Synthesis and characterization of styrene – maleic anhydride copolymer derivatives

Thesis presented in partial fulfillment of the requirements for the degree of

Master of Science (Polymer Chemistry)

By

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Declaration

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Mpitso Khotso

Abstract

In this study, a functional styrene – maleic anhydride copolymer (SMA) was synthesized via reversible addition-fragmentation chain transfer mediated polymerization (RAFT). The obtained copolymer had an alternating structure with well controlled molecular weight. The structure of the copolymer was found to alternating when characterized by NMR and MALDI-Tof-MS.

SMA copolymer is functional polymer due to the presence of reactive maleic anhydride moiety in its backbone. The SMA copolymer was used as a starting material for synthesis of other three copolymers with potential anti-viral activity. These three copolymers are referred to as SMA copolymer derivatives because they were synthesized by reacting either maleic anhydride or styrene moieties with certain chemical compounds. The three derived copolymers are; styrene-maleimde copolymer (SMI), styrene sulfonate-maleic anhydride copolymer (SSMA) and styrene sulfonate– maleimide copolymer (SSMI).

SMI was synthesized by reacting 4-aminomethylbenzene sulfonamide compound with maleic anhydride moieties on the backbone of SMA copolymer. The reaction proceeded in the presence of co-catalysts triethylamine and dimethylamino pyridine to from amide linkages. The copolymer was characterized by NMR spectroscopy, SEC and FTIR spectroscopy.

SSMA copolymer was successfully synthesized by reacting styrene moieties of the SMA copolymers with chlorosulfonic acid. The SSMA copolymer was further reacted with amine compound to synthesize SSMI copolymer. The synthesis of SSMI was achieved by reacting the maleic anhydride moieties in the backbone of the SSMA copolymer with N^1,N^1-dimethylpropane-1,3-diamine. Both copolymers were successfully characterized by FTIR spectroscopy.

Opsomming

'n Funksionele stireen-maleïensuuranhidried (SMA) kopolimeer is berei d.m.v. omkeerbare addisie-fragmentasie ketting-oordrag-beheerde (OAFO) polimerisasie. Die polimere het 'n wissellende struktuur en goed beheerde molekulêre massa gehad. Die wisselende struktuur is bevestig d.m.v. KMR en MALDI-ToF analise.

Die SMA kopolimeer is funksioneel a.g.v. die teenwoordigheid van reaktiewe anhidriedgroepe in die polimeerrugraat. Hierdie SMA kopolimeer is gebruik as uitgangstof vir die bereiding van drie ander kopolimere met potensiele teenvirale-aktiwiteit: stireen-maleïimied kopolimeer (SMI), stireensulfonaat-maleïensuuranhidried kopolimeer (SSMA) en stireensulfonaat-maleïimied kopolimeer (SSMI). Hiedie kopolimere staan bekend as SMA-kopolimeerderivate omdat hulle berei is deur d.m.v. die reaksie van of maleïensuuranhidried of stireengroepe.

SMI is suksesvol berei d.m.v. die reaksie van 4-aminobenseensulfonamied met maleïensuur-anhidriedeenhede op die polimeerruggraat in die teenwoordigheid van die kokataliste trietielamien of dimetielaminopiridien, om sodoende amiedbindings te vorm. Die kopolimere is gekarakteriseer m.b.v. grootte-uitsluitings-chromatografie (SEC), KMR en FTIR.

Die SMMA kopolimeer is suksesvol gesintetiseer d.m.v. die reaksie van die stireeneenhede van die SMMA kopolimeer met chlorosulfoonsuur. Die SSMA kopolimeer is verder gereageer met amienverbindings om die SSMI kopolimeer te lewer. SMMI kopolimere is berei d.m.v. die reaksie van die maleïensuuranhidriedgroepe in die ruggraat van die SSMA kopolimeer met N',N'-dimetielpropaan-1,3-diamien. Albei kopolimere is suksesvol gekarakteriseer m.b.v. KMR en FTIR.

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List of Symbols

C_{tr}	Chain transfer constant
f	Initiator efficiency factor
k_{add}	Addition rate constant
k_d	Dissociation rate constant
k_{frag}	Fragmentation rate constant
k_p	Propagation rate constant
k_t	Termination rate constant
[M]	Monomer concentration
$[M]_0$	Initial monomer concentration
M_M	Molar mass of repeat unit
M_n^{NMR}	M_n determined by NMR
M_n^{SEC}	M_n determined by SEC
M_n^{theor}	Theoretical M_n value
M_w/M_n	Ratio of weight average molar mass to number average molar mass
t	Time
ξ	The reduced super saturation

$[I]_0$	Initial concentration of the initiator
$[RAFT]_0$	Initial concentration of the RAFT agent
W_{RAFT}	Mass of RAFT agent
FW_{RAFT}	Molar mass of RAFT agent
χ_{Sty}	Mole fraction of Styrene
χ_{MAnh}	Mole fraction of Maleic anhydride

List of Abbreviations

ATRA	Atom transfer radical addition
ATRP	Atom transfer radical polymerization
ATR-FTIR	Attenuated total reflectance-fourier transmission infra red spectroscopy
AIBN	Azobis (isobutyronitril)
BPO	Benzoyl peroxide
CTA	Chain transfer agent
CDB	Cumyl dithiobenzoate
CIPDB	Cyanoisopropyl dithiobenzoate
DNA	Deoxyribonucleic acid
DCE	Dichloroethane
DIAD	Diisopropyl azodicarboxylate
DMSO	Dimethyl sulfoxide
DMAPA	Dimethylamino-1-propylamine
DMF	Dimethylformamide
DMFC	Direct methanol fuel cells
ESR	Electron-spin resonance
HCl	Hydrochloric acid
$LiAlH_4$	Lithium aluminum hydride
LRP	Living radical polymerization
MADIX	Macromolecular design via interchange of xanthates

MAnh	Maleic anhydride
NVP	N- vinyl pyrrolidine
NBS	N-bromosuccinimide
NCS	Neocarzinostatin
NMP	Nitroxide mediated polymerization
NMR	Nuclear magnetic resonance spectroscopy
PMMA	Poly (methyl methacrylate)
RAFT	Reversible addition-fragmentation chain transfer polymerization
SEC	Size exclusion chromatography
NaCl	Sodium chloride
NaOH	Sodium hydroxide
SFRP	Stable free-radical polymerization
Sty	Styrene
SSMA	Styrene sulfonate-maleic anhydride
SSMI	Styrene sulfonate-maleimide
SMA	Styrene-maleic anhydride
SMI	Styrene-maleimide
THF	Tetrahydrofuran
ATRP	Transfer radical polymerization
TEA	Triethylamine
Ph_3P	Tri-phenyl phosphine
VAc	Vinyl acetate
MWD	Molecular weight distribution

Chapter one: Introduction

Definition and history of polymers

Polymers can be defined as large molecules consisting of repeating structural units (monomer). The word polymer is derived from Greek, poly meaning "many" and mer, meaning "part".[1] Common examples of polymers are rubbers, plastics, but also deoxyribonucleic acid (DNA), proteins, etc.

Polymers date back to early 18th century. Faraday had discovered C_5H_8 as an empirical formula of rubber. Isoprene (C_5H_8) was identified as the repeating unit of a purified natural rubber.[2] Since the discovery of polymers to date, they have been realized to form an integral part of our lives on a daily basis. Good examples are the polymers which our bodies are made up of, that is, proteins, carbohydrates, nucleic acids, etc. These polymers are classified as natural polymers and our body needs them for essential functions. Other natural occurring polymers such as wood, silk, etc., are used for clothing and building materials among other things. The other class of polymers that play a huge role in our lives are synthetic polymers. Examples are polyethylene, nylon, polystyrene, etc.

Modern life with polymers

Over the years, life has changed dramatically from being simple and nature dependant to complex and technology dependant. Modern life is incomparably different from yester life due to synthetic chemicals called polymers. Common materials like fibers, plastics, elastomers, coatings, adhesives, etc. are all polymers employed to make life easier. Though polymers were discovered in the 18th century, it was during and after World War II that polymers created a really substantial market. Polyethylene was accidentally discovered in the 1930s and due to its many properties; it was used in the World War to insulate the cables needed for the vital radar equipment. Since then the improvements in polymer science have led to the synthesis of simple and complex polymers that are employable in a wide variety of applications. For example, synthetic polymers are employed in life support materials to

medical related applications such drug delivery and many more examples for various applications in different fields.

Purpose of this study

The synthesis of anti-HIV active biocompatible copolymers is the main objective of this study. These materials are synthesized by chemical attachment of compounds of low molecular weight which have anti-HIV activity to copolymers to produce anti-HIV active polymers. This is due to the fact that biocompatible polymers have an advantage of prolonged residence time in the body over low molecular compounds. Styrene-maleic anhydride (SMA) copolymer is a polymer which has reactive sites where the compounds of interest can be attached. The attachment will result in targeted derivatives of the SMA copolymer. A brief outline of the study is given the section below.

The synthesized copolymers will be characterized by nuclear magnetic resonance spectroscopy (NMR), size exclusion chromatography (SEC), attenuated total reflectance-fourier transform infrared spectroscopy (ATR-FTIR) and elemental analysis.

Outline

Chapter one: Introduction

In this section, the history, definition and few applications of polymers have been briefly outlined. Outline of the project is also provided

Chapter two: Historical and theoretical background

Chapter 2 contains a brief discussion about polymerization in general, chemistry of conventional radical polymerization and living radical polymerization (LRP). Controlled/living radical polymerization is discussed in detail, where nitroxide mediated polymerization (NMP), atom transfer radical polymerization (ATRP) and reversible addition-

fragmentation chain transfer mediated polymerization (RAFT) are introduced. RAFT mediated is discussed in greatest detail as it is the method employed in this study. The SMA copolymer and its derivatives are discussed with all the procedures available in literature for their synthesis.

Chapter three: Synthesis of RAFT agents

In chapter 3, a brief literature overview of RAFT agents is discussed along with the organic chemistry used for their synthesis. Procedures for the RAFT agents synthesized for this study are discussed.

Chapter four: Synthesis of SMA copolymer and its derivatives

In Chapter 4, all the synthetic routes used to synthesize styrene-maleic anhydride (SMA), styrene-maleimide (SMI), styrene sulfonate-maleic anhydride (SSMA) and styrene sulfonate-maleimide (SSMI) copolymers are discussed. SMA copolymer is synthesized by RAFT mediated polymerization, while SMI, SSMA and SSMI copolymers are SMA derivatives and the relevant chemistry is discussed.

Chapter five: discussions, conclusions, outlook and acknowledgements

Chapter 5 comprises a general discussion of all the work done in this study. All the problems encountered are also discussed. Conclusions based on the successes and failures during the study will also be drawn. Methods to improve where there has been failure or difficulty will be discussed.

References

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2. Hiemenz, P. C., *Polymer chemistry: The basic concepts*. Marcel Dekker, Inc: New York, 1984.
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Chapter two: Theory and historical

2.1 General introduction to polymerization

2.1.1 History of polymerization

Polymerization is a chemical reaction by which small molecules are linked/combined to form larger molecules.[1, 2, 3] The larger molecule formed from this type of chemical reaction is known as polymer. Staudinger is a pioneer of polymerization reactions, even though his early hypothesis was criticized by other chemists. In 1920 he proposed chain formulas that are being used to describe the polymer structures to date. He came with the hypothesis that large molecules (polymers) are held together by covalent bonds which are very much similar to those of small molecules.[1] His ideas had a controversial decade before being accepted and widely used. However, he did get the Nobel prize for his achievements in 1953.[1]

2.1.2 Classification of polymerization processes

Polymerization processes have been classified into two groups by Carothers. He classified the process into addition and condensation polymerizations.[1] This classification is based on the repeating unit of the polymer chains. In addition polymerization, a polymer has the same atoms as the monomer in its repeating units, whereas in condensation polymerization, a polymer has fewer atoms in its repeating units than monomers due to the formation of byproducts, e.g. H_2O, HCl or CH_3OH.

2.1.2.1 Condensation polymerization

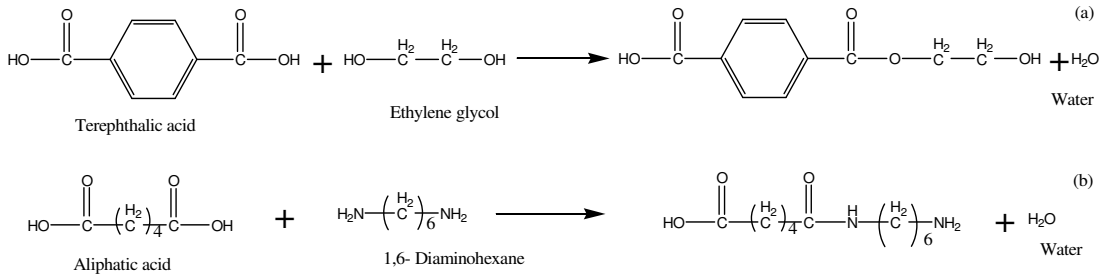
Condensation polymerization is a form of step-growth polymerization which utilizes monomers with complementary reactive groups.[3] This polymerization process follows simple organic condensation chemistry in which a small molecule is formed as a byproduct when a

link is formed between two molecules (monomers). Water, hydrochloric acid and methanol are typical byproducts of condensation reactions.

There are few factors that needs to be considered for a successful condensation polymerization. i.e.

- Steric factor – for monomers with bulky side groups that will prevent the active side of the chain from adding to another monomer unit by hiding active side of the growing chain.
- Intra-molecular factor – for multifunctional monomers which may result in formation of cyclic products.
- Purified monomers – to avoid side reactions of functional groups

Reactions between carboxylic acid and alcohol/amine are widely used in organic condensation. Typical examples are the reactions between an alcohol and an acid to form an ester linkage and an acid and amine reacting to form an amide linkage shown **in scheme 2.1**.[3]

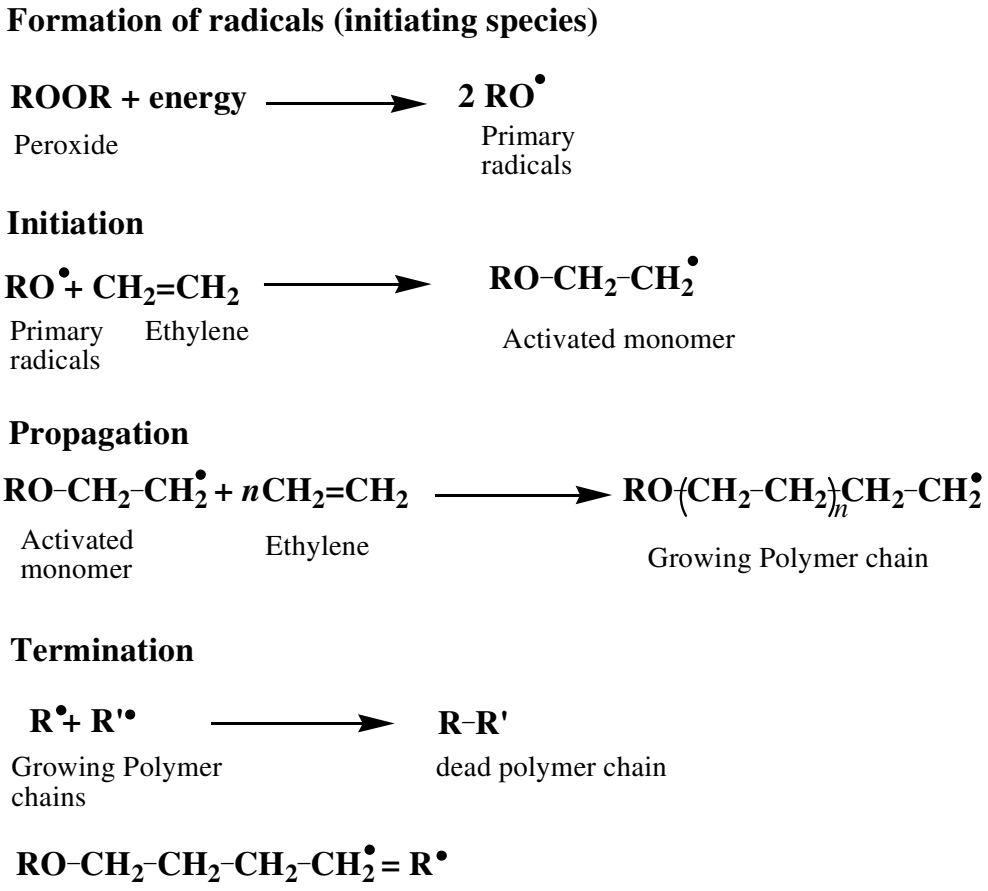


Scheme 2.1 Condensation reactions between (a) Acid and Alcohol (b) Acid and Amine

2.1.2.2 Addition polymerization

Addition polymerization is in many cases is also known as chain growth polymerization. Polymerization of vinyl monomers to give high molecular weight polymers proceeds via a chain growth mechanism. Generally, polymerization of ethylene gives a better understanding of addition polymerization. The monomer contains a pi-bond which opens up to produce two sigma bonds when reacted with an active species (radical, anion, cation, etc). A product of

the reaction is the homopolymer (polyethylene) and the backbone is joined by carbon-carbon links/bonds. The chain growth involves three steps to completion. First step is initiation, followed by propagation and lastly termination as shown in **scheme 2.2**. Formation of radicals produced on thermolysis or photolysis is a requirement as they serve as initiating species. In this case, peroxides were fragmented thermally to yield the radicals. These radicals are unstable and reactive. They initiate (first step) polymerization by attacking the double bond of ethylene and the radical is transferred to the other end of the attacked ethylene monomer. Propagation follows as the monomer with radical attacks another monomer. This goes on so that the chain grows longer. Termination occurs when two growing chains with radicals react bimolecularly, or when the original radical formed by thermolysis reacts with a growing chain.



Scheme 2.2 Addition polymerization of ethylene via a free radical mechanism

Chain growth polymerization encompasses free radical and ionic polymerization of which all have an active site at the end of a growing chain. Ionic polymerization is divided into anionic and cationic polymerization systems.

- **Free radical polymerization** – In this process, a propagating species is a long chain free radical which is usually initiated by the attack of free radicals derived by thermal or photochemical decomposition of unstable compounds (initiators).[4]

- **Anionic polymerization** – In this process, polymerization takes place with monomers possessing electron-withdrawing groups such as carbonyl, nitrile, phenyl, and vinyl. An electron-withdrawing group is required in anionic polymerization to stabilize the propagating anionic species. The stabilization of anionic propagating species for long periods is required to synthesize desirable high molecular weight products.[1, 3, 5]

- **Cationic polymerization** – in this process, polymerization takes place with monomers possessing electron-donating substituents such as alkoxy, phenyl, and 1, 1 dialkyl. Stabilization of propagating cationic species is also necessary for longer periods to synthesize products of high molecular weight.[1, 3, 5]

All these methods of chain growth polymerization share similar polymerization steps. They all have initiation steps in which reactive species are generated. The reactive species attack the first monomer to initiate polymerization. Then a number of propagation steps follow in which typically larger numbers of monomer units are sequentially added to the growing polymer chain. The reactive chain end is retained after addition of each new monomer unit. The last step, which is the termination step where the termination of the reactive chain ends transpires, is missing in anionic polymerization. Details of the above mentioned steps are different between cationic and free radical polymerization even though the names are common .[1, 5]

It should be noted that ionic polymerization is highly selective. High polarity solvents are desirable to solvate ions but they cannot be employed. This is due to the fact that highly polar solvents such as water and alcohols react with and destroy ionic centers. Other polar solvents such as ketones prevent initiation in ionic polymerization by forming highly stable complexes with initiators.[5]

2.1.3 Techniques of polymerization

For various applications, polymers have many different properties. Diversity in properties is brought about by many things, such as molecular weight, molecular structure, functional groups, design of a polymer, nature of polymerization, etc. A number of polymerization processes with different reaction conditions (*i.e.* reaction medium (solvents), temperature, duration, different monomer compositions (feeds) and initiation methods) have been devised to achieve various polymer properties.[1]

Based on the conditions of the systems, polymerization processes have been categorized into solution polymerization, bulk polymerization, dispersion polymerization, suspension polymerization, and emulsion and mini-emulsion polymerizations. The processes are briefly discussed below:

Solution polymerization: In this technique, monomer is dissolved in a non-reactive solvent. Heat produced by the polymerization reaction is absorbed by the solvent and transferred to the reactor wall to control the temperature in the reactor. Choice of solvent is vital as this may result in limitation of molecular weight by the chain transfer reaction. It has few disadvantages and advantages. Solvent may be difficult to remove and there maybe the possibility of chain transfer to the solvent. Advantage is that heat is dissipated easily and the viscosity is low.[1, 6]

Bulk polymerization: also known as mass polymerization is the simplest of the polymerization techniques. Polymerization of the monomer takes place in the absence of any medium, except for accelerator or catalyst. Usually monomers are in liquid form, though gaseous and solid phase monomers can be polymerized. Advantages of this technique are simplicity and the absence of contaminants. Disadvantages; polymerization is exothermic and it is difficult to control the reaction and viscosity increases fast.[1, 6, 7]

Dispersion polymerization is a single step process used to prepare relatively mono-disperse microspheres. The solvent used in this process is readily miscible with the monomer, but is a non-solvent for the resulting polymer (product). Amphiphilic macromolecules are used as stabilizers. These stabilizers are classified into three classes: (i) homopolymers, (ii) macromonomers and (iii) block and graft copolymers.[8, 9]

Suspension polymerization is a process whereby aqueous (continuous) phase and organic phase (monomer-dispersed) which are immiscible, are brought into contact to form a liquid-liquid dispersion by the use of continuous stirring and a suspension agent. The size of the monomer particles dispersed is determined by the agitation intensity and by the suspension agent properties. Polymerization occurs in the monomer droplets which become viscous with conversion. At the end of polymerization the viscosity increase leads to solid particles. Suspension polymerization is the major route for polymerizing vinyl chloride. Its advantage is the ease of heat removal and the disadvantage is the need to separate polymer from the suspending medium and wash off the additives.[1, 6, 10, 11]

Emulsion polymerization also uses two immiscible liquids, *i.e.* aqueous and organic (monomer) phases to form a liquid-liquid dispersion. Surfactant is used to lower the surface tension between the dispersed and continuous phases. A large fraction of the surfactant will form micelles. During polymerization, monomer is transported from monomer droplets (5-10 microns) into the micelles by diffusion. Particle nucleation occurs early in the reaction. This happens via homogeneous nucleation or via entry of free radicals into swollen micelles. Nucleation stops when all the micelles have either been initiated or used for the stabilization

of growing particles. Polymerization subsequently takes place in the nucleated particles.[1, 6, 12, 13]

Mini-emulsion polymerization is similar to emulsion polymerization but particle nucleation and monomer transport are different. The size of the monomer droplets in this case is very small (50-500 nm) hence the name mini-emulsion. A surfactant/co-stabilizer system is used to stabilize the monomer droplets. In this process mass transport of monomer from the droplets is not needed, since in principle droplets will be directly converted into particles. Most surfactant is adsorbed on droplets leaving little surfactant to form micelles. The predominant nucleation mechanism in mini-emulsion polymerization is droplet nucleation in contrast to micellar nucleation in an emulsion process.[12-15]

2.2 Living/Controlled radical polymerization

2.2.1 History and theoretical background

Living polymerization has received immense attention in recent years. However, its first demonstration and current definition is attributed to Szwarc.[4, 16] He defined living polymerization as a chain growth process without chain breaking reactions (transfer and termination). This kind of polymerization provides polymers of controlled composition, molecular weight distribution, precisely designed architectures and nano-structured morphology.[4, 17-19] Even though this kind of polymerization affords end-group controlled polymers; it does not necessarily achieve molecular weight control and low polydispersity. For these kinds of properties to be achieved, consumption of the initiator at the early stages of the polymerization and exchange between species of different reactivity should be fast in comparison to propagation.[18] The term *controlled* has been suggested to be used if the above mentioned criteria are met. The term was proposed for systems in which molecular weight and molecular weight distribution are controlled, but these systems are characterized by chain breaking reactions continuously occurring, just like in a conventional radical polymerization. "*Living*" polymerization can also be used as an optional term due to the fact that chain

breaking occurs continuously with certainty. The term controlled does not define which features are controlled and which are not controlled.[20] Even though living radical polymerization has been known for over a decade, it is now starting to be increasingly used in polymer chemistry. In this sense, to meet industrial requirements of well controlled molecular weight and to attain low polydispersity, it has led to significant efforts to develop and understand living radical polymerization. Entezami *et al*. have discussed briefly the aspects of controlled free radical polymerization.[18] Atom transfer radical polymerization (ATRP), reversible addition-fragmentation chain transfer polymerization (RAFT) and nitroxide-mediated polymerization (NMP) are three methods which serve as the prime examples of living radical polymerization and will be briefly discussed later in this chapter.[21] Living polymerizations are characterized by a linear plot of molecular weight *vs.* conversion due to the fact that they neither undergo termination nor transfer and this is shown in **figure 2.1** below.

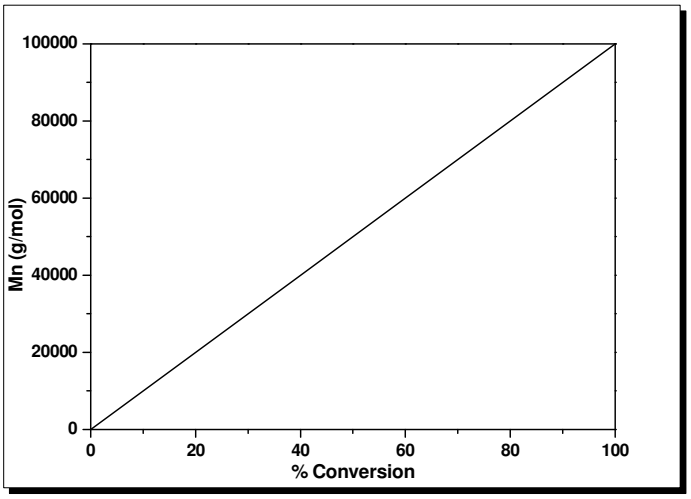
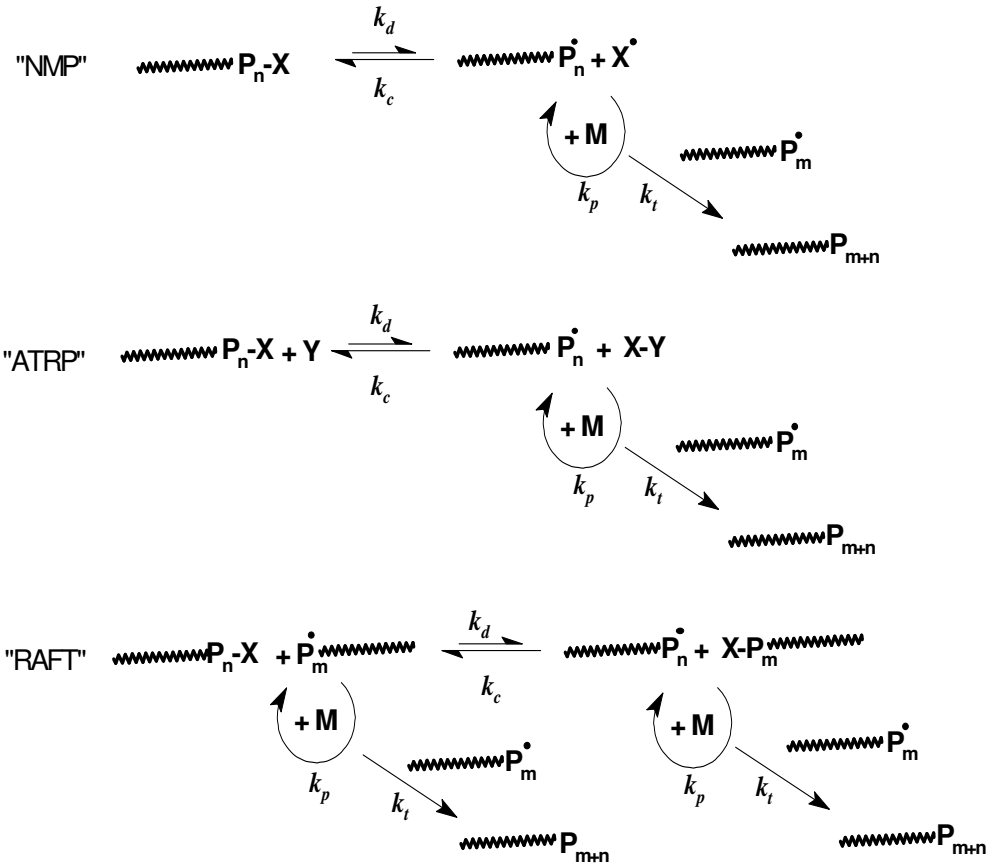


Figure 2.1 Molecular weight vs. conversion typical graph of living polymerization.[18]

Polymer chains grow at the same rate resulting in all chains having similar length, therefore a decrease in polydispersity index is observed as conversion increases. At 100% conversion, the propagating center is dormant and can be further reacted by addition of monomer. Living polymerization was discovered for anionic processes in which suppression of termination and transfer is simple albeit requiring rigorous exclusion of moisture and oxygen. As for control of living radical polymerization, termination and transfer are difficult to suppress due to

various radical chain transfer reactions and favourable coupling of propagating radical centers. Controlled/Living radical polymerizations involve equilibria of growing free radicals and various types of dormant species. The equilibrium ensures simultaneous growth of all chains. The rate of polymerization is controlled by control over this equilibrium.[18] **Scheme 2.3** below shows the mechanisms of three types of controlled radical polymerizations.

