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Ran Wang
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RAFT SYNTHESIS OF WATER-SOLUBLE, STIMULI-RESPONSIVE
AB DIBLOCK COPOLYMERS

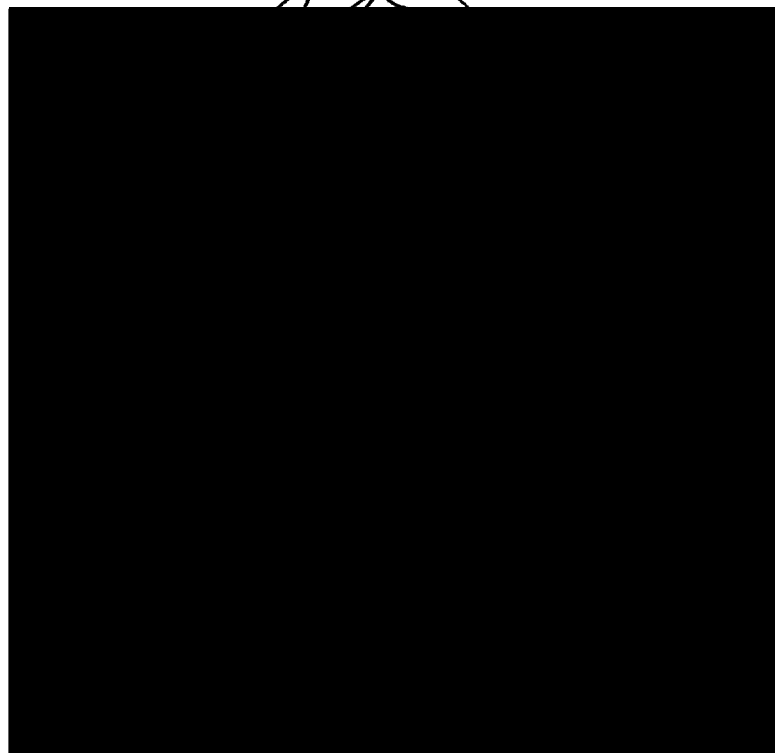
by

Ran Wang

A Dissertation

Submitted to the Graduate Studies Office
of The University of Southern Mississippi
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy

Approved: 



May 2008

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2008

The University of Southern Mississippi

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ABSTRACT

RAFT SYNTHESIS OF WATER-SOLUBLE, STIMULI-RESPONSIVE AB DIBLOCK COPOLYMERS

by Ran Wang

May 2008

A series of water-soluble, stimuli-responsive AB diblock copolymers were synthesized via the reversible addition-fragmentation chain transfer (RAFT) polymerization technique employing 2-(2-carboxyethylsulfanylthiocarbonylsulfanyl)propionic acid (**CTA26**) as the RAFT mediating agent.

First, a series of diacid functional trithiocarbonate chain transfer agents (CTA's) were synthesized and examined for their effectiveness as mediating agents in controlling the polymerization of *n*-butyl acrylate (nBA). Overall, **CTA26** demonstrated good control in the homopolymerization of nBA with respect to the molecular weight and the molecular weight distribution, as well as its ability to form block copolymers with high reinitiating efficiency, and thus was chosen as the CTA for the subsequent synthesis of polymers.

The first series of AB diblock copolymers we synthesized were polyampholytes derived from phosphonium styrenic-based monomers (**M63** and **M106**) and 4-vinylbenzoic acid (VBZ, **M62**). The homopolymerization of the trimethyl/triphenyl phosphonium styrene derivatives proceeds in a controlled fashion as evidenced from the narrow molecular weight distributions and the excellent agreement between the

theoretical and experimentally determined molecular weights. We also demonstrate the controlled nature of the homopolymerization of **M62** in DMSO. We subsequently prepared both statistical and block copolymers from the phosphonium/VBZ monomers to yield the first examples of polyampholytes in which the cationic functional group is a quaternary phosphonium species. We show that the kinetic characteristics of the statistical copolymerizations are different from the homopolymerizations and proceed, generally, at a significantly faster rate although there appears to be a composition dependence on the rate. Given the inherent problems in characterizing such polyampholytic copolymers via aqueous size exclusion chromatography we have qualitatively proved their successful formation via FTIR spectroscopy. Finally, we demonstrate the ability of such pH-responsive block copolymers to undergo supramolecular self-assembly characterized by ^{13}C NMR spectroscopy.

Following this, we synthesized styrenic-based block polyelectrolytes comprised of 4-vinylbenzyltrimethylphosphonium chloride (TMP, **M63**) and *N,N*-dimethylbenzylvinylamine (DMBVA, **M59**) directly in aqueous media under homogeneous conditions. TMP was first homopolymerized and polyTMP was subsequently used as macro-CTA for the polymerization of the DMBVA under buffered conditions (pH 4). Copolymerizations were controlled as judged by the high blocking efficiency and the resulting narrow molecular weight distributions. The pH-dependent self-assembly properties of the AB diblock copolymers were examined using a combination of ^1H NMR spectroscopy, dynamic light scattering, and fluorescence spectroscopy. The size of the polymeric aggregates was demonstrated to be dependent upon the block copolymer composition/molar mass. Such pH-induced supramolecular

self-assembly was also demonstrated to be completely reversible, as predicted given the tunable hydrophilicity/hydrophobicity of the DMBVA block. Finally, we demonstrate the ability to effectively lock the AB diblock copolymers in the self-assembled state via a straightforward core crosslinking reaction between the tertiary amine residues of DMBVA and the difunctional benzylic bromide 1,4-bis(bromomethyl)benzene.

Finally, we made an AB diblock copolymer of *N*-isopropylacrylamide (NIPAM, **M75**) and VBZ (**M62**) via RAFT mediated by **CTA26** in DMF. NIPAM was homopolymerized first and polyNIPAM was treated as a macro-CTA in the subsequent polymerization of VBZ. By virtue of the temperature-responsive properties of the NIPAM block and the pH-responsive nature of VBZ block, this novel AB diblock copolymer was demonstrated to be able to form normal and inverse micelles in the same aqueous solution simply by controlling the temperature and solution pH. As judged by NMR spectroscopy and dynamic light scattering, raising the temperature to 40°C (above the lower critical solution temperature of the NIPAM block), while at pH 12 results in supramolecular self-assembly to yield nanosized species that, presumably, are composed of a hydrophobic NIPAM core stabilized by a hydrophilic VBZ corona. Conversely, lowering the solution pH to 2.0 at ambient temperature results in the formation of aggregates in which the VBZ block is now hydrophobic and in the core, stabilized by the hydrophilic NIPAM block.

To my parents
For their love and support

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CHAPTER I

INTRODUCTION

1. Water-soluble Polymers

Water-soluble polymers are among the most important families of polymers. They range from naturally occurring biopolymers such as proteins and nucleotides, to synthetic polymers such as viscosifiers and soaps. Water-soluble polymers, in general, can be divided into nonionic and ionic species. The majority are ionic materials. Ionic polymers can be further divided into two groups, polyelectrolytes and polyzwitterions, based on the type of ions present. Polyelectrolytes contain either cationic or anionic groups, while polyzwitterions contain both cationic and anionic groups.

1.1 Nonionic water-soluble polymers

A large number of nonionic water-soluble (co)polymers have been synthesized from monomers such as those shown in Figure I-1. The water-solubility is a result of the polar or hydrogen-bonding functional groups on the repeat units. Some important water-soluble polymers are those derived from acrylamide (**M1**),¹ acrylic acid (**M2**),² ethylene oxide (**M3**),³ vinyl alcohol (prepared by alcoholysis/hydrolysis of poly(vinyl acetate) (**M4**),⁴ methyl vinyl ether (**M5**),⁵ *N*-vinylpyrrolidinone (**M6**),⁶ and *N*-(2-methyl-4-oxopentan-2-yl)acrylamide (**M7**). Such hydrophilic polymers usually display inverse temperature water-solubility with a lower critical solution temperature (LCST).⁷

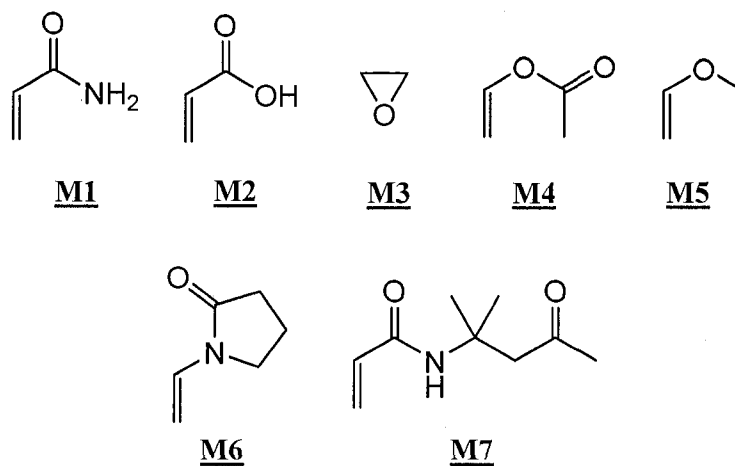


Figure I-1. Examples of nonionic water-soluble monomers.

1.2 *Polyelectrolytes*

Polyelectrolytes are polymers with charged functional groups along the polymer chain. These polymers can be categorized as either polycations (those containing positively charged groups) or polyanions (those containing negatively charged groups), such charged groups are associated with counterions.^{8,9}

Most of the cationic polyelectrolytes in the literature contain amine functional groups or quaternary ammonium groups (Figure I-2). However, other heteroatoms are also capable of bearing a formal positive charge, and monomers with phosphonium, sulfonium, and onium cationic groups are also known.^{2,11-56}

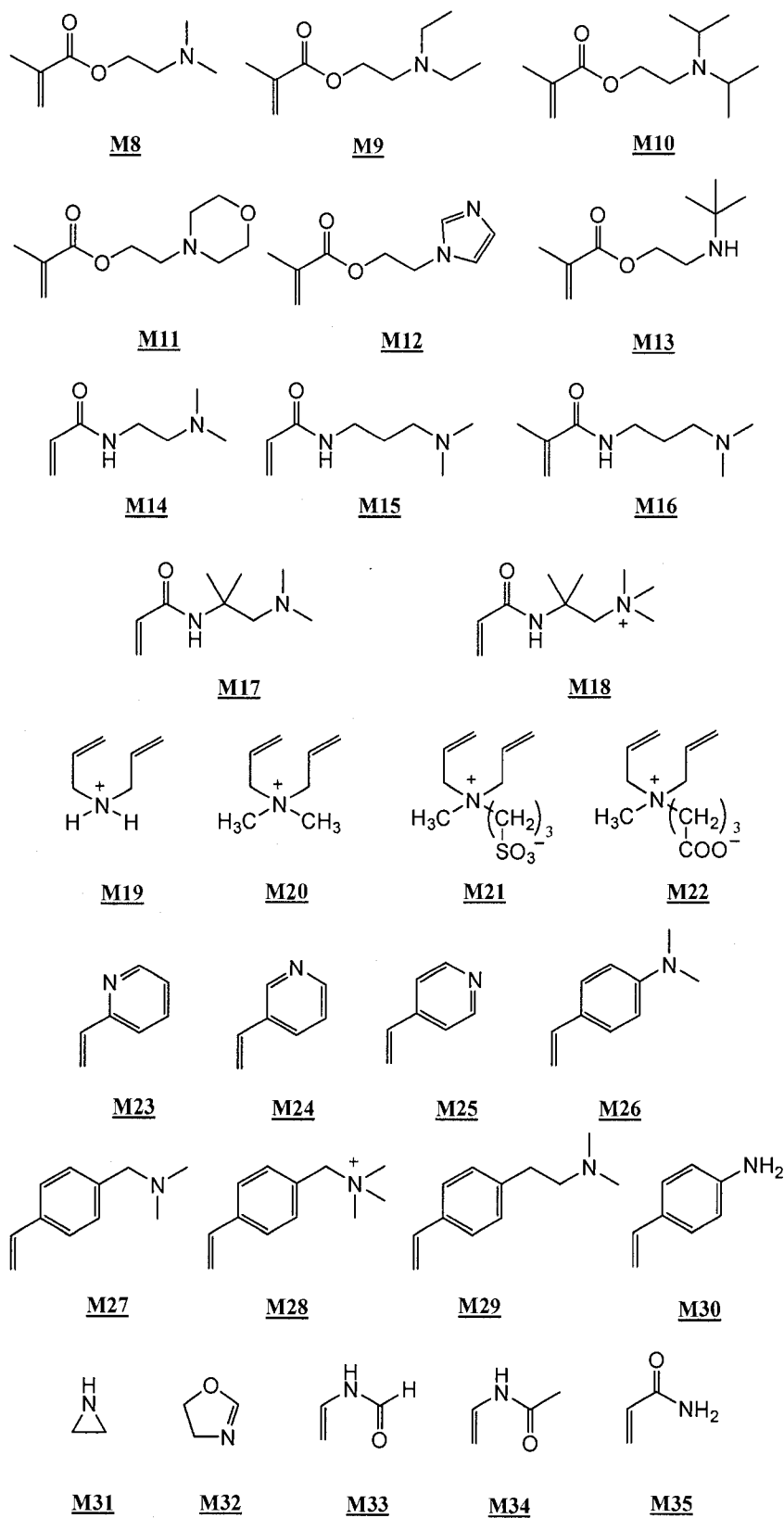


Figure I-2. Chemical structures of common ammine/ammonium-containing monomers.

Typical monomers yielding anionic polyelectrolytes include those containing, for example, functional carboxylate, sulfonate, phosphate groups (Figure I-3).^{2,57-79}

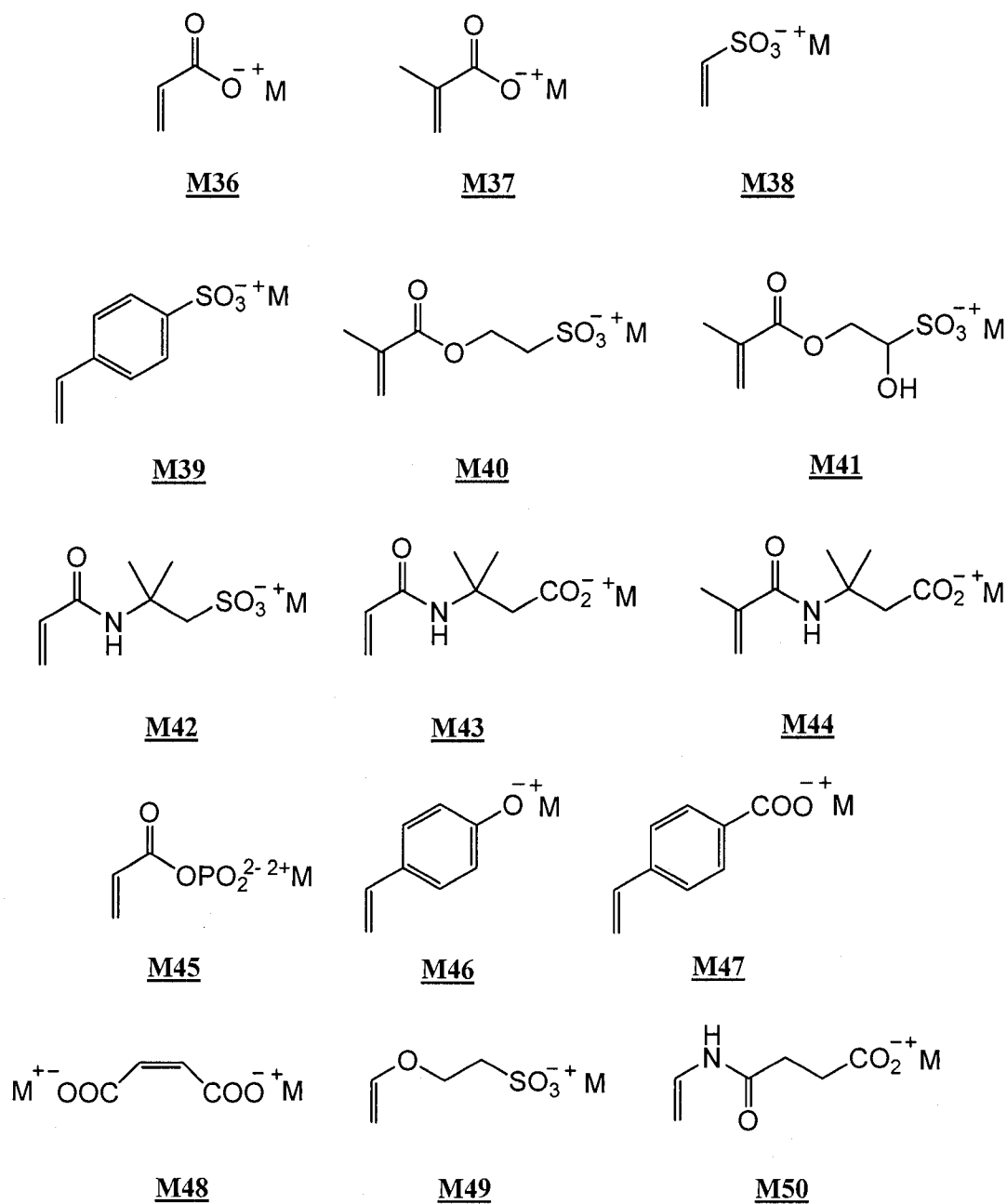


Figure I-3. Chemical structures of common anionic monomers.

An interesting characteristic of polyelectrolytes is chain extension, resulting in large hydrodynamic volumes in deionized water. This is due to the Coulombic repulsions between charged groups along the polymer chains, forcing the polymer into an extended conformation. The addition of low molecular weight electrolytes, such as NaCl, leads to these repulsive electrostatic forces being largely screened and the polymer chain will contract, adopting an entropically more favored conformation. This is known as the *polyelectrolyte effect* (Figure I-4).⁸⁰

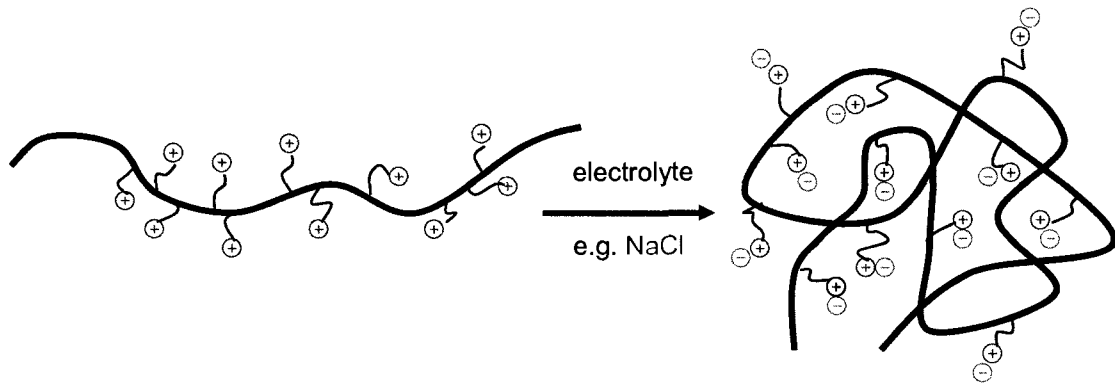


Figure I-4. Schematic illustration of polyelectrolyte effect.

1.3 Polyzwitterions

Polyzwitterions can be divided into polyampholytes and polybetaines according to the number and location of the charged groups. Polybetaines possess both cationic and anionic groups on the *same* monomer unit, and as such are charged balanced.

Polyampholytes have the charges on different monomer units, and may or may not be charged balanced depending on the molar ratio of anionic to cationic monomers.

The solution behavior of polyzwitterions is opposite to that of polyelectrolytes. The conformation of polyzwitterions is usually more compact due to the net attractive

electrostatic forces between the charged groups along the polymer chains in deionized water. The addition of low molecular weight electrolytes can reduce such interactions and result in chain extension and hence promote/enhance solubility. This kind of behavior is known as the *antipolyelectrolyte effect* (Figure I-5).⁸¹

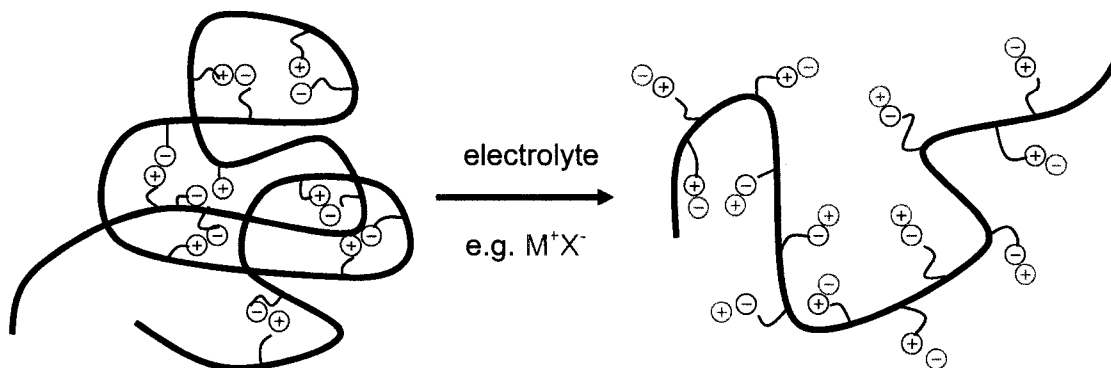


Figure I-5. Schematic illustration of the anti-polyelectrolyte effect.

1.3.1 Polyampholytes

Polyampholytes are of great interests because they are synthetic analogues of naturally occurring biopolymers such as proteins. Polyampholytes possess cationic and anionic residues on different repeating units. Therefore, polyampholytes can be either balanced or unbalanced in overall charge. There are four subclasses of polyampholytes based on their response to pH change in aqueous solution.⁸¹ a) polyampholytes contain both cationic and anionic groups that may be neutralized; b) the cationic group may be neutralized while the anionic groups are insensitive to any change of pH; c) the anionic group may be neutralized while the cationic groups are insensitive to change of the pH; d) both cationic and anionic groups are insensitive to pH changes.

