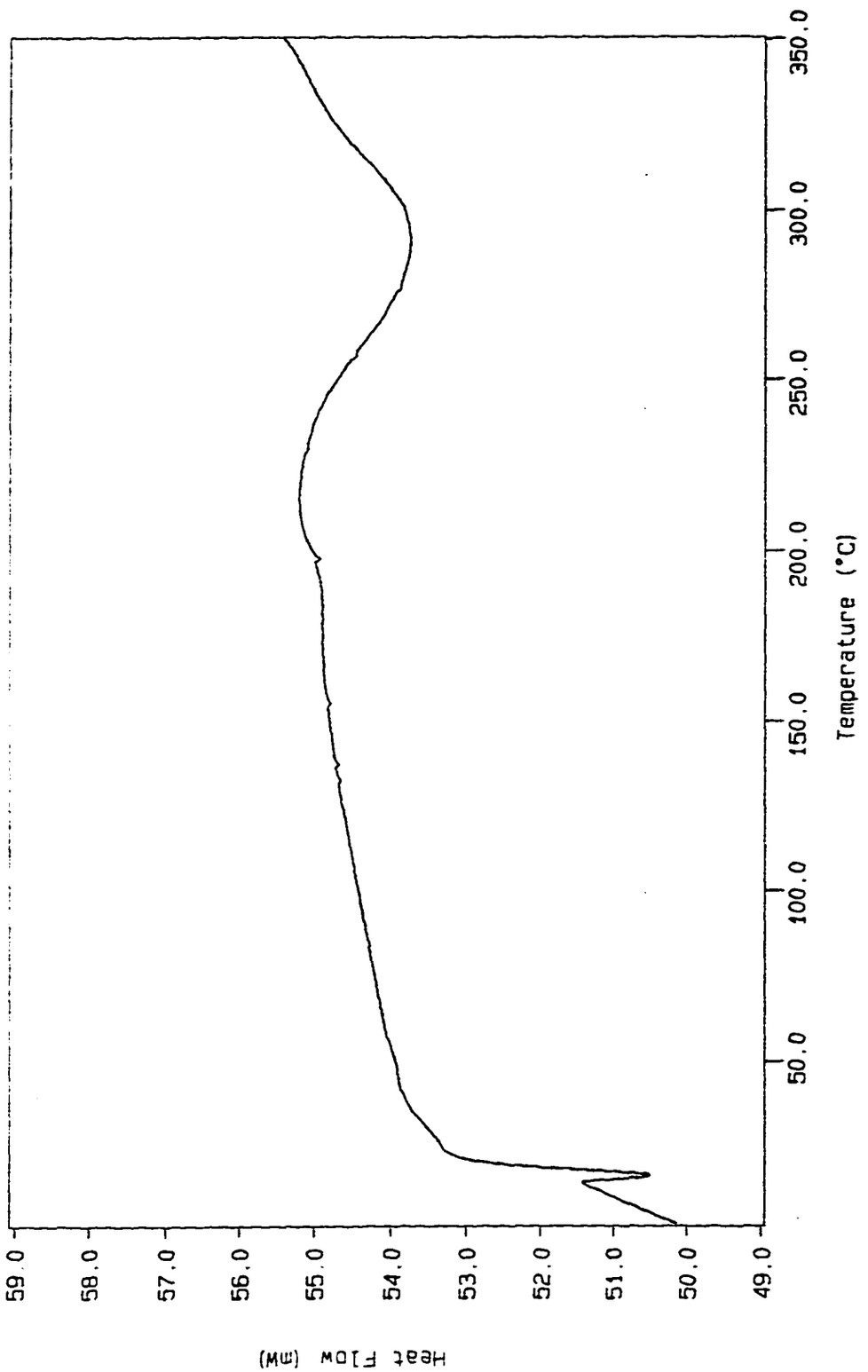

Figure 18. The DSC thermogram of **poly-4**, measured at a scan rate of 20 °C/minute.