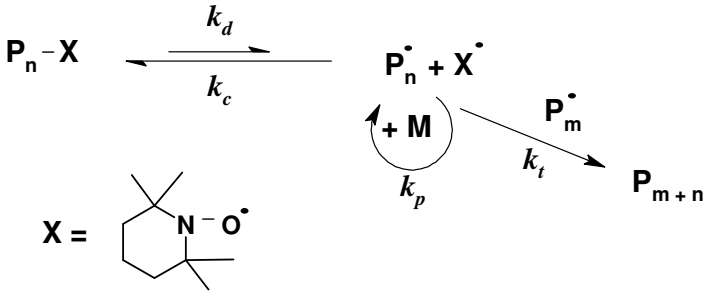


Scheme 2.3 Three different mechanisms of controlled/living radical polymerization methods

2.2.1.1 Nitroxide Mediated Polymerization (NMP)

NMP, which is also known as stable free-radical polymerization (SFRP), is another form of living radical polymerization which was first reported by Rizzardo *et al.*[27] They used a stable radical that reversibly deactivates the propagating radical in the homopolymerization of styrene using different initiators.[27] The use of other nitroxides, 2,2,6,6 trimethylpiperidine-

N- oxyl (TEMPO)[28] being an example to homopolymerize styrene was also successful. TEMPO and other first generation nitroxides could only control the polymerization of styrene and its derivatives and failed to control polymerization of monomer systems such as acrylates[29, 30] and dienes[31]. The versatility of NMP towards other monomer systems such as acrylates and dienes came about with the introduction of acyclic nitroxides bearing a hydrogen atom on the α-carbon. Advancement in NMP was the introduction of alkoxyamines which could serve as both the initiator and mediator. This resulted in desertion of conventional initiators in NMP systems. From the reported routes in the literature towards alkoxyamines synthesis, the ATRA method reported by Matyjaszewski *et al.* has proven to be the most convenient procedure.[32] The general mechanism of NMP is shown in **scheme 2.4** below



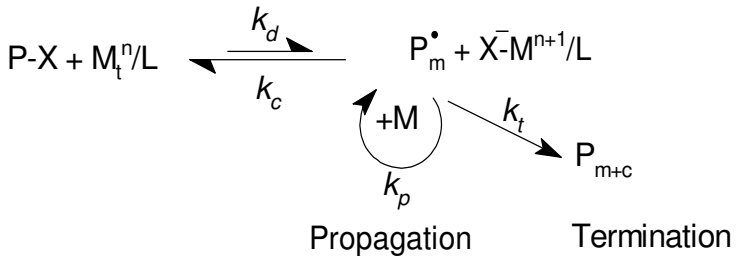
Scheme 2.4 General mechanism of NMP

In this process, the propagating species ($P_n^{\bullet}$) reacts with a persistent radical species ($X^{\bullet}$). Dormant species (P_n—X) is formed as the two react and it reversibly cleaves to regenerate the radicals, ($P_n^{\bullet}$) and ($X^{\bullet}$). Once ($P_n^{\bullet}$) has formed, it reacts with the monomer (M) and propagates further.[18] Nitroxide radical ($X^{\bullet}$) should not initiate any chain growth or react with itself for the NMP system to exhibit living behavior. This nitroxide radical is also required to be stable.

2.2.1.2 Atom Transfer Radical Polymerization (ATRP)

In atom transfer radical polymerization (ATRP), an alkyl halide is activated by a transition metal catalyst to form a radical which can initiate polymerization.[18] The general mechanism for ATRP is shown in **scheme 2.5** to show the formation of radicals by a redox process

involving a transition metal complex.[22] Two catalytic systems for controlling radical polymerization were reported in 1995. These methods were used by organic chemists for atom transfer radical addition (ATRA) and hence the equivalent polymerization was termed ATRP.[20] Of the two catalytic systems, the copper-based one has been shown to be successful in many ATRP reactions.[23] It was successful for styrene, methacrylates, acrylates, acrylonitrile, and other monomers.[24, 25] A $RuCl_3/(PPh_3)_3$ catalyst based method was used to polymerize methyl methacrylate and the reaction was initiated by carbon tetrachloride (CCl_4)[26]. The catalyst appeared to be inactive on its own, and was activated by methylaluminum bis-(2, 6-di-tert-butylphenoxide) [$MeAl(ODBP)_2$].



Scheme 2.5 General mechanism of ATRP

ATRP has numerous advantages, it can be used on a large variety of monomers and it can be carried out over a wide range of temperatures. Its disadvantage is that a metal catalyst must be used which must be removed after polymerization.

2.2.1.3 Radical addition-fragmentation chain transfer (RAFT) polymerization

The RAFT process is a highly advanced and versatile controlled radical polymerization technique. Unlike other controlled radical polymerization techniques, it is applicable to most monomers which can be polymerized under free radical conditions. RAFT polymerization relies on the rapid central addition-fragmentation equilibrium involving dormant chains, propagating radicals and intermediate radicals. The RAFT process will be further discussed in the following sections of this chapter.

2.3 Radical addition-fragmentation chain transfer (RAFT) polymerization

2.3.1 History and theoretical background

RAFT polymerization is another type of controlled/living radical polymerization. It was discovered by Chiefari *et al.* and was first published in 1998.[33] It differs from other controlled/living radical polymerization techniques by its versatility. It is quite tolerant to a wide range of functionalities in the monomers (*e.g.* –OH, –COOH, $–CONR_2$, $–NR_2$, $–SO_3Na$) ,[34] and therefore can be employed to a wide range of monomers and reaction conditions. This RAFT technique is effective over a wide range of temperatures (20-150°C). It offers benefits such as control over molecular weight, low polydispersity, end functionalized polymers, block copolymer and polymers of complex architectures.[33] The success of RAFT polymerization is attributable to chain transfer agents (CTA) also known as RAFT agents.[35] CTAs are thiocarbonyl thio species belonging to one of the following general families of compounds: xanthates,[36, 37] dithioesters, trithiocarbonates[38] and dithiocarbamates.[35] Thiocarbonyl thio species will be discussed briefly in chapter three. The activity of a CTA is influenced by two fragments, the Z-group and the R-group. The Z-group controls the reactivity of the thiocarbonyl group and the R-group should be a good leaving group which should be able to react with monomers to start new polymer chains.[39] The R-group also participates in the stabilization of the radical intermediate, but to a lesser extent.

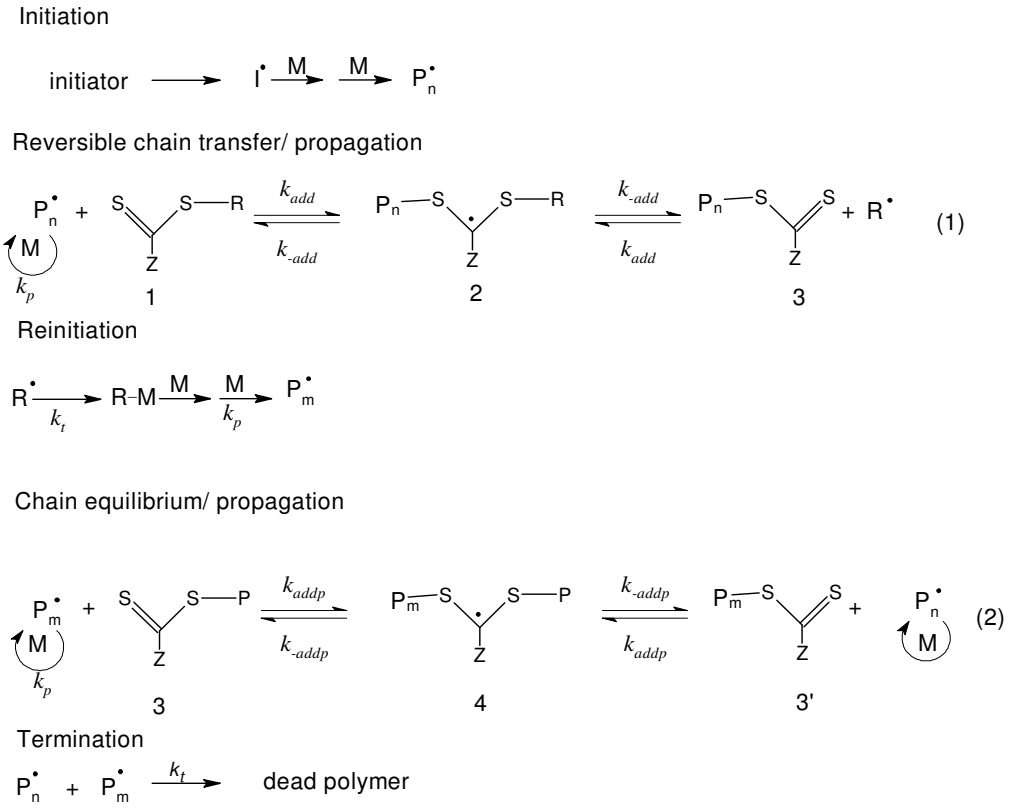
It should be noted that a proper choice of the CTA and reaction conditions plays a vital role in achieving success with the RAFT technique.[40] When choosing a CTA for a certain system, parameters such as polarity, steric hindrance and stability of the generated radical need to be considered.[41] Inappropriate choice of either CTA for monomers and/or reaction conditions could result in retardation, inhibition and/or poor control. When a CTA performs well for a certain system it does not necessarily mean it will function optimally for other systems.

Further on the issue of the choice of CTA and reaction conditions for good polymerization, it is also well known that the presence of oxygen has negative impacts in the polymerization

system. It retards the polymerization rates and it causes inhibition periods.[42] These negative effects are avoided by having an oxygen free system for polymerization. Oxygen is removed from the system by purging with nitrogen or argon. Alternatively freeze-pump-thaw cycles can be used to deoxygenate the system. These processes are expensive for industrial polymerizations; therefore alternative methods are employed on a large scale. Zhang *et al.*[43] have just recently proved that for some systems, polymerizations can be a success while there is a low concentration of oxygen in them. They polymerized MMA with different concentrations of oxygen and compared the results with MMA polymerized in an oxygen free system with similar conditions.[44] It was fascinating to find that oxygen helps to accelerate the polymerization of MMA. They had a good control as polydispersity was relatively low (1.13-1.49). They then followed-up by polymerizing styrene in the presence of oxygen using two different RAFT agents and polymerization rates were higher than that of the deoxygenated systems. However they found that the control was not good as polydispersity index was high. They concluded that the interaction between styrene and oxygen could be acting as an additional initiator besides the thermal auto-polymerization of styrene.[43]

2.3.2 Mechanism of RAFT process

The characteristic feature of the RAFT process is the addition-fragmentation equilibrium sequence in the mechanism of RAFT polymerization as shown in **scheme 2.6**.[33, 45]



Scheme 2.6 Detailed mechanism of RAFT polymerization

Initiation and radical-radical termination occur as in conventional radical polymerization. Initiation has two steps, first being photo or thermal decomposition of the initiator which results in the formation of radicals. These primary radicals initiate polymerization by attacking a monomer unit to form a propagating radical ($P_n^{\bullet}$). The formed propagating radical ($P_n^{\bullet}$) adds to a thiocarbonyl thio compound [S=C(Z)S─R (1)] to form an intermediate radical. This is followed by intermediate radical fragmentation resulting in a polymeric thiocarbonyl thio compound [S=C(Z)S─P_n (3)] and a new radical ($R^{\bullet}$). The radical ($R^{\bullet}$) reacts with monomer to give a propagating radical ($P_m^{\bullet}$). A rapid equilibrium between the active

propagating radicals ($P_n^{\bullet}$ and $P_m^{\bullet}$) and a dormant polymeric thiocarbonyl thio compound (3) provides equal probability for all chains to grow and allows production of low polydispersity polymers. The thiocarbonyl thio end group is retained by most polymer chains when polymerization is complete (stopped) and they are isolated as stable materials. The RAFT mechanism can be evidently shown using ^{1}H NMR and UV/visible spectra which demonstrate the presence of S=C(Z)S─ retained as an end group in the polymeric product.[33]With polymer chains growing concurrently, molecular weight of the chains can be predicted from the amount of polymer produced (conversion) and the initial concentration of monomer(s) and CTA using the following equation:

$$M_n^{theo} = \frac{[Monomer]}{[CTA]} \times FW(M) \times c + FW(CTA) \qquad (2.\ 1)$$

$M_{n,}^{theo}$ is the theoretical number average molecular weight. [Monomer] and [CTA] are initial monomer concentration and CTA concentration respectively. FW(M) and FW(CTA) are molecular weights of monomer and CTA respectively, c is the fractional conversion.[21]This prediction is allowed when first assuming that all CTAs have reacted and chains initiated by primary radicals are neglected.[46]

2.3.3 Factors contributing towards successful RAFT polymerization

There are certain requirements to a good control over the molecular weight distribution during RAFT polymerization. Requirements to be mentioned are equally important. Polymer chains must be initiated simultaneously within a short period of time. Fast initiation is achieved with CTAs that have a high transfer constant (C_{tr}). The probability of chains growing at the same time is favored. The number of monomer units added to the propagating radical per activation/deactivation cycle should be low. This ensures that a similar rate of chain growth for all polymer chains is achieved. Most importantly, any reaction which might lead to formation of dead polymer chains should be suppressed. In this type of polymerization, termination is minimized by having a low concentration of initiating radicals

in the system. A high concentration of primary radicals will surely result in the termination of growing polymer chains.[18, 47]

In RAFT polymerization, both the addition and fragmentation rate should be high and of comparable magnitude to limit the number and the life time of intermediate radicals. The equilibrium between addition and fragmentation is dynamic. The reversible addition – fragmentation pre-equilibrium (scheme 2.6 no. 1) should largely result in the release of the leaving group radicals ($R^{\bullet}$) and formation of dormant chains (scheme 2.6 no 3). The leaving group radicals should be able to initiate new polymer chains rapidly. Dormant species (scheme 2.6 no. 2) should exhibit a high transfer activity to ensure fast transition between dormant and active chains. This means that, the transfer rate of the active species with the CTA should be similar or higher than the propagation rate. Control of RAFT polymerization depends entirely on the efficiency and selectivity of reversible addition – fragmentation reaction and therefore on the RAFT agent structure (R – group and Z – group) relative to the monomer. The influence of the R – group and Z – group in RAFT polymerization has been further discussed by Favier *et al.*[47]

2.3.4 Advantages of RAFT polymerization over other controlled/living radical polymerization techniques

"Living polymers" are polymers retaining their activity after polymerization has been completed and renewing their propagation after the addition of a new monomer feed. They contain at their ends reactive groups called active centers. Anionic polymerization discovered by Szwarc *et al.* is the first technique employed to synthesize "living" polymers.[16] However, anionic polymerization is limited to a certain range of monomers and it is extremely sensitive to impurities, such as water. This resulted in the development of other polymerization techniques that can be employed. NMP, ATRP and RAFT were devised and have proven to be more versatile.

The NMP technique is the simplest method of living free radical polymerization. It has been developed to a state whereby it is compatible with monomers such as styrene, acrylate derivatives, acrylamides, and dienes by development of new nitroxides, particularly acyclic nitroxides.[48] NMP is still incompatible with methacrylic derivatives.[20] ATRP can be used on a large number of monomers. The main disadvantage of ATRP is that the transition metal catalyst used to control polymerization must be removed and recycled if possible.[18] ATRP cannot polymerize (meth)acrylic acids in their protonated form because they destroy the catalyst used to control polymerization by coordinating to it and protonating nitrogen containing ligands.[20, 49] The RAFT technique is more versatile than the other controlled/living radical polymerization techniques.

RAFT technique has relative insensitivity towards the chemistry of functional groups of the monomers, meaning it can be directly applied without protecting the functional groups. Monomers such as (meth)acrylic acids are difficult to polymerize by other controlled/living radical polymerization techniques but can be easily polymerized by the RAFT technique.[50, 51] Polymerizations can be successfully carried out in heterogeneous media (emulsion, mini-emulsion, and suspension) Polymers of complex structures such as stars, blocks, microgel and hyperbranched structures, supra-molecular and other complex architectures can be synthesized with high purity.[45] And most importantly, the RAFT technique is simple and affordable. It just needs a suitable RAFT agent and minor alterations to the typical conventional free radical polymerization system.[46]

2.3.5 Challenges in RAFT mediated polymerization

RAFT mediated polymerization is known to be a conventional free radical polymerization derived process which uses a chain transfer agent/RAFT agent to manufacture academically and industrially desired polymers. It has few advantages over other living radical polymerization systems. However, it has its challenges that are still being debated to date. Retardation of polymerization is by far the most outstanding problem in RAFT polymerization. Retardation can occur at the initial phase of polymerization (induction

period) where polymerization does not take place or polymerization may be slow compared to corresponding conventional radical polymerization without RAFT agent.

Many factors attribute to retardation. Factors of the RAFT mediated polymerization and experimental techniques contribute to rate retardation. Impurities such as residual inhibitor, oxygen, etc. do retard polymerization. However, in the case of dithiobenzoate mediated polymerizations, retardation may also be due to, for example, side-reactions of the intermediate radical.

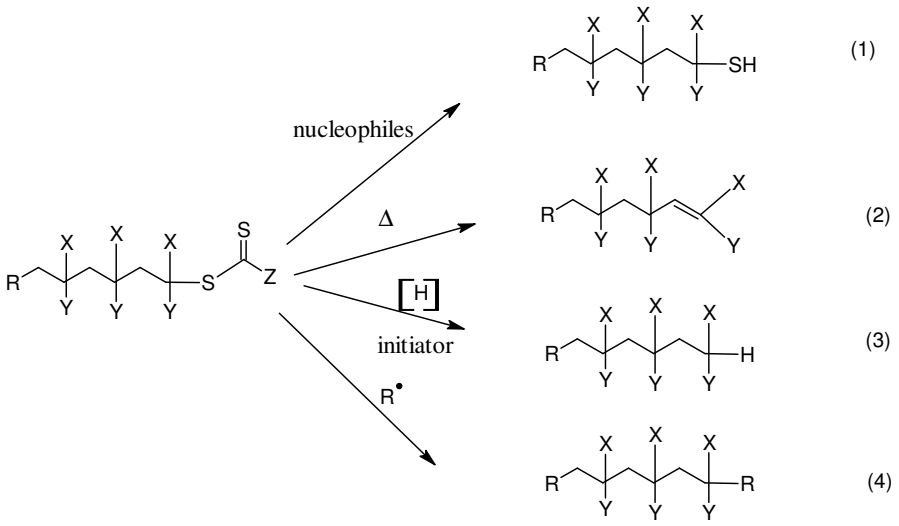
2.4 Thiocarbonyl thio terminus removal

RAFT polymerization, as mentioned in the previous sections, is a recent development or advancement in controlled/living radical polymerization. Controlled molecular weight, low polydispersity polymers, block copolymers, and polymers of complex architectures are some of the benefits from the RAFT technique. The overall process involves insertion of the monomer in the C─S bond of the thiocarbonyl thio compound (CTA) as shown in **scheme 2.6**. When the polymerization is finished, the thiocarbonyl thio groups present in the initial CTA is retained in the final products. This type of polymeric products are said to be "living" polymers. With addition of a new monomer feed and initiator, propagation will be renewed and controlled by the thiocarbonyl thio moiety at the end of the chain. Block copolymers and end functionalized polymers can be synthesized.

Although the presence of the thiocarbonyl thio groups in the polymeric products carries the living character of the RAFT technique, it has some disadvantages if kept in the final product. Applications of the polymers synthesized using this technique serve as a deciding factor whether to leave or cleave the thiocarbonyl thio group. Polymeric products containing this group may be coloured, with colours ranging from violet through red to pale yellow depending on the absorption spectra of the particular thiocarbonyl thio group in the chromophore.[52] The C─S bond is labile,[53] the polymers may in some cases release odor when

the thiocarbonyl thio group decomposes. These are disadvantages during some applications. With a proper choice of the RAFT agent, these problems can be kept to a minimum.

Even though the disadvantages can be mitigated, investigations to remove the thiocarbonyl thio terminus from the polymeric material have been conducted. The chemistry of the thiocarbonyl thio group has been studied and a few methods were developed to remove it from the polymer chains.[52] Methods that can be employed are shown in **scheme 2.7**.



Scheme 2.7 End-group removal processes; [H] Represent H atom donating compounds. Tri-n-butylstannane Bu_3SnH is an example of an [H] donor.

The thiocarbonyl thio group reacts with ionic reducing agents and nucleophiles to give thiols (1).[53] Primary and secondary amines are good nucleophiles as they react rapidly by aminolysis with the thiocarbonyl thio group. Primary and secondary amines reacts rapidly with dithioesters in basic medium, but are less reactive in acidic medium.[54] Borohydrides and hydroxides are good examples of ionic reducing agents. The thiocarbonyl thio group is also sensitive towards UV irradiation.[55] To remove the RAFT moiety, the polymeric material is exposed to any source of UV radiation at room temperature. The C─S bond is very labile, consequently, removal of the group is also achievable by a process called thermolysis (2).[53, 56] In this case a RAFT made polymer is exposed to higher temperatures. The last method for

thiocarbonyl thio group removal is radical induced reduction (3 and 4).[53, 56] Thermolysis and the radical induced reduction method are rated as the best among the four methods studied. Other methods leave reactive end groups which can be an advantage when there is the intention to further react the polymer chain. Thermolysis has limitations as it can only be used for polymers stable at high temperatures. Radical induced reduction processes require a careful selection of compounds to use for the reaction to avoid unwanted and possibly toxic byproducts.

2.5 Complex polymers architectures

With the RAFT process and its advantages outlined earlier, polymeric materials with complex architectures can be easily synthesized.[17] Polymers of architecture are linear, star/multi-armed, comb/brushes, networks and branched polymers, see **figure 2.2**.[17] Even though they are complex, they are synthesized without compromising control of molecular weight and low polydispersity. Lower bulk and solution viscosities of the complex materials compared to the linear analogues of the same molecular weight have triggered the interest in developing them. Generally, these polymers possess properties which their linear analogues do not have.

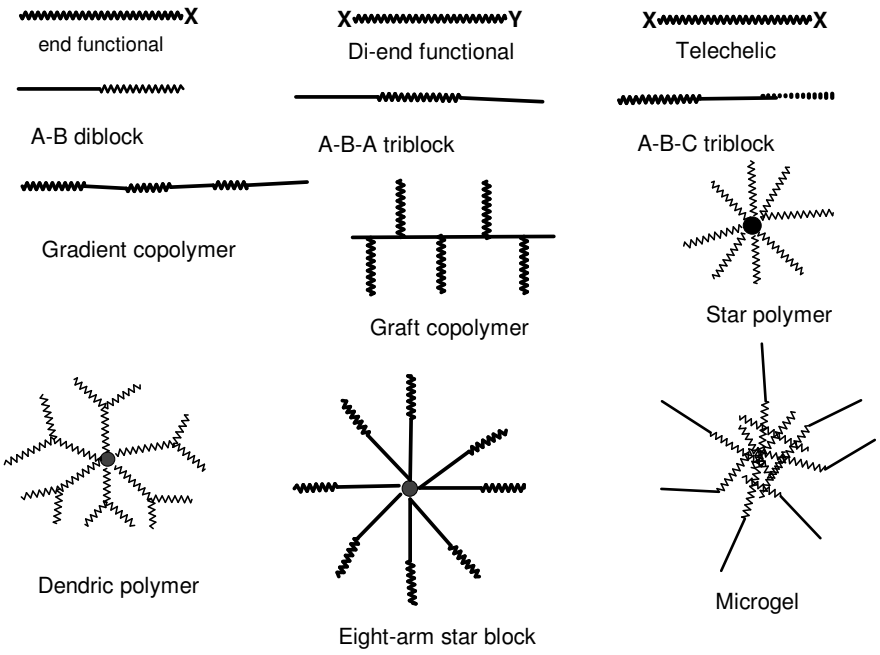


Figure 2. 2 Few examples of complex polymers that can be synthesized by RAFT technique and other LRPs

2.5.1 Star polymers by RAFT polymerization

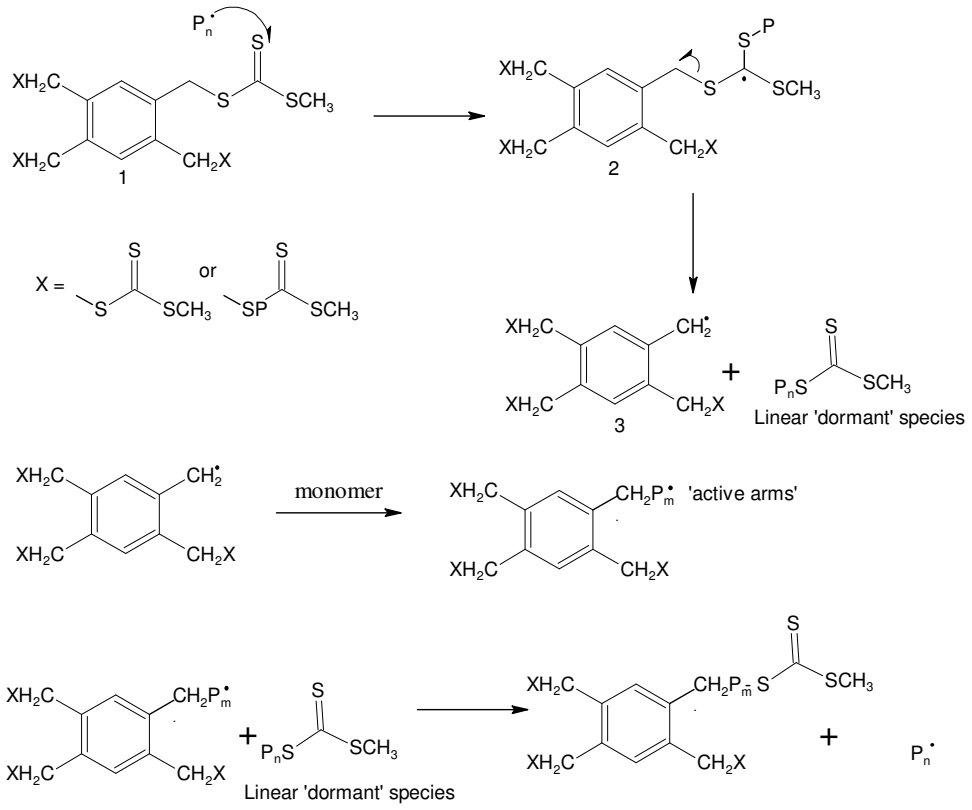
Of all the polymer architectures mentioned above, stars/multi-armed polymers will receive more attention as they are synthesized and modified in this research. They have different hydrodynamic properties compared to the linear polymers of the same composition.[57] They have lower bulk and solution viscosities compared to analogous linear polymers. The decrease in viscosity is credited to the fact that viscosity is dependent on the molecular weight of each arm as compared to the total molecular weight of the star polymer.[58]

In the late 1940s, preparation of star polymers has been documented by Schaefgen and Flory.[59] However, their preparation remained a challenge until the discovery of living polymerization. Morton *et al.* took full advantage of living anionic polymerization to synthesize well defined four armed polystyrene star polymer by neutralizing living polystyryllithium with tetrachlorosilane in 1956. Their work led to many researchers contributing in the synthesis of star polymers via living anionic polymerization. Research of

Morton *et al*.[60] was a success even though the product contained a mixture of three- and four-armed stars. There are two methods that can be employed to synthesize star polymers: that is arms first (i) and core first (ii).[57] In the arm first method, arms are synthesized first followed by binding of the arms using either a multifunctional terminating agent (e.g. tetrachlorosilane) or a tetrafunctional monomer (e.g. divinyl benzene). In the core first approach a multifunctional initiator (core) is first synthesized then monomer is polymerized from it.[61]

With certain advances in polymerization, specifically controlled/living radical polymerization, star polymers synthesis has been well documented.[62] Core and arm first approaches have both been reported via ATRP by Matyjaszewski *et al*.[62] Trollsås *et al*.[63] have contributed towards the core first method by synthesizing branched (star) polymers.