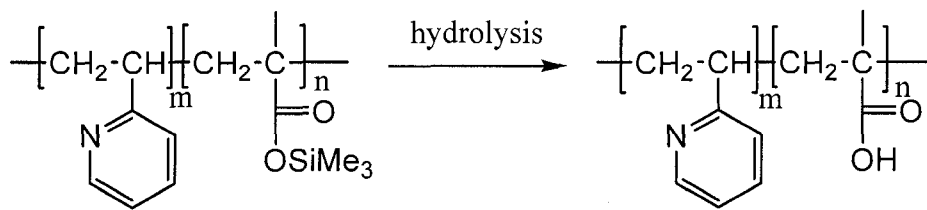


Figure I-6. First example of synthetic block polyampholytes.

Statistical polyampholytes can be prepared by the direct copolymerization of cationic and anionic monomers, typically in aqueous media by conventional free radical polymerization. The first examples of such copolymers were reported in the 1950's.⁸²⁻⁸⁹ However, it was not until the 1970's that the first block polyampholytes were reported.^{90,91} An AB diblock copolymer of 2-vinylpyridine and trimethylsilyl methacrylate was prepared by living anionic polymerization. The protecting trimethylsilyl group was removed post-polymerization by hydrolysis (Figure I-6). However, even today, nearly 40 years after this report there are still only a handful of papers describing the synthesis and solution properties of block polyampholytes with the majority of the syntheses requiring protecting group chemistries. Recently, the development of the controlled/living free radical polymerization techniques, such as stable free radical polymerization (SFRP), best exemplified by nitroxide-mediated polymerization (NMP),^{92,93} atom transfer radical polymerization (ATRP),⁹⁴⁻⁹⁸ and reversible addition-fragmentation chain transfer (RAFT) polymerization,⁹⁹⁻¹⁰¹ have enabled the direct synthesis of such polyampholytes in aqueous media without the need for protecting group chemistry. For example, a block copolymer of sodium-styrenesulfonate with 4-(dimethylamino)methyl styrene has been prepared via TEMPO-mediated SFRP.¹⁰²

The aqueous solution behavior of polyampholytes is dictated by Coulombic interactions between cationic and anionic groups on different monomer units and can be very complex. Polyampholytes can display both polyelectrolyte and antipolyelectrolyte behavior, depending on the solution pH, nature of the anionic and cationic groups, copolymer composition, and the presence/absence of low molecular weight electrolytes. One of the characteristics of polyampholytes that have both weak acid and base groups is the isoelectric point (IEP or pI). The pI is defined as the pH at which polyampholytes are electrically neutral.⁸² The solubility of polyampholytes at the pI depends on copolymer composition and architecture. For example, statistical polyampholytes tend to be soluble at the pI, while block polyampholytes tend to precipitate at/around the pI, but tend to be soluble below or above the pI.¹⁰³ The pI can be determined by either titration or by measuring the reduced viscosity.¹⁰⁴ The pI is the solution pH at which the polyampholytes have the most compact conformation, which is indicated by the minimum of the reduced viscosity.

It is also possible to calculate the pI theoretically.¹⁰⁵ Patrickios has shown:

$$pI = pK_b + \log \left\{ (1/2) \left[(1 - R) / R + \left[((1 - R) R)^2 + (4/R) \times 10^{pK_a - pK_b} \right]^{1/2} \right] \right\} \quad \text{Equation 1}$$

Where K_b is the equilibrium dissociation constant for basic residues, K_a is the equilibrium dissociation constant for acidic residues, $pK_b = -\log K_b$, $pK_a = -\log K_a$, and R is the ratio of acidic to basic residues. This equation is only valid for base-rich polyampholytes, when $R < 1$. For acid-rich polyampholytes when $R > 1$, the equation below needs to be used:

$$pI = pK_a + \log\left\{\frac{1}{2}\left[\frac{(1-R)}{R} + \left[\left(\frac{(1-R)}{R}\right)^2 + \left(\frac{4}{R}\right) \times 10^{pK_a - pK_b}\right]^{1/2}\right]\right\} \quad \text{Equation 2}$$

These equations were first proposed by Ehrlich and Doty in 1954, and solved recently by Patrickios.¹⁰⁵ For some specific compositional ratios, for example, when $R = 1$, $1/2$, and 2 , the calculation of pI can be simplified. When $R = 1$ (equal number of acidic and basic residues), the pI can be calculated as:

$$pI = (pK_a + pK_b) / 2 \quad \text{Equation 3}$$

In this case, the isoelectric point is simply the arithmetic average of the equilibrium constants of acidic and basic residues. At $R = 2$, where acidic residues are as twice as basic residues:

$$pI = pK_a \quad \text{Equation 4}$$

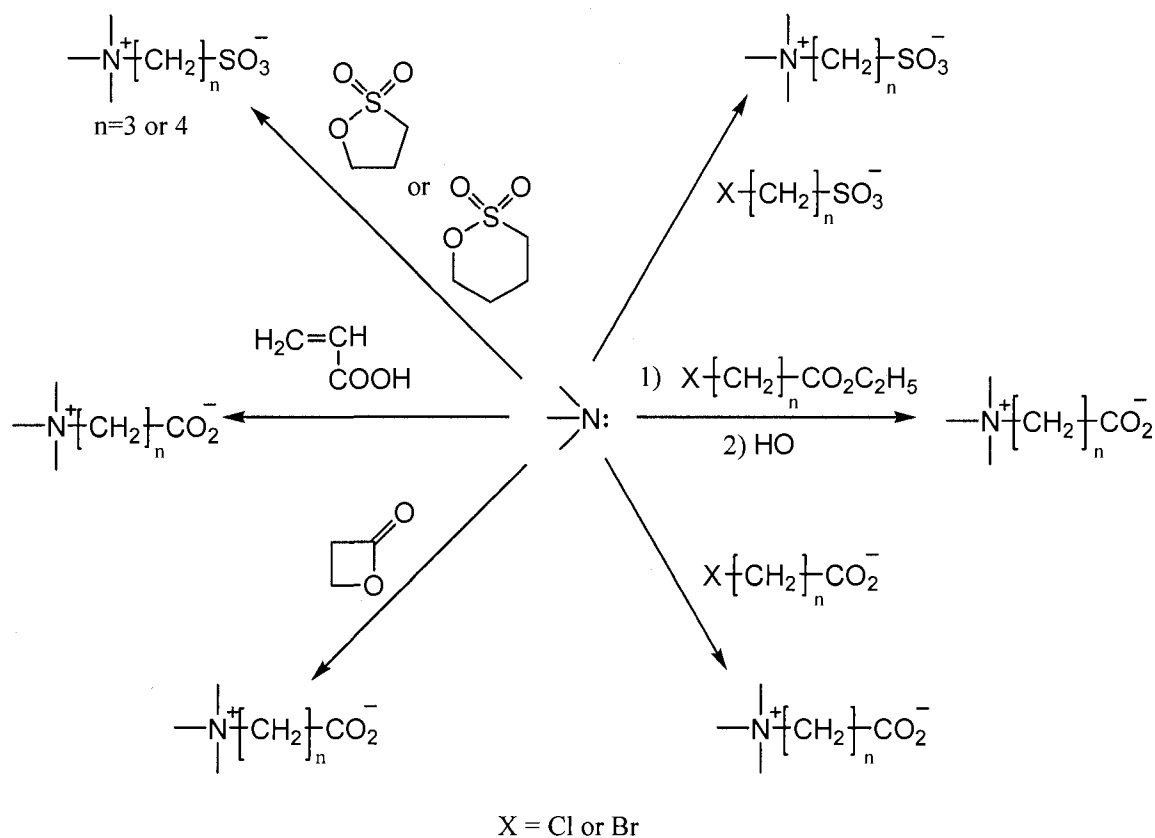
And at $R = 1/2$, where basic residues are as twice as acidic residues:

$$pI = pK_b \quad \text{Equation 5}$$

Experimental data has shown perfect agreement between the calculated and observed values.⁶⁷

1.3.2 Polybetaines

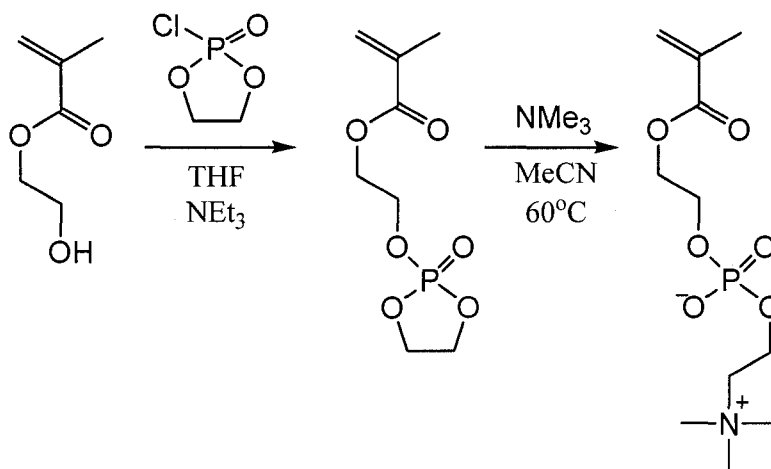
Polybetaines are materials in which the anionic and cationic groups are located on the same repeat unit. A general feature of the aqueous solution behavior of polybetaines is the general lack of solubility in pure water. The insolubility is caused by the intra- and interchain ionic attractions resulting in an ionically cross-linked network structure.



Scheme I-1. General synthetic routes for sulfo/carboxybetaines.

The typical cationic residue in polybetaines is a quaternary ammonium species, while the anionic species can be carboxylate, sulfonate, or a phosphate functional group. Scheme I-1 shows the general synthetic routes available for synthesizing various sulfo/carboxybetaines from a starting monomer bearing a tertiary amine group.

Sulfobetaines can be obtained by reacting the tertiary amine residue with either 1,3-propanesultone or 1,4-butanesultone at room temperature in common solvents such as THF or CH₃CN.¹⁰⁶ Alternatively the tertiary amine can be reacted with a haloalkylsulfonate species.¹⁰⁷ Carboxybetaines may be prepared in the similar way by reacting tertiary amine with a suitable lactone,¹⁰⁸ or with a haloalkylcarboxylate. Another method is through reaction with the corresponding haloalkylester to yield the quaternized species, followed by ester hydrolysis to yield the carboxybetaine.^{109,110} The most common phosphobetaine monomer is 2-(methacryloyloxy)ethyl phosphorylcholine (MPC), which can be prepared from the reaction of 2-hydroxyethyl methacrylate with 2-chloro-2-oxo-1,3,2-dioxaphospholane, followed by ring opening with trimethylamine (see Scheme I-2).¹¹¹ This general procedure can be applied to any alcohol functional monomer to prepare the corresponding phosphobetaine derivative.



Scheme I-2. Synthesis of 2-(methacryloyloxy)ethyl phosphorylcholine (MPC).

Polybetaines are most readily prepared by the direct polymerization of the betaine monomers, usually in aqueous salt solution.¹¹²⁻¹¹⁵ The direct polymerization of betaines

in a controlled fashion has been reported by group transfer polymerization (GTP),¹¹⁶ ATRP,¹¹⁷⁻¹²⁰ and RAFT polymerization.¹²¹⁻¹²⁴ The latter is more versatile with respect to monomer choice with examples of styrenic, methacrylic and acrylamido sulfo- and phosphobetaines, having been reported.

Polymeric betaines have applications similar to those of polyampholytes. Additionally, phosphobetaines have found special application in the biomedical area. For example, copolymers of MPC and alkyl methacrylate have been shown to display good biocompatibility and have found application as coatings for medical devices and for contact lenses.¹²⁵

2. Living Polymerizations

Conventional free radical polymerization is initiated by radicals derived from an initiator. These primary radicals will add to monomer and form propagating chains which are the active species. Polymer chains propagate by adding additional monomer, and terminate by radical combination or disproportionation. The current IUPAC definition of a living polymerization is “a chain growth process that proceeds in the complete absence of termination or chain transfer reactions”. However, in reality, few, if any, polymerizations meet these criteria.¹²⁶

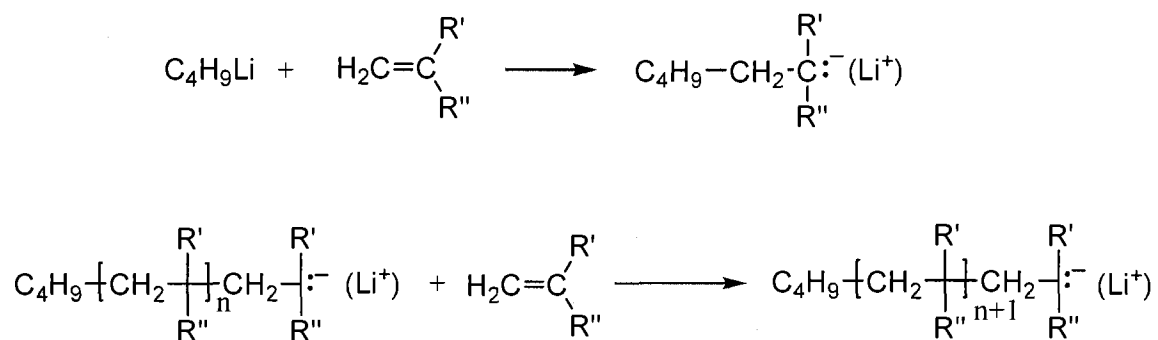
2.1 Evolution of classic living systems

2.1.1 Living anionic polymerization

For about 40 years living anionic polymerization was the main technique to synthesize polymers with well-defined architectures and narrow molecular weight

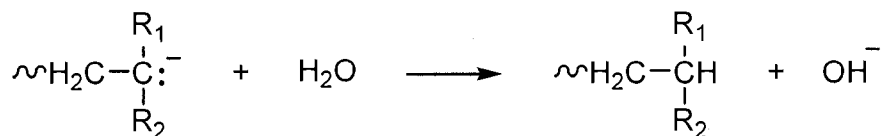
distributions.¹²⁷ This is mainly due to the relative stability of the propagating anionic species compared with free propagating radicals or cations.

A variety of nucleophilic initiators have been used to initiate anionic polymerization.¹²⁸⁻¹³³ For example, alkyllithium compounds are the most commonly employed initiators (Scheme I-3):



Scheme I-3. Initiation and propagation in anionic polymerization with *n*-butyl lithium as an initiator.

Living anionic polymerizations are typically conducted at very low temperature, i.e. -78°C . In many cases, there is no effective termination reaction in a living anionic polymerization system and propagation continues to 100% conversion of monomer(s), forming living polymers which can later chain extend because the propagating anionic centers remain intact. This provides the possibility to synthesize block copolymers and even more complex architectures. However, propagating anions may be terminated by trace amount of moisture present (Scheme I-4).¹³⁴



Scheme I-4. Anionic propagating species terminated by water.

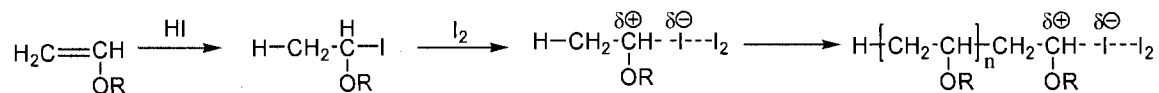
Therefore, a living anionic polymerization system requires all reagents/glassware to be cleaned thoroughly to avoid any water or impurity which has labile hydrogen. Such precautions make living anionic polymerizations synthetically challenging to execute.

2.1.2 Living cationic polymerization

In comparison with anionic polymerization, it is much more difficult to achieve living cationic polymerization (LCP) even in a well-purified system where there is no nucleophile present to terminate the cationic center. This is because of the built-in termination reaction – transfer of β -protons to monomer, counterion or some other basic species in a cationic polymerization system. To achieve LCP, the components such as the initiator, coinitiator, solvents need to be carefully chosen so that there is no nucleophile present in the system which can irreversibly terminate the propagating cationic species. Also, basic components need to be avoided to minimize the β -proton transfer. However, most monomers themselves are basic. Therefore, it is necessary to find other ways to minimize undesirable β -proton transfer reactions.⁵³

The basic approach to suppress such transfer reactions is to establish a reversible equilibrium in which the short-living, unstable cationic centers are converted to stable dormant species (Scheme I-5). The equilibrium between dormant covalent species and active ion pairs is driven toward the dormant species by choice of appropriate initiating

systems. Also, the components of the systems are chosen so that there is a fast and frequent exchange between the active and dormant species. The overall result is much less chance of the transfer side reaction as well as extended lifetime of propagating cations.



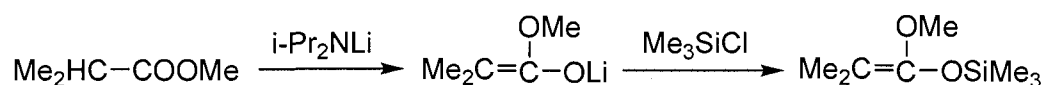
Scheme I-5. Example of living cationic polymerization of vinyl ethers using the HI/I₂ initiating system.

Low temperature is also necessary to achieve LCP. Because the activation energy for β -proton transfer is greater than that for propagation, the exotherm caused by polymerization increases the transfer relative to propagation, resulting in shorter lifetime of the propagating cations and thus a lack of control. Therefore, most LCP's need to be carried out at low temperatures.

Examples of living cationic polymerizations include the polymerization of isobutyl vinyl ether with HI/I₂ as the initiator.¹³⁵⁻¹³⁷ Since vinyl ethers have a strong resonance stabilization of positive charge and thus can form stable carbocations with the propagating species, a relatively weak initiator is used. However, for isobutylene, which has a weaker capability to form carbocations than a vinyl ether, a stronger Lewis acid is required. But it should be noted that none of the living cationic polymerization systems are as long-lived as the anionic systems. The half-lives of the propagating species begin to decay as soon as the monomer is starved. And in the absence of monomer, the half-lives of the cationic centers vary from hours to a day, depending on the temperature.

2.1.3 Group transfer polymerization

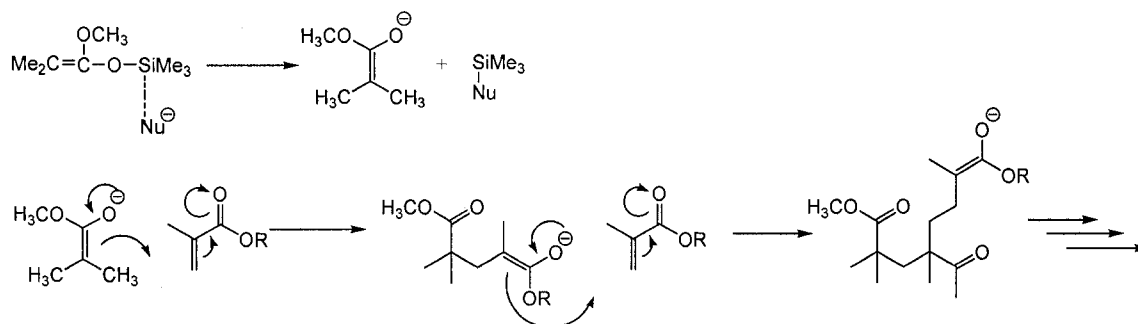
Group transfer polymerization (GTP) was discovered by Webster et al. in the 1980's under Dupont's exploratory research project.¹³⁸ GTP can be viewed as a special form of living anionic polymerization, that is especially effective for (meth)acrylate monomers. However, it has the advantage of being readily conducted at room temperature. The common initiator is a silyl ketene acetal that can be synthesized from an ester enolate (Scheme I-6).⁵³ This initiator is now commercially available.



Scheme I-6. The synthesis of the common GTP initiator, (1-methoxy-2-methylprop-1-enyloxy)trimethylsilane.

GTP needs to be catalyzed by either a nucleophile or Lewis acid. The most common catalysts are $[(\text{CH}_3)_2\text{N}_3]\text{SHF}_2$ (TASHF₂) and tetrabutyl ammonium bibenzoate (TBABB).¹³⁹

Nucleophilic GTP proceeds by a dissociative mechanism in the presence of anionic propagating centers (Scheme I-7). The trimethylsilyl group of the initiator is displaced by the nucleophilic catalyst, forming an enolate, which will propagate by adding to (meth)acrylate via consecutive Michael addition reactions. The overall result is that the anionic center 'transfers' to the end of the chain, which gives the polymerization its name.¹⁴⁰

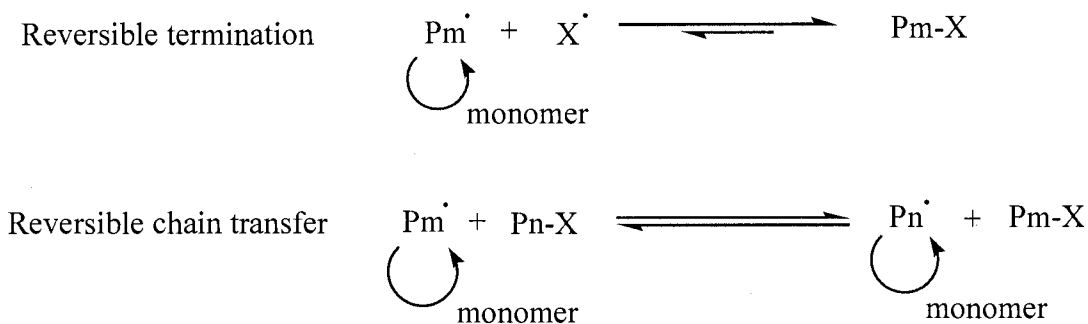


Scheme I-7. Dissociative mechanism of nucleophilic GTP.