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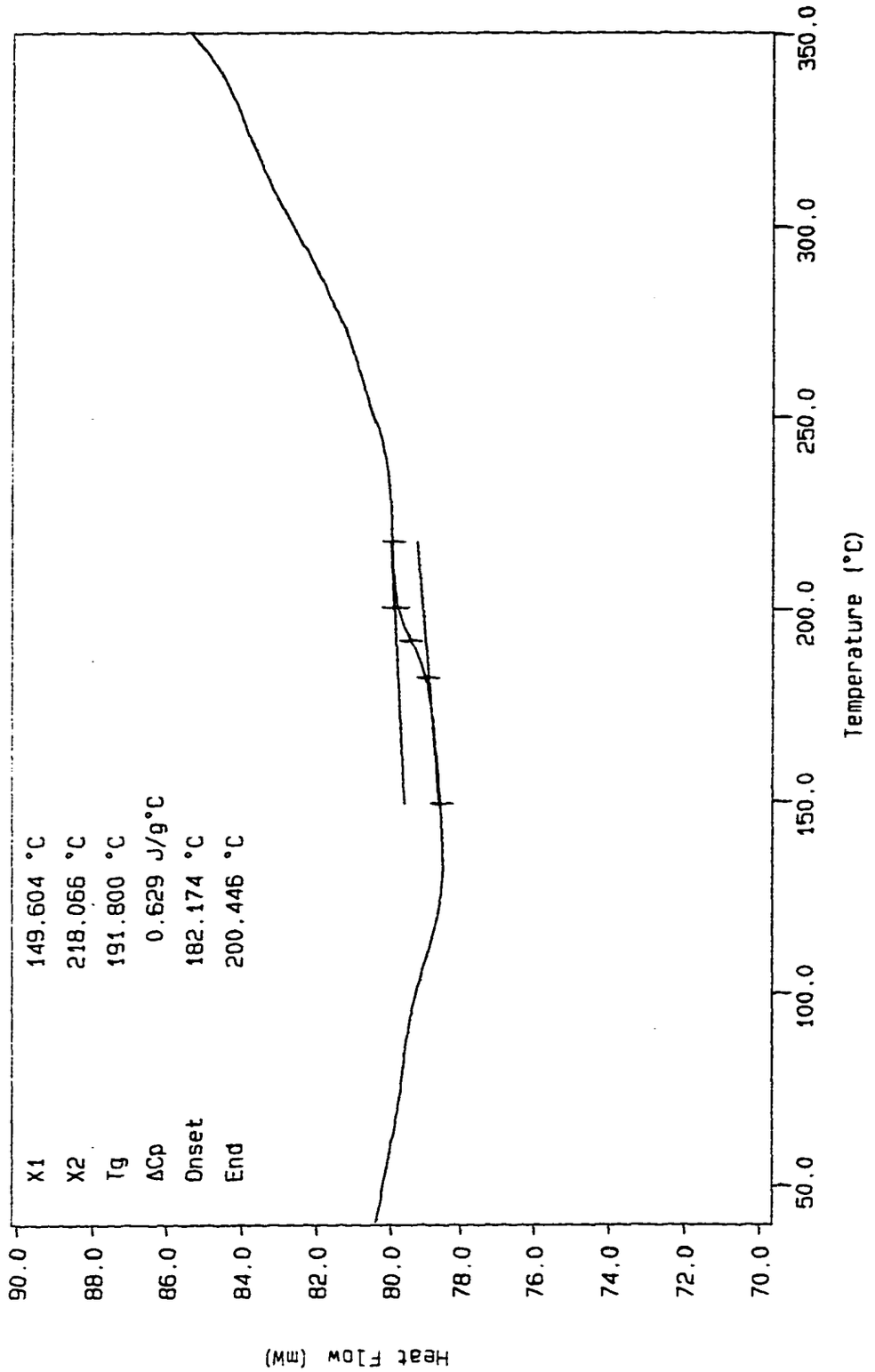

Figure 19. The DSC thermogram of **poly-6a**, measured at a scan rate of 20 °C/minute.