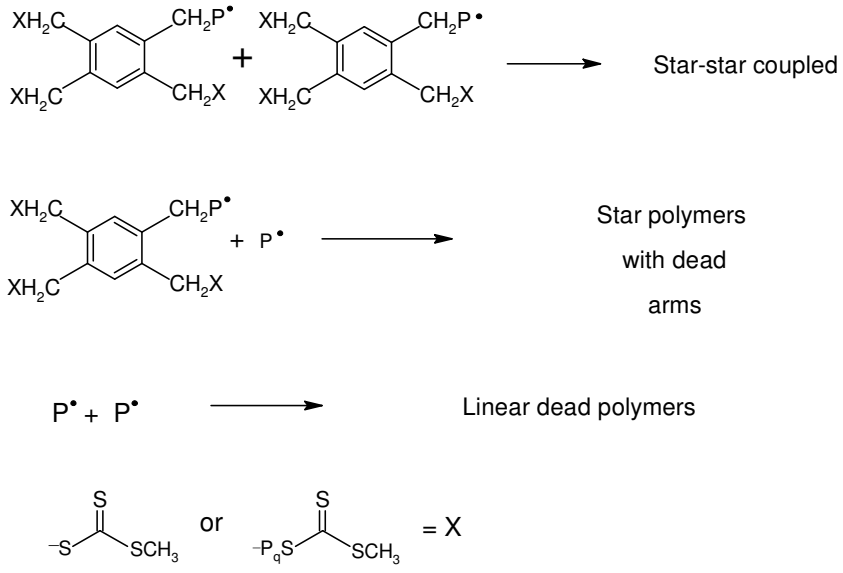
The NMP process has also been used to synthesize star polymers via both the arm and core first methods.[64] The RAFT process is mostly used for a core first approach. There are few limitations to all above mentioned techniques. However, chemical versatility and stability of RAFT agents make the RAFT technique prominent for the preparation of star polymers. Compatibility of the RAFT agent with monomer to be polymerized and polymerization conditions is important. Design of the RAFT agent for an aimed number of arms for the star polymer is also vital. The RAFT process has two principal options for connection to the central core of a multi-functional RAFT agent. The core may be connected to either the R-group (leaving group) or the Z-group (stabilizing moiety). Choice of connecting the core to either the R or Z group is important as both approaches have advantages and disadvantages.



Scheme 2. 8 polymerization mechanism in the case of R-group attachment to the core[65]

When the core is connected to the R-group after the fragmentation of RAFT agent, radical species shown in **scheme 2.8** (radical no.**3**) results. This radical initiates polymerization and propagation of arms attached to the core occurs. Propagation stops either upon exchange of a trithiocarbonate moiety from a linear dormant chain or a dormant chain attached from the core (activating another arm for propagation) or by radical-radical termination. Possible and unwanted terminations are regarded as side reactions because they produce impure polymers. A well known radical-radical termination event in the RAFT process produces star-star coupled polymers, linear dead chains and star polymers with dead arms,[66] all illustrated in **scheme 2.9**. The occurrence of star-star coupling is associated with a broad molecular weight distribution. Broadening of the molecular distribution becomes more pronounced with an increase in coupling of star polymers. In the past few years a lot of effort has been devoted towards improving synthetic routes for accessing star polymers by living radical polymerization methods. It has been found that star-star coupling reactions can be kept minimal by polymerization of low monomer to polymer conversion with low radical fluxes.[67]

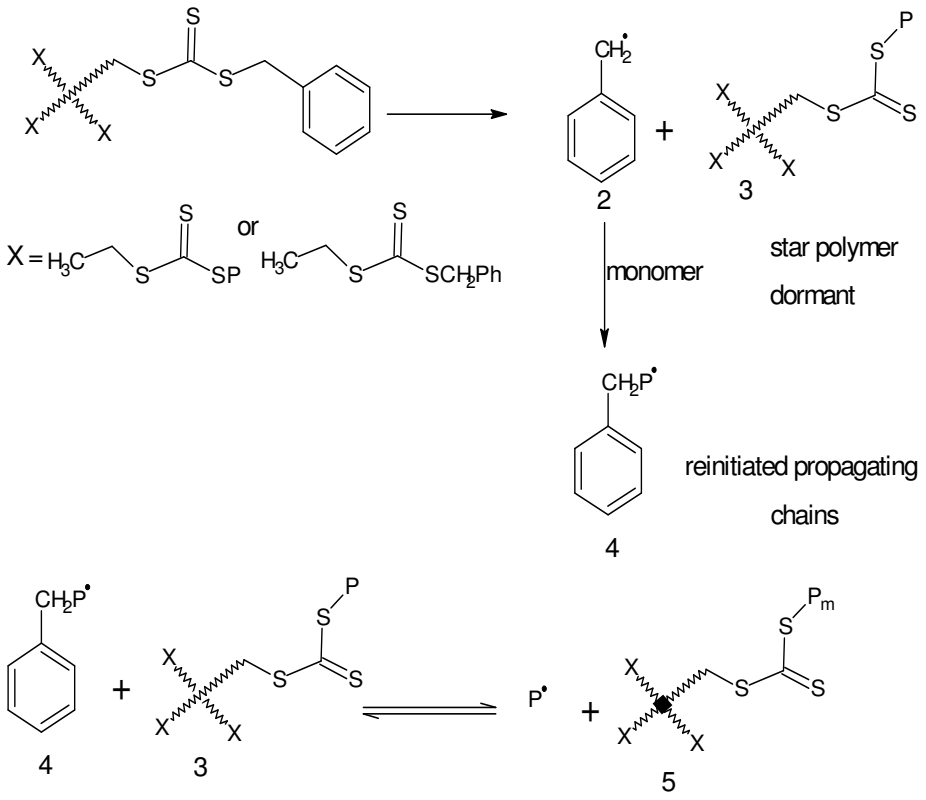
Linear dead chains result in a bimodal molecular weight distribution. Since they (linear chains) grow simultaneously with the arms of the star polymer, (they should have an identical molecular weight to each of the arms attached to the core) they may serve as reference material during characterization.[66]



Scheme 2.9 Side reactions in star synthesis

With the core attached to the Z-group and the R-group detached after fragmentation from the RAFT agent, as shown in **scheme 2.10** (no.2 and no.3), radical no.2 initiates polymerization away from the core resulting in linear propagating chains. When compound **1** in scheme 2.10 or one similar to it is used, the arms of the star polymer will always be dormant when they are attached to the core. Therefore star-star coupling cannot occur. In this case the growing macro-radical is detached and the RAFT group is directly bonded to the core, as shown in scheme 2.10.[65] For a growing radical to participate in the RAFT process, it has to reach the RAFT group which is located in the center of the star near the core. However, this might be difficult with increasing conversion due to a shielding effect.[68, 69] This inability to reach the RAFT moiety might result in the growing macro-radical terminating with another active chain to form a dead linear chain. The molecular weight may deviate from the one theoretically predicted. Bimolecular termination between macro-radicals appears to be less

pronounced with less dense star polymers. This allows larger conversion of monomer and the synthesis of polymers of higher molecular weight.



Scheme 2.10 Polymerization mechanism in the case of Z-group attachment to the core [65]

Considering both methods mentioned above, in this research, design of the RAFT agent is a major factor. Steric and other factors were considered.[6]

2.6 Styrene maleic anhydride copolymer (SMA)

In the past few decades, chemical modifications of polymers to achieve desirable characteristics have been put into practice. This practice has led to the synthesis of polymers in which more than one monomer is used to form copolymers. The copolymers synthesized are named according to the sequence and feed compositions of the added units during

copolymerization. Familiar names are alternating copolymers, random copolymers, statistical copolymers, block copolymers and graft copolymers. A good example of a copolymer is poly (styrene-co-maleic anhydride).[70]

Poly (styrene-co- maleic anhydride) shown in figure 2.3 below, is produced by copolymerizing styrene and maleic anhydride monomers.

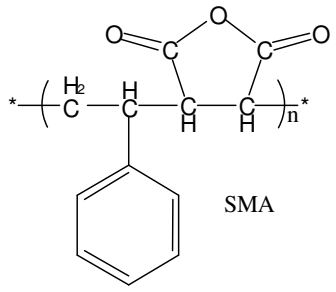


Figure 2.3 Styrene-maleic anhydride copolymer

The importance of styrene-maleic anhydride copolymers is attributed to their usage in a number of areas for various purposes. Its applications comprise additives that are used to upgrade properties of styrenic polymeric material, coating additives, binder application, additives for building materials, microcapsules, blend compatibilizer, adhesion promoter for polyolefin coatings on metals and medical and pharmaceutical applications.[71]

Styrene-maleic anhydride copolymer is also regarded as a functional or reactive polymer. The functionality is brought about by the maleic anhydride in the backbone of the copolymer which is reactive towards nucleophilic reagents (H_2O, alcohols, thiols, ammonia, amines, etc). Introduction of nucleophilic compounds enables the synthesis of new materials.[72]

2.6.1 Medical and pharmaceutical applications

SMA is known to be a biocompatible polymeric material. Its biocompatibility is attributed to the combination of hydrophilic maleic anhydride and hydrophobic styrene units in the backbone of the copolymer. It has been used in many applications such as drug and protein delivery vehicles to the biological environments of different pH.[73] SMA has also been used as male contraceptive.[74] The contraceptive consists of a SMA which is prepared by the step of irradiation at a dose of 0.2 to 0.24 megarad for every 40 g. of the copolymer. The contraceptive consists of an injectable fluid of SMA and pure dimethyl sulphoxide. The polymer has some antiviral activity when tested for anti-HIV virus activity.[75] However, the anti-HIV activity was not as high as that of styrene sulfonate-maleic anhydride derivatives.

2.6.2 Polymer-Protein conjugates

Polymer-protein conjugates are the first polymer therapeutics used as anticancer agents in 1985. Styrene - maleic anhydride neocarzinostatin (SMANCS) conjugate was the first to be introduced into clinical use and lead to development of a new class of anticancer agents. SMANCS is a polymer-protein conjugate synthesized by H. Maeda *et al.* for treatment of tumor.[76, 77 78]They synthesized the polymer-protein conjugate by covalently linking anti-tumor agent/protein neocarzinostatin (NCS) to styrene-maleic anhydride copolymer (SMA). The aim of their study was to develop sufficiently hydrophobic polymer derivative that will promote the dispersion of phase contrast agent lipiodol. Its success has led to it being approved in Japan as a treatment for hepatocellular carcinomas.

2.6.3 Polymerization of styrene-maleic anhydride copolymer

Due to its many applications, styrene-maleic anhydride copolymers have been synthesized for the past few decades by conventional free radical polymerization techniques.[72] Various free radical generating compounds including organic peroxides and azo compounds were employed. In the controlled radical polymerization, the copolymer has been proven to favour

alternating "behavior" during copolymerization when the feed composition ratio of styrene to maleic anhydride ranges from 1:1 to 1:4.[70] Styrene - block - styrene-maleic anhydride copolymer can also be synthesized when the concentration of styrene is high in the feed. Controlled/living free radical polymerization techniques such as NMP and RAFT have been previously reported for the synthesis of styrene-maleic anhydride copolymers as will be reviewed below.

2.6.3.1 NMP

NMP is well known for control of polymerization of different vinyl monomers. It has also been employed in the copolymerization of styrene and maleic anhydride. Park *et al.* have synthesized a copolymer of styrene and maleic anhydride using low amounts of maleic anhydride.[79] The polymerization showed a controlled/living behavior at 120 °C, but when using other temperatures it deviated from it. The conclusion was based on the fact that the copolymerizations deviated from the linear relationship between molecular weight and conversion. Hawker *et al* used TEMPO at 120 °C to synthesize styrene-maleic anhydride copolymer. However, it proved to be fruitless as nonliving behavior was observed under a variety of different conditions with little or no control over molecular weights and polydispersity. They mitigated the problem by using an α-hydrogen bearing nitroxide (second generation) in 5% excess. They made copolymers of high molecular weights and low polydispersity (1.1-1.2). They also showed living behavior of the styrene and maleic anhydride copolymerization by further synthesizing styrene – alt – maleic anhydride – block – polystyrene block copolymer.[80]

2.6.3.2 ATRP

Although the alternating copolymer of styrene and maleic anhydride has been easily synthesized by conventional radical polymerization and other controlled/living radical polymerization techniques, Li *et al.* and Hawker *et al.* have tried it via the ATRP technique, but the polymerization did not take place. The reasonable explanation was that maleic anhydride interferes with the ATRP catalyst such as Cu(I)-2,2′ -bipyridine.[80, 81]

2.6.3.3 RAFT

There have been many reported cases where styrene and maleic anhydride were copolymerized by the RAFT technique to achieve alternating styrene-maleic anhydride copolymer with well controlled molecular weight and low polydispersity.[71, 82, 83]

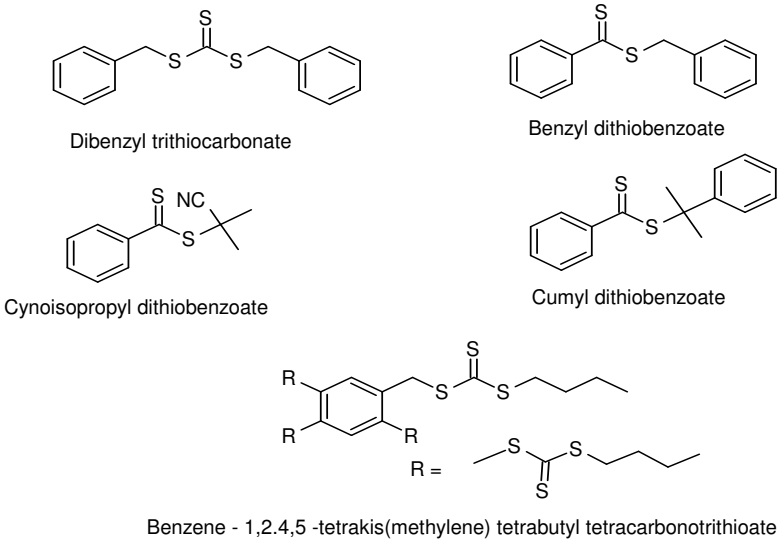


Figure 2. 4 Some of the RAFT CTAs used mediated LRP of SMA

You *et al.* have synthesized styrene-maleic anhydride copolymer in the presence of dibenzyl trithiocarbonate without adding an initiator.[84] In their work cyanoisopropyl dithiobenzoate and benzene-1,2,4,5-tetrakis(methylene) tetrabutyl tetracarbonotrithioate were used to control the copolymerization of styrene and maleic anhydride. Styrene-maleic anhydride copolymers with PDI of 1.09 - 1.20 and molecular weight ranging from 2500 to 5000 were obtained.

Benzyl dithiobenzoate has been used by E. Chernikova *et al.* to control the copolymerization and determine how the monomer feed composition of styrene and maleic anhydride affects the polymerization rates.[84, 85] They found that a higher concentration of styrene results in lower polymerization rates compared with feed composition ratio of 1:1, while higher maleic anhydride concentrations resulted in an increase in PDI. ^{13}C NMR was used again to confirm

the alternating structure of the synthesized copolymer. Du *et al.* also used benzyl dithiobenzoate to control the copolymerization of styrene and maleic anhydride to determine the alternating structure of copolymer formed by electron-spin resonance (ESR).[86] They found that in conventional radical polymerization, the rate of polymerization is too high and the detected ESR spectra were too complicated to interpret the structure of the propagating radical. However, when a CTA was added, propagation rate was reduced and the formation of a relatively stable radical was observed. They found that this intermediate radical during the RAFT mediated polymerization of styrene and maleic anhydride had maleic anhydride radical units at both sides of the dithio compound. de Brouwer *et al.* also used cumyl dithiobenzoate to control the copolymerization of styrene and maleic anhydride before further modifying it for intended use.[71] Further work on RAFT polymerization of styrene-maleic anhydride will be discussed in chapter 4.

2.7 Styrene maleic anhydride copolymer derivatives

2.7.1 Styrene N-substituted maleimide copolymer (SMI)

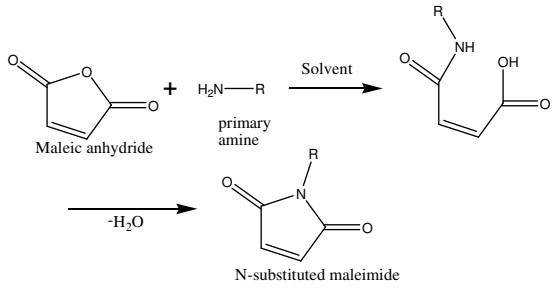
Styrene- maleimide copolymers just like styrene-maleic anhydride copolymers are often alternating in nature. They can be synthesized by copolymerizing styrene and maleimide monomers or alternatively, by imidization of a styrene maleic anhydride copolymer.[87]

2.7.1.1 Synthesis of styrene N-substituted maleimide

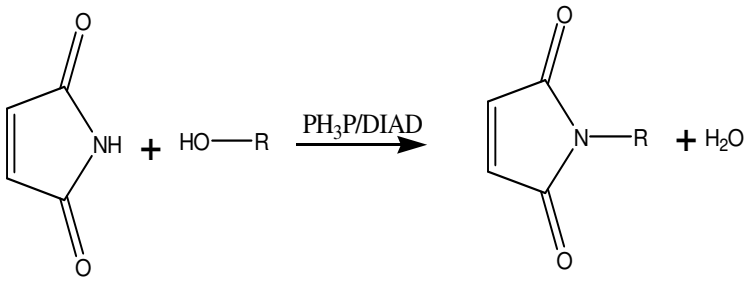
Copolymerization of styrene and maleimides has been previously studied. Xu *et al.* have reported the synthesis of SMI via an anionic polymerization method.[88] The SMI copolymer has also been synthesized by controlled/living radical polymerization techniques. Lokaj *et al.*[89, 90] have reported the synthesis of SMI block copolymer via nitroxide mediated polymerization (NMP), while Li *et al.*[91] reported the synthesis of the alternating copolymer via atom transfer radical polymerization (ATRP). In these studies, the synthesis of the maleimide compound (monomer) was the first step.

Maleimides are generally prepared by a traditional two step procedure, including ring-opening addition between a primary amine compound and maleic anhydride to get maleiamic acid, followed by cyclodehydration. The other method that has been reported for synthesis of maleimides is that of direct alkylation of alcohols with maleimide (scheme 2.11). This method is possible when using Mitsunobu reaction conditions. The method is said to complement condensation/dehydration addition method because the starting material is an alcohol instead of an amine. The yields of this method are low. Walker claimed to have improved the yields of this method by introducing tri-phenyl phosphine (Ph_3P), diisopropyl azodicarboxylate (DIAD) and diethyl azodicarboxylate as catalysts.[87]

Modification of the SMA copolymer can also be used to synthesize SMI. The synthesis can be achieved by reaction of the maleic anhydride residue on the backbone of the copolymer with an amine compound. Vermeesch *et al.* have reported the modification (imidization) by the use of reactive extrusion.[92] The imidization reaction was done under melt condition, whereby the copolymer was melted and reacted with the amine compound. They determined the degree of imidization by titrating residual maleic anhydride with methanol/sodium hydroxide solution. They also measured the glass transition of the modified copolymer which has shown to increase with the degree of imidization depending on substituent.



Scheme 2. 10 Two step procedure for synthesis of N- substituted maleimides



Scheme 2. 11 Mitsunobu reaction (synthesis of N-substituted maleimide by direct alkylation)

2.7.1.2 Properties and applications of N-substituted maleimides copolymers

Polymers of N-substituted maleimides and their derivatives can be classified as high performance engineering plastics, polyimides and a class of rigid polymers because of imide rings in the backbone. They show enhanced mechanical and thermal properties.[93, 94] Due to their good properties, a variety of maleimides were incorporated in vinyl copolymers and have been studied in several fields for various applications. Typical examples are the applications that relates to their good optical properties, dielectric properties and Langmuir Blodgett film-forming properties.[95, 96, 97].

2.7.2 Styrene sulfonate-maleic anhydride (SSMA) copolymer derived from SMA

2.7.2.1 Synthesis of SSMA

SSMA is a copolymer of styrene sulfonate acid or salt with maleic anhydride. There are quite a few methods that can be employed to synthesize the copolymer of styrene sulfonate-maleic anhydride. The most common method for preparing this copolymer is reported in U.S. Pat. No. 3 072 619. The styrene-maleic anhydride copolymer is homogeneously dissolved in a liquid chlorinated aliphatic hydrocarbon such as dichloroethane, carbon tetrachloride or methylene chloride and then treated with sulfur trioxide complex. The sulfonated product precipitates from the solution and is easily recovered by decanting the solution or filtering the

copolymer. Sulfonation can also be achieved by chlorosulfonic acid or sulphuric acid. In other papers, preparation of styrene sulfonate-maleic anhydride copolymer is accomplished by first sulfonating the styrene monomer followed by copolymerization with maleic anhydride.

2.7.2.2 Properties and applications of SSMA

In the last few decades, homopolymers and copolymers of styrene sulfonate have been synthesized for various applications. Polymers containing sulfonic acid groups have high proton conductivity, thermal stability and chemical stability. Because of these properties, they are often used in polyelectrolyte membranes, reverse osmosis and nanofiltrations.[98] They are also used in direct methanol fuel cells (DMFC) because of their resistance to methanol.[99] Styrene sulfonate-maleic anhydride is an example of sulfonate styrenic copolymer which has many applications. Polystyrene sodium sulfonate and low molecular weight sulfonated styrene-maleic anhydride have also been tested for anti-HIV activity and antiviral activity against other enveloped viruses. Low molecular weight styrene sulfonate and pure styrene-maleic anhydride showed low antiviral activity when tested against the HIV virus compared to styrene sulfonate-maleic anhydride.[100] SSMA has many more applications in various fields: i.e.

- Improves soil structure (soil conditioning),[101]
- Improves flow properties of slurry cement,[102]
- it enhances drug solubility and comfortability at a selected pH range,[103, 104]
- used in leather modification to provide resistance to ultraviolet,[105]
- It is used as additive in laundry detergent (prevent redeposition of soil on the stains)[106]

2.7.3 Styrene sulfonate N-substituted maleimide (SSMI)

2.7.3.1 Synthesis of SSMI

SSMI is a copolymer of styrene sulfonate and N-substituted maleimide. Looking into the chemistry of the copolymer itself, there are numerous ways that can be used to synthesize it. However, some methods are quite challenging. The most common and simplest procedure to synthesize SSMI is by first polymerizing styrene and the maleimide of choice in the solvent like dichloroethane followed by sulfonation of the resulting copolymer.[107-109]

2.7.3.1 Properties and applications

The copolymer itself has not been cited in the literature and therefore it has no reported applications and properties. What is important for this study is that it is expected to have anti-microbial activity.

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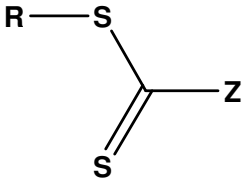
Chapter three: Synthesis of RAFT agents

3.1 Thiocarbonyl thio compounds

Thiocarbonyl thio RAFT agents are used as chain transfer agents in RAFT mediated polymerization. They offer exceptional versatility and produce polymers of controlled molecular weight and low polydispersity (M_w/M_n usually < 1.2, sometimes < 1.1).[1] There are several classes of sulfur containing species (thiocarbonyl thio compounds) that are used as chain transfer agents in RAFT mediated polymerization.[2] These thiocarbonyl thio compounds include dithiocarbamates, trithiocarbonates, dithioesters and xanthates. The classification is brought about by the different Z-groups they possess as illustrated in figure 3.1. The key structural features of RAFT agents are the Z and R groups. The Z group largely controls the reactivity of the RAFT agent. It has two fundamental roles during polymerization, *i.e.* it determines the general reactivity of C=S bond towards radical addition and it is a major factor affecting the lifetime of the intermediate radical resulting from addition of a radical species across the C=S bond.[2, 3] The R group should be an excellent free radical (homolytic) leaving group and should be a good reinitiating radical.[3, 4] More details about the thiocarbonyl thio compound and specific examples regarding types of RAFT agents and the polymerization reactions that they have been successfully employed in, has been discussed to a greater extent by G. Moad *et al.*[5]



R = Leaving group

Z = Alkoxy (xanthate)
N,N-dialkylamine (dithiocarbamate)
Alkyl or aryl (dithioester)
Thio alkoxy (trithiocarbonate)

Figure 3.1 RAFT agent structure as well as common stabilizing Z-groups

3.1.1 Dithiocarbamates

Dithiocarbamates are dithio derivatives with (S=C(Z)S─R) as a general structure. Their preparation and reactivity have been widely investigated.[6] They are not only photo iniferters[7], but also RAFT agents. Dithiocarbamates differ from other RAFT agent by the Z-group. Z-group is a dialkylamino ($\mathbf{R_2N}$).[9] Rizzardo *et al*. found that electron withdrawing substituents on the N of dithiocarbamates can significantly enhance the activity of dithiocarbamates.[8-10] The R-group does not differ from the one used by other species of RAFT agents. It can be cumyl, cyanoisopropyl, propionate ester moiety, etc.[4] Dithiocarbamates in which the nitrogen lone pair is less available for delocalization with the C=S by virtue of being part of an aromatic ring or by having adjacent electron withdrawing substituent have advantage over the dithiocarbamates with nitrogen attached to simple alkyl species. They function effectively for monomers such as styrene and (meth) acrylates. Dithiocarbamates with the nitrogen attached to simple alkyl species works effectively for non-conjugated monomer substrates, such as VAc and NVP.[3, 5]

3.1.2 Trithiocarbonates

Trithiocarbonates are typical RAFT agents which are often characterized by high transfer coefficients.[11, 12] They are generally less effective than dithiobenzoate and similar RAFT agents but they provide a good control over polymerization of (meth)acrylic and styrenic monomers. Substantially, they give less retardation and are less prone to hydrolytic degradation. The Z-group is an alkyl thiol and R-group is a substituted alkyl or aryl group. They are relatively easy to synthesize and purify compared to some other RAFT agents.[5, 13]

3.1.3 Dithioesters

Historically, dithioesters were the most commonly used RAFT agents. Generally, they are oily and have an unpleasant odour.[14] The Z-group can be alkyl or aryl group, such as phenyl, benzyl or methyl. Generally dithioesters are most susceptible to radical addition, especially when the Z-group is phenyl.[3] There have been many publications where functionality is incorporated in the 'R' fragment. Functional groups include hydroxyl, sulfonic acid,

carboxylic acid, siloxane, azide and olefin.[5] A large number of authors have contributed to the studies of RAFT polymerization given that it has been developed to a stage where it is being used in industries for commercial purposes, mainly trithiocarbonates. For example, van den Dungen *et al.* have investigated the initialization behavior of RAFT polymerization of MA using dithioester RAFT agents with different R-groups. They have proven that they all have different initialization periods.[15] With a good choice of R-group dithioesters give a good control over polymerization of (meth)acrylic and styrenic monomers. However, when used in high concentrations they can give retardation.