2.2 Controlled/living free radical polymerization: An introduction

In conventional free radical polymerizations, the steady state concentration of propagating radicals is $\sim 10^{-7}$ M and each chain grows for about 1 –5 seconds before it is terminated either by combination or by disproportionation. In the whole system, chains are continuously generated, propagate and terminate. The molecular weight of polymer chain formed is higher at the early stage but reduces with the conversion because of the depletion of monomer(s). Thus, the molecular weight distribution is broad and the polydispersity index (PDI) is usually larger than 1.5.⁵³

The past few years have witnessed the development of the controlled/living free radical polymerizations, such as SFRP, best exemplified by nitroxide mediated polymerization (NMP),^{92,93} ATRP,⁹⁴⁻⁹⁸ and RAFT.⁹⁹⁻¹⁰¹ All these techniques utilize a dormant species that can react with propagating radicals either by reversible termination (NMP and ATRP) or reversible chain transfer (RAFT), largely suppressing the undesired radical-radical termination reactions (Scheme I-8). The rapid equilibration between the dormant species and the active propagating radicals ensures that all chains get an equal chance to grow. Such conditions allow for the control of molecular weight and typically result in materials with narrow molecular weight distributions.



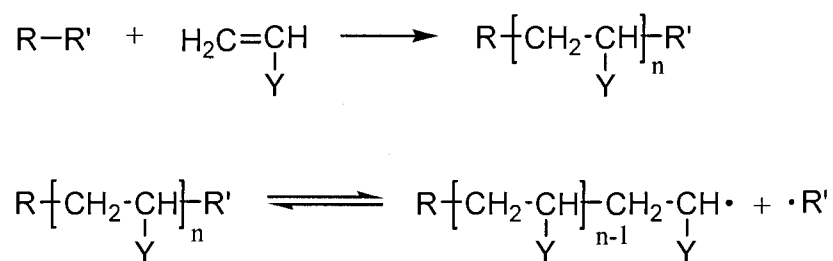
Scheme I-8. General strategies for achieving living radical polymerization.

3. Living Radical Polymerizations

The synthesis of polymers with well-defined architectures and functionalities has always been of great interest in polymer chemistry. However, traditional free radical polymerization offers very limited control over either molecular weight or architecture due to the termination reactions between propagating radical chains. Until living radical polymerization was developed recently, ionic polymerizations were the only ‘living’ techniques available that could provide polymers of controlled molecular weight, low polydispersity, and defined chain ends, although such techniques are inapplicable to many functionalized vinylic monomers because of the incompatibility of the active center (anionic or cationic) with certain monomer families and/or functional groups. In addition, they require stringent conditions, such as ultrapure reagents and the complete exclusion of water. Therefore, it is important to develop techniques that can offer both versatility and controllability, which is the reason of the development of living radical polymerizations.

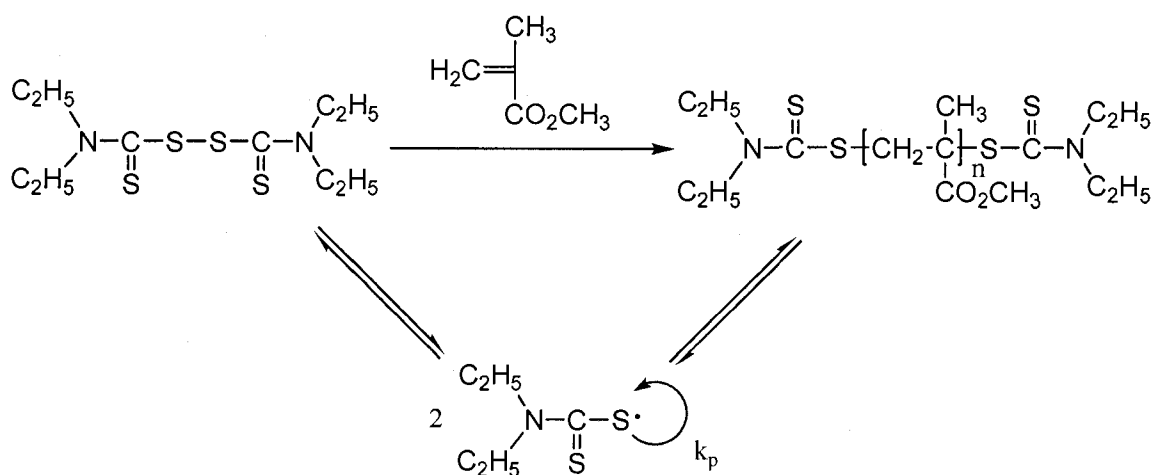
3.1 *Iniferter polymerization*

The concept of a living radical polymerization (LRP) was first introduced by Otsu in the early 1980's through his investigation of iniferters.^{141,142} The term 'iniferter' was defined as compounds that can **initiate**, **transfer**, and **terminate** a radical polymerization (Scheme I-9) by analogy to the 'inifers' used by Kennedy in cationic polymerization.¹⁴³



Scheme I-9. General mechanism of an iniferter system.

For example, tetraethylthiuram disulfide was used as the iniferter to mediate the polymerization of methyl methacrylate (Scheme I-10).¹⁴²



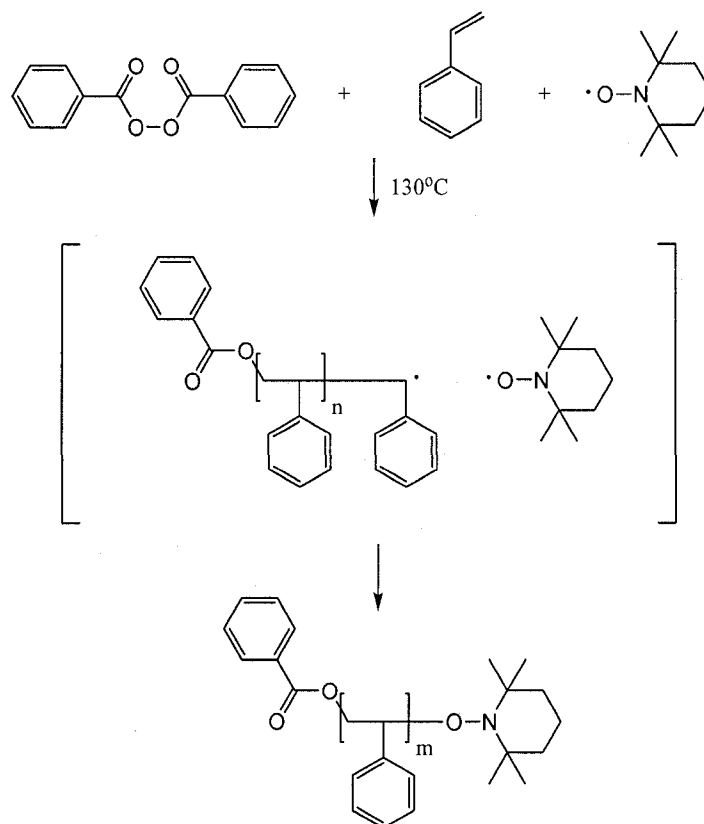
Scheme I-10. Iniferter used to mediate polymerization of methyl methacrylate.

Using this method, the preparation of block polymers by the sequential addition of monomers becomes possible. Although not very efficient, this early work provided a model for the later development of living radical polymerization techniques.

3.2 Nitroxide mediated polymerization (NMP)

3.2.1 **Introduction**

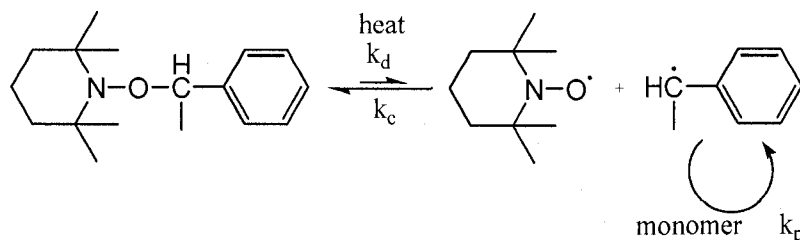
Nitroxides are well known for their ability to rapidly combine with carbon-centered radicals to yield alkoxyamines. Therefore, such stable radicals are often used as a radical scavenger to detect or identify radical species in reactions. The idea of utilizing nitroxides as mediators instead of inhibitors in free radical polymerization systems was first reported by Rizzardo in the 1980's.⁹² They synthesized low molecular weight oligomers of acrylates at 80-100°C, in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). Although the polymerization was considered living, it was poorly controlled with respect to molecular weights and polydispersities. Later the Georges group at Xerox reported the successful synthesis of low polydispersity polystyrene (PDI = 1.20) using the same nitroxide but at 130 °C.¹⁴⁴ The system consisted of benzoyl peroxide as the initiator and TEMPO at a molar ratio of 1.3:1 (Scheme I-11). This work displays many fundamental characteristics of a living polymerization process, such as the linear growth of number average molecular weight (M_n) with conversion, as well as low PDI values (1.2), which is significantly lower than the theoretical lower limit for a conventional free radical process (1.5).



Scheme I-11. Nitroxide-mediated polymerization of styrene at 130 °C.

3.2.2 Basic mechanism

The work reported by Georges et al. is a bimolecular system, in which an external radical source was used. However, such a system is poorly defined and the concentration of the initiating species is unknown. This prompted the development of unimolecular systems, based on the fact that the C-O bond of the small molecule alkoxyamine is thermotically unstable and decomposes to yield an initiating radical (α -methyl benzyl in Scheme I-12), as well as the mediating nitroxide radical, in the correct 1:1 stoichiometry.¹⁴⁵ The advantage of unimolecular system is that all polymer chains are terminated by nitroxide species, and thus the molecular weight can be accurately controlled, and the synthesis of more advanced architectures can be achieved.



Scheme I-12. Mechanism of TEMPO-mediated NMP.

The mechanism of NMP is known as reversible termination. During the polymerization, the propagating radicals, tends to combine with the nitroxide and be converted reversibly into the dormant, non-propagating species. The equilibrium favors the formation of dormant species by several orders of magnitude and the concentration of dormant species is about 6 orders of magnitude greater than that of propagating radicals. The overall result is that the instantaneous radical concentration in the system is low and thus the undesirable bimolecular termination reactions can be largely suppressed. The stable radical is often called the persistent radical, and its suppression effect is called the persistent radical effect.

3.2.3 Suitable monomers

The application of NMP mediated by TEMPO is limited, due to the high temperatures (125-145 °C) required, long polymerization time, and incompatibility with many monomer families.¹⁴⁶

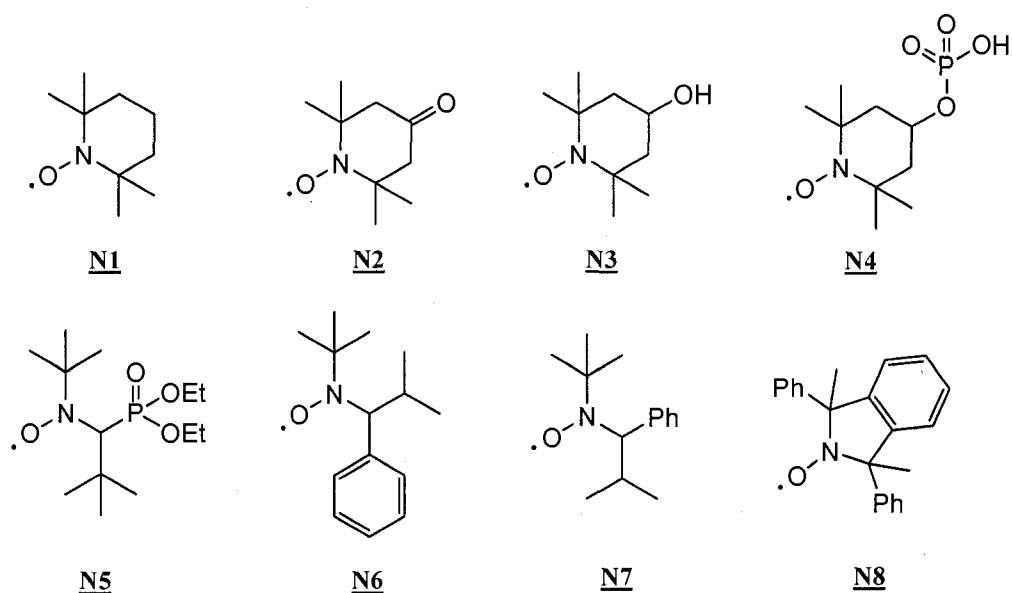


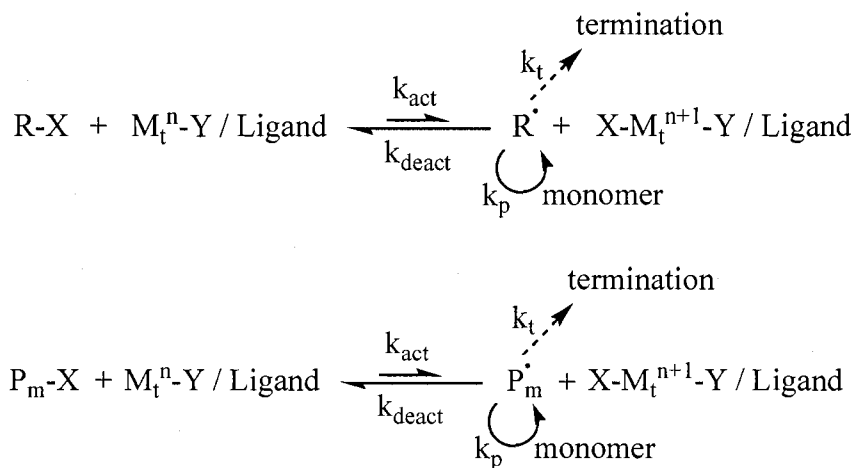
Figure I-7. Examples of nitroxides employed in NMP.

The position of the main equilibrium ($K = k_d / k_c$) is mainly determined by the type of nitroxide used. Therefore, it is important to explore new effective nitroxides to improve the technique. Figure I-7 shows a few types of nitroxides that have been reported in the literature.¹⁴⁷⁻¹⁵² Of them the most important breakthrough is the design of acyclic, nonquaternary nitroxides, best exemplified by **N5**¹⁴⁷ and **N6**¹⁴⁸ in Figure I-7, introduced by Gnanou et al. and Hawker et al. respectively. These nitroxides have been shown to permit the controlled polymerization of a wide variety of monomer families, such as acrylates, acrylamides, 1,3-dienes, and acrylonitriles.

3.3 Atom transfer radical polymerization (ATRP)

3.3.1 Introduction

In the mid-1990's atom transfer radical polymerization (ATRP) was simultaneously reported by Matyjaszewski and co-workers,^{94,95} and Sawamoto and co-workers.⁹⁶⁻⁹⁸



Scheme I-13. Mechanism of transition metal catalyzed ATRP.

The general mechanism of ATRP is shown in Scheme I-13. The radicals are generated through a reversible redox reaction catalyzed by a transition metal catalyst $\text{M}_t^n\text{-Y}$, where Y may be the counterion or another ligand. The catalyst undergoes a one electron oxidation and abstracts a (pseudo)halogen atom, X, from R-X, which is the dormant species in the system. This process has a rate constant of activation, k_{act} , and deactivation, k_{deact} . Typically, k_{act} is far less than k_{deact} , and thus the equilibrium favors the reverse reaction much more than the forward reaction. Polymer chain grows when the intermediate radical $\text{R}\cdot$ or $\text{P}_m\cdot$ is released in the manner similar to conventional radical polymerization, with the rate constant of k_p . Termination reactions also occur in ATRP,

mainly through combination or disproportionation, forming dead polymers. However, in successful ATRP polymerizations, the amount of terminated dead polymer is very small, no more than 5% of the total propagating chains. The process of ATRP also operates based on the so-called ‘persistent radical’ effect, which refers to the oxidized metal complex, $X-M_t^{n+1}$, which will combine with the propagating radicals and thus minimize the concentration of radicals as well as the chance of termination reactions between them.¹⁵³ By such fast and frequent activation and deactivation, all polymer chains get an equal chance to grow, and the side reactions involving radicals are largely suppressed.

The ability of each monomer to polymerize by ATRP under certain conditions can be determined from the equilibrium constant $K_{eq} = k_{act} / k_{deact}$, which describes how the equilibrium favors the reverse reaction over the forward reaction.¹⁵⁴ ATRP polymerization will not occur, or occur very slowly, if the equilibrium constant is too small. In contrast, if K_{eq} is too large, it will lead to large number of radicals in the system, and thus a large chance of termination reactions, i.e. a non-controlled polymerization.

ATRP is commonly initiated by alkyl halides, R-X. If the termination and chain transfer reactions are negligible, the number of polymer chains will be equal to the number of R-X molecules. Therefore, the number-average molecular weight (M_n) of polymers prepared by ATRP can be calculated as:

$$M_{n,theo} = m_{monomer} \times [M]_0 / [Initiator]_0 \times \text{conversion} \quad \text{Equation 6}$$

Where $[M]_0$ is the initial concentration of monomer, $[\text{Initiator}]_0$ is the initial concentration of initiator, and m_{monmer} is the molecular weight of monomer. This equation indicates that the molecular weight grows linearly with conversion.¹⁵⁵

In order to get good control of a polymerization and a narrow molecular weight distribution, the initiator should be consumed fast. This depends on the choice of the R and X groups. A good X group should be able to migrate between the propagating radical and the transition metal complex frequently and rapidly. The literature shows that chlorine and bromine are good choices for X,¹⁵⁵ while fluorine is never used because the C-F bond is too strong to be cleaved homolytically. Iodine can work with acrylate polymerization under copper-mediated ATRP¹⁵⁶ and styrene polymerizations under ruthenium-/rhenium-based ATRP.^{157,158} An alkyl group with activating substituents on the α -carbon, such as aryl, carbonyl, or allyl groups, is favored because it facilitates the formation of the R radical. Some compounds with a weak R-X bond, such as N-X, S-X and O-X, can also be used.

The most important component in an ATRP is the transition metal catalyst. It is the key that determines the position of the equilibrium and the dynamics of exchange between the dormant and active species. Some general prerequisites for an efficient ATRP catalyst are: a) the metal center should have at least two oxidation states differing by one electron; b) the metal center should have reasonable affinity towards halogen; c) the co-ordination sphere around the metal center should be expandable to accommodate the halogen. The main task is to find/design a transition metal catalyst system that has an appropriate equilibrium position and dynamics which fit specific monomer and polymerization conditions. A variety of transition metal complexes with various ligands

have been studied as ATRP catalysts, and include molybdenum,¹⁸⁷ rhenium,¹⁵⁷ ruthenium,⁹⁷ iron,¹⁷⁴ rhodium,¹⁸⁶ nickel,¹⁸⁶ palladium,¹⁷⁶ and copper^{94,160,166} (Figure I-8). Copper catalysts are superior in ATRP in terms of versatility and cost, and it has proven to be effective in polymerizations of styrenes, (meth)acrylate esters and amides, and acrylonitrile. Iron catalysts have been used for the polymerization of styrenes and methacrylates. The majority of ligands used for iron-mediated ATRP are nitrogen or phosphine based ligands. A mixed ligand system is often used in the iron-mediated ATRP polymerization of styrene, allowing for improved polymerization rates and lower PDI's. Ruthenium catalysts have been used for the polymerization of styrenes and (meth)acrylates. Ruthenium-based catalysts usually contain RuCl_2 complexed to suitable ligand(s), such as a phosphorous ligand. Some ruthenium-based catalysts can directly catalyze ring-opening metathesis polymerization (ROMP) (**C9** in Figure I-8), which provides a convenient way to combine ATRP with ROMP.⁴¹⁹

ATRP can be conducted either in bulk, in solution, or in a heterogeneous system such as emulsion or suspension. The choice of solvents may be determined by several factors: a) chain transfer to solvent; b) interaction between solvent and catalyst; c) catalyst poisoning by solvent and d) solvent-assisted side-reactions.

3.3.2 Suitable monomers

A variety of monomers have been successfully polymerized by ATRP, including styrenes,¹⁵⁷⁻¹⁶⁵ (meth)acrylates,¹⁶⁷⁻¹⁷⁷ (meth)acrylamides,¹⁷⁸⁻¹⁸³ and acrylonitrile.^{184,185}

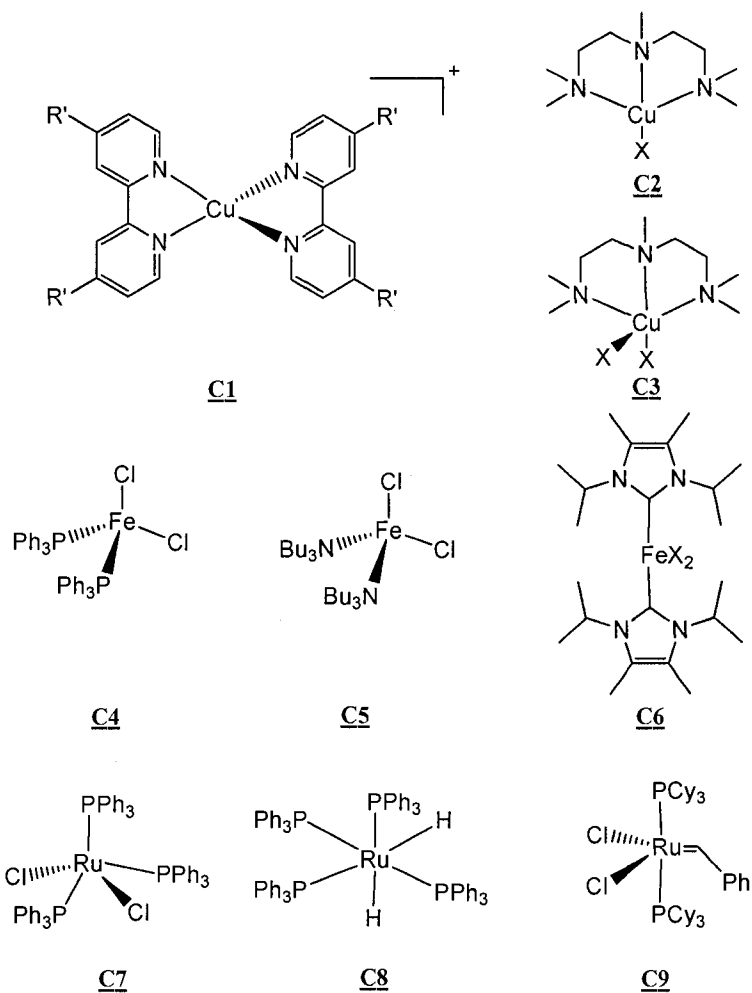
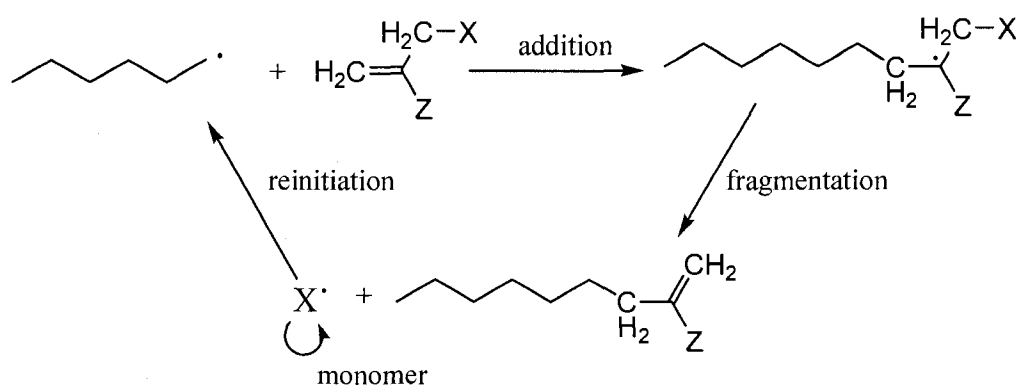


Figure I-8. Examples of ATRP catalysts.