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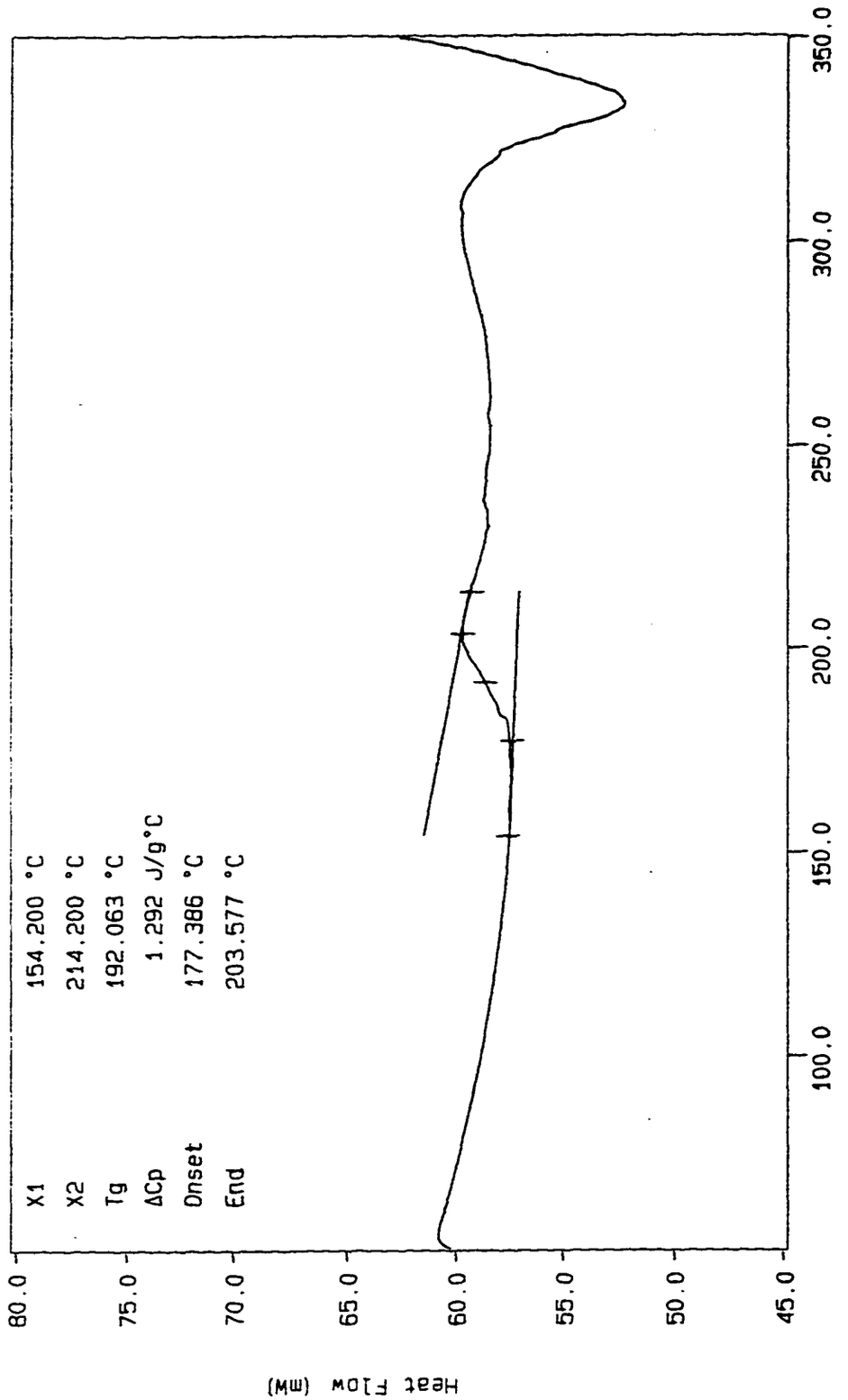

Figure 20. The DSC thermogram of **poly-1**, measured at a scan rate of 20 °C/minute.