3.1.4 Xanthates

Xanthates are also chain transfer agents. However, living radical polymerization where they are employed is rather called macromolecular design via interchange of xanthates (MADIX).[16-18] MADIX is among the newest and fastest growing techniques.[16] From a mechanistic point of view, RAFT and MADIX are identical. The general structure of the RAFT agent can be used to describe the structure of xanthates with the appropriate choice of the Z-group.[17] The Z-group of xanthates is an alkoxy moiety. [17, 18] O-alkyl compounds have been extensively used in RAFT polymerization of VAc, NVP and related monomers (such as N-carbozole, N-vinylindole). Xanthates generally have low transfer constants when employed for polymerization of styrenic and acrylic monomers. They fail to control polymerization of methacrylic polymers.[5, 6]

3.2 Synthesis of RAFT agents

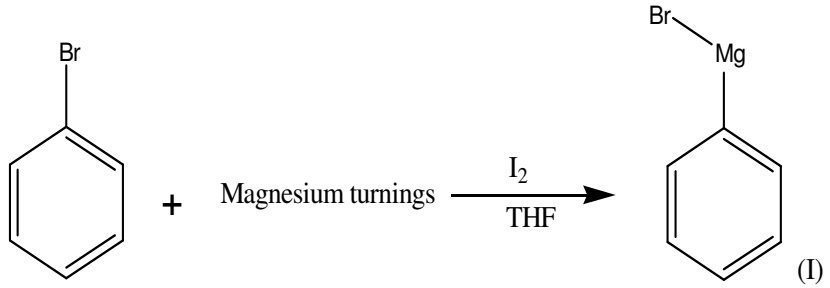
3.2.1 Linear RAFT agent / Cyanoisopropyl dithiobenzoate (CIPD)

3.2.1.1 Chemicals

Magnesium turnings 99% were dried overnight in an oven before use. iodine crystals (Merck), bromobenzene 99% (Acros) were used as received. THF (Merck) was freshly distilled from lithium aluminum hydride (LiAlH4) (Sigma-Aldrich) and kept over molecular sieves. hydrochloric acid 32% (Merck), carbon disulfide 99% (Labchem), dimethyl sulfoxide > 99% (Merck) were used as received. 2,2 azobis (isobutyronitril) (Sigma-Aldrich), ethanol (Sasol), diethyl ether, pentane, heptane and ethyl acetate (all from Merck). All the solvents were distilled under standard conditions at different temperatures.

3.2.1.2 Procedure

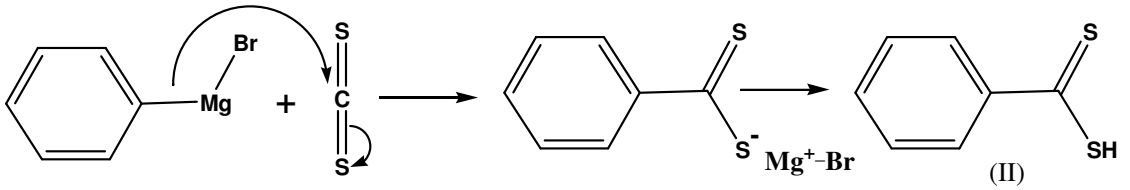
The Grignard reagent, phenyl magnesium bromide, was prepared from magnesium turnings and bromobenzene. All the glassware was dried at 150 °C overnight. Magnesium turnings (4.0 g, 0.16 mol) were weighed and placed in a three necked round bottomed flask (reaction vessel). A few iodine crystals and THF (20 ml) were also added to the reaction vessel. Iodine is used as a catalyst to activate the magnesium substrate.[19] Bromobenzene (25 g, 0.16 mol) and THF (100 ml) were placed in two separate additional dropping funnels. Approximately 10% of THF and bromobenzene were added to the reaction vessel and heat was applied from a heat gun until the reaction started. The brown iodine colour changes to colorless to confirm that the reaction has started. Bromobenzene and THF from the dropping funnels were then added dropwise into the reaction vessel at such rates that the reaction is kept going and the temperature was also kept below 40 °C with the aid of an ice bath. Upon completion, the reaction was allowed to run until no further heat was produced. The reaction mixture was dark greenish in colour, which is a typical Grignard reagent colour.



Scheme 3.1 Grignard agent (I) synthesis with bromobenzene used as halide

Dithiobenzoic acid

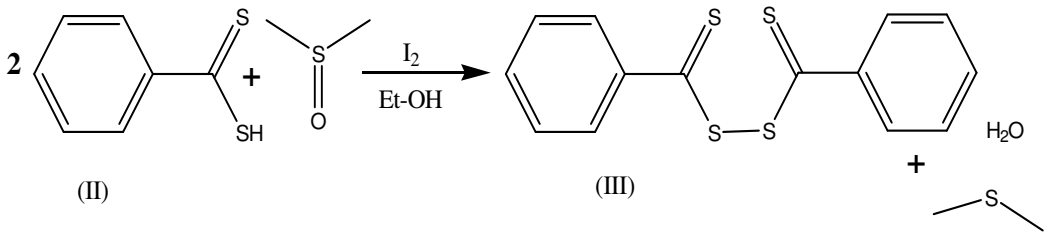
The dropping funnels were charged with carbon disulfide (12.2 g, 0.16 mol) and water (50 ml) respectively. Carbon disulfide was added dropwise into the reaction vessel containing Grignard reaction product. During the addition of carbon disulfide, the reaction mixture turned red-brown signaling the formation of the dithiobenzoate salt. Temperature was monitored as the reaction is exothermic and the temperature of the reaction mixture was kept below 35 °C by using an ice bath. When the addition was complete and the mixture had cooled, water was added dropwise terminating the reaction. HCl (32%) was added as donor of H+ ions to produce dithiobenzoic acid until the red/brown colour changed to purple. The reaction mixture was placed in a separating funnel. Dithiobenzoic acid was extracted with three portions of diethyl ether (40 ml) from water. The extracts were combined and concentrated by removing diethyl ether via rotary evaporation under reduced pressure.



Scheme 3.2 Nucleophilic addition of (I) to CS2 to give dithiobenzoic acid (II)

Dithiobenzoic acid was used to synthesize bis(thiobenzoyl) disulfide (III). Scheme 3.3 shows the synthesis. A round bottomed flask containing dithiobenzoate acid was placed in an ice bath. A stirrer bar was placed in the flask. Catalytic iodine (a few crystals) and ethanol (24.0 ml) were added. DMSO (6.625 g, 0.08 mol) was added dropwise from a dropping funnel

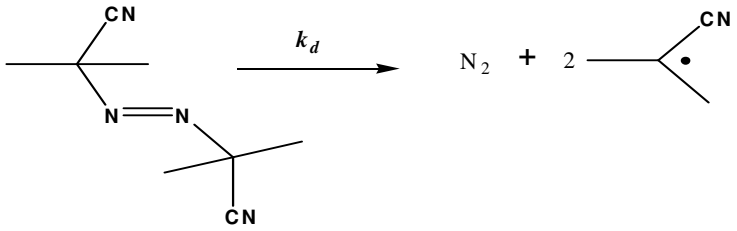
while stirring. A few minutes after addition of DMSO, pinkish-maroon crystals were formed. They were filtered using a sintered glass filter, washed with cold ethanol and dried overnight in a vacuum oven at room temperature. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 (dd, 4H, meta position) 7.61 (m, 2H, para position) 8.09 (d, 4H, ortho position)



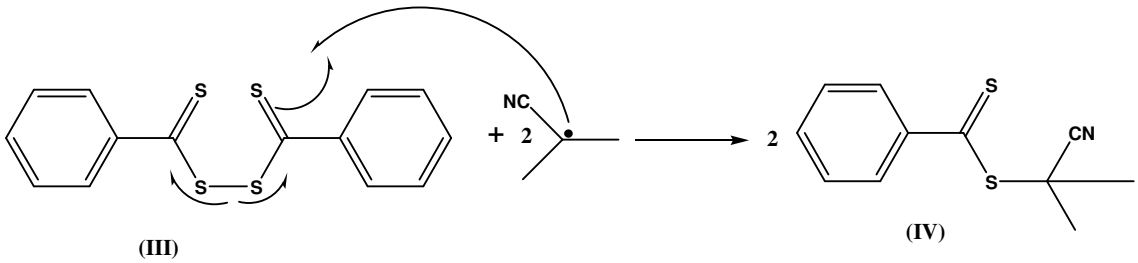
Scheme 3.3 Bis(dithiobenzoyl) disulfide (III) is formed from dithiobenzoic acid (II)

Cyanoisopropyl dithiobenzoate

In a three necked round bottomed flask equipped with a stirrer, appropriate amounts of bis(thiobenzoyl) disulfide (4 g, 0.013 mol) and AIBN (3.25 g, 0.019 mol) were placed. Ethyl acetate (30 ml) was added as a solvent. The mixture was refluxed under nitrogen atmosphere for 30 minutes. Then the solution was stirred overnight at 70 °C. Ethyl acetate was removed under reduced pressure and a red oil was obtained as a product. It was further purified by column chromatography on silica using volume ratios of 9:9:2 pentane: heptane: diethyl ether. The yield was 55% after purification. The complete synthesis is shown in **schemes 3.4** and **3.5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.93 (s, 6H, CH_3) 7.40 (m, 2H, aromatic) 7.55 (m, 1H, aromatic) 7.90 (d, 2H, aromatic). the purity of the compound was 97%. Fig 3.1 shows the ^{1}H NMR spectrum.



Scheme 3.4 Decomposition of 2, 2 azobis (isobutyronitril)



(III) (IV)

Scheme 3.5 Radical addition of initiator fragment to bis(dithiobenzoyl) disulfide (III)

3.2.2 Three armed RAFT agent (benzene-1, 3, 5-triyltris (methylene) tributyl tricarbonotrithioate)

3.2.2.1 Chemicals

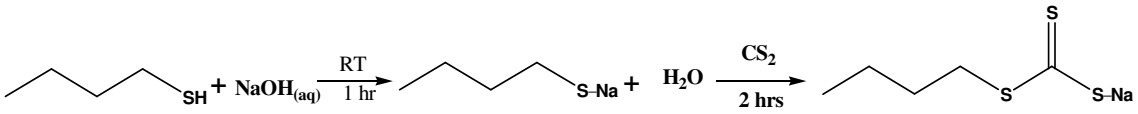
1,3,5 Trimethyl benzene (mesitylene) > 99.0 (Fluka), N-bromosuccinimide > 99%, 2,2 azobis (isobutyronitrile) recrystallized from methanol, benzene > 99.9%, butane thiol were purchased from Sigma Aldrich and used as received. sodium chloride (NaCl) 99.5% (Scienceworld, magnesium sulphate ($MgSO_4$) > 99.0% (Scienceworld), sodium hydroxide (NaOH) > 97% (Saarchem), carbon disulfide(CS_2) > 99% (Labchem) were used as received, diethyl ether (Merck), ethyl acetate (Sasol chemicals), petroleum ether (Kimix) were distilled under standard conditions before use. Water was distilled before use.

3.2.2.2 Procedure

Preparation of sodium butanetrithiocarbonate

A 250 ml three-necked round-bottomed flask equipped with magnetic stirrer, reflux condenser and two dropping funnels, was charged with 19 ml distilled water and sodium hydroxide (NaOH) (5.5 g, 0.13 mol). The contents were stirred until the NaOH was completely dissolved. Dropping funnels were charged with butane thiol (9.99 g, 0.25 mol) and carbon disulfide (7.85 g, 0.10 mol) were both diluted with diethyl ether (50 ml) respectively. From the first dropping funnel, butane thiol was added dropwise over a 30 minutes period and thereafter the reaction was left to stir for 1 hour at room temperature.

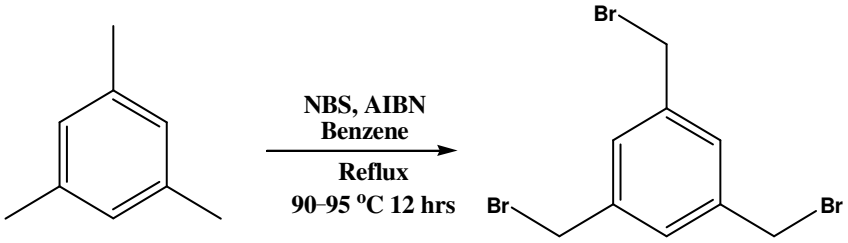
Dropwise addition of carbon disulfide diluted with diethyl ether followed over a period of 30 minutes. The reaction mixture was stirred for 2 hours. The solvent was removed by rotary evaporation. The residue was extracted three times with ethyl acetate. Ethyl acetate was removed by rotary evaporation to afford a yellow powder (product) with a yield of 70%. The crude product was used without further purification.



Scheme 3.6 Synthesis of sodium butanetrithiocarbonate

Synthesis of 1,3,5-tribromomesitylene

10 ml (0.072 mol) of mesitylene, 44.8 g (0.252 mol) of N-bromosuccinimide (NBS), 8.75 g (0.036 mol) of benzoyl peroxide (BPO), and 200 ml of benzene were charged into a 500 ml three necked round bottomed flask equipped with a magnetic stirrer. The reaction mixture was refluxed for 12 hours at 90-95 °C then allowed to cool. The cooled reaction mixture was washed with water and dried over magnesium sulphate. Solvent was removed under vacuum to get a pale yellow solid. The crude product was recrystallized from a 1:1 mixture of ethanol and hexane.[20, 21] Yield was 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.34 (s, 6H, methylene), 6.78 (s, 3H, aromatic). The purity was 98%.

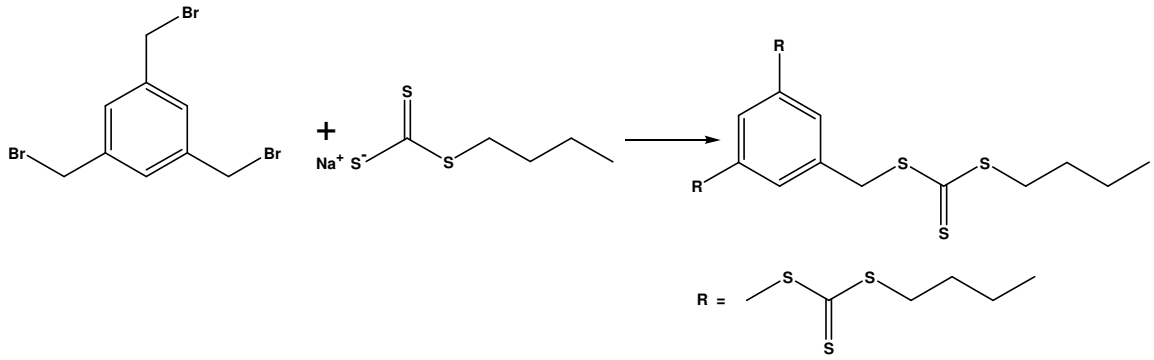


Scheme 3.7 Synthesis of 1,3,5-tribromomesitylene

Benzene-1,3,5-triyltris(methylene) tributyl tricarbonotrithioate

A round-bottomed flask equipped with magnetic stirrer was charged with a partially soluble suspension of sodium butanetrithiocarbonate (6.33 g, 0.034 mol) in THF (20 ml). A solution

of 1,3,5-tribromomesitylene (4.0 g, 0.011 mol) in THF (5 ml) was added dropwise from a dropping funnel to the round-bottomed flask over a period of 30 minutes. The solution was allowed to stir for 12 hours before adding 30 ml of water and 30 ml of ethyl acetate. Using a separating funnel, the organic phase was separated and the aqueous layer was extracted with ethyl acetate (2 x 40 ml). The solution of combined organic phases was washed with saturated NaCl solution, dried with $MgSO_4$, and filtered. The solvent was evaporated under vacuum to afford a crude product (yellowish oil). The product was purified by chromatography on silica, using 20 % ethyl acetate in petroleum ether as an eluent. ^{1}H NMR: δ*:* 0.9 (9H, -CH3), 1.45 (6H, methylene -CH_2-), 1.68 (6H, methylene -CH_2-), 3.4 (6H, methylene S-CH_2-), 4.4 (6H, benzyl CH2), 7.35 (3H, Aromatic H). The yield was 51% and the purity was 94%. Figure 3.2 shows the ^{1}H NMR spectrum.



Scheme 3.8 Benzene-1,3,5-triyltris(methylene) tributyl tricarbonotrithioate

3.2.3 Four armed RAFT agent (Benzene-1,2,4,5-tetrayltetrakis(methylene) tetrabutyl tetracarbonotrithioate)

3.2.3.1 Chemicals

1,2,4,5-Tetramethylbenzene, N-bromosuccinimide > 99.0%, carbon disulfide > 99.0%, Butane thiol (Sigma-Aldrich), sodium hydroxide (NaOH) > 97% (Saarchem), benzene > 99.9% were all purchased from Sigma-Aldrich and used as received. AIBN was recrystallized from methanol (Sigma-Aldrich). Sodium chloride (NaCl) (Merck), magnesium sulphate ($MgSO_4$) > 99.0% (Scienceworld) were used as received. THF (Merck) freshly distilled from

lithium aluminum hydride ($LiAlH_4$) (Aldrich) and kept over molecular sieve, Diethyl ether (Merck), ethyl acetate (Sasol chemicals) were distilled under standard conditions before use.

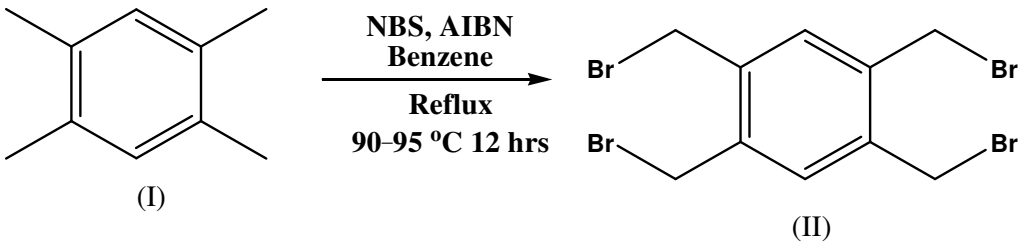
3.2.3.2 Procedure

Preparation of Sodium butanetrithiocarbonate

This was synthesized by the method described earlier in section 3.2.2.2. The crude product was used without further purification.

Preparation of 1, 2, 4, 5- Tetrakis-(bromomethyl) benzene

A 500 ml three-necked round-bottomed flask equipped with magnetic stirrer was charged with 1, 2, 4, 5-tetramethylbenzene (10.73 g, 0.08 mol), N-bromosuccinimide (57.66 g, 0.324 mol) AIBN (4.27 g, 0.026 mol) and benzene (100 ml). The solution was refluxed with stirring for 12 hours under nitrogen atmosphere. After cooling to room temperature, the mixture was slowly poured in a 500 ml beaker containing water (100 ml). The product was extracted with benzene and dried over anhydrous magnesium sulphate. The mixture was filtered to remove magnesium sulphate. Solvent was removed under vacuum and cream-white oily crystals were obtained. Product was recrystallized from hexane and methylene chloride (1:1) to afford white crystals.[22] The synthesis is represented by scheme 3.9. ^{1}H NMR: δ*:* 4.6 (8H, CH_2, benzyl) 7.4 (2H, aromatic H). The yield was 60% and the purity was 98%.



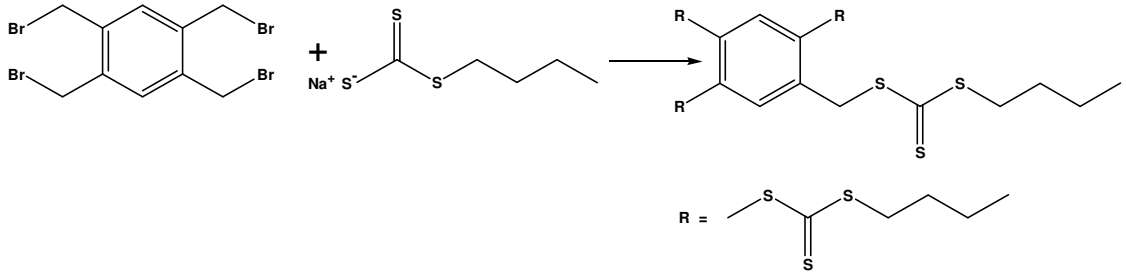
(I) (II)

Scheme 3.9 synthesis of 1, 2, 4, 5- Tetrakis-(bromomethyl) benzene

Benzene-1,2,4,5-tetrayltetrakis(methylene) tetrabutyl tetracarbonotrithioate

A round-bottomed flask equipped with magnetic stirrer was charged with a partially soluble suspension of sodium butanetrithiocarbonate (3.11 g, 0.165 mol) in THF (15 ml). Using a dropping funnel, a solution of 1, 2, 4, 5- tetrakis-(bromomethyl) benzene (4.0 g, 0.9 mmol) in

THF (30 ml) was added dropwise to the round-bottomed flask over period of 30 minutes. The solution was allowed to stir for 12 hours before adding 30 ml of water and 30 ml of ethyl acetate respectively. The organic phase was separated using a separating funnel and the aqueous layer was extracted with ethyl acetate (2 x 40 ml). The solution of combined organic phases was washed with saturated NaCl solution, dried with $MgSO_4$ and filtered. The solvent was evaporated under vacuum to afford a crude product (yellow crystals). The product was purified by chromatography on silica, using 20 % ethyl acetate in petroleum ether (80%) as an eluent. ^{1}H NMR: δ*:* 0.9 (12H, -CH3), 1.4 (8H, methylene -CH_2-), 1.65 (8H, methylene -CH_2-), 3.4 (8H, methylene S-CH_2-), 4.6 (8H, benzyl CH_2), 7.4 (2H, Aromatic H). The yield was 53% and purity was 93%.



Scheme 3.10 Benzene-1,2,4,5-tetrayltetrakis(methylene) tetrabutyl tetracarbonotrithioate

3.3 Conclusions

Three RAFT agents for the copolymerization of styrene and maleic anhydride were successfully synthesized. NMR spectroscopy was used to confirm their structures and purity. The four armed star RAFT agent and cyano isopropyl dithiobenzoate had a purity above 95% and the three armed star RAFT agent had a purity above 90%. Further purification would have resulted in too large losses of RAFT agents.

^{1}H NMR spectra of RAFT agents

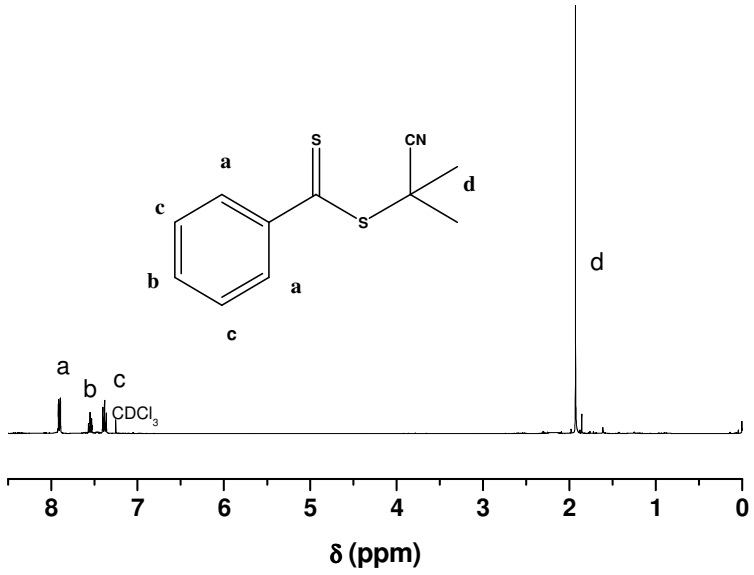


Figure 3. 1 ^{1}H NMR spectrum of cyanoisopropyl dithiobenzoate

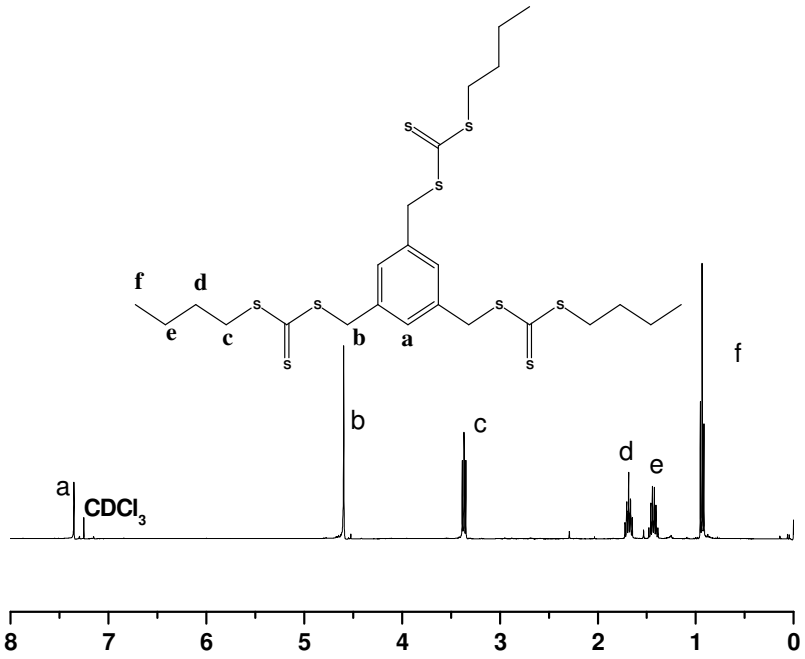


Figure 3. 2 ^{1}H NMR spectrum of benzene-1,3,5-triyltris(methylene) tributyl tricarbonotrithioate

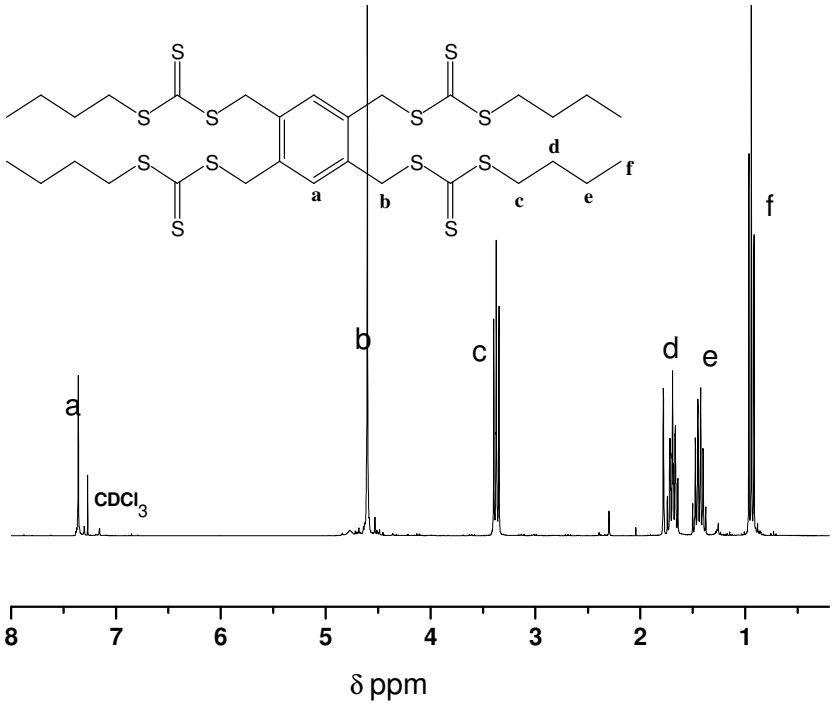


Figure 3. 3 ^{1}H NMR spectrum of benzene-1,2,4,5-tetrayltetrakis(methylene) tetrabutyl tetracarbonotrithioate

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Chapter four: Experimental and discussion

4.1 Introduction

In this work, four different copolymers were synthesized. Styrene maleic anhydride copolymer (SMA) was the first to be synthesized of the four copolymers. The other three, which are styrene maleimide copolymer (SMI), styrene sulfonate maleic anhydride copolymer (SSMA) and styrene sulfonate maleimide copolymer (SSMI), were synthesized by modifying the SMA copolymer.