3.4 Reversible addition-fragmentation chain transfer (RAFT) polymerization

The basic concept of RAFT/MADIX (Macromolecular Design via the interchange of xanthates) was first introduced by two groups in the late 1980's. In 1986, the Industrial Research Organization (CSIRO) group reported the use of poly(methyl methacrylate) (PMMA) macromonomers as chain transfer agent in radical polymerization (Scheme I-14).¹⁹¹ The process was first called *addition fragmentation chain transfer* (AFCT) and the agent was called the *addition fragmentation chain transfer agent* (AFCTA). In the system, the propagating radicals can add to the PMMA macromonomer

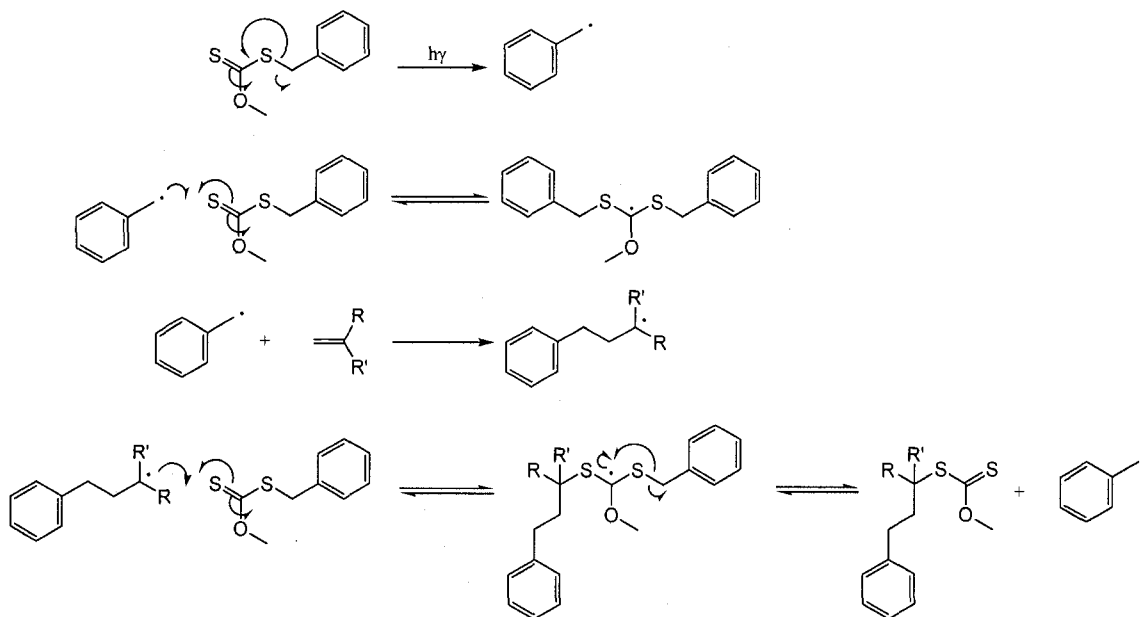
and form a new propagating radical and a new alkene-ended macromonomer by chain transfer. A variety of AFCT agents with similar structures were reported later, including allyl sulfides, allyl bromides, allyl peroxides, vinyl esters and thionoesters. However, in most cases, the molecular weight distributions are broad. In 1998, the CSIRO group reported the use of a thiocarbonylthio compound, that can be used to prepare polymers with predetermined molecular weight, narrow molecular weight distributions, and the functional end group was retained after the polymerization, which is an essential feature of a living polymerization system.⁹⁹



Scheme I-14. Early-studied addition fragmentation chain transfer (AFCT) process.

At about the same time, Zard's group reported the degenerative transfer of radicals to xanthates (Scheme I-15).¹⁸⁸ The photo-induced benzyl radical can either add directly to the xanthate to form a symmetric intermediate radical or add to the monomer, forming a new radical which would also add to the xanthate. The intermediate radical can fragment to form a radical and a xanthate, and the overall reaction is degenerative. This technique was first used to synthesize organic compounds^{189,190} and later was adapted for

polymer synthesis. The research team termed the process “**Macromolecular Design via the Inter-change of Xanthates**” (MADIX).¹⁹²



Scheme I-15. Proposed mechanism of degenerative transfer in the presence of xanthate.

3.4.1 Introduction

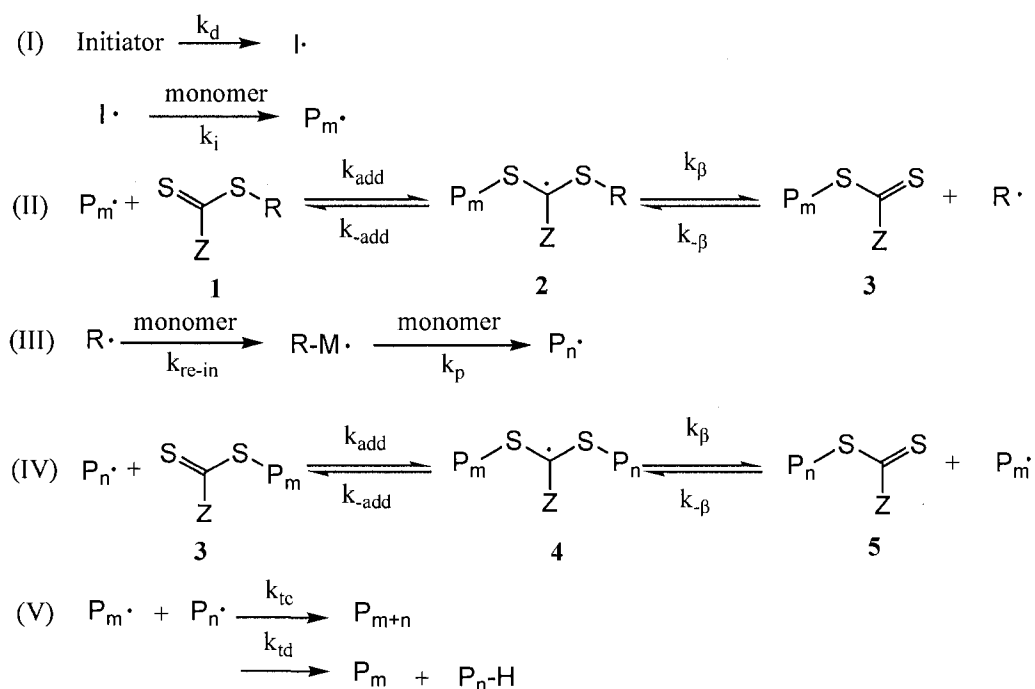
Reversible addition-fragmentation chain transfer (RAFT) polymerization was first reported in the open literature in 1998 by CSIRO in Australia. It is a relatively new living radical polymerization method mediated by thiocarbonylthio compounds ($ZC(=S)SR$). RAFT has proven to be one of the most versatile techniques to prepare various polymers with well-defined architectures, including homo-, gradient, diblock, triblock, star polymers, microgels and polymer brushes.

RAFT polymerization, as one of the living/controlled radical polymerization techniques, has both merits of radical polymerization and living/controlled polymerizations. As a radical polymerization, RAFT can be used with a large variety of

monomers including styrenics, (meth)acrylates, (meth)acrylamides, and vinyl esters. It is also tolerant to various functional groups (e.g. COOH, NR₂, CONR₂, OH) and reaction conditions (bulk, solution, emulsion, miniemulsion, suspension and impurities). However, unlike conventional free radical polymerization, RAFT can provide polymers with control of the molecular weight, molecular weight distribution, composition, and architectures.

3.4.2 RAFT mechanism

Although RAFT is one of the common controlled/living radical polymerization (CLRP) techniques, its mechanism differs greatly from that of NMP or ATRP. RAFT is based on the concept of reversible chain transfer between propagating chains, while NMP and ATRP are based on the concept of reversible termination.



Scheme I-16. Mechanism of RAFT polymerization.

Scheme I-16 shows the generally accepted mechanism of a RAFT polymerization. The controlled features observed in RAFT are achieved by a sequence of addition-fragmentation equilibria. As with conventional radical polymerization, RAFT requires the generation of primary radicals at the very start of polymerization to trigger the degenerative chain transfer reactions that dominate the whole polymerization process. Generally, radicals in a RAFT system can be generated by decomposition of an appropriate initiator such as an azo compound, external sources can be used such as UV or γ -ray radiation, or by simple thermal initiation in the case of styrene. After generation, these primary radicals will add to a few monomers and form propagating chains. The propagating chains, due to the high transfer constant of the RAFT chain transfer agents, will add across the C=S double bond of the CTA and form the intermediate C-centered radical. The intermediate radicals are not stable, and thus may either fragment back to the original propagating radical and CTA, or fragment 'forward' to form a new macro thiocarbonylthio compound and a new released radical, $R\cdot$, as shown in step II (Scheme 16). Which direction the fragmentation of the intermediate radicals choose is determined by the relative stability between the new released radical ($R\cdot$) and the original propagating radical derived from the monomer.

The newly released radical $R\cdot$, if capable, will add to a few monomers to reinitiate the polymerization. After all CTA is consumed (preferably fast), the polymerization will proceed into the main equilibrium (step IV), in which only macro-CTA is present. In the main equilibrium, different propagating chains, through rapid and frequent addition to CTA and fragmentation of new propagating chains, get an equal chance to propagate, leading to a narrow molecular weight distribution. And because RAFT polymerizations

are usually conducted at a high ratio of [CTA]:[Initiator], the dormant species in the system is the thiocarbonylthio end-capped polymer chain, while only a small amount of propagating chains are active. This strategy effectively eliminates the chances of side reactions such as termination or chain transfer reactions.

However, since RAFT is a radical polymerization, the side reactions involving radicals, although largely suppressed, cannot be completely avoided. Common side reactions include chain transfer from propagating radicals or intermediate radicals to monomers, polymer chains (both propagating and dead chains), or solvent (if used), and termination reactions between propagating radicals and intermediate radicals by combination or disproportionation, resulting in dead chains.

From the mechanism above, the following remarks can be made:

- 1) RAFT polymerization is naturally a free radical polymerization. The polymerization needs to be triggered by a radical source. An increase in the radical concentration will increase the rate of polymerization, but may also increase the chance of radical side reactions, resulting in broader molecular weight distributions and overall reduced control.
- 2) The majority of the polymer chains are initiated by the R group of the CTA and not by primary initiator-derived radicals.
- 3) Polymers are end-capped by the thiocarbonylthio functional group, which facilitate the synthesis of more complex architectures.
- 4) The molecular weight of the polymer can be predicted/tuned based on the ratio of CTA to monomer.

3.4.3 Chain transfer agents (CTA)

The living characteristics of RAFT polymerizations are achieved simply by the addition of a small amount of RAFT CTA to an otherwise conventional free radical polymerization system. Since RAFT was first introduced in 1998, a wide range of CTA's have been reported. All CTA's have the general structure $ZC(=S)SR$. Based on the nature of the Z-group, CTA's can be divided into four general families, which are dithioesters,⁹⁹ trithiocarbonates,²⁰¹ dithiocarbamates,²⁰⁰ and xanthates¹⁹² (Figure I-9).

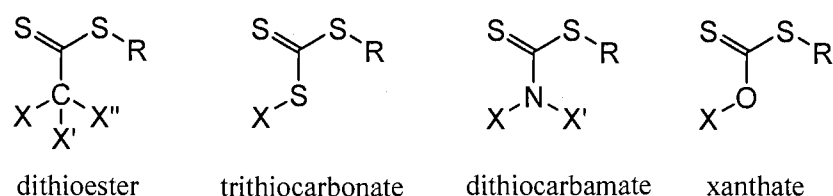


Figure I-9. General families of RAFT chain transfer agents.

From the mechanism, we can see that RAFT is comprised of a series of equilibria. Actually, RAFT can be viewed as a complicated balance of many factors, including the rate of initiation (k_i), reinitiation (k_{re-in}) and propagation (k_p), the equilibrium position of addition ($K_{add} = k_{add} / k_{-add}$) and fragmentation ($K_{\beta} = k_{\beta} / k_{-\beta}$) in both step II and IV. Of these factors the most important one(s) may be the equilibrium of CTA initiation (step II) and exchanges between polymer chains (step IV), which can be tuned by the choice of CTA. In fact, the most important key to successful RAFT polymerization is the choice /design of an appropriate CTA based on monomer and polymerization conditions. Generally, a good CTA should a) have a reactive $C=S$ double bond (high k_{add}); b) fragment rapidly and favor the new released radical $R\cdot$ ($k_{\beta} > k_{-add}$); c) the newly released

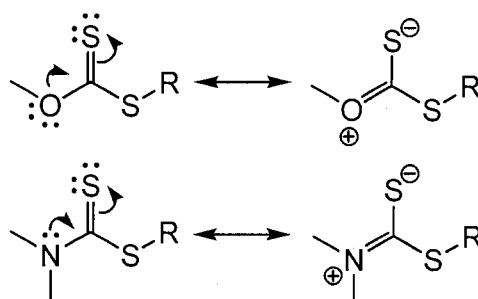
radical $R\cdot$ should efficiently re-initiate polymerization. Since all CTA's have the general structure $ZC(=S)SR$, specifically, it becomes the choice of Z and R group of the CTA that determines its overall effectiveness.

Z is the activating group of the CTA. It is the main factor that determines the reactivity of the $C=S$ bond toward attack from radicals, and it also strongly influences the stability of the intermediate radicals. Generally, strong stabilizing groups enhance the stability of the intermediate radical and thus enhance the reactivity of the $C=S$ bond towards radical attack. However, if the intermediate radical is too stable, the fragmentation step will not be favored and thus the chance of chain transfer or termination reaction with intermediate radicals will be greatly increased. Therefore, the choice of Z group needs to be tuned in order to find a balance between rates of addition and fragmentation.

Several groups have examined the effect of different Z groups on a variety of monomers.¹⁹³⁻¹⁹⁹ Among them, a phenyl group is believed to be a good choice for most monomers as it balances the rate of addition and fragmentation. For dithioester CTA's, for example, the phenyl group has a better stabilizing effect than a benzyl group. Therefore, the fragmentation step of the latter occurs more easily. This may explain that there is almost no retardation in polymerization of styrene when utilizing benzyl as the Z group (this will be discussed later in kinetics). But it may lead to poor control of bulkier monomers such as methyl methacrylate.¹⁹⁸

In the case of dithiocarbamates and xanthates, the Z group is OR or NRR' , respectively. The nonbonded electron pairs on these heteroatoms are delocalized with the $C=S$ double bond. This reduces the double bond character of the $C=S$ bond (Scheme I-

17), making it less susceptible to radical addition, leading to poor control of the growing polymer chains.¹⁹² But this type of CTA is especially effective with some fast propagating monomers with less stable corresponding propagating radicals, such as vinyl acetate.¹⁹² This is because the formed intermediate radical is relatively stable and thus facilitate the addition to C=S double bond.



Scheme I-17. Some canonical forms of xanthates and dithiocarbamates.

On the other hand, if the nonbonded pair of electrons is conjugated with other electron-withdrawing substituent, or the heteroatom is part of an aromatic ring, the stability of the intermediate radical will be increased and the reactivity of the C=S double bond towards radical species will be enhanced.^{195,197} For example, styrene,^{194,195,197,199} methyl acrylate,^{194,195,197} ethyl acrylate,¹⁹⁷ methyl methacrylate,^{195,197} and *N*-isopropyl acrylamide²⁰⁰ have all been polymerized in a controlled manner mediated by such CTA's.

A specific case of Z group is associated with the trithiocarbonates, where Z is -SR. In this case, the C=S double bond is reactive enough towards attack from propagating radicals to favor addition, and the intermediate radical is not as stable as that of a typical dithiobenzoate, which ensures rapid fragmentation without any rate retardation. Trithiocarbonates also offer other advantages: a) the synthesis of trithiocarbonates is

usually much easier than that of dithioesters. Many of them can be prepared by a straightforward one-step reaction; b) trithiocarbonates usually have a yellow color, which will not affect the color of the final product as greatly as dithiobenzoates; c) the Z group can be utilized to prepare a variety of complex architectures in a much more convenient manner (see section on polymer architectures). A variety of monomers have been successfully polymerized by RAFT mediated by trithiocarbonates, including styrenic monomers,^{199,201-205} acrylates (including acrylic acid),^{201-203,205-207} acrylamides,^{208,205,209,202,210} methacrylates,^{201,202,205} dibutyl itaconate, and dicyclohexyl itaconate.²¹¹

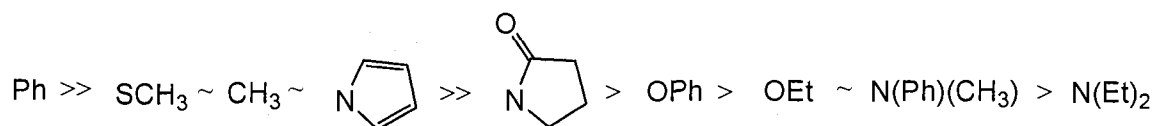


Figure I-10. Guidelines for selection of Z group of CTA. Addition rates decrease and fragmentation rates increase from left to right.

In conclusion, a general order of Z groups decreasing in the versatility is as follows: dithiobenzoates > trithiocarbonates ~ dithioalkaneates > dithiocarbamates (where the nonbonded pair of electron on N atom is conjugated by electron-withdrawing group) > xanthates > dithiocarbamates (Figure I-10).^{193,194,195-199,212} However, xanthates are especially effective for the RAFT polymerization of vinyl acetate and other non-activated substrates.

The R group is the free radical leaving and reinitiating group. From the mechanism of RAFT polymerization, we can see that in order for the intermediate radical to proceed forward to release the R group and a new macro-CTA, R must be a

comparative or better homolytic leaving group in comparison with the propagating radicals. The leaving ability can be interpreted as the stability of corresponding R• radical. Generally, a tertiary R group has a better leaving ability than a secondary R group, which is better than a primary R group. It can also be affected by the electron-withdrawing/electron-donating substituents of R since the electron-donating substituent tends to stabilize the formed radical. R is also required to be a good re-initiating species. Therefore, there are suggestions that the R group be designed to mimic the propagating polymeric radical. But this may not be true when R is a tertiary group when the penultimate unit effect cannot be neglected. For example, this idea does not work with methacrylate derivatives, as the polymethacrylate radicals are more stable than the single methacrylate unit, and thus the fragmentation of polymethacrylate radicals will be favored.^{213,214} Previous studies suggest that the cumyl and cyanoisopropyl groups seem to be the most efficient R groups.¹⁹⁷ A general guideline for the selections of the R group for a CTA is shown in Figure I-11:²¹⁵

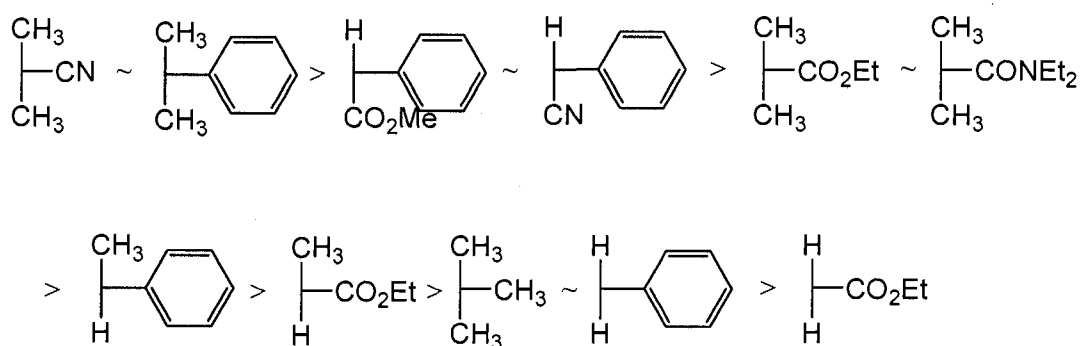
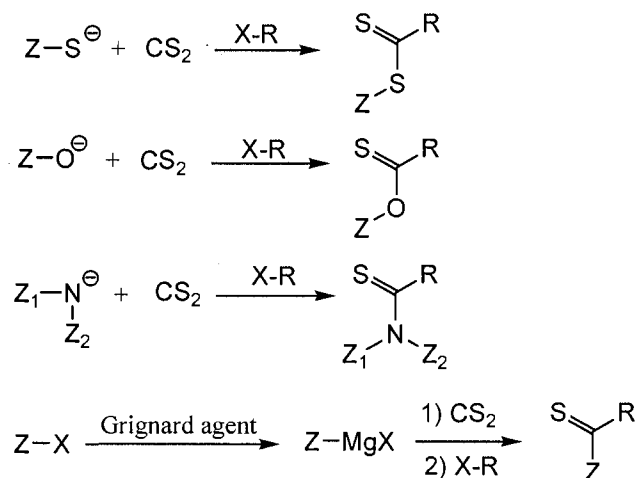


Figure I-11. General guideline for the selection of R group for CTA with decreasing stability.