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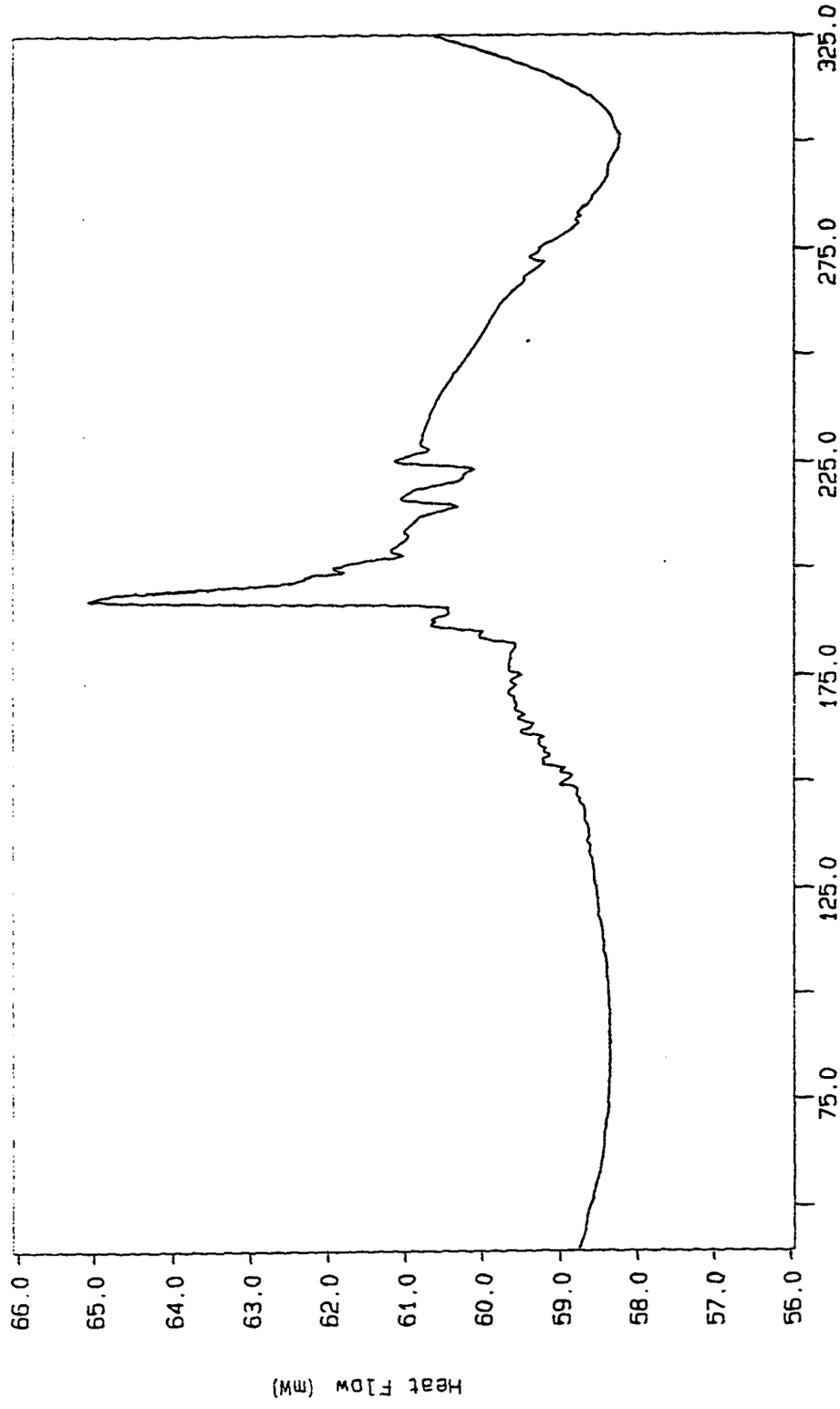

Figure 21. The DSC thermogram of **poly-4-co-6a** at 1:1 ratio, measured at a scan rate of 20 °C/minute.

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PART II. DEVELOPMENT OF A POLYMER LABORATORY FOR UNDERGRADUATE STUDENTS

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Introduction and Purpose

According to L. J. Mathias,[71] since most industrial B.S. chemists will spend a majority of time at the bench during their careers, and 35 to 65 % of them will be working with monomers and polymers, chemistry students need polymer laboratory experience. If both synthetic and characterization experience are provided to the student in the polymer lab at MTSU, the student will have the opportunity to refine and expand his/her laboratory and instrumental skills, which will be useful throughout his/her chemical career.