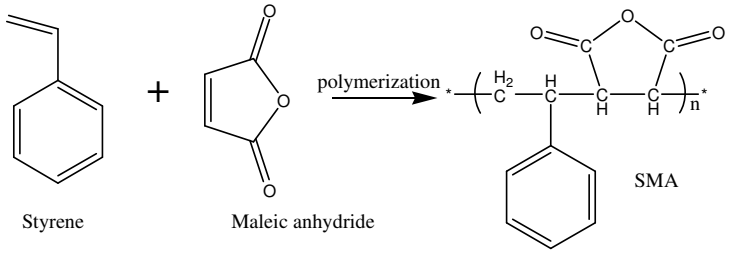
4.1.1 SMA copolymer

SMA copolymer can be easily synthesized by conventional radical polymerization. The SMA copolymer results from the copolymerization of styrene and maleic anhydride and it has a tendency to give an alternating structure.[1-4]

In this study, the reversible addition-fragmentation chain transfer mediated polymerization (RAFT) technique was employed due to its ability to produce polymers with controlled molecular weight and narrow molecular weight distribution. As was briefly discussed in Chapter two, there have been many reports of successful RAFT mediated copolymerization of styrene and maleic anhydride. Van den Dungen *et al*. have studied the initialization behaviour of the copolymerization using two different RAFT agents (*i.e.* cyanoisopropyl dithiobenzoate (CIPDB) and cumyl dithiobenzoate (CDB)). Both RAFT agents provided good control and an alternating copolymer was obtained.[5] They proved that the choice of RAFT agent has an influence on initialization rates and on which monomer unit will be found at the alpha terminus of the chain.

Although good control over molar mass distribution and an alternating structure are obtained by the use of the RAFT technique, the feed composition ratio of the monomers in the

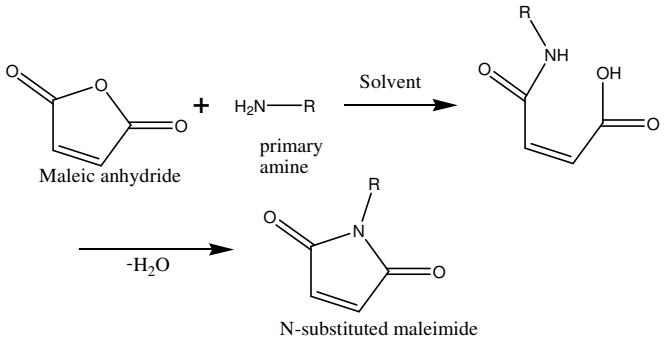
polymerization system has to be 1:1 (Sty:MAnh).[6] It has been reported that, when the amount of styrene to maleic anhydride is too high in the feed (9:1 to 22:1) a block copolymer (poly(styrene-alt-maleic anhydride-block-styrene)) is obtained.[7] In the present study, the RAFT technique and a co-monomer feed ratio of 1:1 are used to obtain alternating copolymers with good control of molecular weight. Scheme 4.1 depicts the copolymerization of styrene and maleic anhydride. Details of the polymerization are discussed in the experimental section.



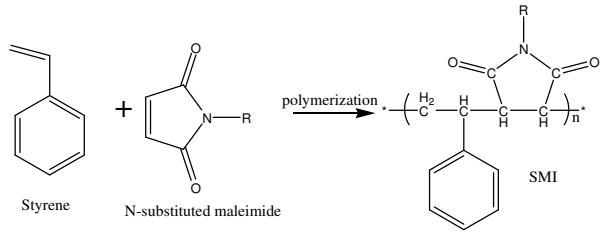
Scheme 4.1 styrene-maleic anhydride copolymer synthesis

4.1.2 SMI copolymer

Methods to synthesize SMI copolymers have been previously discussed in Chapter two. The first method consists of the synthesis of N-substituted maleimide as a monomer. This synthesis consists of a two step procedure shown in scheme 4.2, followed by copolymerization with styrene monomer (scheme 4.3).[8-12]

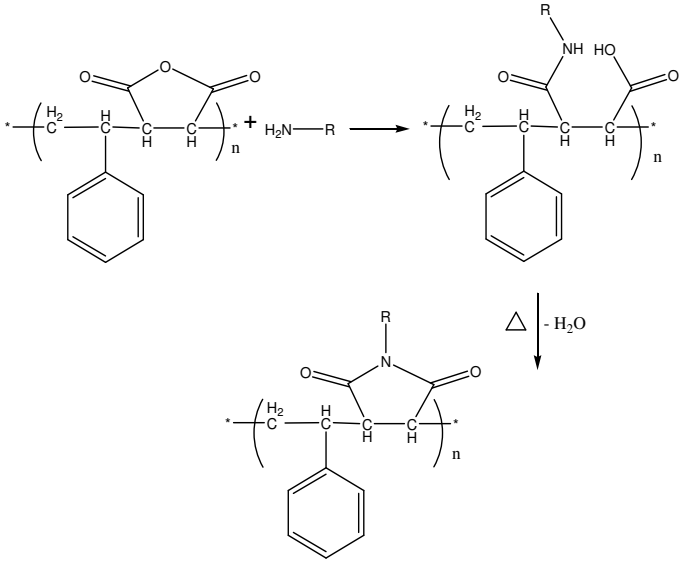


Scheme 4. 2 Synthesis of N-substituted maleimide



Scheme 4. 3 Styrene-maleimide copolymer synthesis via direct copolymerization of monomers

Another prominent method used to synthesize SMI copolymer is by initial synthesis of SMA copolymer followed by reacting maleic anhydride residues on the backbone of the copolymer with primary amine compounds to form an imide (scheme 4.4).[13]

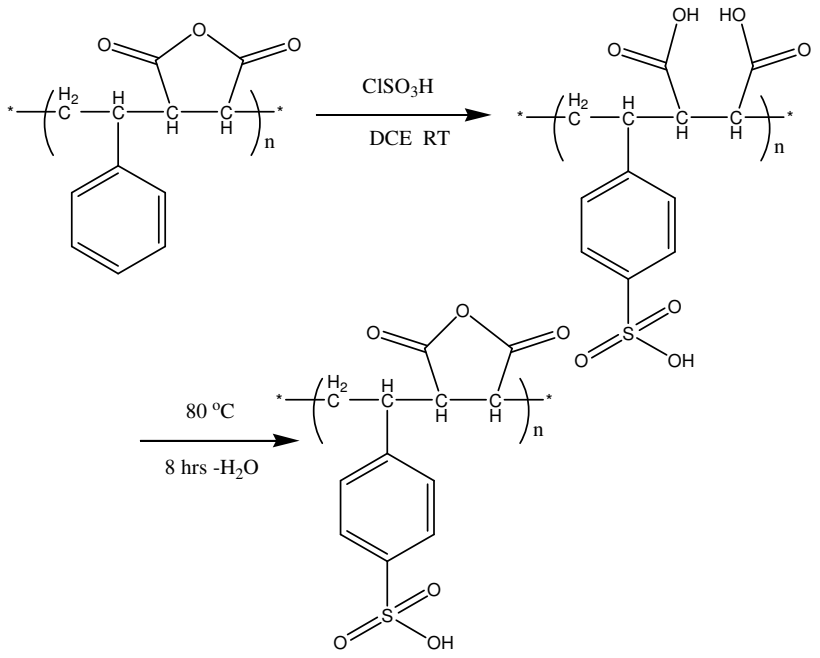


Scheme 4.4 Modification of SMA to SMI by reaction with primary amine

4.1.3 SSMA copolymer

In this study, for the synthesis of the SSMA copolymer, sulfonation of SMA copolymer with chlorosulfonic acid was the method of choice. Our aim is to synthesize a copolymer of controlled molecular weight and narrow molecular weight distribution using the RAFT technique. Copolymerization of styrene sodium sulfonate and maleic anhydride in the

presence of a RAFT agent was not successful. The reason behind this was not investigated, however the reaction will be further considered in future work. Synthesis of SSMA has been reported in a reasonable number of publications. The procedure to be followed in the present project is shown in Scheme 4.5



Scheme 4.4 Schematic representation of sulfonation of SMA copolymer to produce SSMA copolymer

4.1.4 SSMI copolymer

Styrene sulfonate-maleimide is a copolymer of styrene sulfonate and maleimide monomers. There are a few methods that can be used to synthesize this type of copolymer. The first approach can be the synthesis of the monomers, styrene sulfonate and maleimide (scheme 4.2) followed by the copolymerization. The other approach is the synthesis of SMA copolymer (scheme 4.1) followed by stepwise modification of each monomer unit. First, SMA copolymer is modified to SSMA copolymer followed by a reaction of the maleic anhydride with an amine compound to form the SSMI copolymer. The procedures used to modify styrene of SMA copolymer to styrene sulfonate and maleic anhydride to maleimide had been previously discussed in Sections 4.1.2 and 4.1.3. The final structure of the SSMI copolymer is shown by figure 4.1.

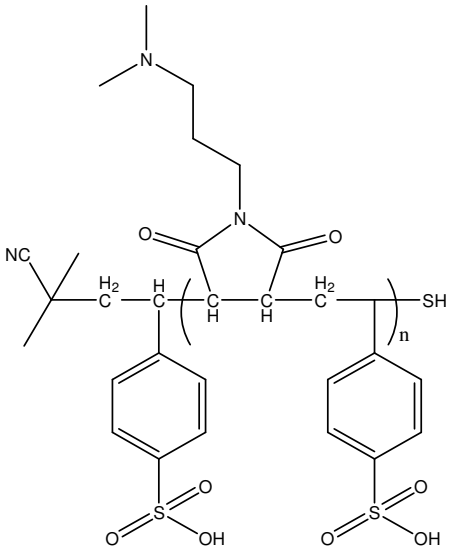


Figure 4.1 Structure of SSMI copolymer

4.2 Synthesis of copolymers

4.2.1 Materials

Styrene (Sigma-Aldrich) was purified from inhibitor by subsequently washing with 10% aqueous solution of sodium hydroxide (NaOH) and with water. After drying over $MgSO_4$, it was filtered and distilled under vacuum and stored at low temperatures before use. Maleic anhydride 99%+ (Merck) was used as received. Azobis(isobutyronitrile) (AIBN) (Merck) was recrystallized from methanol 99.9% (Merck). Methyl ethyl ketone 99% (MEK) (Sigma-Aldrich) was used as received, tetrahydrofuran (THF) was distilled from lithium aluminium hydride ($LiAlH_4$) and kept over molecular sieves. Hexane was distilled under standard conditions before use. The RAFT agents were synthesized as discussed in Chapter three. Isopropanol class 3 Grade (Sasol solvents) was used as received. 3-(*N*, *N*-dimethylamino)-1-propylamine > 98% (DMAPA) purchased from Fluka was used as received. 4-(N,N-dimethylamino)pyridine 99% (DMAP), 4-aminomethylbenzene sulphonamide hydrochloride 95% (4-AMBSA), dimethylformamide 99% (DMF) and triethylamine +99.5 % (TEA), chlorosulfonic acid 98 % +, dichloroethane 99.0% + (DCE) were purchased from Sigma-Aldrich and used as received.

4.2.2 SMA copolymer

For the synthesis of SMA copolymer the RAFT mediated polymerization of styrene and maleic anhydride was carried out. The polymerization reactions were all conducted in solution at 60°C.

Table 4.1 RAFT mediated solution polymerization of SMA copolymer with three different transfer agents (i), (ii) and (iii) listed below to afford linear and star copolymers.

Run	RAFT agent type	Time (hrs)	$[M]_0$:[RAFT]:[I]	[a]Conv. (%)	[b]$M_n^{cal.}$ (g/mol)	M_n^{NMR} (g/mol)
1	(i)	10	250:5:1	83.2	8595	7886
2	(i)	7	250:5:1	64.1	6691	6046
3	(i)	5	250:5:1	48.2	5078	3943
4	(ii)	10	250:5:1	96.2	10315	—
5	(ii)	7	250:5:1	61.3	6752	—
6	(iii)	10	250:5:1	91.3	9953	—
7	(iii)	7	250:5:1	61.0	6930	—

RAFT agents (see chapter three)	**Formula**
(i) – Cyanoisopropyl dithiobenzoate **(ii)** – Benzene-1,3,5-triyltris(methylene) tributyl tricarbonotrithioate **(iii)** – Benzene-1,2,4,5-tetrayltetrakis(methylene) tetrabutyl tetracarbonotrithioate	[a]**Conv.** – %Yield = mass of polymer (g)/ [RAFT + monomer + initiator] (g) [b]$\mathbf{M_n}$ – M_n values calculated by equation 4.1 – M_n values could not be determined from ^{1}H NMR spectra

The experimental procedure was standard for the runs 1-7, the only difference was the duration of the polymerization taken for each run and the type of RAFT agent employed. For example, the first run was carried out as follows (1): Styrene (13.02 g, $1.25 \cdot 10^{-1}$ mol), maleic anhydride (12.26 g, $1.25 \cdot 10^{-1}$ mol), AIBN (0.0821 g, $0.5 \cdot 10^{-3}$ mol), the RAFT agent (i) (1.107 g, $5.0 \cdot 10^{-3}$ mol) and MEK (50 ml) were placed in a 250 ml three necked round bottomed flask equipped with magnetic stirrer bar and condenser. The contents were purged with nitrogen for 30 minutes, and the 250 ml flask was placed in an oil bath at a temperature of 60 ºC. Polymerization was stopped after 10 hours by removing the flask from the oil bath and letting it cool to room temperature. The polymer was precipitated by adding the contents

of the round bottomed flask dropwise into a beaker containing 400 ml isopropanol and stirred for three hours to dissolve unreacted material. Precipitated copolymer was collected by filtration as a pink powder. The copolymer was re-dissolved in THF and precipitated in hexane three times.

Theoretical values of molecular weights were calculated using equation 4.1[14], which is the simplified version of equation 4.2,[15] where $[I]_0$, $[RAFT]_0$ and $[M]_0$ are the initial concentrations of the initiator, RAFT agent and monomer respectively. ξ is the fractional conversion; M_0 and FW_{RAFT} are the molecular weights of the monomer and the RAFT agent respectively. *f is* the initiator efficiency factor and k_d is the rate constant for initiator decomposition. *f* values for AIBN range between 0.5 and 0.6 at 60 °C in conventional free radical polymerization.[16] However, *f* values are not constant and they are lower in highly viscous media. Conversion of monomer to polymer leads to an increase in the viscosity of the system hence resulting in a decrease of *f* values. This value can be below 0.5 in viscous media and the second term in the denominator in equation 4.2 becomes arguably small.[17] Equation 4.1 is therefore used for convenience.

$$\overline{M_n} = FW_{RAFT} + {[M]_0}/{[RAFT]_0} \times \xi \times M_0 \qquad (4.1)$$

$$\overline{M_n} = FW_{RAFT} + \frac{[M]_0}{[RAFT]_0 + 2f[I]_0\left(1 - e^{-k_d t}\right)} \times \xi \times M_0$$

(4.2)

$$\xi = \frac{W_{pol} - W_{RAFT}}{W_{monomer}} \qquad (4.3)$$

Conversion of monomer to polymer is calculated by equation 4.3 where W_{pol}, W_{RAFT}, $W_{monomer}$ are the weight of polymer formed, the RAFT agent and monomer used respectively. ^{1}H NMR was also used to calculate the molecular weight of SMA copolymer with the aid of end-group peaks.[18] Only molecular weight of the linear chain SMA copolymer could be determined and it was in acceptable agreement (section 4.1)with the other methods such as SEC and MALDI

– ToF (for low molecular weight SMA) used to determine the molecular weight. For the star polymers, the end-group peaks were part of the broad proton peaks of styrene and maleic anhydride, therefore molecular weight could not be determined.

4.2.3 SMI copolymer

For modification of SMA copolymer to SMI (runs 1-5), the following procedure was typical: SMA from run 1 (3.21 g), 4-AMBSA (3.35 g, 1.5 x 10^{-2} mol), DMAP ($2.0 \cdot 10^{-3}$ g, $1.6 \cdot 10^{-2}$ mol), TEA (0.016 g, $1.6 \cdot 10^{-4}$ mol) and DMF (30 ml) were placed in a 100 ml round bottomed flask equipped with magnetic stirrer bar and condenser. The 100 ml flask was placed in an oil bath at a temperature of 85 ºC. The reaction was stopped after 4 hours by removing the flask from the oil bath and letting it cool to room temperature. Then 1 ml of ammonia solution (30 %) was added to the round bottomed flask at room temperature and the reaction mixture was stirred for another 4 hours. Ammonia reacts with unreacted maleic anhydride moieties in the backbone of SMA copolymer to form maleimide. The reaction of maleic anhydride and ammonia improves solubility of the newly synthesized SMI copolymer. The copolymer was precipitated by adding the contents of the round bottomed flask drop-wise into a beaker containing 200 ml isopropanol and stirred for three hours to dissolve unreacted material. The precipitated copolymer was left to settle at the bottom of the beaker and isopropanol was decanted. The copolymer was cream-white when wet. The product was dried in vacuo overnight at 100 ºC to afford a cream-yellowish powder.

Table 4.2 The quantities of reagents used to modify SMA to SMI. SMI copolymers were prepared from SMA copolymers prepared from run 1, 4 and 6 in table 4.1

Run	SMA Mass (g) (run no. Table 4.1)	*Maleic anhydride Mol x 10^{-2}	4-AMBSA Mass(g): mol x 10^{-2}	DMAP Mass (g): mol x 10^{-2}	TEA Mass (g) x 10^{-2}: mol x 10^{-4}	Ammonia solution (30%)/ml
1. Linear SMI	3.21 (1)	1.58	3.35 : 1.50	2.00 : 1.64	1.60 : 1.58	1.00
2. Linear SMI	1.02 (1)	0.49	0.80 : 0.36	0.58 : 0.47	0.50 : 0.49	0.50
3. Linear SMI	1.01 (1)	0.49	1.10 : 0.49	0.77 : 0.63	0.60 : 0.59	0.50
4. Three armed SMI	3.05 (4)	1.51	3.69 : 1.66	1.60 : 1.31	1.30 : 1.28	1.00
5. Four armed SMI	3.00 (6)	1.48	3.30 : 1.48	1.80 : 1.47	1.40 : 1.38	1.00

(1), (4) and (6) are all the run numbers from which SMA copolymers were prepared from (Table 4.1).

* Moles of maleic anhydride available for modification (imidization)

4.2.4 SSMA copolymer

The typical procedure for the runs 1-5 to modify SMA to SSMA was followed: (e.g. for run 1) a 100 ml round-bottomed three-necked flask equipped with magnetic stirrer, 100 ml dropping funnel and a reflux condenser, was charged with dichloroethane (40 ml) and linear SMA copolymer (6.02 g). Chlorosulfonic acid (3.46 g, 2.96 x 10^{-2} mol) diluted with dichloroethane (10 ml) was added to the dropping funnel. At room temperature while the contents in the round-bottomed flask were stirred, a solution of chlorosulfonic acid was added dropwise from the dropping funnel until finished. The copolymer started to precipitate out of the solution with the addition of the chlorosulfonic acid solution. The reaction was kept stirring until hydrochloric acid (HCl) in the form of a gas was no longer released. The temperature was raised to 70 °C using an oil bath for 1 hour. Then the reaction mixture was cooled down and the solvent was decanted. Distilled water (100 ml) was added to the dropping funnel, and then dropwise added to the layer of the polymer at the bottom of the round-bottomed flask. When the addition of water was completed, the temperature was

increased to 90 °C for a period of 2 hours. Then the round bottomed flask with its contents was removed from the oil bath and cooled down to room temperature. The cold copolymer solution was poured into a 500 ml round bottomed flask with one neck and frozen by using liquid nitrogen. The round bottomed flask with frozen contents was attached to the freeze dryer overnight to remove water under vacuum. The dried copolymer was put in an oven for maleic anhydride ring closing at 80 °C for eight hours. When the maleic anhydride ring has been closed by the use of oven, a black product was obtained. The copolymer was analyzed without ring closing the maleic anhydride ring. The copolymer was characterized by NMR, FTIR and SEC.

Table 4.3 Quantities of reagents used to modify SMA to SSMA

Run (SSMA)	SMA Mass(g)	*Styrene mol x 10^{-2}	Chlorosulfonic acid Mass(g) : mol x 10^{-2}
1. Linear (1)	6.02	2.98	3.46 : 2.96
2. Three armed (4)	6.08	3.01	3.50 : 3.00
3. Four armed (6)	6.05	2.88	3.48 : 2.98

(1), (4) and (6) are all the run numbers from which SMA copolymers were prepared from (Table 4.1).

* Moles of styrene available for modification (sulfonation)

4.2.5 SSMI copolymer

The following procedure was typical for synthesis of SSMI from SSMA: SSMA (from run 1 table 4.3) 3.10 g was dissolved in 20 ml DMF and charged in a 100 ml round bottomed flask equipped with magnetic stirrer. 1.60 g (15.0 mmol) DMAPA diluted with 5 ml DMF was added dropwise from a dropping funnel into the solution of SSMA. The reaction mixture was stirred for 5 hours at room temperature. The resulting copolymer was precipitated by dropwise addition of the reaction mixture into a beaker containing 200 ml isopropanol. The precipitate in isopropanol was stirred for an hour to extract unreacted material and subsequently left to settle at the bottom of the beaker. The solvent was decanted and the precipitate was filtered and dried overnight in a vacuum oven at room temperature.

Table 4.4 Quantities of reagents used to modify SSMA to SSMI.

Theoretical M_n of SSMA was used to calculate required amount of amine

Run (SSMI)	SSMA M_n^{th}	SSMA Mass(g)	*Maleic anhydride mol x 10^{-2}	DMAPA Mass(g) : mol x 10^{-2}
1. Linear (1)	11366	3.10	1.09	1.60 : 1.56
2. Three armed (2)	15963	3.15	1.11	1.63 : 1.58
3. Four armed (3)	11825	3.05	1.08	1.62 : 1.58

(1), (2) and (3) are all the run numbers from which SSMA copolymers were prepared from (Table 4.3).

* Moles of maleic anhydride available for modification (imidization)

4.2.6 Purification of Copolymers by dialysis

Dialysis is an analytical process of separating smaller molecules from larger molecules in solution by means of their unequal diffusion rates through semi-permeable membrane. Dialysis is employed to remove low molecular compounds to have polymers free of impurities or low molecular compounds.

Procedure

Dialysis tubing (Snake skin pleated dialysis tubing, Pierce, 3.500 MWCO). The copolymers were dialyzed against distilled water.

The synthesized copolymers were dissolved in distilled water at a concentration of 0.025 $g \cdot ml^{-1}$ and dialyzed for 48 hours at room temperature. The polymers recovered after freeze drying were placed in an oven for 5 hours at a temperature of 80 °C.

4.3. Characterization techniques

4.3.1 NMR

NMR spectroscopy was used to elucidate the chemical structures of the synthesized compounds and to determine their purity. One dimensional ^{1}H and ^{13}C NMR spectra were acquired with a Varian Unity Inova 600MHz NMR spectrometer with 5 mm broad band probe at 293K in DMSO-d_6 unless specified otherwise. For both ^{1}H and ^{13}C NMR a relaxation delay of 1 second was used. The frequency for ^{1}H is 600 MHz and the frequency for ^{13}C is 150 MHz. Spectra were internally referenced to TMS. All peaks are reported downfield of TMS.

4.3.2 FTIR/ATR

Infrared spectroscopy was used to identify the functional groups present in synthesized compounds. All the polymer samples were dried prior to analysis. A Smart Golden Gate Diamond attenuated total reflection FT-IR with ZnSe lenses from Thermo nicolet coupled to a Nexus FT-IR was used. The powder sample was placed and pressed between the ZnSe lenses and analyzed by averaging 32 scans with a wavenumber resolution of 4 cm^{-1}.

4.3.3 Size Exclusion Chromatography (SEC)

Size exclusion chromatography is a chromatographic method in which polymer chains are separated based on their size, or more precisely, their hydrodynamic volume. It is applied to large molecules such as organic polymers and proteins. It is used to determine the molecular weight and molecular weight distribution.

Dry polymer samples were dissolved in DMF (5 mg/ml) and filtered through a 0.45 µm nylon filter. The SEC instrument consisted of Waters 117 plus autosampler, Waters 600 E system controller (run by Millenium V 3.05 software) and a Waters 610 fluid unit. A Waters 410 differential refractometer and Waters 2487 dual wavelength absorbance detector were used at

30 °C as detectors. DMF (HPLC grade) containing LiCl (20 mM) was sparged with IR grade helium and was used as eluent at a fixed flow rate of 0.7 ml/min. The column oven was kept at 30 °C and the injection volume was 100 μL. Two PL gel 5 μm mixed-C columns and a precolumn (PL gel 50 μm Guard) were used. The system was calibrated with narrow poly (methyl methacrylate) (PMMA) standards ranging from 850 to 342 900 g/mol. All molecular weights were reported relative to PMMA standards.

4.3.4 MALDI TOF Mass spectroscopy

MALDI TOF mass spectra were recorded on a Voyager-DE STR (Applied Biosystems, Framingham) equipped with a nitrogen (N_2) 337 nm laser in the reflector mode, at 25 kV accelerating voltage and delayed extraction. Potassium trifluoro acetate (KTFA) was used as cationizing agent and trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene]malonitrile was used as the matrix. The sample was prepared by individually making 40 mg/ml matrix, 5mg/ml KTFA and 1mg/ml sample in THF solvent. They were mixed with the ratio 4:1:4 and thereafter placed on the target plate in the form of spots. The spots were left to dry by evaporation of THF.