Unfortunately, very few effective CTA's are commercially available at this time. There are, however, several synthetic methods available for preparing CTA's in moderate to high yield:

1) Preparation via alkylation

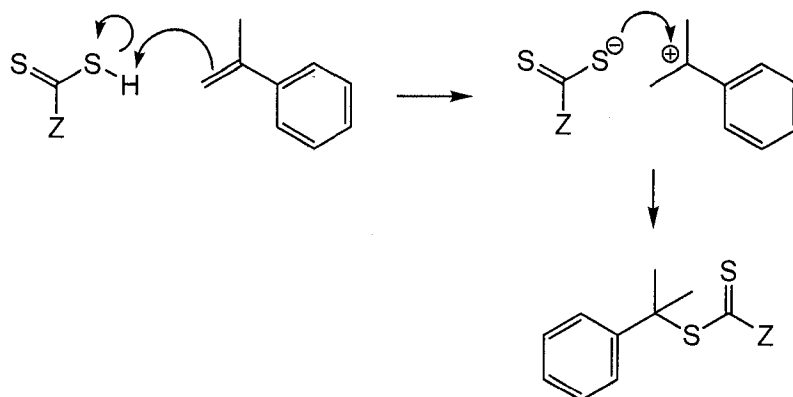
One of the most widely used synthetic methods to prepare CTA's is alkylation of a thiocarbonylthio salt with an alkyl halide (Scheme I-18). For trithiocarbonates,²¹⁶ dithiocarbamates,¹⁹⁷ and xanthates,¹⁹² thiolate salts, amines, and alkoxides are used respectively. For dithioesters, Grignard reagents are usually reacted with carbon disulfide to form a thiocarbonylthio salt and then reacted with an appropriate alkyl halide.²¹⁷ CTA's prepared by this method can be obtained with high yields.



Scheme I-18. Alkylation of thiocarbonylthio groups.

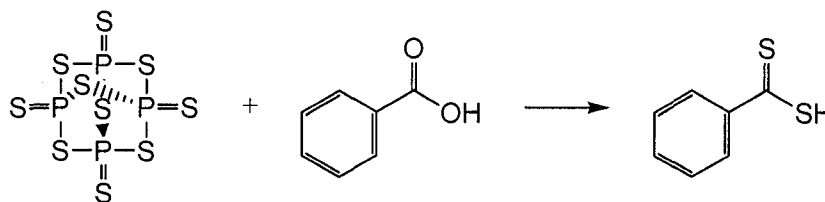
The drawback of this approach is that CTA's with tertiary R groups cannot be synthesized due to the steric hindrance and competing elimination.

- 2) Addition of a dithioacid to an olefinic double bond – Markovnikov addition. This is the method of choice for the synthesis of cumyl dithiobenzoate (Scheme I-19).²¹⁸



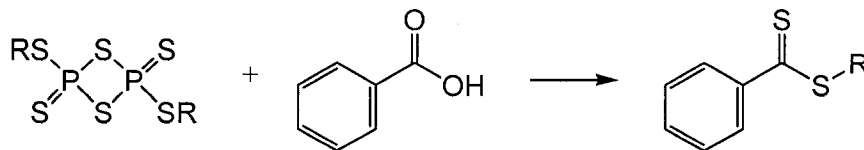
Scheme I-19. Synthesis of cumyl dithiobenzoate from α -methyl styrene via Markovnikov addition.

- 3) Sulphuration of a thioester or a carboxylic acid by cyclic tetrathio phosphates.



Scheme I-20. Thionation of benzoic acid by using P_4S_{10} .

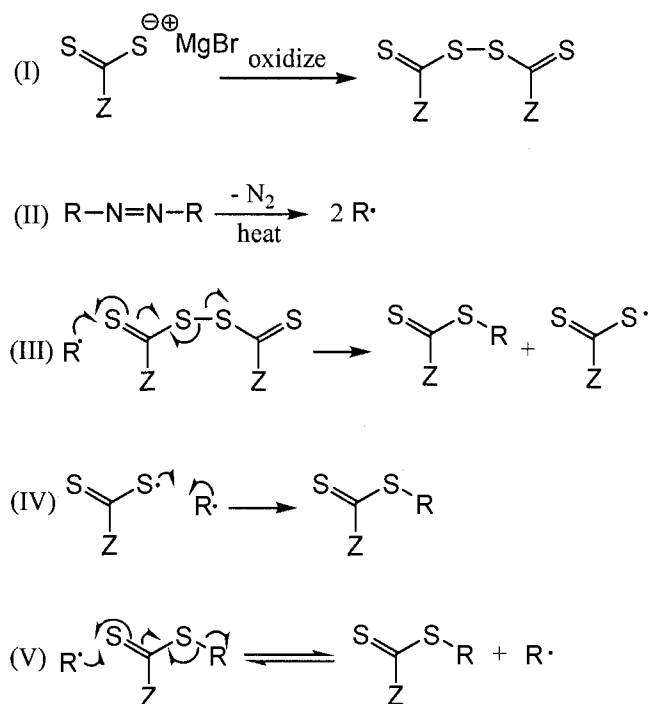
Dureault et al. first reported the use of cyclic tetrathio phosphates to sulphurate the carboxylic acid or thioesters.²¹⁸ Scheme I-20 shows the reaction of P_4S_{10} with benzoic acid to form dithiobenzoic acid. This approach is very useful to prepare precursors to a variety of dithioesters.



Scheme I-21. Thionation of benzoic acid by Davy reagents.

The same group also reported the use of the Davy reagent in reactions with benzoic acid to prepare the dithioester CTA with R group from the Davy reagent (Scheme I-21).^{218,219}

4) Preparation from a bis(thiocarbonyl) disulfide via radical addition-fragmentation reactions.



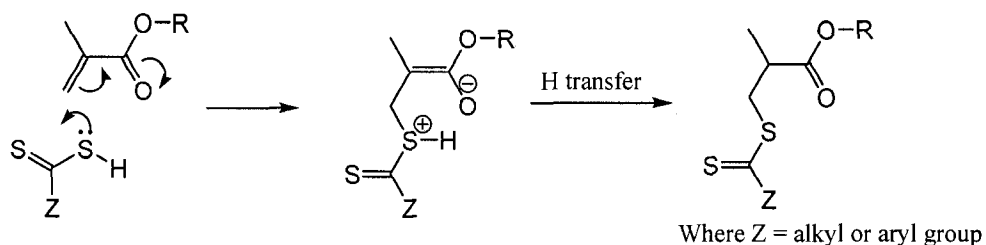
Scheme I-22. Proposed mechanism for synthesis of CTA's via addition-fragmentation reaction between bi(thiocarbonyl) disulfide and azo compound.

A bis(thiocarbonyl) disulfide is first prepared by oxidation of a thiocarbonylthio salt. These compounds can be further reacted with a free radical source, usually a symmetric azo compound,^{210,211} via a series of radical addition-fragmentation reactions, leading to the formation of the RAFT CTA. The mechanism (Scheme I-22) is similar to that of a RAFT polymerization, except that the newly released radical is the thiocarbonylthio radical, which combines with the primary radical from the initiator to form the target molecule. The yields obtained with this method are moderate to good. This method can also be used to generate CTA in situ.²¹²

A modification of this method is to add a free radical source to an already formed CTA to 'exchange' the R group. To obtain a good yield, the R group of the precursor CTA should be a better leaving group with respect to that of the targeted CTA product. In other words, the free radical added must be less stable than the R group of the precursor CTA.

5) Michael Addition

Michael addition is one of the most popular reactions to add alkenes onto carbonyl groups. It can also be applied to the synthesis of CTA's by reacting a dithiocarboxylic acid with a (meth)acrylate-type compound (Scheme I-23).²¹⁸ It is noteworthy to mention that the Markovnikof addition synthetic approach cannot be applied to prepare such CTA's with methacrylate radicals as the leaving groups.



Scheme I-23. Mechanism of preparation of CTA's via Michael addition.

3.4.4 Kinetics of RAFT polymerization

The kinetics of RAFT polymerization is the same as that of conventional free radical polymerization, under steady-state conditions. A linear relationship between $\ln([M]_0/[M]_t)$ and polymerization time could be drawn. The fact that the straight line passes through the origin indicates that there is no inhibition or induction time.

$$r_p = - d [M] / d t = k_p [R\cdot] [M] \quad \text{Equation 7}$$

where r_p is the rate of polymerization, $[M]$ is the monomer concentration, k_p is the rate coefficient, and $[R\cdot]$ is the radical concentration. Therefore,

$$- [M] / d [M] = 1 / (k_p [R\cdot] d t) \quad \text{Equation 8}$$

$$\ln ([M]_t / [M]_0) = k_p [R\cdot] t \quad \text{Equation 9}$$

Under the steady-state assumption of radical polymerization,²²³ $[R\cdot]$ is constant during the polymerization. k_p is the propagating rate constant of the monomer, which can also be treated as constant under certain polymerization condition. Therefore, the term $k_p [R\cdot]$ can be replaced by K_p , which is called apparent rate constant.

$$\ln ([M]_t / [M]_0) = K_p t, \text{ where } K_p = k_p[R\cdot] \quad \text{Equation 10}$$

The equation above clearly shows a linear relationship between $\ln([M]_0/[M]_t)$ and polymerization time, with the value of slope equal to K_p (Figure I-12).

Although it is possible to calculate the amount of radicals decomposed from the initiator knowing the amount of initiator added, the half life of the initiator, and the initiating efficiency, there are always side reactions such as terminations reactions that occur in RAFT polymerization, and therefore the precise concentration of radicals in polymerization system is undetectable, and thus the calculation of k_p in RAFT is difficult even though the value of apparent rate constant can be calculated.

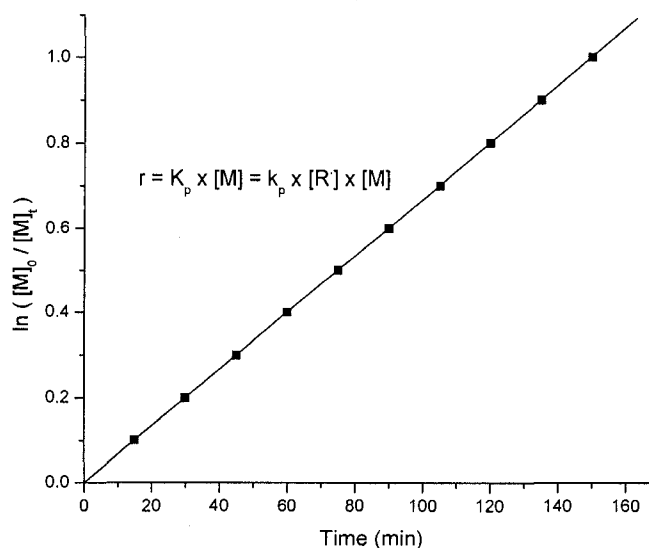


Figure I-12. Example of ideal kinetics of RAFT polymerization.

Deviations from the ideal linear relationship between $\ln([M]_0/[M]_t)$ and polymerization are often observed experimentally. For example, the red line in Figure I-

13 with small slope at the beginning indicates slow initiation, while the blue line with decreasing slope starting from the mid-term of polymerization indicates radical-radical termination. This is because the value of the slope is equal to the apparent constant K_p , which is $k_p[R\cdot]$. If we assume that k_p doesn't change during the polymerization, a decreasing in K_p indicates the decreasing in the concentration of radicals in the polymerization system.

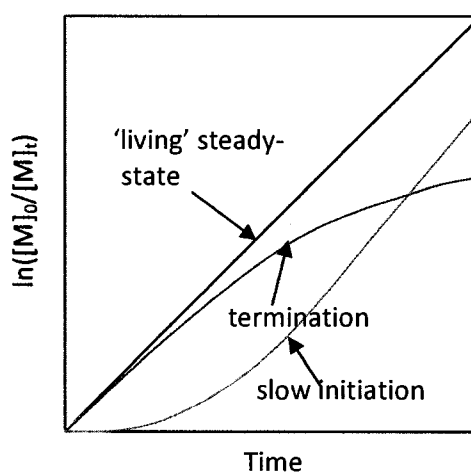


Figure I-13. Ideal and possible deviations in RAFT kinetic plots.

RAFT operates on the principle of degenerative addition-fragmentation chain transfer. For each radical consumed by addition to the C=S double bond, a new radical is generated through fragmentation. If the addition-fragmentation process is fast enough, the degenerative chain transfer process should have no effect on the overall polymerization rate. Therefore, the kinetics of a RAFT polymerization should follow that of a conventional free radical polymerization, which is half-order with respect to the concentration of initiator and be independent of the concentration of CTA. However, it is

surprising to find slower kinetics of RAFT polymerization, compared with conventional free radical polymerization under similar conditions. Furthermore, it is also observed that the rate of RAFT polymerization may be decreased when the concentration of CTA is increased. These kinds of retardation effects are more commonly observed with the use of dithiobenzoates,²²⁵⁻²²⁸ as opposed to aliphatic dithioesters,^{196,198} trithiocarbonates,²⁰¹ or xanthates.¹⁹² To date, the cause of the retardation effect is still under debate. There are generally two representative justifications:²²⁴

1) Side reactions involving the intermediate radicals

The intermediate radicals may be involved in a variety of side reactions during polymerization. Monteiro et al. first proposed the possibility of intermediate radical coupling with a propagating radical to form a three-armed star structure.²²⁹ Later, Fukuda's group confirmed Monteiro's idea by isolating and characterizing three-armed stars by a variety of analytical techniques.^{226,230-232} Venkatesh et al. reported the observation of both three-armed and four-armed star structures, the latter of which are formed by the combination of two intermediate radicals.²³³ On the other hand, the Center for Advanced Macromolecular Design (CAMD) team could not isolate any three-arm or four-arm stars by combination of size exclusion chromatography and ESI mass spectrometry techniques.

It is noteworthy that most experiments in which the three-armed and four armed star structures were observed were set up as model systems, in which a high concentration of radicals are present. To date, there is no direct evidence of such reactions in ordinary RAFT polymerization systems.

Other possible side reactions involving intermediate radicals include reactions with residual oxygen, or other impurities, and chain transfer to monomers or polymer chains.

2) Slow fragmentation of the intermediate radicals

The CAMD group has developed a computer simulation system which calculated the lifetime of the intermediate radicals in the polymerization of styrene mediated by cumyl dithiobenzoate. The result shows that the intermediate radical is very stable and has a lifetime of more than 10^{-5} seconds.^{198,227,234-238} They suggested that the retardation of polymerization rate in RAFT, especially mediated by cumyl dithiobenzoate, can be caused by the slow fragmentation of the intermediate radicals. But such a result suggests a very high concentration of intermediate radicals (10^{-4} M), which is in direct contradiction to the experimental ESR data, which suggested the concentration of intermediate radical was lower than 10^{-7} M.^{225,239-243}

Recent use of ab initio molecular orbital calculations has shown that dithiobenzoate derived intermediate radicals are more stable than that of aliphatic dithioesters and trithiocarbonates,^{215,244,245} suggesting that the retardation of methyl acrylate and styrene mediated by cumyl dithiobenzoate may be attributed to the slow fragmentation of the intermediate radical.

In many RAFT polymerizations, a certain degree of inhibition/induction period is observed. This behavior also occurs more with dithiobenzoates than with trithiocarbonates or aliphatic dithioesters, and inhibition period increases with the concentration of CTA. This effect may also be caused by the slow fragmentation of the

intermediate radical **2** in Scheme I-15.^{217,228,240} Another explanation may be the slow reinitiation of the released leaving group R·.^{200,246-249} Finally, it can also be attributed to the impurities in the system, such as residual oxygen which kills the radicals.²⁵⁰

3.4.5 Molecular weight control

From the mechanism of RAFT polymerization, we can see that all polymer chains are either initiated by primary radical I· or by the released group R·. Therefore, the number-averaged molecular weight (M_n) can be calculated according to Equation 11:

$$M_{n,theo} = [M]_0 m_{monomer} \rho / ([CTA]_0 + 2f[I]_0(1 - e^{-k_d t})) + m_{CTA} \quad \text{Equation 11}$$

Where $m_{monomer}$ is the molecular weight of the monomer, m_{CTA} is the molecular weight of the CTA, $[M]_0$ is the initial concentration of the monomer, $[CTA]_0$ is the initial concentration of CTA, $[I]_0$ is the initial concentration of initiator, ρ is the fractional conversion of monomer, k_d is the initiator decomposition rate constant, and f is the initiator efficiency.

Because RAFT polymerization is usually conducted at a high ratio of $[CTA]:[I]$, the small number of chains initiated by primary radicals can be neglected. Thus, Equation 11 can be simplified to:

$$M_{n,theo} = [M]_0 m_{monomer} \rho / [CTA]_0 + m_{CTA} \quad \text{Equation 12}$$

This is the most often used equation to calculate the M_n of polymers prepared by RAFT. However, some deviations from the ideal molecular weight may occur. For example, the green line in Figure I-14 shows slow initiation of the CTA while the blue line indicates the occurrence of normal, undesirable chain transfer reactions.

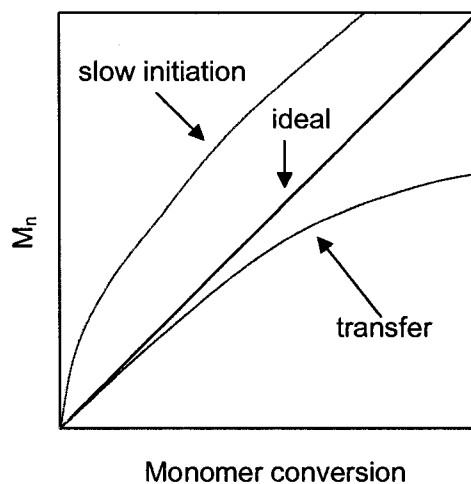


Figure I-14. Example of ideal MW evolution and diagnostics of slow initiation and conventional chain transfer in RAFT.

3.4.6 Conditions

Since RAFT polymerization only requires the introduction of a small amount of CTA to an otherwise conventional free radical polymerization system, theoretically, it is possible to perform RAFT polymerization under the same conditions as those for conventional free radical polymerization. To date, RAFT polymerization has been performed under a variety of conditions, including bulk, solution, emulsion, miniemulsion, in ionic liquids, in supercritical carbon dioxide, and at high pressure.

1) Bulk polymerization

Bulk polymerization is the simplest process for conducting RAFT polymerizations. However, the increase in viscosity may cause side reactions when polymerization proceeds to high conversion. Polymerization in bulk is generally faster than in solution. For example, Zhu et al. showed that the polymerization of glycidyl methacrylate at 60°C reached 96.7% conversion in bulk and 64.3% in benzene (50 vol%) after the same reaction time.²⁵¹ However, they do not necessarily lead to higher PDI's. For example, the polymerization of 4-acetoxystyrene and isobutyl methacrylate in bulk gives polymers with lower PDI's than those obtained from solution under the same polymerization conditions.²⁵²

2) Solution

Solution polymerization is adopted when the viscosity produced during the polymerization becomes a problem. The solubility of monomer(s), initiator(s), the resulting (co)polymer(s), and CTA need to be considered when choosing an appropriate solvent. Possible side reactions between radicals and solvents, i.e. transfer reactions, also need to be considered.

Of particular importance is direct homogeneous aqueous RAFT polymerization. Such polymerizations have been investigated extensively by the McCormick group and the Lowe group.^{57,123} A variety of monomers have been successfully (co)polymerized via aqueous RAFT, including acrylamides,^{58,59,122-124,208,210,253} methacrylamides,²⁵⁵ styrenic derivatives,⁶¹ vinyl pyridines,⁴² glycomonomers,²⁵⁷ acrylic acid,^{254,258} and 2-(dimethylamino)ethyl methacrylate.²⁵⁹ Ideally, a water-soluble CTA should be used in

such polymerizations. However, CTA's that are not fully water-soluble but soluble in water-monomer mixtures can also be used. A recent study by Thomas et al. shows that dithioesters may undergo hydrolysis and/or aminolysis at high pH in aqueous media.²⁵⁶ They evaluated cyanopentanoic acid dithiobenzoate (CTP) and its corresponding macro-CTA and concluded that the rates of hydrolysis and aminolysis both increase with increasing pH and decrease with increasing molecular weight of the dithioester. This could result in higher than predicted molecular weights, or even complete loss of control.

3) Emulsion

Emulsion polymerization is widely used in industry because it provides good heat transfer as the viscosity of the system remains low. RAFT emulsion polymerization was first reported by the CSIRO group with the polymerization of butyl methacrylate (BMA).⁹⁹ Subsequently it was applied to the polymerization of styrene and methyl methacrylate.²⁶⁰ Various other research groups have also examined the polymerization of styrene,²⁶¹⁻²⁶⁸ styrenic derivatives,²⁶⁹ MMA,²⁶⁰ butyl acrylate,^{261,270} and vinyl acetate.²⁷¹ A general problem occurring during the polymerization is the difficulty in controlling the molecular weight growth or the colloidal stability. This may be attributed to a number of issues such as the occurrence of two phases in the reaction mixture leading to phase partitioning of the CTA, rate retardation, water sensitivity of some CTA's, transport of the CTA between phases, surface activity of some CTA's, and particle nucleation.^{264,269,271-274}

4) Ionic liquids

Perrier et al. demonstrated the use of an ionic liquid (butylmethylimidazolium hexafluorophosphate) at room temperature as an alternative to traditional organic solvents, in the RAFT polymerization of methyl methacrylate (MMA) and methyl acrylate (MA).²⁷⁵ Both control of molecular weight and narrow molecular weight distributions were achieved.