At MTSU, polymer chemistry is an elective course for advanced students whose major or minor is chemistry. It has been taught since 1975, and a separate polymer chemistry lab course has been offered since Spring 1996.

The purpose of the lab is to supplement the theoretical material by providing a practical demonstration of scientific principles and to educate the student in the techniques particular to the field. This laboratory course fulfills part of the requirements for an ACS-credited Bachelor of Science degree in Chemistry.

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The laboratory curriculum includes polymer syntheses and polymer property determinations. Typically, nine polymer experiments were completed during the semester. They were based on a schedule of eleven 4-hour laboratory periods. Most of the experiments were intended to be performed by a pair of students. A lab report was required after each experiment. Each of the experiments were written by Dr. Friedli or taken from the literature[72] under the presumption that the students were aware of the fundamentals of physical and organic chemistry. All of the experiments presented were tested and revised by the author. As an observer of and assistant for the Spring 1996 Laboratory, the author prepared notes for the future teaching assistants, since there will be a different teaching assistant each semester.

This course has been offered for two semesters. There were three students enrolled in the first semester and five students enrolled in the second semester.

For the purpose of determining the students' attitude toward this course, a qualitative survey was distributed and completed by the students after the class.

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Introduction to the Polymer Experiments and Notes for Teaching Assistants

The experiments were assembled in the home-written manual lab book, "Making, Measuring, and Manipulating Macromolecules". For more information about the content of the laboratories, this manual should be consulted.

Since the students were advanced (juniors or seniors), the introduction and descriptions of procedures were kept brief in most experiments. In order to teach the students to write scientific papers, questions were assigned in each experiment, and discussion of the results was required. There are two types of lab report format provided, a short and a long report. The format of the short report was based on a typical organic lab write-up, while the long reports were written in the style of a journal article. Thus, the students were exposed to scientific journal writing, especially polymer journals.

As part of this project, brief guides to the experiments and brief notes for the graduate teaching assistant (GTA) were written. They were written in the present tense as instructions for future GTAs.

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Experiment 1. Introduction to Polymer Properties[73]

This experiment introduces students to physical properties of polymers and teaches them how to use these properties to identify a polymer. The experiment involves measurement of solubility and density, which are classical methods, and IR and NMR spectroscopy, which are more modern methods, to determine the identity of polymers.

A flow chart for the identification of a polymer from solubility, a flow chart for the density determination of selected polymers, densities and approximate molecular weights for some common solvents at room temperature, characteristic infrared absorption frequencies, characteristic proton chemical shifts and carbon-13 NMR chemical shifts were provided in the manual. A list of possible unknown polymer samples were also given to each student.

Students were encouraged to find useful information from reference books and handbooks, such as Polymer Handbook, CRC, ASTM Stardard methods, and the Aldrich catalog.

To prepare the experiment, the GTA should choose the polymer samples which are composed of large particles or films for the students to use in the determination of polymer

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density and should not choose samples containing entrapped bubbles.

During the experiment, the GTA should direct students to make films for IR on a AgCl plate or glass (for water soluble polymers) once a suitable solvent is found.

Experiment **2.** *Synthesis and Molecular Weight of Poly(vinyl alcohol)* [74]

This experiment introduces functional group reactions on existing polymers. It can be done conveniently with polyvinyl acetate.

Before providing this experimental procedure to the students, several procedures were tested. Instead of asking the students to make polyvinyl acetate themselves, commercial polyvinyl acetate was provided to allow the experiments to be completed within the lab period and to avoid doing two radical polymerization reactions.

Both H^+ and OH^- can catalyze hydrolysis of polyvinyl acetate to polyvinyl alcohol. However, it was found that under acidic conditions, it took much longer (6 to 8 hours) and the yield was low.

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Before lab, the GTA must prepare polyvinyl acetate, methanol and sodium before the class and review the safety procedures with the students for handling sodium metal.

In the second part of this experiment, the oldest and most popular method of determining molecular weight, viscometry, was introduced. An Ubbelohde viscometer was chosen because dilutions can be made in the viscometer.