4.4. Results and discussion

4.4.1 SMA copolymer

4.4.1.1 ^{1}H NMR analysis

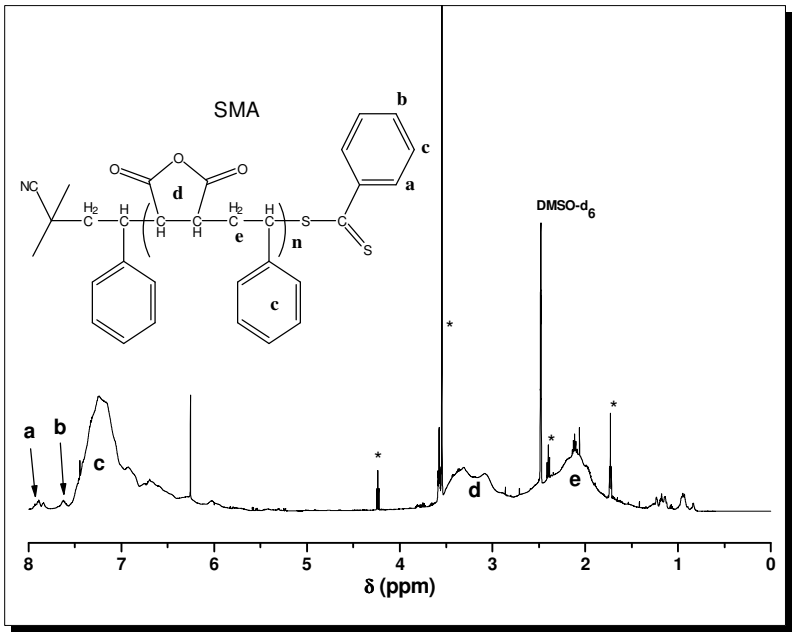


Figure 4.2 ^{1}H NMR spectrum (DMSO-d_6) of SMA copolymer synthesized via RAFT mediated polymerization of Sty and MAnh at 60 °C with the initial mass ratio of 125:125:5:1 for Sty, MAnh, RAFT agent and AIBN respectively. (run 1 Table 4.1)

In the ^{1}H NMR spectrum of SMA, (Figure 4.2) broad overlapping peaks between 1.3 and 2.5 ppm (e) and peaks between 5.9 ppm and 7.6 ppm (c) are due to methylene/methine and aromatic ring hydrogens of styrene respectively. The methine proton peaks of maleic anhydride appear between 3.1 and 3.7 ppm (d).[19, 20] The peaks marked by THF are due to tetrahydrofuran solvent. The signals at 7.9 ppm (a) and 7.7 (b) ppm are attributed to the phenyl protons of the Z – group of the RAFT agent located at the ω – chain end of the copolymer. The signal at 7.9 ppm (a) was used to calculate the number-average molecular weight (M_n) of the copolymer. The peaks marked with the asterisk are solvent peaks. The M_n

value was determined by dividing the integration value of the signal between 5.9 ppm and 7.6 ppm (c) by the integration value of the RAFT chain end (a). This is shown in equation 4.4.

$$M_n^{NMR} = \frac{c/5}{a/2} \times 202.206 \frac{g}{mol} \qquad (4.4)$$

M_n^{NMR} is the number average molecular weight value of the copolymer. 202.206 g/mol is the sum of the molecular weight of styrene and maleic anhydride (which can be considered as the repeat unit of the alternating copolymer). The signals *c* and *a* were used because they are clearly resolved from the other peaks. Signal *c* is due to five phenyl protons of styrene while signal *a* is due to two phenyl protons of the RAFT Z – group. The integration of *c* is divided by the integration of *a* to get the degree of polymerization. The M_n^{NMR} values are shown in table 4.1 (section 4.2.2). There are few factors that affect the accuracy of the number average molecular weight determined via NMR: i.e.

- polymer peaks are broad and overlap with each other
- The characteristic Z – group is used for determination of M_n^{NMR}, but some chains terminate during the process and therefore do not possess Z – group.

4.4.1.2 SEC of SMA copolymer

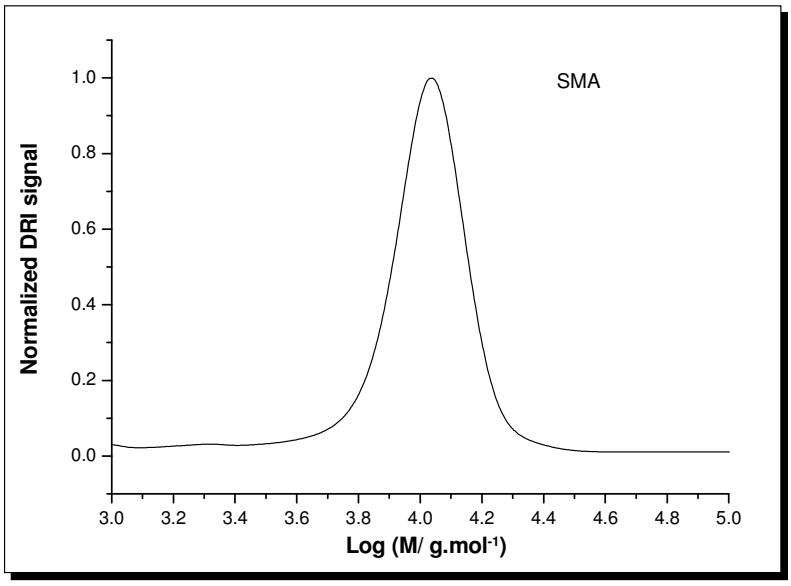


Figure 4.3 MWD of SMA copolymer synthesized via RAFT mediated polymerization of Sty and MAnh at 60 °C with the initial mole ratio of 125:125:5:1 for Sty, MAnh, RAFT agent and AIBN respectively. (Run 1 in Table 4.1)

The MWD plot of SMA copolymer is shown in Fig 4.3 above. A symmetrical peak and a narrow molecular weight distribution are typical for a polymer synthesized via controlled radical polymerization. UV at 320 nm is normally used to show the presence of the thiocarbonyl thio moiety at the end of the polymer chains. In most cases, the presence of the thiocarbonyl thio moiety at the end of polymer chains notifies that the polymerization was controlled. In this study the UV response obtained was not as good as expected; therefore the RAFT moiety could not be traced to further confirm the control of polymerization. The DMF solvent was suspected to be the possible reason for bad UV-vis spectra as it was used to dissolve the polymers. Appendix A and B shows MWD plots of SMA copolymer dissolved in DMF and THF solvents respectively. From the appendixes it was observed that UV response in DMF showed a strange peak shape (at maximum normalized DRI signal) compared to the normal peak obtained when THF was used. The only reason why THF could not be employed was because only SMA dissolves in it and other copolymers synthesized in this study are

insoluble (SMI, SSMA and SSMI). Even though the UV was not suitable to prove the presence of the RAFT moiety at the end of the copolymer chains, information obtained from SEC, such as a low polydispersity index still proved that the polymerization was controlled.

4.4.1.3 Alternating structure and architecture (stars) of SMA copolymer

Alternating SMA copolymer characterized by ^{1}H NMR

It has been proven previously that copolymerization of styrene and maleic anhydride results in an alternating copolymer when the co-monomer ratio Sty:MAnh is kept in the range of 1:1 to 3:1.[5, 21, 22] To confirm the alternating structure of SMA copolymer, equations 4.5 and 4.6 are used. These equations are used to determine the composition of the copolymers from ^{1}H NMR spectra with a probable relative error of ± 10%.[18, 23, 24] The method requires a well resolved resonance peak of a functional group in one of the monomer units in the spectra. In this case the phenyl ring of styrene is well resolved from all other peaks. The mole fractions of maleic anhydride and styrene calculated for SMA copolymers synthesized are shown in table 4.5. The calculated values agree reasonably well with the expected alternating structure of the copolymer.[18, 24] Figure 4.2 provides the typical spectrum of the SMA copolymer.

$$X_{Sty} = \frac{5I_{total} - 8I_{phenyl}}{5I_{total} - 6I_{phenyl}} \tag{4.5}$$

$$X_{MAnh} = \frac{2I_{phenyl}}{5I_{total} - 6I_{phenyl}} \tag{4.6}$$

- I_{total} is the total integration intensity of all protons (peaks assigned "**c**", "**d**" and "**e**" were integrated, see Fig 4.2)
- I_{phenyl} integration intensities of styrene phenyl protons (peak assigned "**c**", see Fig 4.2)

In the above equations X_{Sty} and X_{MAnh} are the mole fractions of styrene and maleic anhydride in the SMA copolymer. Equations 4.5 and 4.6 are used to calculate mole fraction of MAnh (X_{MAnh}) and mole fraction of the styrene (X_{Sty}) in the SMA copolymer and the calculated values are shown in table 4.5 below.

Table 4.5 The mole fractions of Sty and MAnh for alternating SMA copolymers

	SMA runs from table 4.1						
Exp. no.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
$\mathbf{X_{Sty}}$	0.50	0.55	0.44	0.55	0.56	0.55	0.50
$\mathbf{X_{MAnh}}$	0.50	0.45	0.56	0.45	0.44	0.45	0.50

Alternating SMA copolymer characterized by MALDI ToF MS

The SMA copolymers ware further analyzed by MALDI ToF MS. Figure 4.4 shows a typical MALDI ToF mass spectrum of SMA copolymer synthesized in this study. The m/z region between 3900 and 4400 is expanded to illustrate the phenomenon to be explained. The peaks in the main distribution have intervals of approximately 104.14 and 98.06 mass units in between. The two intervals alternate, and this shows that the addition of the two different monomers was in an alternating manner. This clearly proves that an alternating SMA copolymer was synthesized. Potassium trifluoro acetate was added as the cationizing agent. The potassium ion accounts for 39.10 Da of the experimental molecular weights.

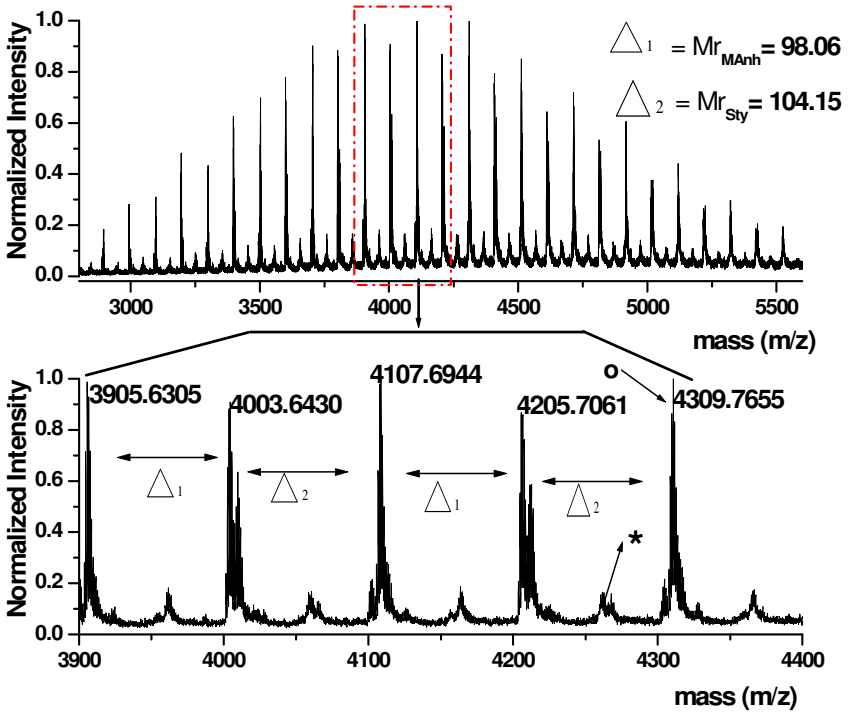


Figure 4.4 MALDI ToF mass spectrum of SMA copolymer synthesized via RAFT mediated polymerization of Sty and MAnh at 60 °C with the initial mole ratio of 125:125:5:1 for Sty, MAnh, RAFT agent and AIBN respectively (run 3 in Table 4.1).

4.4.1.4 Formation of star polymers

The chemical versatility inherent in RAFT agents makes RAFT mediated polymerization a suitable procedure for the preparation of star polymers. For star polymers to be synthesized, a RAFT agent with several thiocarbonyl thio moieties attached to a central core is required. The mechanism of RAFT mediated polymerization allows the formation of star polymers in the presence of multifunctional RAFT agents. It is known that star polymer growth is accompanied by parallel growth of linear chains initiated from the initiator derived primary radicals. These linear chains should have a similar molecular weight and molecular weight distribution as the arms attached to the core. The phenomena can be easily understood by studying the mechanism of RAFT polymerization.[25]

Figure 4.5 shows the molecular weight distributions (MWDs) of three and four armed star copolymers of SMA. The four armed star copolymer with lower molecular weight is shown

by a dotted line while the three armed copolymer with higher molecular weight is represented by a drawn line.

The tailing and a small peak ($M_w \approx 2000$ g/mol) in the low molecular weight region of the MWD is believed to be due to linear dormant chains and due to polymer formed from radical-radical termination of the linear propagating radicals.[25, 26] This behaviour in RAFT polymerization of stars is expected as some chains are not attached to the core (chains initiated by the initiator). In this work, impurities resulting from linear chains and from star-star coupling were expected. [27] The formation of star-star coupling was expected to occur under conditions of high radical concentration, and/or at high monomer conversion. On the basis of the obtained SEC chromatograms, it is judged that star-star coupling did not occur to a significant extent as there is no shoulder on the high molecular weight region. Hence, the linear chains are the only impurity.[27, 28]

The low molecular weight shoulder appears at the same region for both three and four armed copolymers irrespective of the small difference in molecular weight. The reason could be the similarity in the conditions of the polymerization of both star copolymers and the fact that the RAFT agents used are trithiocarbonates transfer agents. The only difference is the number of arms.

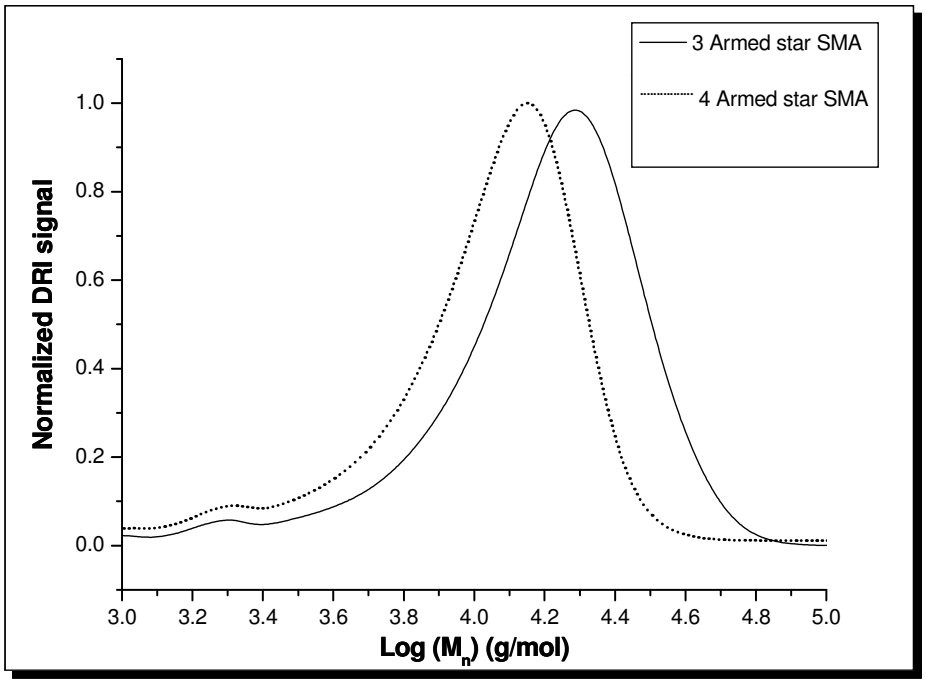


Figure 4.5 SEC MWDs of a four armed star copolymer and a three armed star copolymer synthesized via RAFT mediated polymerization of Sty and MAnh at 60 °C with the initial mole ratio of 125:125:5:1 for Sty, MAnh, RAFT agent and AIBN respectively (run 4 and 6 respectively in table 4.1).

4.4.1.5 Chain endgroup analysis

Copolymers with low degrees of polymerization were synthesized in order to study their end groups. Low molecular weight polymers have a high concentration of end groups and they give a better resolution of endgroup signals when characterized by ^{1}H NMR. The presence of the thiocarbonyl thio end group at the end of the polymer chain proves that the polymer was synthesized via RAFT mediated polymerization. The presence of the RAFT moiety at the chain ends has already been proven by ^{1}H NMR in section 4.4.1.1. In this section MALDI ToF MS will be used to identify the SMA end groups.

MALDI ToF MS

MALDI ToF mass spectra offer an opportunity to explore the finest structural details in polymers, such as molar mass distribution; determination of repeat units structure and end group identification.

The polymer end groups can be calculated from a polymeric series in a mass spectrum using equation 4.7.

$$M_{peak} = M_{end1} + [(M]_{monomer})n + M_{end2} + M_{cation} \quad (4.7)$$

M_{peak} is the molar mass value of selected peak, M_{end1} and M_{end2} are molar mass values of initiating group and end-capping group, $M_{monomer}$ is the molar mass of the repeating units and M_{cation} is the molar mass of the cation attached in the ionization process.

The plot of M_{peak} against n should give a straight line and the slope of the line represents $M_{monomer}$. Few peaks with greatest signal intensity were chosen to determine the end groups of the chains. The formula weight of all the peaks could be determined; they all had similar formula with the only difference being the number of the repeating unit (n). Equation 4.8 was used to determined the theoretical isotopic distribution.[29, 30]

$$M_{peak} = M_{end1} + [(M]_{mon1})n_1 + [(M]_{mon2})n_2 + M_{end2} + M_{cation} \quad (4.8)$$

Figure 4.6 shows an expansion of peak labeled "**O**" in figure 4.4 with the molecular weight of 4310.76 g/mol. Equation 4.8, which is derived from of equation 4.7, was used to theoretically determine the structure and molecular weight of the peaks based on figure 4.4. As shown in figure 4.6 there was an agreement between the experimental and theoretical

isotopic distributions. The theoretically determined peak corresponds with the chain capped with the RAFT end moiety.

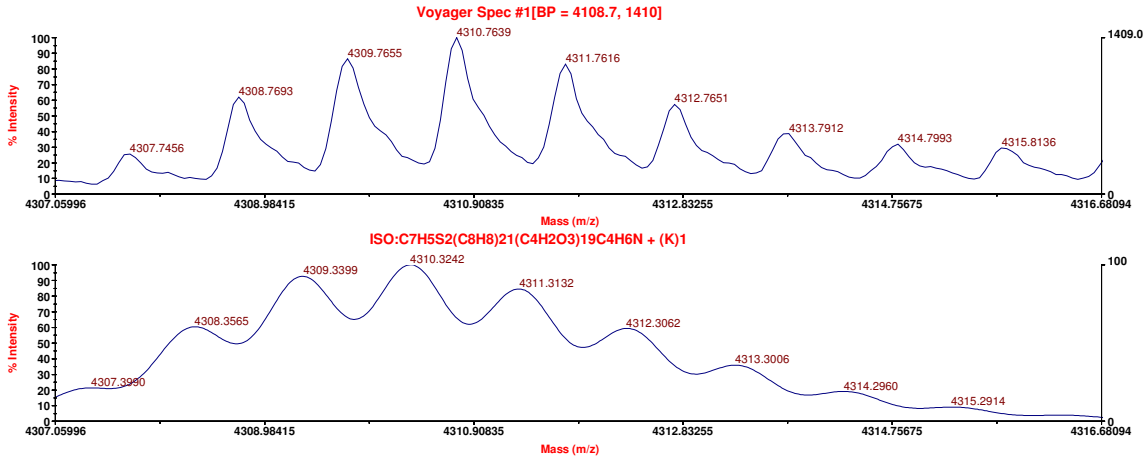


Figure 4.6 MALDI ToF mass spectrum of SMA copolymer with RAFT moiety at the chain end (run 3, Table 4.1) showing experimental isotopic distribution (top) and theoretical isotopic distribution (bottom)

During the ionization process, a fraction of polymer chains loses the RAFT end moiety due to the laser used. Figure 4.7 shows an expansion of smaller peaks which are at placed at the base of the isotopic distribution. These peaks have the lowest signal intensity and the possible reason for the low signal intensity could be that quantitatively there are very few chains of this kind. The peak labeled with asterisk/"*" in figure 4.4 has the molecular weight of 4261.74 g/mol and the molecular weight of the peak was theoretically determined.

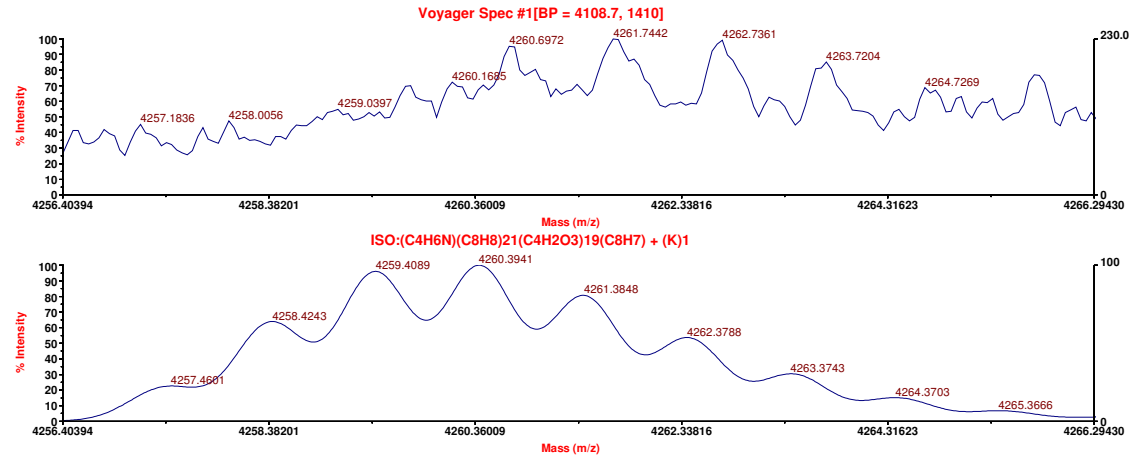


Figure 4.7 MALDI ToF mass spectrum of SMA copolymer without RAFT moiety at the chain end (run 3, Table 4.1) showing experimental isotopic distribution (top) and theoretical isotopic distribution (bottom)

4.4.2 SMI copolymer

4.4.2.1 NMR

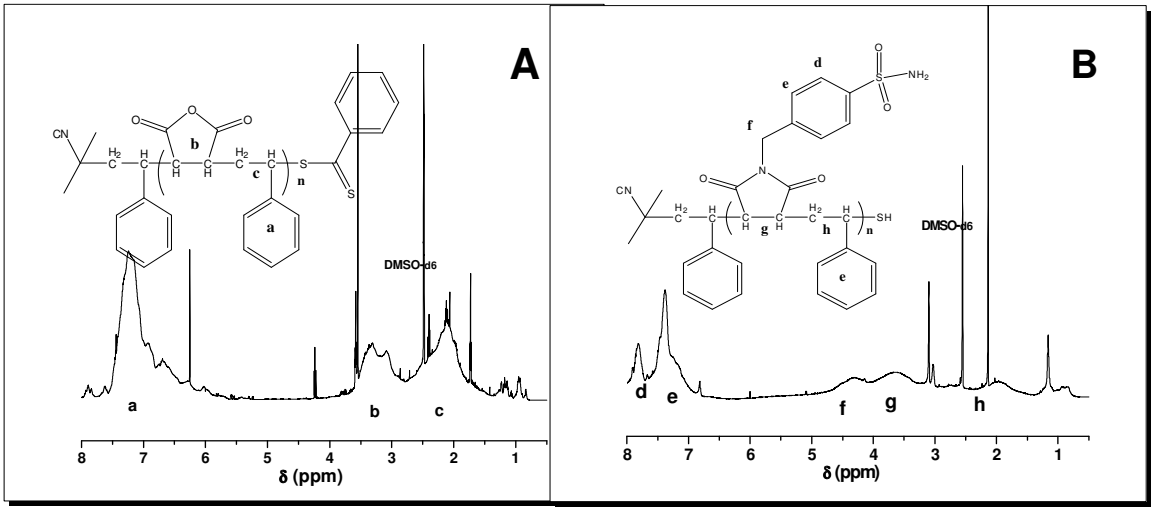


Figure 4. 8 ^{1}H NMR spectra of SMA (A) copolymer and SMI (B) copolymer prepared by reaction of the amine compound with SMA copolymer at 85 °C in DMF for 8 hrs. (Run 3 in Table 4.2)

In the ^{1}H NMR spectrum of SMA and SMI (Figure 4.8), broad overlapping peaks between 1.3 and 2.5 ppm and peaks between 6.9 and 7.6 ppm are due to methylene/methine and aromatic ring hydrogens of styrene/benzene sulphonamide respectively. The methine proton peaks of maleic anhydride appear between 3.1 and 3.7 ppm.[19, 20] The ^{1}H NMR spectrum of SMI shows a broad peak between 7.6 and 8.0 ppm which is due to aromatic protons of benzene sulphonamide in the ortho position to the sulphonamide group. Again in the spectrum of SMI there is a new peak between 4.0 ppm and 4.6 ppm which is due to methylene protons between benzene sulphonamide and the newly formed imide. The former maleic anhydride protons, now being imide protons, have their peak shifted to the downfield region between 3.2 ppm and 4.0 ppm. The peak between 7.6 and 8.0 ppm and the peak between 4.0 and 4.6 ppm were integrated and compared to verify that the SMA copolymer was modified to SMI copolymer. The integration ratio was 1:1 as anticipated because they both belong to newly introduced amine compound with two protons in two different environments.

The ^{13}C NMR spectra of SMA and SMI (appendix C), show the characteristic peaks of methylene/methine and aromatic ring carbons of styrene at 40 and 130 ppm respectively. In the ^{13}C NMR spectrum of SMI, there are two aromatic peaks. The peak between 125 ppm and 127 ppm is due to the aromatic carbons of benzene sulphonamide and the peak between 127 ppm and 129 ppm is due to aromatic carbons of styrene. The interpretations of ^{1}H and ^{13}C NMR spectra hold for linear and star SMA and SMI copolymers.

4.4.2.2 ATR/FTIR

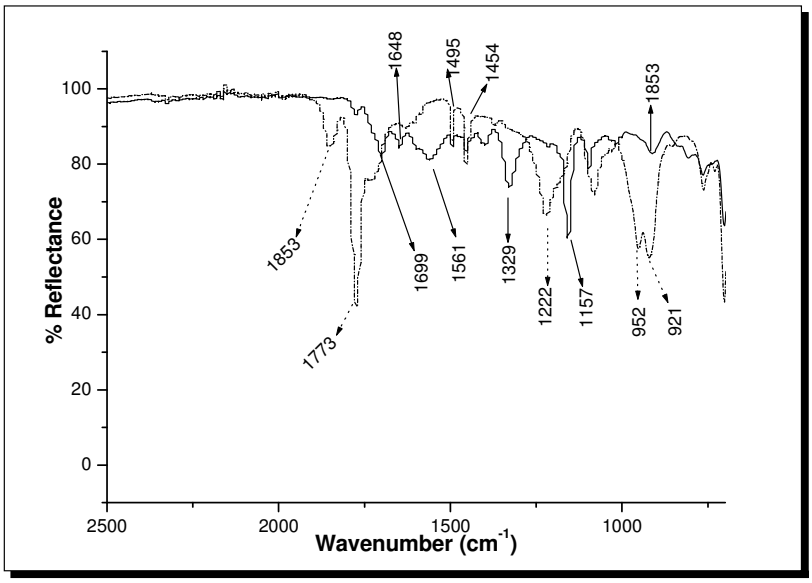


Figure 4. 9 ATR/FTIR spectra of SMA (dashed line) and SMI (solid line) copolymer prepared by reaction of the amine compound (4-AMBSA) with SMA copolymer at 85 °C in DMF for 8 hrs. (Run 1 in Table 4.2)

In the ATR/FTIR spectrum of SMA copolymer (Figure 4.9), the bands at 1853 cm^{-1} and 1773 cm^{-1} are assigned to the cyclic anhydride (C=O) and 1222 cm^{-1} is due cyclic ring ether (C-O-C).[12, 31] The band at 1495 cm^{-1} is a styrenic band.[20]Aromatic C─C stretching vibrations appear at 1454 cm^{-1} and 1157 cm^{-1}.[32] The ATR/FTIR spectrum of the SMI copolymer has similar bands to the one of the SMA copolymer except for the disappearance of all maleic anhydride bands and appearance of the imide carbonyl (C=O) band at 1648 cm^{-1} and the imide band at 1561 cm^{-1}.[33] The band that appears at 1329 cm^{-1} is characteristic for the sulfonate functional group of sulphonamides.