5) Supercritical CO₂

Supercritical CO₂ is another environmentally friendly alternative to organic solvents. Arita et al. first reported the RAFT polymerization of styrene²⁷⁶ and methyl acrylate²⁷⁷ in supercritical CO₂. The polymers were made with well controlled molecular weights, but the polymerization rates seemed to be slower than that in solution.

6) High pressure

Several RAFT polymerizations at high pressure have been reported.²⁷⁸⁻²⁸⁰ The use of high pressure (1.8 kBar) resulted in higher polymerization rates and a reduced number of dead chains compared to those observed at atmospheric pressure in the RAFT polymerization of styrene. A higher pressure (5 kBar) was applied to the solution polymerization of MMA, resulting in extremely high molecular weight ($M_n > 10^6$ g/mol), and PDI's as low as 1.03.²⁷⁹ Another example, reported by Arita et al., is the bulk polymerization of styrene at pressure up to 2.5 kBar.²⁸⁰ The overall rate of polymerization was found to increase by a factor of three, and the PDI was reduced from 1.35 to 1.1.

3.4.7 Monomers

Since RAFT was first introduced in 1998, it has proved to be arguably most versatile CLRP technique with regard to monomer choice. A variety of styrenics, (meth)acrylics, (meth)acrylamido, vinyl acetate, vinyl formamide, and their derivatives have been successfully polymerized by RAFT.

1) Styrene and styrenic derivatives

Styrenic monomers are the most studied monomers in RAFT polymerization. The relative stability of the propagating radicals, however, makes styrenic monomers one of the slowest monomers to polymerize. This allows the RAFT polymerization of styrenic monomers to be controlled by most CTA's (dithioesters, trithiocarbonates and dithiocarbamates).

A variety of polymers have been prepared from styrenic derivatives via RAFT (Figure I-15), including styrene (**M51**),^{99,193,241,255,259,269} *p*-chlorostyrene (**M52**),²⁸¹ divinylbenzene (**M53**),²⁸²⁻²⁸⁴ *p*-methylstyrene (**M54**),²⁸¹ *p*-methoxystyrene (**M55**),²⁸¹ *p*-acetoxystyrene (**M56**),²⁶⁹ *p*-vinylbenzoate (**M57**)⁶¹ and *p*-*tert*-butoxycarbonyloxystyrene (**M58**).²⁸⁵ A variety of water-soluble styrenic polymers have also been prepared via RAFT, including polymers containing *N,N*-dimethylvinylbenzylamine (**M59**),^{61,286} *p*-(vinylbenzyl) trimethylammonium chloride (**M60**),^{61,259} sodium (4-styrenesulfonate) (**M61**),⁶¹ the anionic form of 4-vinylbenzoic acid (**M62**),^{287,289} trimethyl 4-vinylbenzylphosphonium chloride (**M63**),^{287,288} and 3-((4-vinylbenzyl)dimethylammonio)propane-1-sulfonate (**M64**).¹²⁴

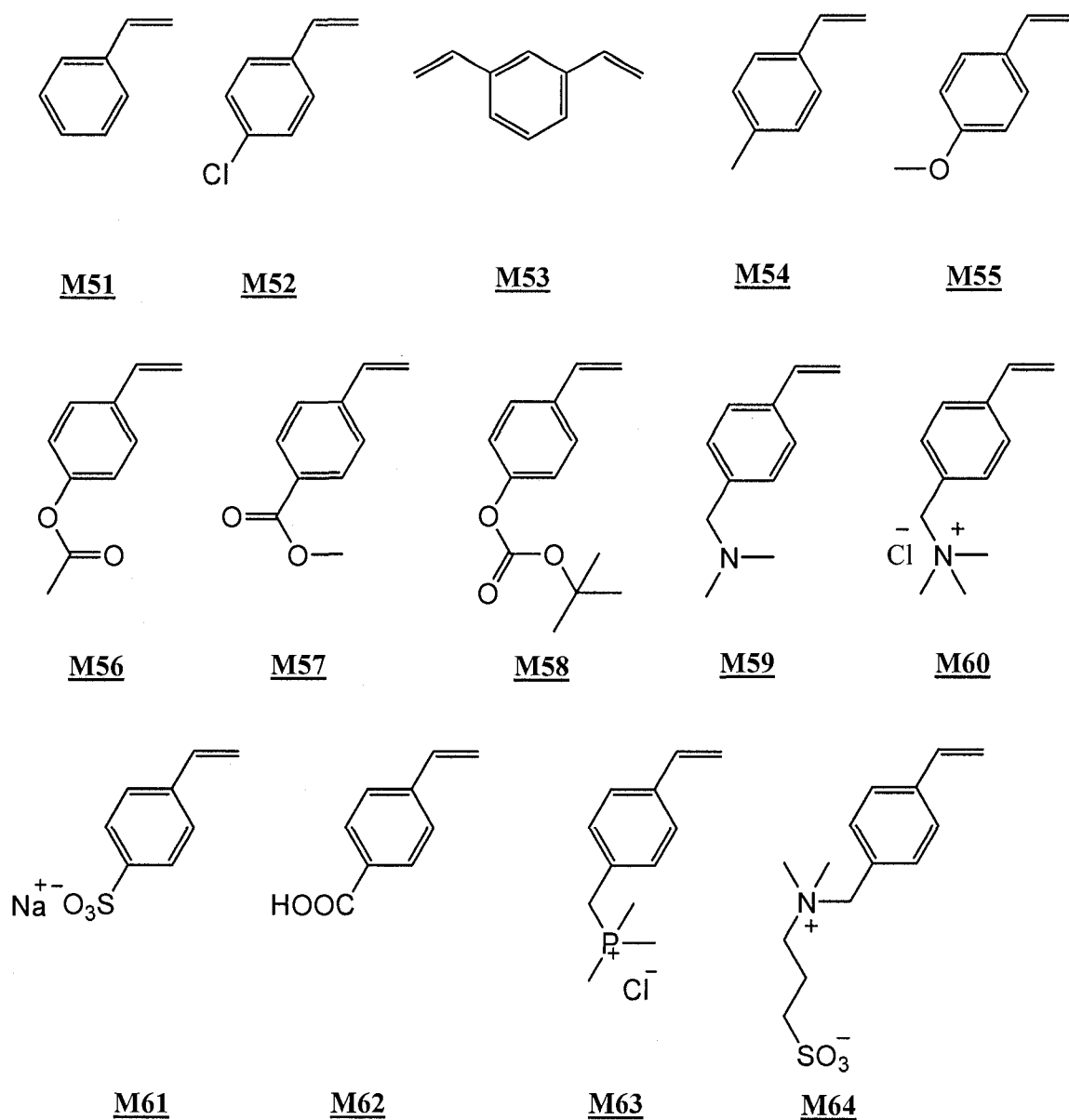


Figure I-15. Styrenes and styrenic derivatives polymerized by RAFT.

2) Acrylates and acrylamides

Acrylates and acrylamides are very fast propagating species due to their reactive propagating radicals and general low steric bulk. Their polymerizations via RAFT have been widely studied, and they typically yield polymers with very well controlled

molecular weights and narrow molecular weight distributions. The RAFT polymerization of acrylates and acrylamides are usually mediated by dithioesters and trithiocarbonates, while the use of xanthates or dithiocarbamates leads to broader molecular weight distributions.

A variety of functional acrylate and acrylamide derivatives have been polymerized by RAFT (Figure I-16). Acrylates reported successfully by RAFT include: acrylic acid (**M65**),^{206,207,258,266,270} methyl acrylate,^{196,205,213,217,247-249,275} ethyl acrylate,²⁹⁰ *n*-butyl acrylate,^{203,213,233,240,263,270} *tert*-butyl acrylate,²⁹¹ octyl acrylate,²⁹² octadecyl acrylate (**M66**),²⁹³ *p*-nitrophenyl acrylate (**M67**),²⁹⁴ 1,1,2,2,-tetrahydroperfluorodecyl acrylate (**M68**),²⁹⁵ 2-(*N*-butyl perfluorooctane-fluorosulfonamido) ethyl acrylate,²⁰⁹ 12-acryloyloxydodecanoic acid (**M70**),²⁹⁶ poly(ethylene oxide) methyl ether acrylate (**M71**),²⁹⁷ and 2-acryloyloxyethyl phosphorylcholine (**M72**).²⁹⁸ Acrylamides polymerized via RAFT include acrylamide (**M73**),^{208,258,299} *N,N*-dimethylacrylamide (**M74**),^{205,209,246,253} *N*-isopropylacrylamide (**M75**),^{200,210,289} *N-tert*-butyl acrylamide (**M76**),³⁰⁰ *N*-octadecyl acrylamide (**M77**),^{296,300} *N*-diphenylmethylacrylamide (**M78**),³⁰⁰ diacetone acrylamide (**M79**),³⁰¹ *N*-acryloylmorpholine (**M80**),³⁰²⁻³⁰⁴ 3-[2-(*N*-methylacrylamido)-ethyl-dimethylammonio] propane sulfonate (**M81**),^{122,124} 2-acrylamido-2-methylpropane-1-sulfonate (**M82**), sodium 2-acrylamido-2-methylpropanesulfonate (**M83**),^{58,59} 11-acrylamidoundecanoic acid (**M84**),²⁹⁶ and sodium 6-acrylamidohexanoate (**M85**).³⁰⁵ It is also noteworthy that controlled polymerization of acrylic acid, although successfully achieved by RAFT, is difficult by ATRP because the carboxylic acid functionality tends to deactivate the catalyst used in ATRP system.¹⁵⁵

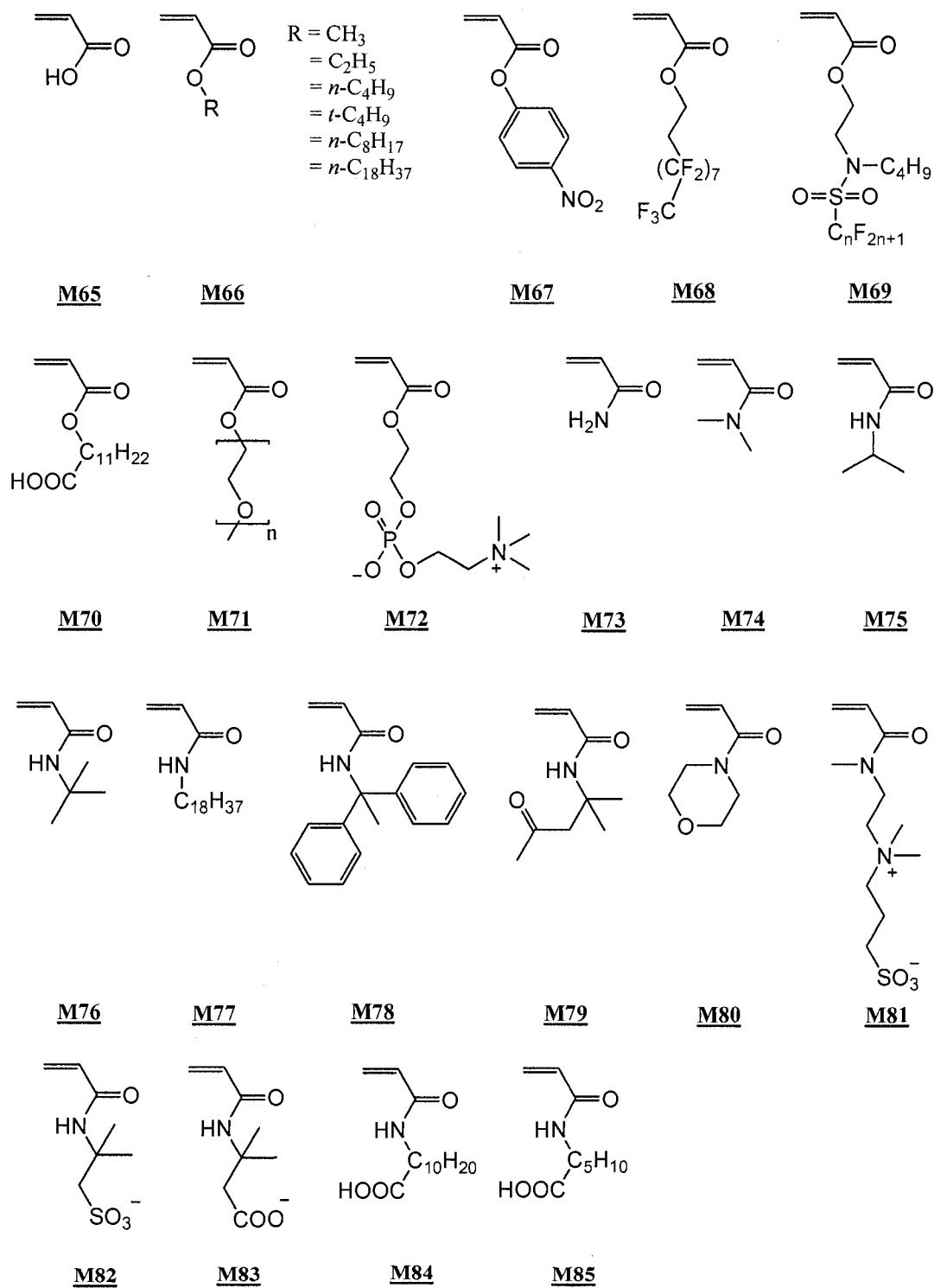


Figure I-16. Various acrylates and acrylamides derivatives polymerized via RAFT.

3) Methacrylates and methacrylamides

Steric hindrance of the propagating radicals generated from methacrylates and methacrylamides makes them difficult to add to the C=C double bond of the CTA. In order to favor the addition and thus the formation of the intermediate radicals, a strong stabilizing Z group is required. Therefore, methacrylates and methacrylamides are best polymerized via RAFT mediated by dithiobenzoates, although some aliphatic dithioesters, trithiocarbonates and dithiocarbamates are also effective.^{195,306} Xanthates usually offer very poor control. The choice of R group also needs to be carefully considered in this case. An R group is required to be of comparable or greater stability with respect to the propagating radicals in order for the intermediate radical to favor the fragmentation forward to release the R group. But the stability should also be balanced with its ability to reinitiate the polymerization. The idea that R group mimics the methacrylic propagating species does not work in this case due to the penultimate unit effect.²¹³ To date, cumyl dithiobenzoate and cyanoisopropyl dithiobenzoate have proved to be the best CTA's for conducting RAFT polymerizations of such monomers.³⁰⁶ It is also noteworthy that methoxycarbonylphenylmethyl dithiobenzoate²⁰⁵ and α -cyanobenzyl dithioester,³⁰⁷ although the R groups of which are secondary, still offers good control over the polymerization of methacrylic monomers.

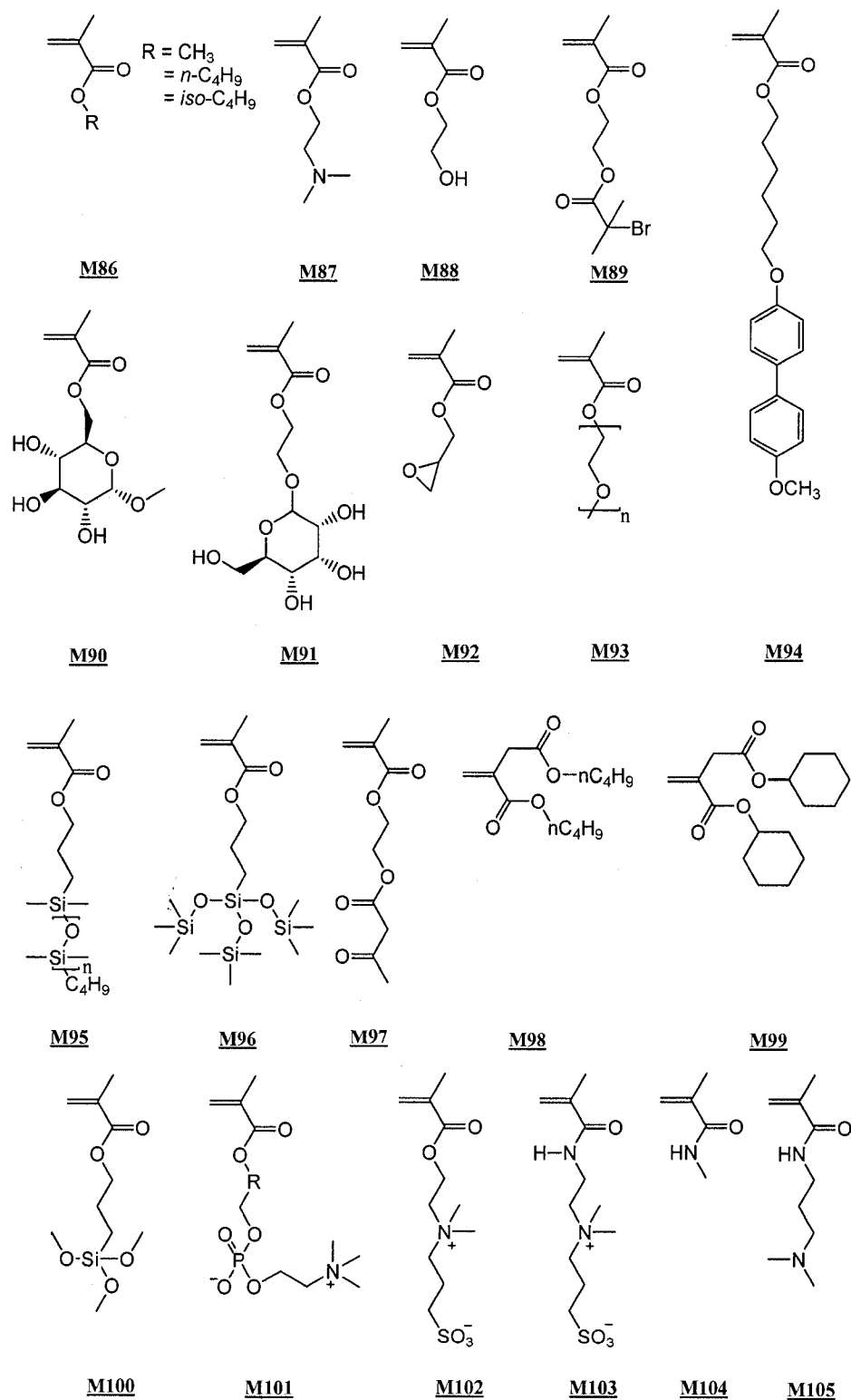


Figure I-17. Various methacrylate and methacrylamide derivatives polymerized via RAFT.

A variety of functional methacrylate and methacrylamide derivatives have been reported successfully polymerized via RAFT (Figure I-17), including: methyl methacrylate (MMA),^{195,198,201,205,213,217,231,271,279} *n*-butyl methacrylate,^{225,292} isobutyl methacrylate (**M86**),²⁵² 2-(dimethylamino)ethyl methacrylate (**M87**),²⁵⁹ hydroxyethyl methacrylate (**M88**),³⁰⁸ 2-(2-bromoisobutyryloxy) ethyl methacrylate (**M89**),³⁰⁹ methyl 6-*O*-methacryloyl- α -D-glucoside (**M90**),³¹⁰ 2-methacryloxyethyl glucoside (**M91**),²⁵⁷ glycidyl methacrylate (**M92**),²⁵¹ poly(ethylene glycol) methyl ether methacrylate (**M93**),^{309,311} 6-[4-(4'-methoxyphenyl)phenoxy]hexyl methacrylate (**M94**),^{312,313} poly(dimethylsiloxane) methacrylate (**M95**),^{314,315} 3-[tris(trimethylsilyloxy) silyl] propyl methacrylate (**M96**),³¹⁶ 2-acetoacetoxyethyl methacrylate (**M97**),^{317,318} dibutyl itaconate (**M98**) and dicyclohexyl itaconate (**M99**),²¹¹ γ -methacryloxypropyltrimethoxysilane (**M100**),³¹⁹ 2-methacryloxyethyl phosphorylcholine (**M101**),³²⁰ 3-[*N*-(3-methacrylamidopropyl)-*N,N*-dimethyl]ammonio propane sulfonate (**M102**),¹²¹ *N*-methylmethacrylamide (**M103**),¹²⁴ *N*-methyl methacrylate (**M104**),³²¹ *N*-[3-(dimethylamino)propyl methacrylamide] (**M105**).²⁵⁵

4) Vinyl acetate

The controlled polymerization of vinyl acetate has been a challenge by CLRP because of the very high reactivity and low steric bulk of the propagating radicals. To date, RAFT is the only technique that can mediate the polymerization of vinyl acetate in a controlled manner by utilizing xanthates or dithiocarbamates as the CTA.^{192,197,250,271,306,322,334,358} However, the intermediate formed by dithioesters or trithiocarbonates are relatively stable and the rate of fragmentation is slow relative to the

rate of propagation, resulting in poor control of the polymerization. Therefore, while xanthates and dithiocarbamates do not confer control with most types of monomers due to the poor stability of the intermediate radicals, they perform extremely well with vinyl acetate and other non-conjugated substrates. Poly(vinyl acetate) with PDI below 1.2 can be produced using a xanthate with $Z = \text{OEt}, \text{OCH}_3, \text{OCH}_2\text{CH}_3, \text{OCH}(\text{CH}_3)_2,$ or $\text{OC}_6\text{H}_4\text{OCH}_3$.³²³ Dithiocarbamates where $Z = \text{N}(\text{Ph})(\text{CH}_3)$ and $\text{R} = \text{CH}_2\text{CN}$ can yield poly(vinyl acetate) with PDI as low as 1.24.³⁰⁶

5) Miscellaneous monomers

RAFT has also been used to control the polymerization of a range of less common vinyl monomers. For example, *N*-acryloxysuccinimide has been copolymerized with *N*-acryloylmorpholine,³²⁴ *N,N*-dimethylacrylamide,³²⁵ butyl methacrylate,³²⁶ and *N*-isopropylacrylamide,³²⁷ in some instances, resulting PDI's below 1.1 when *tert*-butyl dithiobenzoate³²⁴ or cyanoisopropyl dithiobenzoate³²⁷ were employed as the CTA.