No special chemicals need to be prepared in this part. However, the GTA should measure the minimum and maximum volume of the viscometer. Since the t/t_0 is desirable in the range of 1.2-1.5, experimentation is necessary to find out a proper starting concentration for an unknown sample.

Experiment ***3****. Thermogravimetric Analysis* [75-77]

Experiment ***4****. Differential Scanning Calorimetry* [78]

Experiment ***5****. Dynamic Mechanical Analysis* [79]

These three experiments involved measurement of thermal properties of polymers. In these experiments, students used TGA to analyze the composites of hybrid materials, DSC to compare polyethylene terephthalate (PET) samples from different parts of Coca-Cola bottle, and DMA to observe

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stress/strain curve of pencil leads, dynamic viscosity of Silly Putty and Cookie dough.

Polymer samples for thermal analysis need to be free from monomer, water, solvents or other impurities. Most of them are available from a grocery store, or from industry. The GTA should also prepare two polysiloxanes from trimethoxypropysilane and ethyltrimethoxysilane. This can be done as follows: (1) for acid-catalyzed hydrolysis, add 0.01 M HCl to 15.0 mL silane/ethanol (1:1) solution until the pH is 3 and stir for 2 hours. A vacuum oven is used to completely dry the samples. (2) for base-catalyzed hydrolysis, add 0.01 M NH_4OH to 15.0 mL silane/ethanol (1:1) solution until the pH is 10 and stir it for 2 hours. Put the sol-gel in the vacuum oven until it is completely dry.

Prior to lab period, the GTA needs to calibrate the DSC with indium and zinc metal and clean the oven by heating it to 600 °C for 10 minutes. The TGA is cleaned by heating the sample pan to 1000 °C.

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Experiment ***6.*** *Structure/Property Correlations in Polyurethane Foams* [73]

In this experiment, prepolymer is provided to the students to make semi-rigid foams and minimize contact with the toxic TDI. Thermal property measurements by DSC, TGA and DMA are required. This helps students review what they did in Experiments **3**, **4**, and **5**. Densities of the foam are also measured in this experiment and the microstructure of the foam is observed under a microscope.

Before lab, the GTA should provide microscope slides, microscope lens paper, knife, razor, blade, and the following chemicals: toluene diisocyanate, castor oil, polyethylene glycol (MW = 400), diethylaminoethanol(DEAE), triethylamine(TEA), buffered DEAE (35 mg DEAE + 16.6 mL conc. HCl + 33 mL H_2O), L-520 (Union Carbide Silicone Surfactant), glycol and glycerol. These reagents are dispersed from dropper bottles.

Since toluene diisocyanate(TDI) is extremely toxic, the prepolymer is made by the GTA. The prepolymer is made immediately before class. The modified literature procedure[73] should be carried out in a fume hood:

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Introduce toluene diisocyanate (55 g) into a three-neck flask. Raise the temperature to 55 °C. While stirring, dropwise add the mixture of castor oil (42.5 g) and polyethylene glycol (15 g, MW = 400) to the flask through a separatory funnel. Maintain the reaction temperature below 70 °C for 1 hour.

Experiment **7.** *Introduction to Polymer Synthesis*

This introductory experiment is a survey of polymer synthesis which consists of three short syntheses: Bakelite [80] (thermoset polymer formed by phenol-formaldehyde), Nylon Rope Trick [81] (condensation polymerization, interfacial polymerization of 1,6-hexane diamine and adipoyl chloride), and slime[82] (crosslinking of polyvinyl alcohol and sodium borate). These experiments were not only interesting, but helped students thoroughly understand the concepts about a polymer and its polymerization that they learned in classroom through demonstrations.

Before lab, the GTA should provide the following chemicals and supplies:

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a. Bakelite: phenol, formaldehyde(37 %), ammonium hydroxide, acetic acid, disposable test tubes, pipets, heaters, wooden applicators.

b. Nylon 66: 1,6-hexanediamine 5 % aq, adipoyl chloride 5 % cyclohexane solution, NaOH 20 % aq, beakers, spatula, copper wire.

c. Slime: 4 % aqueous polyvinyl alcohol, (prepare by adding PVA powder to boiling water stirred in a large Erlenmeyer flask), 4 % aqueous $Na_2B_4O_7.10\ H_2O$, food coloring (for fun), wooden applicators, beakers.