4.4.2.3 SEC

Table 4.6 Molecular weights of SMI and SMA copolymers from which they were prepared from.

Polymer (SMI) type	SMA M_n^{SEC}	$*M_n^{theor.}$	M_n^{SEC}	M_w/M_n
Linear	8606 (1)	18082	12596	1.21
3 armed star	12087 (4)	25397	20429	1.20
4 armed star	8954 (6)	18814	16984	1.16

(1), (4) and (6) are the SMA run numbers from which SMI copolymers were prepared from (Table 4.1).

$*M_n^{theor.}$ Is the expected molecular weight of SMI at 100% modification

Table 4.7 shows the molecular weight of the SMA before modification and after. The molecular weight of the modified SMA which is SMI has an increase of about 60 %.

Figure 4.10 shows the MWDs of SMA and SMI copolymers. Modified SMA copolymer (SMI) has a higher molecular weight than unmodified SMA copolymer. The chemical composition affects the hydrodynamic volume of copolymers. SMA copolymer has a constant and uniform copolymer composition and its hydrodynamic volume should be consistent with the structure and hence the results should be reproducible. However, when the composition of the copolymer is not uniform, i.e. fixed chain length but different monomer ratios/fractions, the hydrodynamic volume will vary due to unequal interactions between co-monomers and solvent and among co-monomers themselves. In case of SMI, due to the uniform structure of the parent copolymer (SMA), it is expected that the copolymer has a relatively consistent structure. However, its hydrodynamic volume should differ from the one of SMA and hence different apparent molecular weight was obtained.

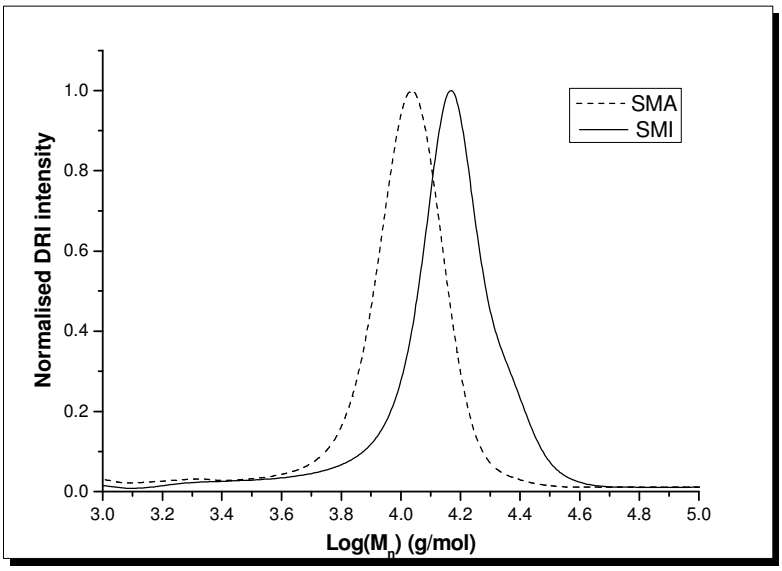


Figure 4.10 MWDs of SMA copolymer (dashed line) prepared from RAFT polymerization (run 1 in Table 4.1) and its derivative SMI copolymer (solid line). SMI is prepared by imidization reaction of SMA and 4-AMBSA in DMF solution at 85 °C for 8 hrs. (Run 1 in Table 4.2)

4.4.2.4 Determination of SMA to SMI reaction extent

There are few methods that can be employed to determine the degree/extent that a chemical reaction has progressed. The most favorable method is tracking of the changes that occur during chemical reaction (from the start until the end of reaction). In situ experiments using FTIR or NMR instrument has been practiced for many chemical reactions, RAFT polymerization being an example to track the changes that occur during the reaction.[34, 35] The other reliable methods are to characterize the synthesized product by techniques such as elemental analysis, titration, NMR, etc.

4.4.2.4.1 Quantification by ^{1}H NMR

NMR is a principal tool that can be used to obtain quantitative, qualitative, chemical, physical, electronic and structural information of the molecules. In this section, quantification of the SMI copolymer formed will be carried out by NMR.

The quantification was achieved by integrating the peak of the SMI copolymer which has a well resolved resonance. Figure 4.11 shows the ^{1}H NMR spectra of SMI used to quantify the amount of maleic anhydride converted to maleimide (degree of imidization). The peaks between 6.9─7.6 ppm and 7.6─8.0 ppm are due to aromatic protons of styrene and of benzene sulphonamide respectively.

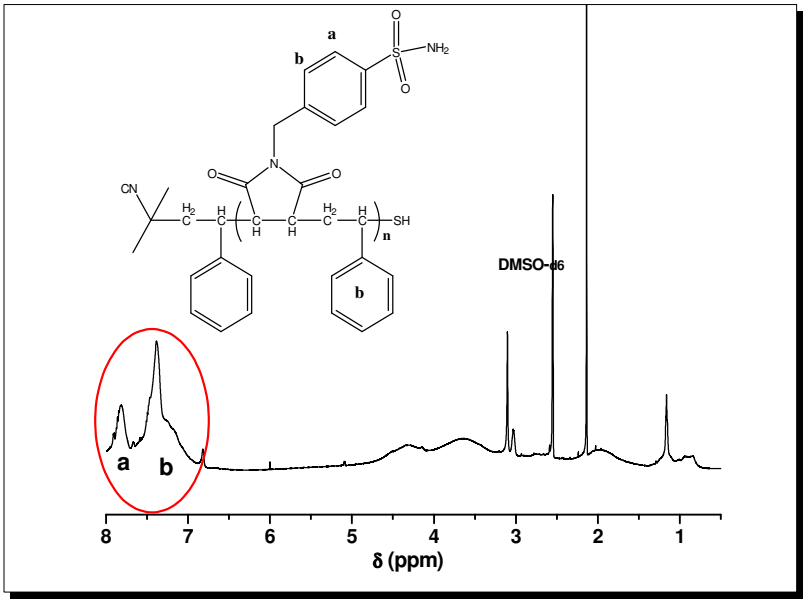


Figure 4.11 The ^{1}H NMR spectrum of SMI copolymer with the red circle indicating the peaks integrated to determine the degree of modification. SMI copolymer was prepared by reaction of the amine compound (4-AMBSA) with SMA copolymer at 85 °C in DMF for 8 hrs. (Run 3 in Table 4.2)

$$a = A \times 2x \tag{4.9}$$

$$b = A(5 + 2x) \tag{4.10}$$

$$\% \, x = \frac{5a}{2b - 2a} \times 100\% \tag{4.11}$$

In the above equations which were used to calculate the fraction of the maleic anhydride residues that were converted into maleimide residues.

- *a* is the integral of peak assigned "**a**"
- *b* is the integral of peak assigned "**b**"
- *x* is the calculated fraction of modified MAnh to maleimide
- *A* is an arbitrary factor that controls the overall integrals, i.e. related to polymer concentration, instrument setting, and data manipulation.

Equation 4.11 was used to determine the degree of imidization as a percentage. Table 4.7 contains the values of MAnh fraction converted to maleimide through the imidization reaction of SMA copolymer. It was found that with increase in the amount of the amine compound used to modify the SMA copolymer, there was an increase in modification percentage. When 100% modification was targeted, maximum of 73% was obtained for all reactions ran.

Table 4.7 Quantified SMI products from different reactions of SMA and amine compound

SMI run no.	SMA (g)	Amine (g)	Mol (10^{-3}) MAnh : amine	Modification percentage (%)
1	3.21	3.35	15.83 : 15.04	63.9
2	1.02	0.80	4.95 : 3.59	43.8
3	1.01	1.10	4.95 : 4.94	73.5
4	3.05	3.69	15.33 : 16.57	73.5
5	3.00	3.30	16.32 : 14.82	71.4

4.4.2.5 Solubility

The SMI copolymer initially synthesized in this work was insoluble in water and most organic solvents. It could only be dissolved in solvents such as DMF and DMSO. These solvents are toxic and they are difficult to remove from the product. The copolymer became

soluble in water at neutral and basic pH after addition of ammonia to the reaction mixture (see section 4.2.1). Ammonia was introduced to react with the unreacted maleic anhydride moieties in the backbone of the SMI copolymer.

4.4.3 SSMA copolymer

In this section the results of all the SSMA copolymers, i.e. linear, three and four armed copolymers will be discussed in comparison to their parent SMA copolymers. Linear SSMA copolymer results will be discussed in more detail.

4.4.3.1 NMR

The ^{1}H NMR spectrum of SSMA (figure 4.12) clearly shows that the polymer is derived from the parent SMA copolymer. The broad peaks labeled "**c**" between 1.5 and 2.3 ppm and the peak labeled "**b"** between 2.3 and 3.7 are assigned to the methylene protons of styrene and maleic anhydride respectively. The peak labeled **"a"** between 6.8 and 7.6 ppm is due to aromatic protons of styrene and it has a shoulder indicating not all the aromatic protons have same environment. The two protons located in the ortho position to the sulfonic group are the ones causing the split or the presence of the shoulder.

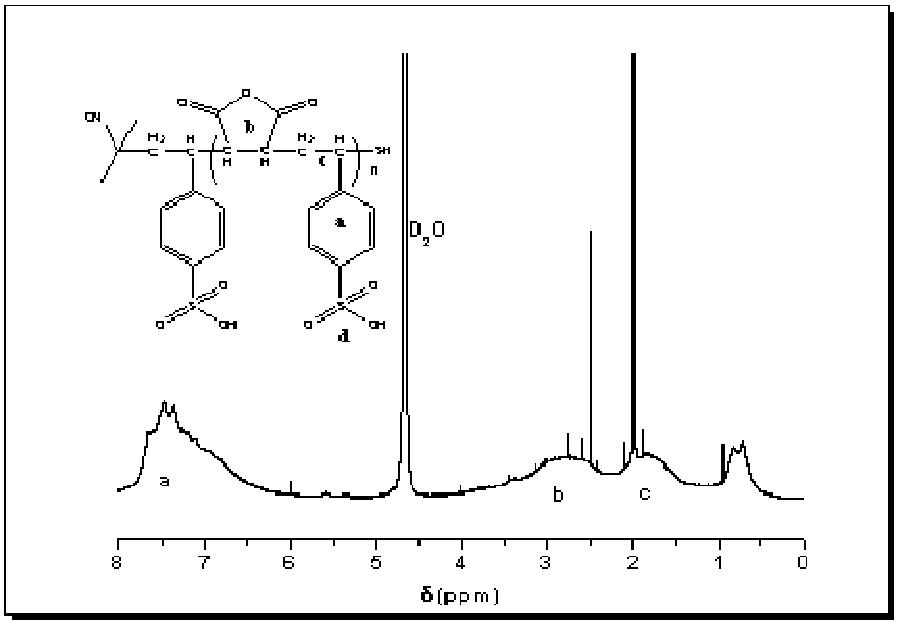


Figure 4.12 ^{1}H NMR spectra of SSMA copolymer synthesized by sulfonation reaction of SMA copolymer and chlorosulfonic acid at room temperature. (Run 2 Table 4.3)

4.4.3.2 ATR/ FTIR

Figure 4.13 shows the ATR/FTIR spectra of the sulfonated SMA copolymer. The sulfonated copolymer has new broad bands at 1000 cm^{-1}, 1030 cm^{-1} and 1160 cm^{-1}.[36-38] These bands can be ascribed to the symmetric and asymmetric vibrations of the SO_3H attached to the phenyl ring.[39, 40] The intensities of these bands have been proven to increase with the increase in degree of sulfonation by Elabd *et al.*[41] The broad band around 3380 cm^{-1} is associated with the stretching mode of the OH bonds of the SO_3H. The band at 3380 cm^{-1} is also due to -OH group of ring opened maleic anhydride moieties. This is also shown by disappearance of maleic anhydride bands at 1853 cm^{-1} and 1773 cm^{-1} which are present in the spectra of SMA.

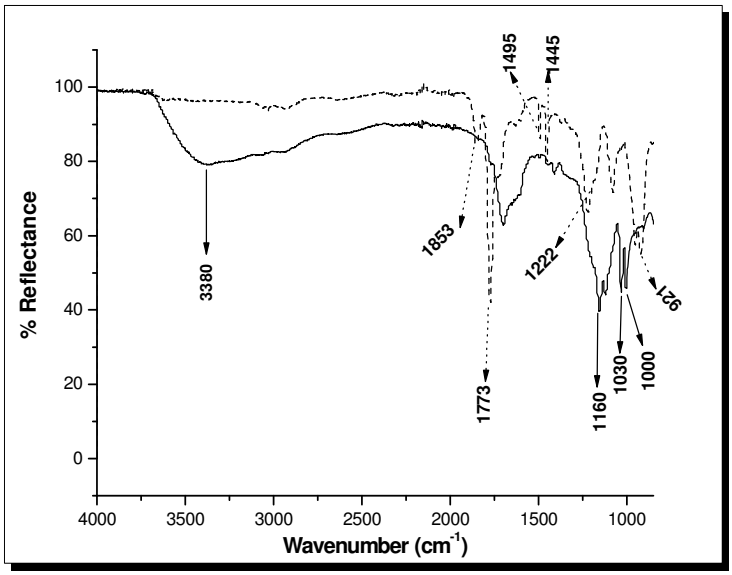


Figure 4.13 ATR/FTIR spectra of SMA (dashed line) and SSMA copolymer synthesized by sulfonation of SMA copolymer (solid line) with chlorosulfonic acid at room temperature. (run 2 Table 4.3)

4.4.3.3 SEC

Table 4. 8 Molecular weights of SSMA and SMA copolymers from which they were prepared from

Polymer (SMI) type	SMA M_n^{SEC}	$*M_n^{theor.}$	M_n^{SEC}	M_w/M_n
Linear	8606 (1)	12053	20669	1.21
Linear	8606 (1)	12053	19634	1.17
Linear	8606 (1)	12053	25629	1.26
3 armed star	12087 (4)	16929	32244	1.62
3 armed star	12087 (4)	16929	42734	1.75
3 armed star	12087 (4)	16929	43371	1.73
4 armed star	8954 (6)	12541	24591	1.31
4 armed star	8954 (6)	12541	26518	1.33
4 armed star	8954 (6)	12541	26531	1.33

(1), (4) and (6) are all the run numbers from which SMA copolymers were prepared from (Table 4.1).

$*M_n^{theor.}$ Is the expected molecular weight of SSMA at 100% modification

Table 4.8 shows molecular weight data of SSMA copolymers obtained via SEC characterization. The molecular weight obtained from SEC was higher than expected. The possible reason for this deviation could be the effect of chemical composition on hydrodynamic volume. There is no unique relationship that can be used to link hydrodynamic volume and chain length of copolymers having different compositions. In this case it is not clear whether all the styrene rings were modified with a sulfonic group. The SMA copolymer has a uniform structure and with the higher conversion of styrene unit to styrene sulfonate, the uniform structure from the parent polymer (SMA) will be obtained. However, if less styrene unit is converted, the final polymer will consist of three different units, i.e. styrene, styrene sulfonate and maleic anhydride (terpolymer).The introduction of the acid brings about change in the copolymer composition and this brings changes on the hydrodynamic volume of the SSMA copolymer. The relationship between Mark-Houwink parameters and the composition of SSMA has not been established as yet. But the possible reason(s) for higher molecular weight obtained will be investigated in future work.

4.4.3.4 Solubility

A water solubility test for the SSMA copolymer was conducted just to confirm its solubility in different pH conditions. The SSMA copolymer is highly hygroscopic and it dissolves easily in water under neutral and basic pH conditions. However, it is insoluble in most organic solvents.

4.4.4 SSMI copolymer

4.4.4.1 NMR

Figure 4.14 shows the ^{1}H NMR spectrum of the SSMI copolymer and the spectrum of the parent SSMA copolymer from which SSMI was derived. The ^{1}H NMR peaks for SMA derived polymers are broad. The methylene protons of the newly formed maleimide labeled "**d**", "**e**", "**g**" and "**h**" are all assigned to the broad peak between 2.2 and 3.5 ppm, while the peak between 1.3 and 2.0 ppm is due to styrenic methylene protons labeled "**c**" and "**f**".[42] The peak between 6.5 ppm and 7.9 ppm, peak labeled **"a",** is due to four aromatic protons..

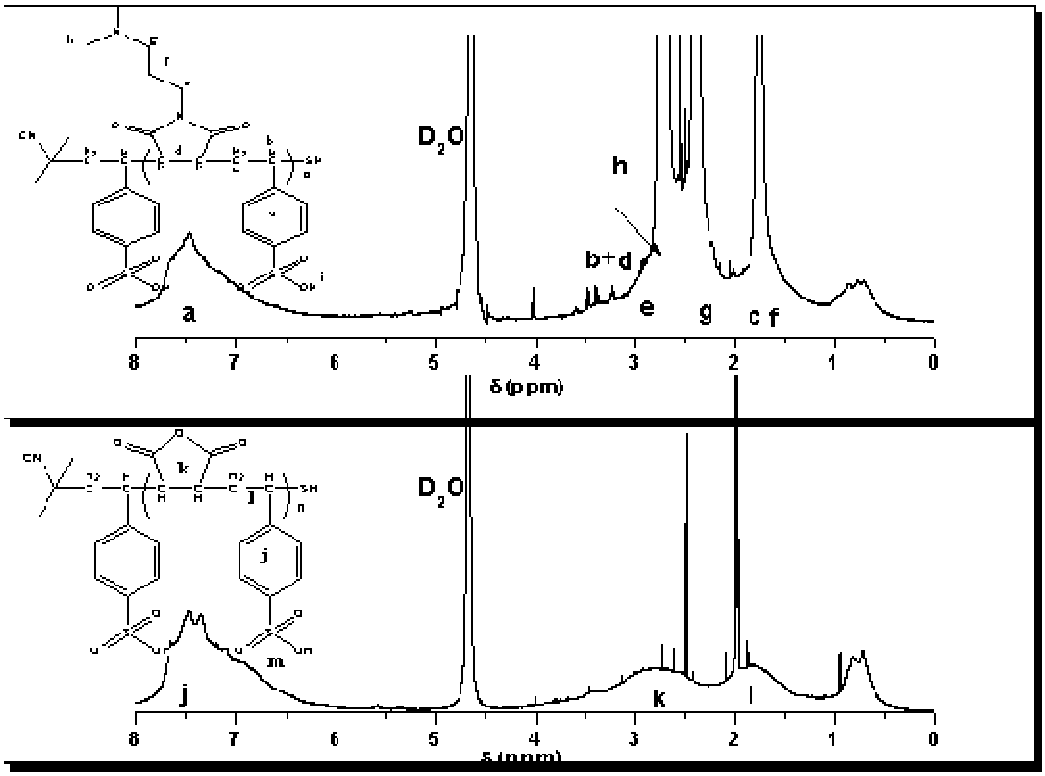


Figure 4.14 ^{1}H NMR spectra of SSMI (above)[42] copolymer prepared by reaction of SSMA copolymer with DMAPA (run 2 in Table 4.4) and SSMA copolymer (below)(run2 Table 4.3).

4.4.4.2 ATR-FTIR

Figure 4.15 shows the ATR/FTIR spectra of SMA and SSMA copolymers. For the synthesis of SSMA, an increase in degree of sulfonation results in broad bands of ATR/FTIR spectra of the sulfonate compound. During the sulfonation reaction, the maleic anhydride ring opens. The copolymer was then reacted with primary amine compound (DMPDA) for the formation of an imide. The imide carbonyl functional group band at 1650 cm^{-1} and the imide band 1546 cm^{-1} proved that the imidization of maleic anhydride was a success.[33, 42, 43] The bands at 1008 cm^{-1}, 1033 cm^{-1}, 1067 cm^{-1} and 1176 cm^{-1} are characteristic bands of the sulfonate functional group.

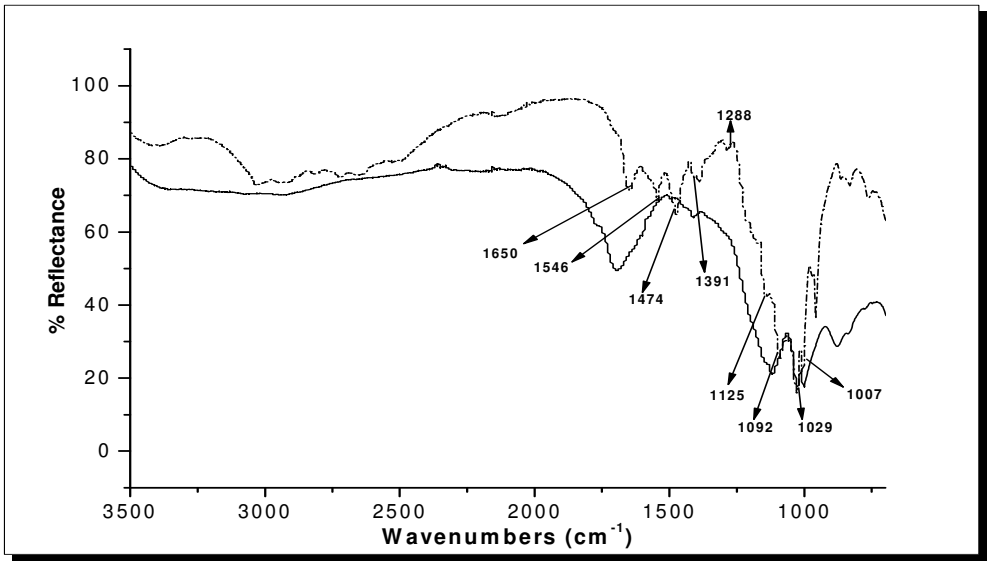


Figure 4.15 ATR/FTIR spectra of SSMA (solid line) and SSMI (dashed line) copolymer prepared by reaction of SSMA copolymer with DMAPA. (Run 2 in Table 4.4)

4.4.4.3 SEC

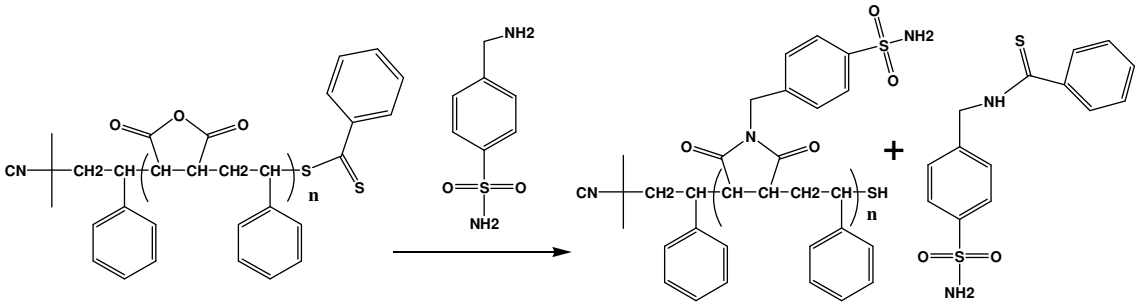
The SSMI copolymer could not be characterized by SEC due to its insolubility in solvents (DMF and THF) used for SEC. Therefore molecular weight of the copolymer could not be determined.

4.4.4.6 Solubility

Similar to its parent copolymer (SSMA), SSMI copolymer is hygroscopic and dissolves in water at neutral and basic pH medium and it is insoluble in most organic solvents.

4.4.5 Thiocarbonyl thio terminus removal

RAFT agents are very important when it comes to the synthesis of well defined polymers with controlled molecular weight and low polydispersity. But the thiocarbonyl thio terminus present in RAFT synthesized polymers possess poor stability which may lead to the release of odorous compounds. In addition, the RAFT moiety is often strongly coloured. In Chapter two, some reactions via which the thiocarbonyl thio group can be removed have been discussed.[44-46] In this study, the RAFT moiety was removed while the polymer was being modified by an amine compound. Scheme 4.7 shows the general reaction of the thiocarbonyl thio terminus removal by an amine compound.[47] This procedure is also applicable to the trithiocarbonate end-groups of the three and four armed star copolymers. The colour disappearance was the first sign to indicate that the thiocarbonyl thio moiety was removed. Polymers synthesized in this project by RAFT agents changed their colours from pink (linear SMA) and yellow (star SMA) to off-white when reacted with the amine compounds, which in this case was for the synthesis of SMI copolymers.



Scheme 4.5 General reaction of RAFT end group removal by nucleophilic attack. Amine compound was in excess and the reaction took place at 90 °C in solution.

When sulfonation of SMA to SSMA was carried out, the polymers changed from pink and yellow to brown. In this case, colour change did not signal the removal of the thiocarbonyl thio moiety but the formation of the SSMA copolymer. The reaction between the RAFT moiety and amines is known to yield a thiol and therefore NMR and Ellman's method were used to prove its conversion to the thiol.

4.4.5.1 End group of SMI copolymer

^{1}H NMR analysis confirms the removal of the thiocarbonyl thio moiety. In figure 4.16, a comparison of the unmodified and the modified SMA copolymers shows the disappearance of the RAFT end group. Even though some of the peaks in the spectra overlap, peaks (a), 7.9 ppm and (b), 7.6 ppm in the spectrum of the unmodified copolymer (SMA) are due to the thiocarbonyl thio moiety. The peak at 7.9 ppm has clearly disappeared in the spectrum of the modified copolymer (SMI).[47]

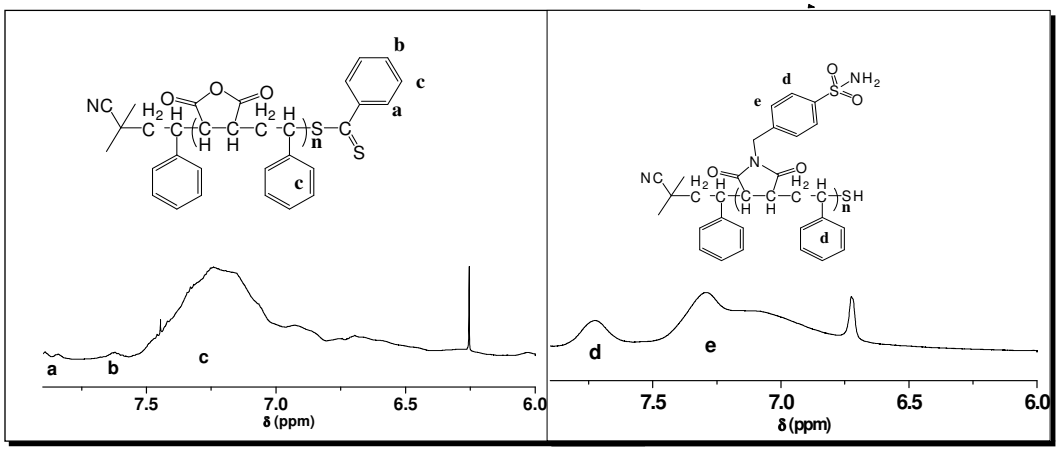


Figure 4.16 ^{1}H NMR spectrum of SMA (left) run 1 in table 4.1 and SMI (right) run 1 in table 4.2

4.4.5.2 End group analysis of the SSMA copolymer

Figure 4.17, shows the ^{1}H NMR spectra of SMA and SSMA. Due to the chlorosulfonic acid and water used for sulfonation of the SMA, the RAFT end group is removed by acid hydrolysis and it is evidently shown by the disappearance of peaks 7.9 ppm and 7.6 ppm in the SSMA spectra.