2-Vinyl-4,4-dimethyl-5-oxazolone and *N*-methacryloxysuccinimide have been successfully homopolymerized via RAFT with cyanoisopropyl dithiobenzoate as the RAFT CTA. The resulting PDI's were around 1.1.³⁰¹

2-Vinylpyridine and 4-vinylpyridine have both been homopolymerized and block copolymerized by RAFT with cumyl dithiobenzoate as CTA to yield polymers with PDI's ranging from 1.1 to 1.25.⁴² 4-Vinylpyridine has also been homopolymerized with dibenzyl trithiocarbonate, and ABA triblock copolymers with styrene with PDI below 1.25 were also reported.³²⁸

The polymerization of acrylonitrile mediated by cyanoethyl dithiobenzoate in ethylene carbonate yielded polymers with PDI's below 1.3. The resulting homopolymer was successfully blocked with *n*-butyl acrylate.³²⁹

The copolymerizations of 1-hexene, 1-octene, and 1-decene with methyl acrylate mediated by benzyl 1-pyrrolcarbodithioate, and 1-octene with methyl acrylate mediated by *S,S'*-bis(α,α' -dimethyl- α'' -acetic acid) have also been reported. The molecular weights were close to theoretical values and PDI's ranged from 1.1 to 1.5.^{330,331}

3.4.8 Polymer Architectures

The tolerance to a wide range of functional groups and the retention of thiocarbonylthio functionality makes RAFT an efficient technique for the preparation of a variety of polymer architectures, including statistical, block, gradient, branched, star, and network (co)polymers (Figure I-18).

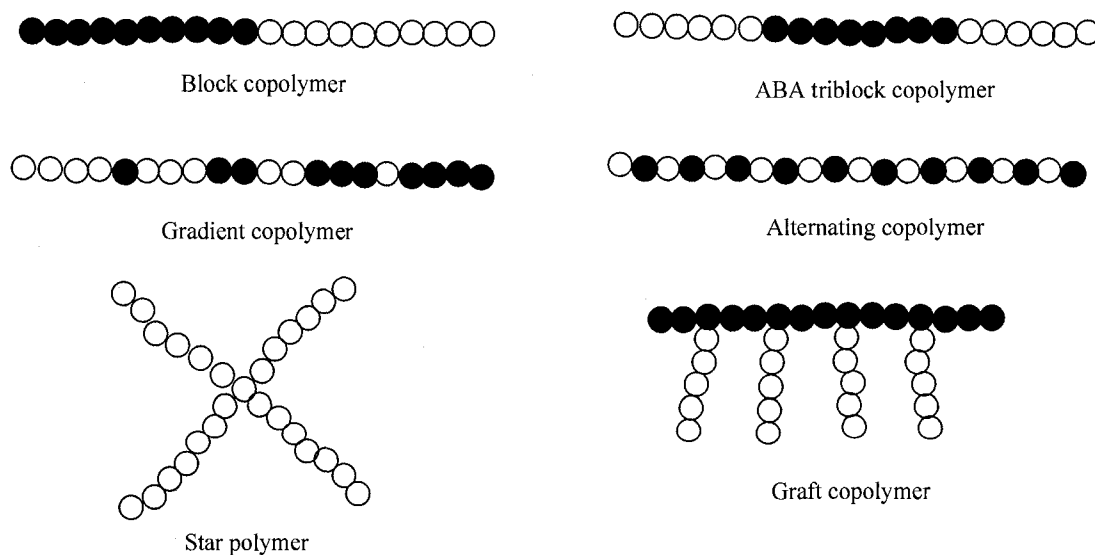


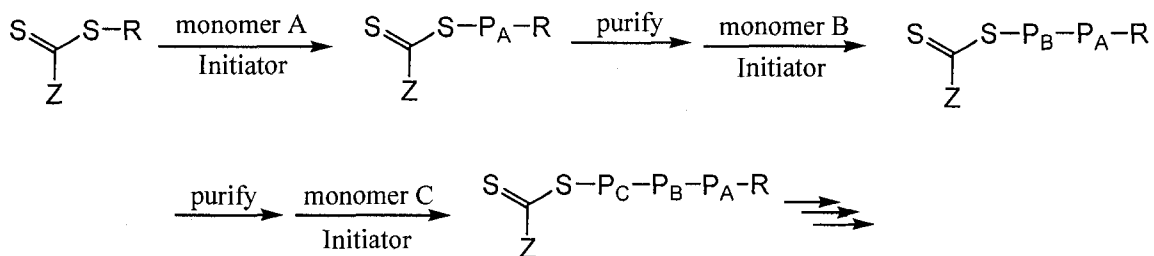
Figure I-18. Structural representation of polymer architectures.

1) Block copolymers

Block copolymers are the simplest and most widely studied materials with advanced architectures prepared by RAFT and other living radical polymerization techniques.

a) AB diblock copolymers

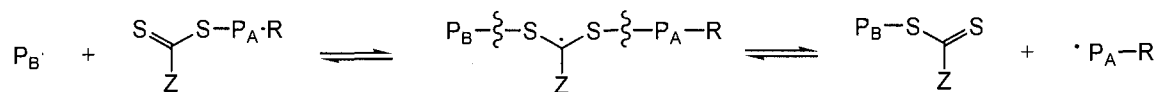
Since the majority of polymers prepared by RAFT retain the thiocarbonylthio functionality as an end-group, these polymers, after purification, can be treated as a so-called macro-CTA to mediate the subsequent polymerization of a second monomer, resulting in AB diblock copolymers (Scheme I-24).



Scheme I-24. Synthetic strategy for block copolymers by sequential addition of monomers.

The sequence of monomer addition (blocking order) needs to be carefully considered. After the propagating radical $\text{P}_\text{B}\cdot$ adds across the $\text{C}=\text{S}$ double bond and forms a polymeric intermediate radical, in order for macro-CTA to be effective, the 'R' group, which is $\text{P}_\text{A}\text{R}\cdot$ in this case, must be a comparable, or better leaving group than $\text{B}_n\cdot$ (Scheme I-25). Thus, when synthesizing AB diblock copolymers via RAFT, the monomer whose corresponding propagating chain has a better leaving ability should be

polymerized first in order to achieve high blocking efficiency. The general order of monomer addition should be acrylonitrile > methacrylate > styrenes ~ acrylates if switching between different classes of monomers.



Scheme I-25. Competitive fragmentation of intermediate radical in the second step of AB diblock copolymer synthesis.

Theoretically, the (co)polymer chain prepared via RAFT can be continually extended as long as the thiocarbonylthio end group functionalities are retained. Thus, multiblock copolymers can be prepared by the sequential addition of monomers.

b) ABA block copolymers

Of particular interest is the synthesis of ABA triblock copolymers using a difunctional CTA (Figure I-19). Difunctional CTA's facilitate the synthesis of ABA triblocks in a two-step process as opposed to the three required if a monofunctional CTA is used. There are generally two types of difunctional CTA. One has difunctional R group and the other difunctional Z group. Difunctional R CTA has the general structure of $ZC(=S)SRSC(=S)Z$, where the polymer chains grow inward to the core and the thiocarbonylthio functionality groups are retained at the chain ends. By sequential addition of monomer A and B, BAB triblock copolymer can be obtained.

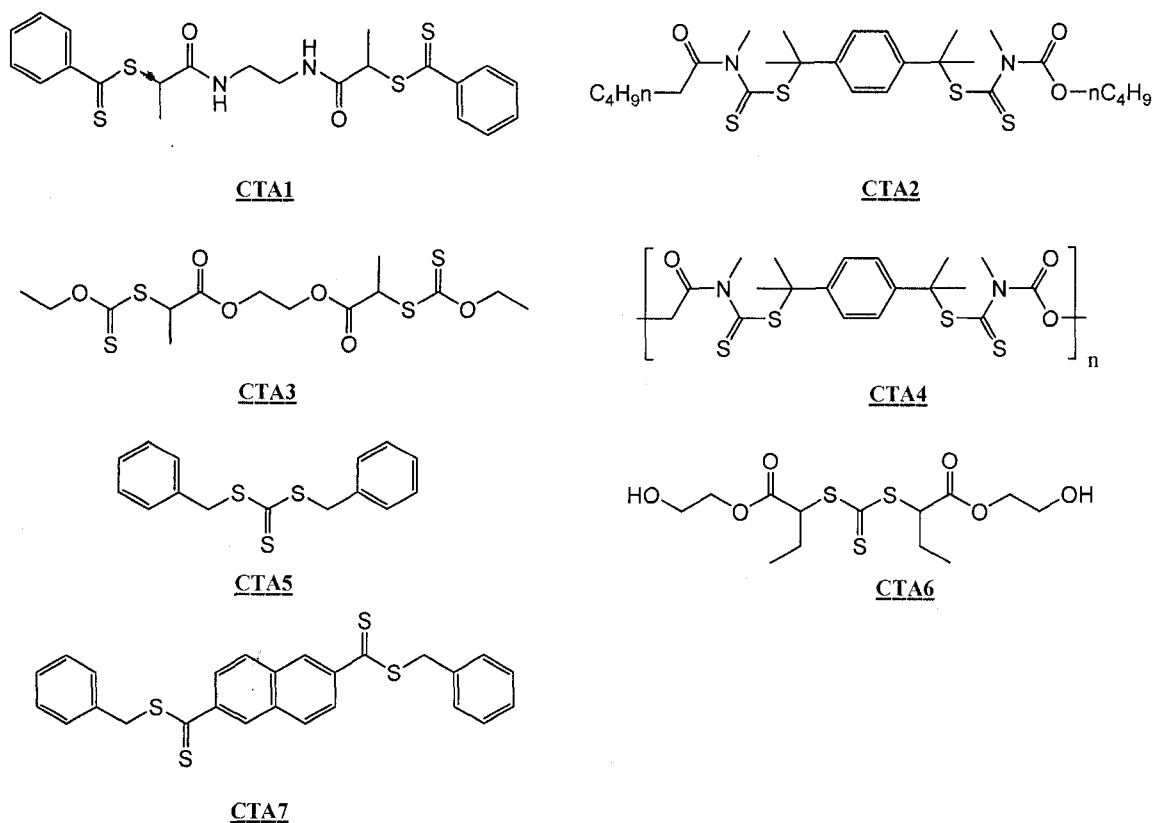


Figure I-19. Difunctional CTA's for the production of ABA triblock copolymers.

Difunctional Z CTA's have a general structure of $RSC(=S)ZC(=S)SR$. By sequential addition of monomer A and B, ABA triblock copolymers can be formed. For example, Dureault et al. used dibenzyl naphthalene-2,6-bis(carbodithioate) (**CTA7**) to synthesize poly(*tert*-butyl acrylate-*block*-styrene-*block*-*tert*-butyl acrylate).²⁹¹ One particular type of this difunctional Z CTA are symmetric trithiocarbonates, that have a general structure of $RSC(=S)SR$, where the polymer chains grow outward on both ends of the trithiocarbonate. For example, Mayadaune et al. reported the synthesis of poly(styrene-*block*-*n*-butyl acrylate-*block*-styrene) by use of dibenzyl trithiocarbonate (**CTA5**) as the CTA.²⁰¹ Yuan et al. used the same CTA to prepare poly(styrene-*block*-4-vinyl pyridine-*block*-styrene) and poly(4-vinylpyridine-*block*-styrene-*block*-4-

vinylpyridine) with PDI's below 1.25.³²⁸ A drawback of this technique is the location of the thiocarbonylthio functional group in the center of the formed polymer, which makes it difficult for propagating radicals to attack the C=S double bond due to the steric hindrance when the molecular weight gets too high.

2) Gradient copolymers

Conventional free radical polymerization of two or more monomers, due to the slow rate of initiation relative to propagation and chain breaking reactions, results in a mixture of copolymers with very different compositions. However, in RAFT polymerization, all the polymer chains are initiated early and grow throughout the polymerization, and thus all chains have similar composition, leading to the formation of gradient copolymers. Examples of gradient copolymers prepared via RAFT include copolymerization of MA and VAc ($r_{MA} \sim 9$, $r_{VAc} \sim 0.1$) mediated by O-ethyl S-cyanomethyl xanthate, and copolymerization of styrene with *N*-phenylmaleimide (NPMI) ($r_S \sim 0.02$, $r_{NPMI} \sim 0.04$) with an excess of styrene, resulting in the formation of poly(NPMI-*alt*-styrene)-*block*-polystyrene.²²³

3) Star polymers

Star polymers can be prepared via RAFT by utilizing multifunctional CTA's. Basically, there are two types of strategies to make star polymers via RAFT. If the core of the multifunctional CTA functions as the R group and polymer chains grow away from the core, it is called the R-approach or attach-to approach. Alternatively, if the core of the

multifunctional CTA acts as the Z group, it is called the Z-approach or away-from approach. The latter is a unique feature of RAFT for synthesis of star polymers.

The R-approach is similar to ATRP or NMP. A variety of molecules have been modified into multifunctional CTA's (Figure I-20). Examples are hexakis(thiobenzoylthiomethyl) benzene (**CTA8**) to mediate the polymerization of styrene (six arms),³³² 2,4,5-tris({[methylsulfanyl]-carbonothioyl}sulfanyl)methyl)benzylmethyl trithiocarbonate (**CTA9**) to mediate the polymerization of styrene and methyl acrylate (four arms).³³³ The synthesis of depentaerythritolhexakis(phenyl-S-methyltrithiocarbonyl methanoate) (six arms) and its three-, four- and eight-arm equivalents were also reported, but they were not used in the polymerization.²¹⁶ Pentaerythritol and 1,1,1-tris(hydroxymethyl)propane were modified with xanthate groups and used to mediate the polymerization of vinyl acetate (four- and three arms, respectively).³³⁴ The main side reaction by this approach is the star-star coupling since the propagating radicals are attached to the cores. To avoid such side reactions, both radical concentration and conversion of monomers should be kept low.

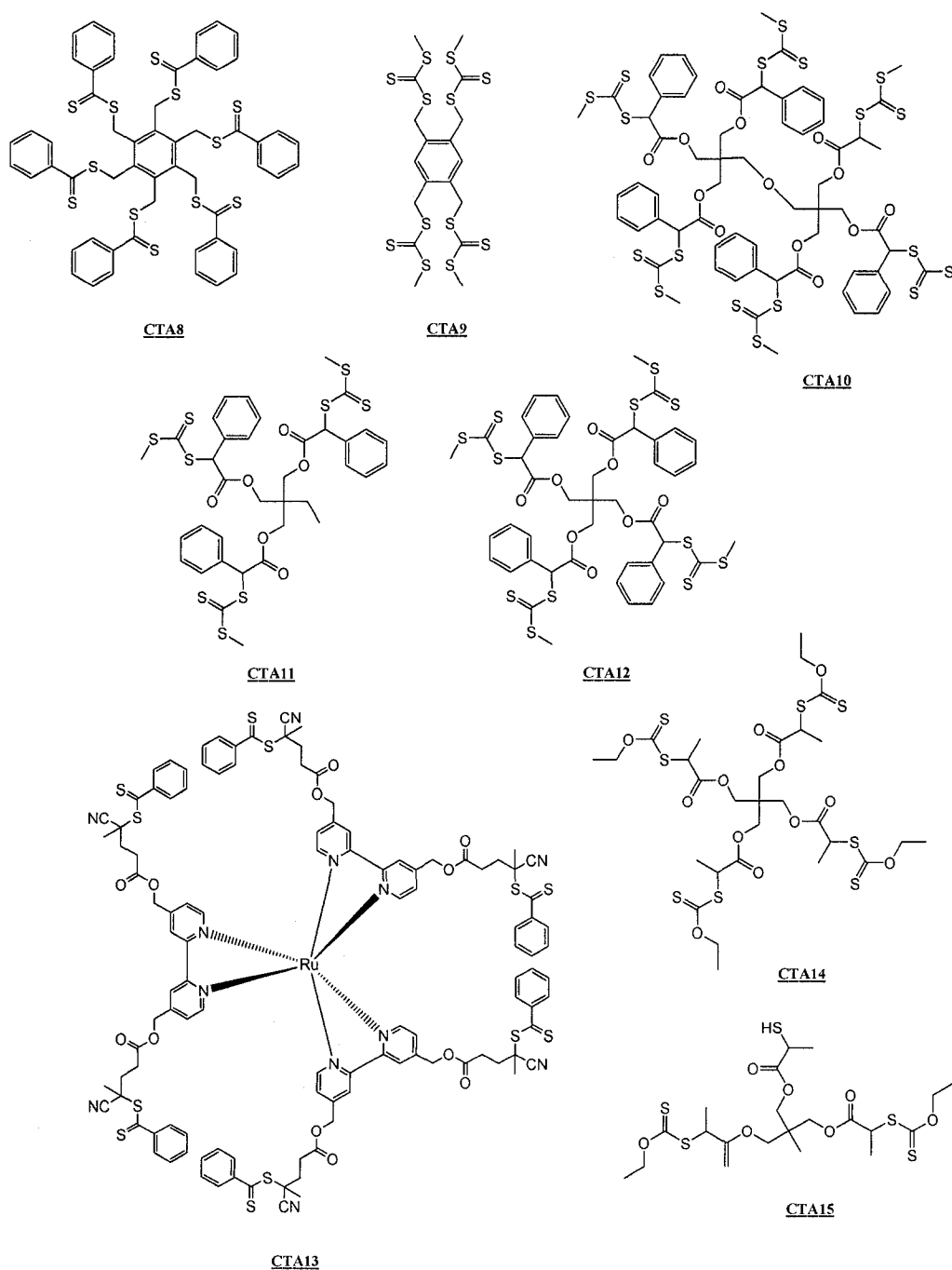


Figure I-20. Functional CTA's for the synthesis of star polymers: the R approach.

In the Z-approach, the polymer chains are detached from the core while they grow, and react back to the core via addition-fragmentation chain transfer. In this case, the coupling reactions occur only between polymer arms. Therefore, star polymers prepared

in this way usually have very narrow molecular weight distributions, with PDI's reported as low as 1.1. The polymerization, unlike the R-approach, can be taken to a higher conversion, but steric hindrance may affect the ability of the arms to attack back to the core when the molecular weight is high. Examples of this approach (Figure I-21) include the use of pentaerythritoltetrakis[3-(*S*-benzyltrithiocarbonyl)propionate] (**CTA12**) to mediate the polymerization of methyl acrylate, styrene and their block copolymers,^{216,333} and depentaerythritolhexakis[3-(*S*-benzyltrithiocarbonyl) propionate] (**CTA11**) was also synthesized, although it was not used in the polymerization.²¹⁶ β -Cyclodextrin was modified into a trithiocarbonate heptafunctional β -cyclodextrin (**CTA17**) to mediate the polymerization of styrene.³³⁵ Xanthates tetrakis(benzyl-sulfanyl-thiocarbonyloxymethyl)methane (**CTA19**), [1-(phenyl-ethyl)-sulfanyl-thiocarbonyloxymethyl]methane (**CTA20**), and tetrakis[(2-phenyl-ethyl)-sulfanyl-thiocarbonyloxymethyl]methane (**CTA21**) were all used to mediate the polymerization of vinyl acetate and vinyl propionate.²⁰⁰