Experiment 8. Radical Chain Copolymerization of Styrene and Methyl Methacrylate[73]

This experiment introduces radical mechanisms and reactivity ratios. In this experiment, students copolymerize styrene and methyl methacrylate in an oxygen-free atmosphere. Instead of using Kontes tubes, students uses ordinary test tubes and rubber septa. This was a two-week experiment. During the second part, students determined the composition of copolymer they made by UV spectroscopy using the 262 nm absorption of the phenyl chromophore of the styryl repeat unit.

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The GTA must prepare styrene and methyl methacrylate before the class. Because these two monomers contain inhibitors, they are prepared as follows: styrene and methyl methacrylate were washed with 10 % NaOH three times and with deionized water several times until it is neutral and dried with Na_2SO_4. The monomers are distilled right before the polymerization. Styrene is distilled under nitrogen at a pressure of 20 mm Hg (b.p. 40-43 °C). Methyl methacrylate is distilled at 60 mm Hg (b.p. 33-35 °C). As a inhibitor, cuprous chloride is added during the distillation.

Experiment 9. Electronic Effects in Polydiacetylene [83]

The last experiment is a fun and relatively easy way to end the semester. Polydiacetylene consists of a highly conjugated backbone. It changes color from blue to red or yellow, with temperature, pH, solvent, mechanical stress, and light because of electronic effects.

Before lab, the GTA must provide the following chemicals and supplies for this experiment:
5,7-Dodecadiyn-1,2-diol bis(butoxycarbonylmethylurethane) (4BCMU)-ethanol solution (0.1 g in 5 ml ethanol), ethanol, hexane, CH_2Cl_2, chlorobenzene, 0.2 M KOH in ethanol, 0.01 M

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HCl, 0.01 M KOH, saturated Br_2 in H_2O, filter paper, heat gun, UV lamp, tubes, sticks, cover slide, and pipettes.

Other experiments, such as sol-gel preparation of silica gel sensors[84] and polyoxymethylene synthesis[73] were also tested as backup experiments in the event of equipment breakdown.

Survey Results

A survey was conducted at the end of the course by the lecture of the polymer course. And the results are illustrated in Table 4.

The students' responses were anonymous and the students understood that the survey would not affect their grades. A total of 7 surveys were collected. From the Table, more than 86 % of the students thought that the lab helped them understand material covered in class, made polymers seem more relevant to everyday life, and expanded their experimental techniques. All of the students who took the lab course believed that the lab expanded their instrumental skills and helped them learn more about polymers. Seventy- two percent of the students thought that the polymer lab expanded their wet experiment skills. Eighty-six percent of the students felt that the handouts were

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	Agree	Not sure	Disagree
The lab helps me understand material covered in class	6	1	0
The lab made polymers seem more relevant to my everyday life	6	1	0
The lab expanded my wet experimental skills	5	2	0
The lab expanded my instrumental skills	7	0	0
I understand more about polymers because of the polymer synthesis experiments	7	0	0
I understand more about polymers because of the polymer characterization experiments	7	0	0
The handout for polymer lab is clear and understandable	6	1	0
The post-lab write-up helps me understand more about the experiments	6	1	0
The lab is important for my career plans.	6	1	0

Table 5. The survey results from polymer laboratory.

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clear. Most of them believed that the lab was important for their career plans. According to the survey, the students thought that the post-lab write-up helped them understand more about the polymer lab.

Since this is a small group of students, the survey will be conducted each semester until a larger database is collected, which will make the analysis meaningful. Space will be added in the survey for the students to write their comments.

Future Development

Overall, the polymer experiments tested were efficient and successful. At least one change will be made to replace the copolymer experiment by another experiment utilizing IR to measure molecular weight using end-group analysis. In order to challenge the more advanced students, a more demanding procedure, such as polymerization using a Ziegler-Natta catalyst, may be developed in the future.
Although no directly correlation between the students lab grades and class grades was found so far, this issue will be studied in the future.

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