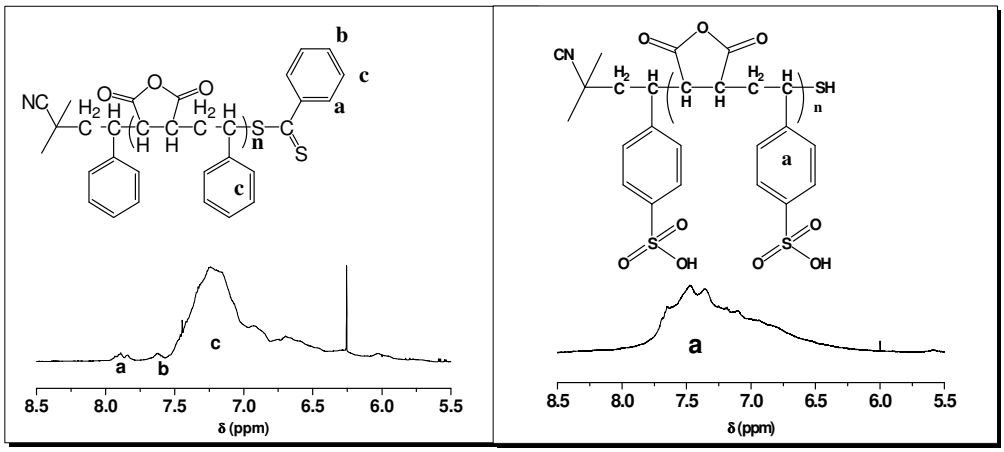


Figure 4.17 ^{1}H NMR spectra of SMA before modification, run 1 in table 4.1 (right) and SSMA run 1 in table 4.3 (left).

4.4.6 Ellman's method

Ellman's method is used to determine the concentration of thiol in organic compounds and in this study it is used to confirm the presence of the thiol by reacting the endgroup of modified copolymers with 5,5 -dithiobis(2-nitrobenzoic acid). 5,5 -dithiobis(2-nitrobenzoic acid) reacts quantitatively with many thiols (mercaptans) to give p-nitrobenzenethiol which is yellow in color.[48, 49]

4.4.6.1 Method

A 0.1 M phosphate buffer (pH 7.6 - 8.0) was prepared by dissolving sodium hydrogen phosphate (0.125 mol) and sodium dihydrogen phosphate (0.025 mol) in 250 ml de-ionized water. Ellman's reagent (0.4 mg/ml, 1.0 mmol/ml) was prepared by dissolving 5, 5 -dithiobis(2-nitrobenzoic acid) in 10 ml phosphate buffer. 4.6 mg of a SMI copolymer to be analyzed was dissolved in de-ionized water (3 ml). The resulting solution was diluted with 6 ml buffer and 1 ml Ellman's solution/reagent. A blank control solution was prepared by adding 1 ml Ellman's reagent to 9 ml phosphate buffer. UV-vis measurements were taken. The same procedure was followed for Ellman's test of SSMA copolymer.

4.4.6.2 Results

The solution of SMI copolymer, Ellman's reagent and phosphate buffer gave a deep yellow colour which indicated the presence of thiol. The yellow colour resulted when a thiol reacts with 5, 5 -dithiobis(2-nitrobenzoic acid).[48] This proves that the thiocarbonyl thio group was converted into a thiol through the aminolysis and acid hydrolysis reactions for SMI and SSMA copolymers respectively. Figure 4.18 shows the UV-vis spectra of Ellman's results. The absorption at 420 nm due to p-nitrobenzenethiol which was released from reaction of 5, 5 –dithiobis(2-nitrobenzoic acid). Using equation 4.8 the concentration of the thiol endgroup was determined. The fraction of thiol end-groups from SMI copolymer using the Ellman's method was found to be 70 %. The UV-vis absorption spectra of SSMA show a lower absorption compared to the SMI spectra. This could mean that there is less concentration of thiol formed during acid hydrolysis instead there are unidentified side products.

$$E = \frac{A}{bc} \tag{4.12}$$

$$c - \frac{A}{Ec} \tag{4.13}$$

$$\frac{c = \frac{A}{13{,}600} moles}{l} \tag{4.14}$$

Where A = absorbance, b = path length in centimeters, c = concentration in moles/liter. b = 1 cm and E = 13, 600 $M^{-1}cm^{-1}$. When these are substituted in equation 4.13, equation 4.14 is derived which is a standard equation for determination of the thiol concentration using Ellman's method.

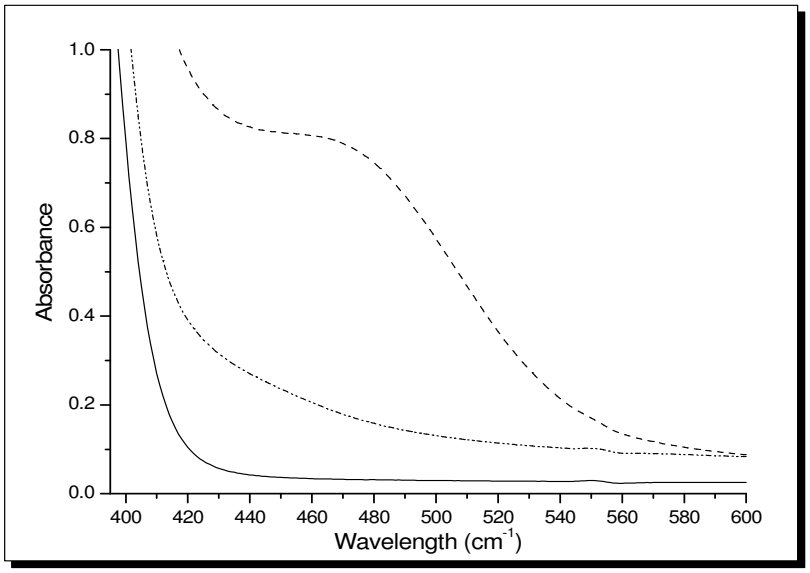


Figure 4.18 UV spectra of Ellman's test for thiol end groups in SMI (run 1 table 4.2) and SSMA (run 1 table 4.3) copolymers, blank curve (solid line), SMI curve (dashed line) and SSMA curve (dotted line)

4.4.7 Quantification of copolymers by elemental analysis

Elemental analysis is a process by which mass fractions of the elements in a compound are determined. Table 4.9 represents theoretical elemental composition of the various repeat units. Table 4.10 provides an overview of the experimentally determined elemental composition.

Table 4.9 Weight percentage of the elements

Polymer	**Unit Mw**	**Weight %**					
		Carbon	**Sulphur**	**Nitrogen**	**Hydrogen**	**Oxygen**	**Total**
SMA	202.21	71.28	0.00	0.00	4.98	23.74	100.00
SMI	370.42	61.61	8.66	7.56	4.90	17.28	100.00
SMI **(with NH_3)**	370.42 + 204.24	64.90	5.59	7.32	5.15	16.73	100.00
SSMA	282.27	51.06	11.36	0.00	3.57	34.01	100.00
SSMI	366.43	55.72	8.75	7.64	6.05	21.83	100.00

Table 4.10 Processed elemental analysis results obtained

polymer type	Lab	C %	S %	N %
SMA Linear	A	65.40		0.40
	B	69.15	0.99	0.04
SMA 3 Star	**A**	63.20	1.54	0.13
SMA 4 Star	**A**	70.10	3.36	0.04
SMI Linear	**A**	59.20	2.92	9.43
	B	54.29	3.54	9.33
SMI 3 Star	**A**	58.00	4.00	9.14
SMI 4 Star	**A**	57.90	1.97	8.67
SSMA Linear	**A**	38.10	3.12	0.27
	B	32.57	10.17	0
SSMA 3 Star	**A**	32.80	9.59	0.04
SSMA 4 Star	**A**	38.30	10.19	0.10
SSMI Linear	**A**	41.10	5.21	8.51
	B	40.01	6.83	8.88
SSMI 3 Star	**A**	44.70	2.46	10.60
SSMI 4 Star	**A**	43.10	7.92	9.09

A = BEM lab (Somerset West) B = University of Cape Town geology lab

The theoretically determined elemental composition provides an overview of the mass fractions of the elements in the unmodified SMA copolymer and in SMA derivatives at 100% modification/conversion. Main elements that are being traced to confirm the success of the reaction and the degree of modification are nitrogen and sulphur. These two elements are present in SMA in very small (negligible) quantities. They are due to RAFT agent derived end groups. In the SMA derivatives, these elements are present at reasonably high quantities. The quantity of nitrogen and sulphur increases due to the introduction of the 4-aminomethylbenzene sulphonamide compound and ammonia solution to the parent SMA copolymer to synthesize the SMI copolymer. The sulfonation of the SMA to SSMA results in an increased quantity of sulphur. Lastly the imidization of SSMA copolymer to SSMI by

introduction of 3-dimethylamino-1-propylamine resulted in an increase in the quantity of nitrogen.

SMA and SMI copolymers

Theoretically and experimentally determined elemental compositions shown in tables 4.9 and 4.10 were compared for copolymers to determine the extent of modification. When comparing the experimental elemental composition of SMA and SMI copolymers, the nitrogen and sulfur compositions of SMI are higher than that of SMA copolymer. The increase in quantities of these two elements shows that introduction of the amine compound was successfully accomplished. However, when determining the extent of modification by comparing theoretical (compositions at 100% modification) and experimental compositions of the nitrogen and sulfur in SMI copolymer, the experimental quantities of nitrogen were found to be higher than theoretical/expected quantities. Because of high quantities, the possible sources of excess nitrogen content were looked into. Sources of nitrogen from the reaction are ammonia, DMF solvent and the catalyst system (TEA and DMAP). The catalyst compounds and unreacted ammonia were found to be soluble in DMF and isopropanol (used to precipitate the copolymer) and therefore they were extracted from the products. DMF was also removed when precipitating the copolymer and during the oven drying. Figure 4.8 (A) depicts the ^{1}H NMR spectrum of SMI copolymer and the peaks for all the compounds used in the modification reaction are absent. Due to high nitrogen quantities, the mass ratio between N and S per SMI chain is not 0.7:1.0 but 1.0: 0.3.

SSMA and SSMI

The quantification of SSMA copolymer also proved to be unsuccessful because the experimental carbon quantity is lower than the theoretical quantity. The quantities of oxygen could result in decreased carbon quantities. The sources of oxygen are water and chlorosulfonic acid. Water was removed through freeze drying while the unreacted acid is soluble in the solvent used for sulfonation reaction. Therefore, their removal was not difficult. Due to the hygroscopic nature of the copolymer, moisture absorption was the other factor that

could contribute to low carbon quantities due to increase in oxygen quantity. To avoid moisture absorption the copolymer was stored in an air tight sample container. Results are shown in tables 4.9 and 4.10.

SSMI copolymer is also hygroscopic and also here an air tight container was used to keep it dry. The experimental content of nitrogen in SSMI copolymer exceeded the theoretical value, while the carbon quantity was found to be too low. The source of nitrogen is DMAPA, but it is soluble in isopropanol hence extracted when copolymer was precipitated. The other source of nitrogen was DMF, but with the aid of ^{1}H NMR. DMF was found to be completely removed from the product (Figure 4.14). The results obtained from quantification of the SSMI could not be used because the weight fraction of elements was not in agreement with theoretical values. Quantities are shown in Tables 4.9 and 4.10.

4.4.8 General discussions

Styrene maleic anhydride copolymer was synthesized via RAFT mediated polymerization. Molecular weight of the alternating SMA copolymers synthesized was determined by ^{1}H NMR and by SEC. The results obtained from both techniques were comparable (table 4.1) with polydispersity indexes ranging between 1.05 – 1.27. RAFT mediated copolymerization of styrene and maleic anhydride was successful and targeted molecular weights for different SMA were obtained.

The SMA copolymer was further used in the synthesis of SMI copolymer by imidization reaction. The extent of imidization of maleic anhydride units was determined by ^{1}H NMR. The reaction proceeded with the aid of the catalysts and ammonia solution was used as additional reagent. Ammonia was introduced to react with unreacted maleic anhydride units, and this promoted the solubility of the synthesized SMI copolymer in water. The SMI copolymers were characterized and quantified by ^{1}H NMR spectroscopy and from the results obtained, about 70 % on average of the maleic anhydride was successfully modified to maleimide.

SSMA copolymer was the third to be synthesized by sulfonation reaction of the SMA copolymer. The synthetic procedure of this polymer is straight forward but its characterization by most techniques at disposal was limited by being insoluble in most organic solvents. The copolymer could not be quantified by NMR because the end group peaks overlapped with other polymer peaks. ATR-FTIR was mainly used to determine the presence of sulfonic acid functional groups, which were found to be present.

SSMI copolymer was synthesized by imidization of maleic anhydride moieties of SSMA to maleimides by DMAPA. The synthesized copolymer was characterized by NMR and ATR-FTIR with reproducible results. Molecular weight of the copolymer could not be determined because the copolymer is insoluble in THF and DMF. NMR and ATR proved that the synthesis of the copolymer was successful.

Solubility of the polymers

The copolymers synthesized in this work are insoluble in most organic solvents. They only dissolve in less user friendly solvents such as DMF and DMSO. These solvents are toxic and they are difficult to remove from the product. Because the copolymers synthesized will be tested for anti-HIV activity, complete removal of organic solvents used is vital and the pH range they dissolve at is of utmost importance. For this purpose the most common and important solvent is water, therefore the copolymer solubility test in water at different pH ranges has been carried out. Table 4.11 shows the solubility results of these polymers in water.

Table 4.11 Solubility tests of all synthesized copolymers in water at different pH ranges

Polymer	Acidic pH (1-6)	Neutral pH (7)	Basic pH (8-14)
SMA	Insoluble	Insoluble	Soluble
SMI	Insoluble	Soluble	Soluble
SSMA	Insoluble	Soluble	Soluble
SSMI	Insoluble	Soluble	Soluble

The results of solubility tests are positive against the background of the application of the copolymers because they are all soluble in water at neutral and basic pH range. SMI copolymer was initially insoluble in water at neutral or basic pH, they were only soluble at acidic pH. It was after the treatment with ammonia solution in water when they became soluble in water.

Dialysis

Dialysis was employed to purify the synthesized copolymers removing low molecular weight. The process was successful because all the polymers were soluble in water.

Elemental analysis

Elemental analysis was used to determine the extent of modification reactions conducted to synthesize SMI,SSMA and SSMI copolymers from SMA copolymer. The extent of the reactions was measured by determination of elemental composition of newly formed polymers. Table 4.9 with theoretical quantities and table 4.10 with experimental quantities were compared to determine closeness of experimental values to true values. With the aid of ^{1}H NMR, an average of 70 % for modification of SMA to SMI copolymer has been estimated. The quantities obtained from experimental data for certain elements were found to exceed the maximum quantities determined theoretically. In conclusion, the extent of

reactions whereby the SMA copolymer was modified into SMI, SSMA and SSMI copolymers was unsuccessful when elemental analysis was employed for quantification purposes.

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Chapter five: Summary and Outlook

5.1 Summary

In chapter three, the synthetic procedure of three different RAFT agents was described and they were characterized by ^{1}H NMR. Their purity was determined by ^{1}H NMR and it was found to be ≥ 93 %. Additional purification by column chromatography on silica using different solvent systems resulted in mass loss of these RAFT agents and therefore it was decided to dismiss further purification.

In chapter four, styrene-maleic anhydride copolymer (SMA) was synthesized via reversible addition-fragmentation chain transfer (RAFT) mediated polymerization. This copolymer had all the characteristics of polymers synthesized via living radical polymerization. Characteristics observed include controlled molecular weight and narrow molecular weight distribution. The presence of thiocarbonyl thio group at the ω-chain end was confirmed by ^{1}H NMR. SMA copolymer at higher molecular weight does not fly when analyzed by MALDI-Tof MS, and therefore the synthesized polymers could not be characterized by this technique. The SMA copolymer was synthesized to serve as a parent polymer for a number of derived copolymers.

The three copolymers that were derived from SMA copolymer are styrene-maleimide copolymer (SMI), styrene sulfonate-maleic anhydride copolymer (SSMA) and styrene sulfonate –maleimide copolymer (SSMI). SMI copolymer was synthesized by imidization of maleic anhydride to yield maleimide using primary amine (4-aminomethylbenzene sulfonamide). SSMA was synthesized by reaction of aromatic ring of styrene and chlorosulfonic acid. The SSMI copolymer was synthesized by reaction of maleic anhydride in the backbone of the SSMA copolymer with *N,N*-dimethylamino propylamine. All these polymers were characterized by ^{1}H and ^{13}C NMR, SEC and FTIR.

Styrene-maleimide copolymer was synthesized by reacting SMA copolymer with 4-aminomethylbenzene sulfonamide. Imidization reaction between maleic anhydride and the amine proceeded with the aid of DMAP and TEA co-catalysts. The resulting copolymer was insoluble in water at pH 7-8; it could only dissolve in strongly basic medium. To improve the solubility of the SMI copolymer, unreacted maleic anhydride moieties in the backbone were converted to maleimide by reacting them with ammonia. Maleimide is soluble in water at neutral pH and therefore the copolymer became soluble. The copolymer was characterized by NMR, SEC and ATR/FTIR. NMR analysis showed a successful modification of SMA via imidization. Because 4-aminomethylbenzene sulfonamide is a primary amine, thiocarbonyl thio end-group was converted into the thiol group my aminolysis. NMR analysis of polymer end groups proved that the thiocarbonyl thio was quantitatively removed. This was shown by the disappearance of the thiocarbonyl thio endgroup peaks.

Styrene sulfonate-maleic anhydride copolymer (SSMA) was synthesized by reacting the styrene aromatic ring of SMA with chlorosulfonic acid. This method was employed because the copolymer could not be synthesized by RAFT mediated copolymerization of styrene sodium sulfonate and maleic anhydride. SSMA was mainly characterized via ATR/FTIR, NMR and SEC. ATR/FTIR and NMR are two methods that proved the success of the sulfonation reaction. ATR/FTIR technique does not give the structure of the compounds but it only notifies of the functional groups present. Sulfonate functional groups were proven to be present in the modified polymer. Results obtained from the SEC were unexpected because the molecular weight values obtained were too high. The possible explanation for the bad results could be that there is interaction of the copolymer with the column. SSMA dissolves easily in water but it is insoluble in most organic solvents. The degree of sulfonation could not be determined by the following techniques; NMR, ATR/FTIR and elemental analysis. With the NMR technique, there is no change in the proton signals during and after sulfonation reaction. Elemental analysis results were found to be different from what was excepted when comparing theoretical and experimental values. High percent of sulfonation was targeted, but the chances of 100 % were low as the copolymer precipitate out of the solution as soon as there was formation of styrene sulfonate not given enough time for all the styrene units to modified. Elabd *et al.* have conducted research where they proved that sulfonation reach a limit point even if access quantity of acid has been used. The thiocarbonyl thio end group was converted into thiol by acid hydrolysis. The removal of thiocarbonyl thio endgroup was

confirmed by NMR technique. The endgroup peaks were absent in the NMR spectra of SSMA. The UV-vis was also used during Ellman's method, however conclusive results were not obtained as p-nitrobenzenethiol absorption was very low and it is assumed that instead of thiol formation during hydrolysis, unidentified side reactions occurred.

Styrene sulfonate-maleimide copolymer (SSMI) was synthesized by reacting SSMA with 3-(*N*, *N*-dimethylamino)-1-propylamine. The copolymer was characterized by NMR and ATR/FTIR. ATR/FTIR mainly proved the presence of both sulfonate and amide groups while NMR gave the spectra of polymer with methylene hydrogens being more visible compared the SSMA copolymer. The SSMI copolymer could not be characterized by SEC because it was insoluble in solvents used to dissolves samples for characterization (i.e. THF and DMF). The copolymer could not be quantitatively characterized due to the solubility restrictions.

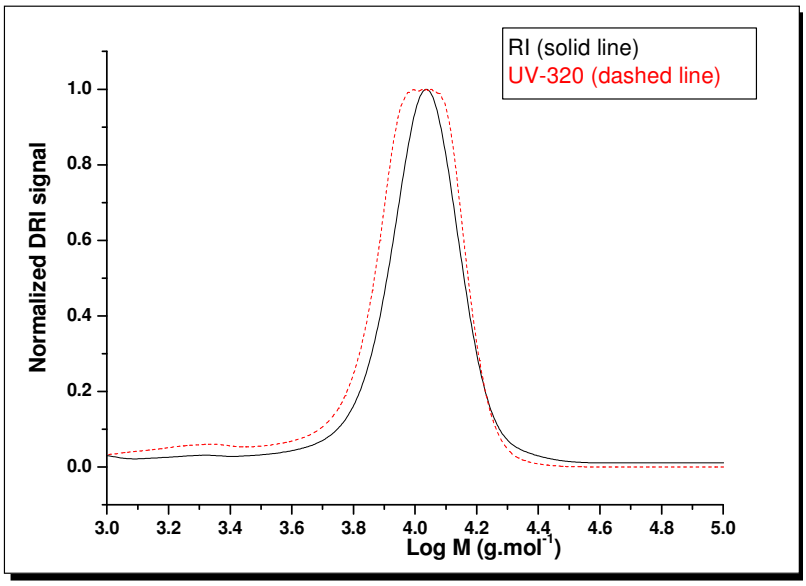
The thiocarbonyl thio end-group was quantitatively removed when SMA was modified to SMI and SSMA copolymers. The thiocarbonyl thio endgroup is labile and it gives coloured polymers. It reacts with nucleophiles to give thiols. During modification of SMA copolymers, the pink colour was lost which is one way of showing that the end group is being removed. NMR analysis confirmed that the end-group has been removed. The Ellman method which is normally used to determine the concentration of thiol was employed to quantitatively determine the presence of thiol at the end of polymer chains. This method quantitatively confirmed the presence of about thiol end-group by UV absorption. Looking at the UV spectra of both SMI and SSMA copolymers for the thiol absorption, the thiol absorption for SSMA was not observed for SSMA and the thiol absorption for the SMI copolymer gave low percent yield of the present end groups (thiol). The results are not conclusive of the thiol end groups quantity for both copolymers.

Elemental analysis was used to quantitatively analyze the synthesized copolymers. The methods did not work quite well as the elemental composition determined experimentally was outside the theoretical boundaries. Therefore it was decided that this method cannot be used to determine the degree of modification in copolymers derived from SMA copolymer.

The entire study is based on the synthesis of copolymers with potential anti-HIV activity. All the copolymers must be water soluble at neutral pH. All the polymers will be tested for anti-HIV activity. Similar materials with a range of molecular weights and different architectures will be synthesized.

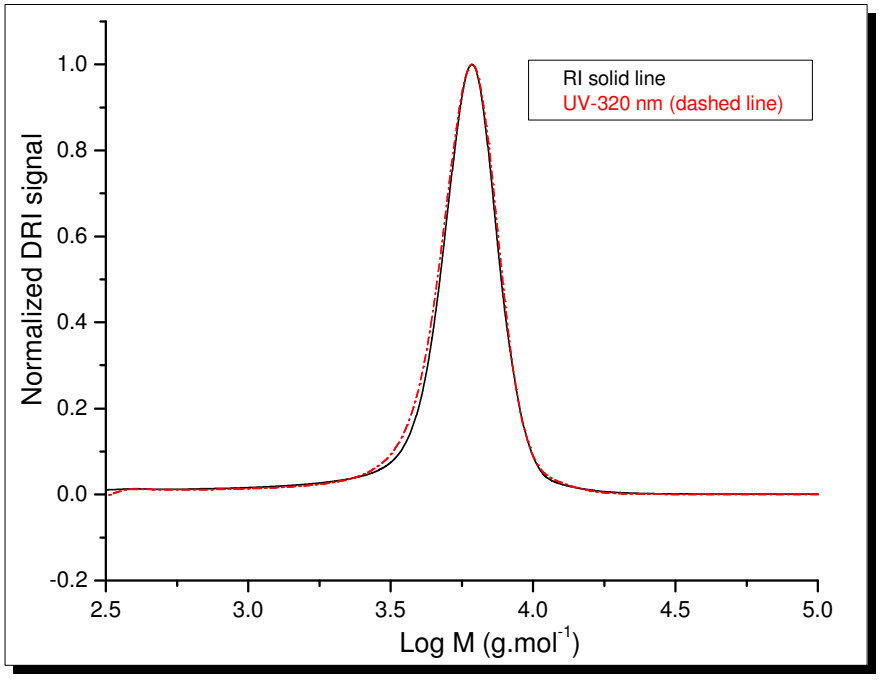
Appendix A

SEC chromatogram of SMA with UV at 320 nm showing the presence of RAFT end group. The UV curve in this chromatogram has a broad shape at maximum normalized DRI signal and the RI curve has a sharp. The phenomenon is strange and it is observed to all SEC chromatogram of copolymers dissolved in DMF. (Run 1 Table 4.1)



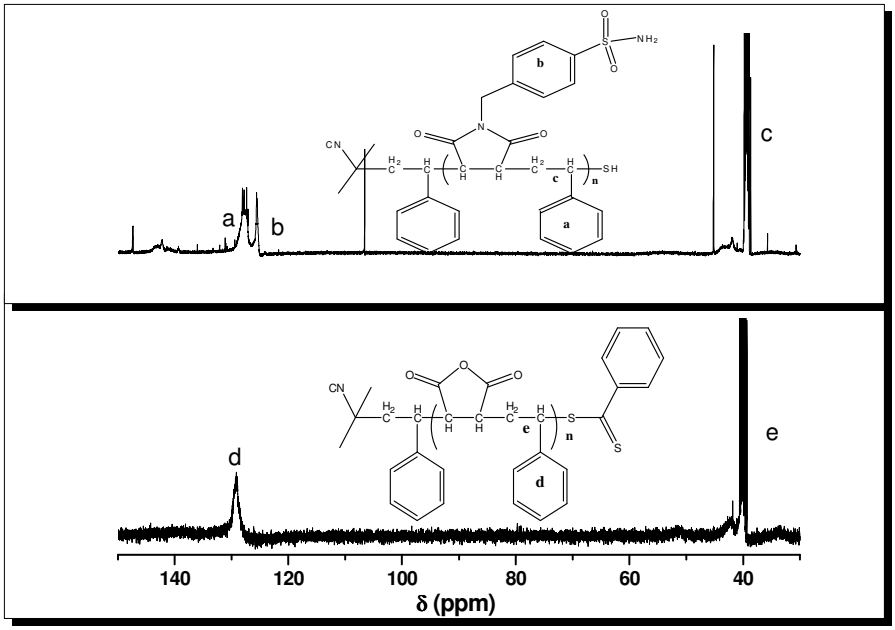
Appendix B

SEC chromatogram of SMA in THF with UV at 320 nm showing the presence of RAFT end group. The UV and RI curves have similar peak shapes. (Run 1 Table 4.1)



Appendix C

^{13}C NMR spectra of SMA (below, DMSO-d_6) of SMA copolymer synthesized via RAFT mediated polymerization of Sty and MAnh at 60 °C. (Run 1 Table 4.1) and SMI copolymer (above, DMSO-d_6) prepared by reaction of the amine compound with SMA copolymer at 85 °C in DMF for 8 hrs. (Run 3 in Table 4.2)



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