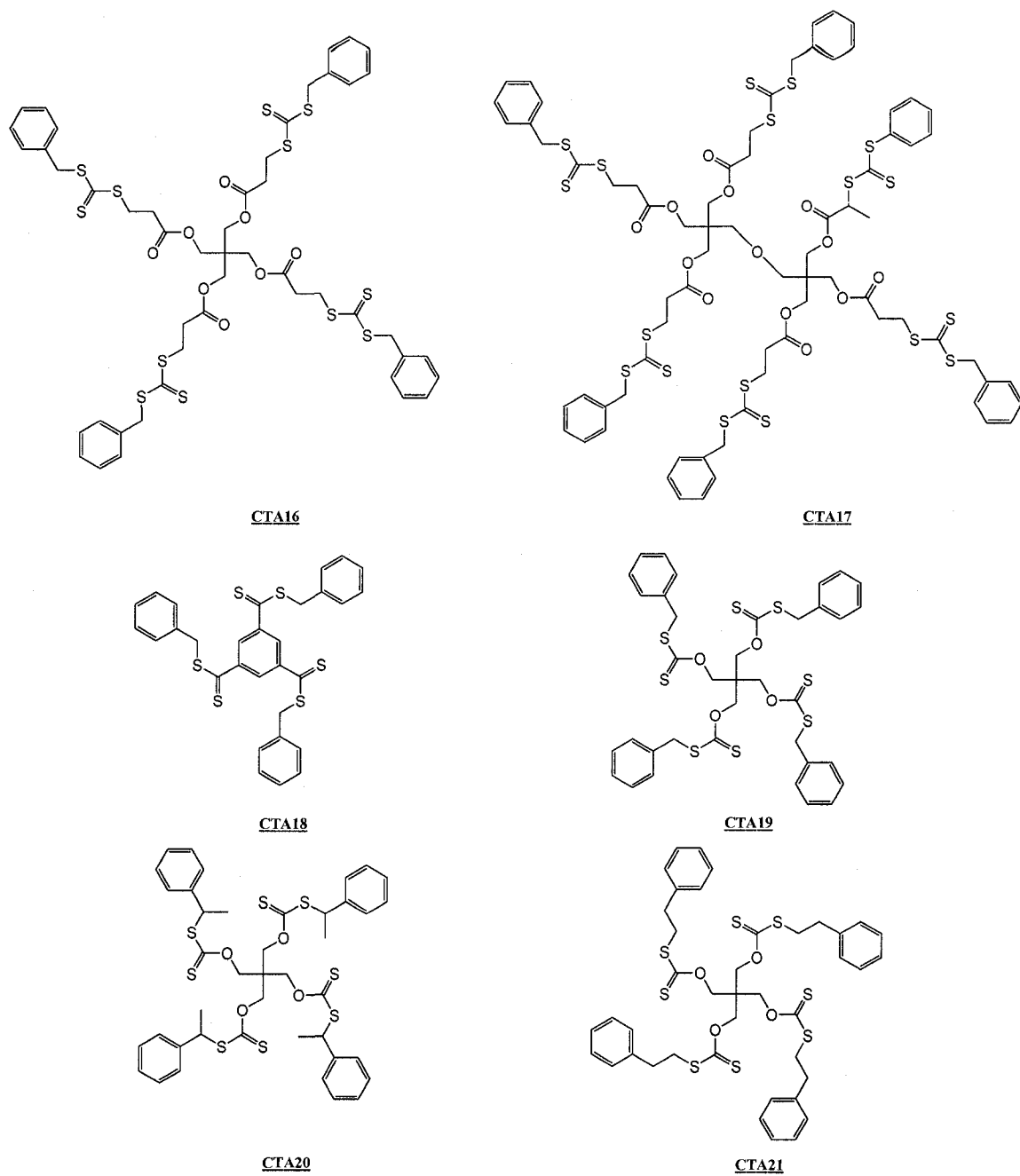
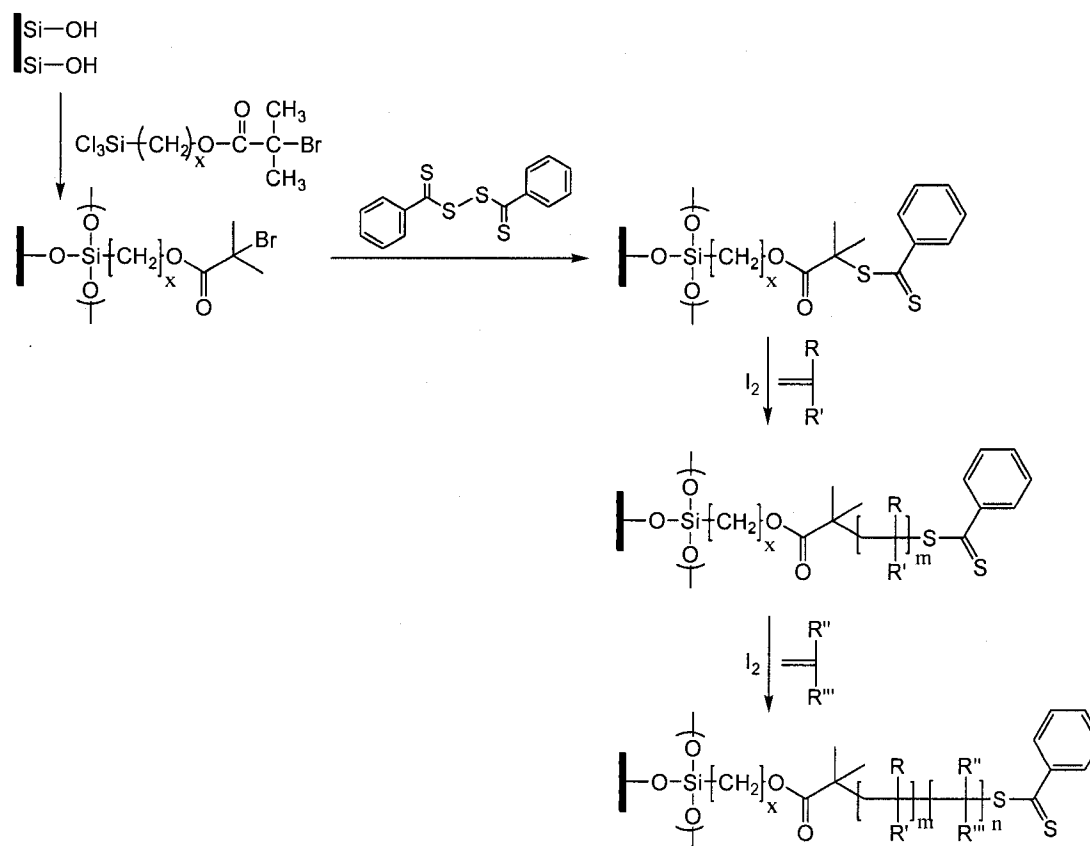


Figure I-21. Functional CTA's for the synthesis of star (co)polymers via the Z-approach.

4) Polymer brushes/Surface-grafted polymers

Polymer brushes/surface grafted polymers are attracting more and more interest. The most common CLFR polymerization technique used to produce polymer brushes is ATRP. However, RAFT has recently been successfully employed.^{420,421}

As with the preparation of star (co)polymers via RAFT, the preparation of polymer brushes initiated from surface also has two general approaches: the 'grafting-to' approach and the 'grafting-from' approach. Scheme I-26 shows an example of the preparation of highly functional polymer brushes via the 'grafting-to' mechanism.



Scheme I-26. Examples of preparation of polymer brushes via RAFT.

Boyes et al. recently reported the synthesis of a variety of well-defined diblock copolymer brushes, including poly(methyl methacrylate) (PMMA)-*b*-poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA), PMMA-*b*-poly(styrene) (PSty), and PSty-*b*-poly(methyl acrylate), achieved via surface immobilized RAFT polymerization (Scheme I-26).³³⁶ Initially, silicon surfaces were modified with CTA's by utilizing a modified atom transfer addition reaction involving a silicon wafer modified with (11-(2-bromo-2-methyl)propionyloxy)undecyltrichlorosilane and dithiobenzoyl disulfide. Diblock copolymer brushes were then prepared via sequential surface initiated RAFT polymerization from the immobilized CTA.

5) Modification of gold surfaces

Lowe et al. reported the first example of colloidal stabilization by polymers prepared via RAFT (Figure I-22).³³⁷ A series of water-soluble polymers prepared via RAFT were evaluated, including poly(sodium 2-acrylamido-2-methyl propane sulfonate) (PAMPS), poly(*ar*-vinylbenzyl)-trimethylammonium chloride (PVBTAC), poly(*N,N*-dimethylacrylamide) (PDMA), and poly(3-[2-*N*-methylacrylamido]-ethyl dimethyl ammonio propane sulfonate-*block-N,N*-dimethylacrylamide) (PMAEDAPS-*b*-PDMA), representing anionic, cationic, neutral and zwitterionic families, respectively. (Co)polymer-stabilized nanoparticles based on transition metal complex (Au (HAuCl₄ sol), Ag (AgNO₃), Pt (Na₂PtCl₆·6H₂O), and Rh (Na₃RhCl₆)) were prepared using NaBH₄ as the reducing agent. The NaBH₄ simultaneously reduced both dithioester end group of the (co)polymer and metal complex. The reduced polymer with thiol end group immediately adopted to the metal, resulting in a polymer-metal complex, which provided

steric and electrostatic stabilization to prevent aggregation of insoluble metal nanoparticles. The simultaneous reduction of thiocarbonylthio end-capped (co)-polymer chains and metal salts affords a facile process for the preparation of (co)polymer-stabilized metal nanoparticles.

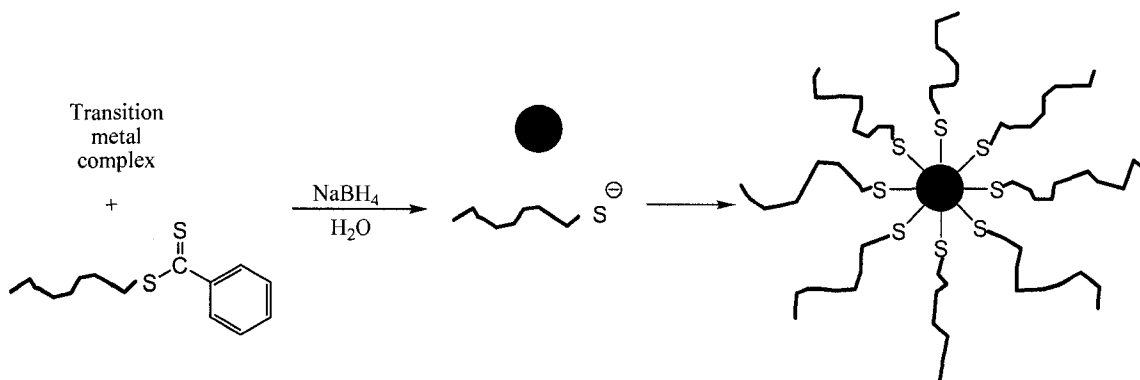


Figure I-22. Stabilization of gold nanoparticles by polymers prepared via RAFT.

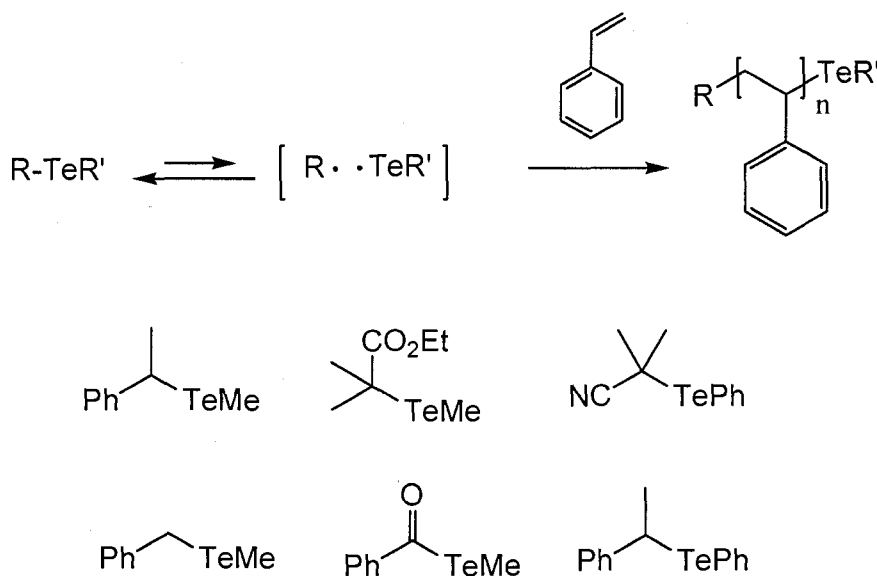
3.5 TERP/QTRP

Some other new living radical polymerization techniques recently disclosed include tellurium-mediated radical polymerization (TERP) and quinone transfer radical polymerization (QTRP).

3.5.1 Tellurium-mediated radical polymerization (TERP)

In 2002, Yamago et al. reported another form of controlled/living radical polymerization system.³³⁸ Based on the fact that organotellurium compounds can undergo reversible carbon-tellurium cleavage upon thermolysis and photolysis, a similar process

to NMP was developed utilizing the organotellurium compounds as unimolecular initiators to achieve living polymerizations (Scheme I-27).



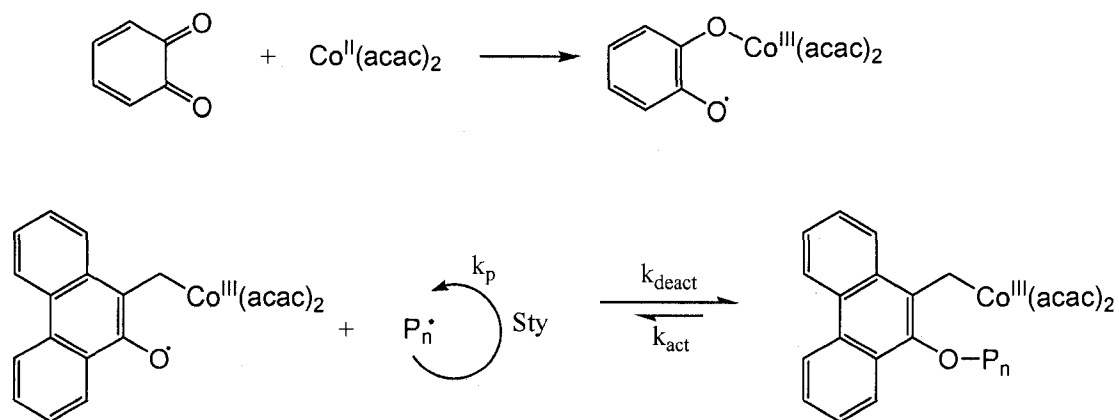
Scheme I-27. Mechanism of tellurium-mediated radical polymerization (TERP) and tellurium mediators.

A variety of monomers have been polymerized by TERP in a controlled manner, such as styrene,³³⁸ butyl acrylate, acrylonitrile, *N,N*-dimethyl acrylamide, and *N*-isopropylacrylamide.³³⁹ One big advantage of TERP over other CLRP techniques is the tolerance of the order of monomer addition when synthesizing block copolymers. For example, the AB diblock copolymer of styrene and MMA can be prepared from either the polystyrene homopolymer or the PMMA homopolymer as the macro-mediator.³⁴⁰

3.5.2 Quinone transfer radical polymerization (QTRP)

In 2004 Caille et al. reported a new process for the controlled/living radical polymerization of styrene based on a complex of ortho-quinone and a catalytic cobalt(II)

acetylacetonate system.³⁴¹ The organometallic species Co(II)(acac)_2 is oxidized by ortho-quinone, forming a oxygen-centered radical, which functions as a persistent radical to combine with a propagating radical (Scheme I-28).



Scheme I-28. Mechanism of quinone transfer radical polymerization (QTRP).

Since the majority of polymer chains are end-capped by the ortho-quinone, the targeted molecular weight of polymer is determined by the amount of ortho-quinone added. This process is more like ATRP, but the amount of metallic catalyst required is small, usually with a ratio of $[\text{Co(II)(acac)}_2]:[\text{PhQ}]$ of 0.01 or even less. Efforts are now being made to extend to other ortho-quinones and metallic catalysts to evaluate the potential and limitations of this technique.

methylbutanoate (AMBA) (Figure I-23) via aqueous RAFT.⁵⁹ At high pH, both AMPS and AMBA blocks are ionized (hydrophilic) and the block copolymer exists as unimers in water. As the pH is decreased, the AMBA block becomes protonated (below its pK_a) and becomes hydrophobic while the AMPS block remains hydrophilic. As such, the unimers self-assemble to form polymeric micelles with the insoluble AMBA block in the core and the soluble AMPS block as the stabilizing corona. This behavior is completely reversible, and raising the pH results in micelle-breakup and unimeric dissolution.

It is important to point out that such reversible micellization behavior can only occur above the so-called critical micellization concentration (cmc).

4.1.2 Micelles formed by ‘schizophrenic’ block copolymers

‘Schizophrenic’ block copolymers are also referred to as doubly ‘smart’ copolymers, and are polymers in which both blocks are tunably hydrophilic/hydrophobic. At present, this represents the least studied of the amphiphilic block copolymers.

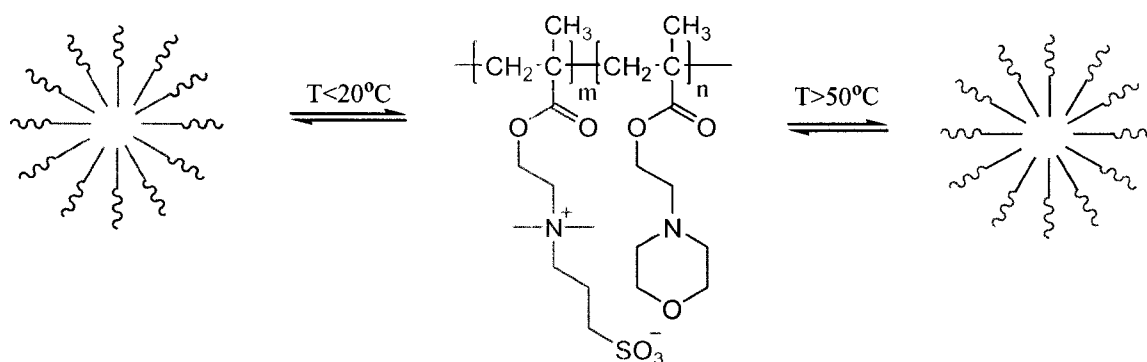


Figure I-24. Example of ‘schizophrenic’ AB diblock copolymer.

One example of such a schizophrenic AB diblock copolymer is shown in Figure I-24, which consists of 2-(*N*-morpholino)ethyl methacrylate (MEMA) and a polysulfobetaine derived from 2-(dimethylamino)ethyl methacrylate (DMAEMA).³⁴² At temperatures between 30 – 40 °C, both blocks are hydrophilic and thus the block copolymer exists as molecularly dissolved unimeric chains. If the temperature is raised above the cloud point of the MEMA block, the copolymer self-assembles to form polymeric micelles with the hydrophobic MEMA block residing in the core and the sulfobetaine block in the corona. However, if the temperature is lowered to below 20 °C, the sulfobetaine block begins to phase separate as it reaches its upper critical solution temperature (UCST) and thus the polymeric micelles are formed with the now hydrophobic sulfobetaine block in the core and hydrophilic MEMA block in the corona.

4.1.3 Core and shell cross-linking micelles

Polymeric micelles formed by block copolymers described above are usually dynamic in the sense that there exists an equilibrium between polymeric micelles and unimers in the aqueous solution. Upon the application of appropriate stimuli, the polymeric micelles are formed; after the removal of the stimuli, the polymeric micelles will be dissociated into unimers. Under some circumstances, the structure of the polymeric micelles, once formed, need to be ‘locked’ even after the stimuli were removed. One method to achieve this is via cross-linking either the core or the corona of the polymeric micelles.

Shell cross-linked micelles, also called knedel or SCK micelles, were first reported in 1997 by Wooley et al.^{343,344} Subsequently, Armes et al. reported the

preparation of so-called Type I and Type II zwitterionic SCK micelles from block copolymers of 2-(dimethylamino)ethyl methacrylate (DMAEMA) with 2-tetrahydropyranyl methacrylate (THPMA) (Figure I-25).^{66,67,345} When dissolved in a water/THF mixture, micellization occurs with the hydrophilic DMAEMA blocks as the corona. Addition of the cross-linking agent bis-(2-iodoethoxy)ethane linked the tertiary amine residues via a quaternization reaction. Subsequent hydrolysis of the THPMA residues in the locked micelles leads to the formation of the Type I SCK species, with the hydrophilic PMMA in the core. Alternatively, the block copolymer can be initially hydrolyzed, followed by heating a solution of the resulting polymer above the cloud point of DMAEMA, which results in the formation of inverse polymeric micelles with the hydrophobic DMAEMA block in the core and hydrophilic PMAA in the corona. Addition of bis-(2-iodoethoxy)ethane results in the formation of Type II SCK micelles via esterification reaction, of the MAA residues.

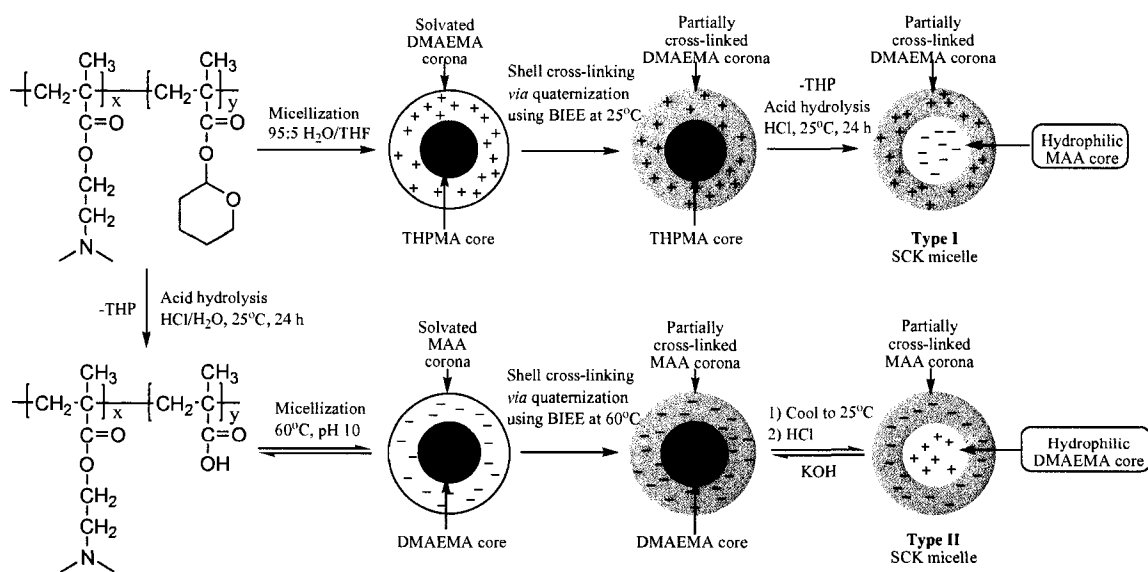


Figure I-25. Reaction scheme for the synthesis of Type I and Type II zwitterionic SCK micelles.

It is noteworthy that such cross-linking needs to be performed in relatively dilute solution, or inter-micelle cross-linking would occur. Such a drawback can be avoided in the situation of polymeric micelles formed by ABC triblock copolymers, with the C block in the core, the A block as the outer corona, and B block as the inner corona, so that the outer A corona could act as steric barrier to protect the inner cross-linking in B block.^{346,347}

Example of core cross-linking was reported with pH-responsive AB diblock copolymer of permanently hydrophilic DMA and tunably hydrophilic/hydrophobic DMVBA. At high pH, polymeric micelles are formed with the DMBVA block in the core. The hydrophobic 1,4-bis-bromomethylbenzene, after being added, is sequestered in the core where it can react with tertiary amine residues via a Menshutkin reaction, resulting in core cross-linking micelles.²⁸⁸

4.2 *Methods for studying self-assembly*

Some of the important parameters to characterize polymeric micelles are:³⁴⁸

K – the equilibrium constant of unimers \leftrightarrow micelles

CMC or CMT – the critical micelle concentration or the critical micelle temperature.

N_{agg} – The aggregation number (association number), which is the average number of polymeric chains in a micelle.

R_g – The radius of gyration of a polymeric micelle.

R_h – The hydrodynamic radius of a polymeric micelle.

R_c – The radius of the micelle core (insoluble block).

L – The thickness of the micelle shell (soluble block).

Not these parameters alone, but also a combination of them, can be utilized to characterize the polymeric micelles. For examples, the ratio of R_g/R_h can give us information about the shape of the micelles.

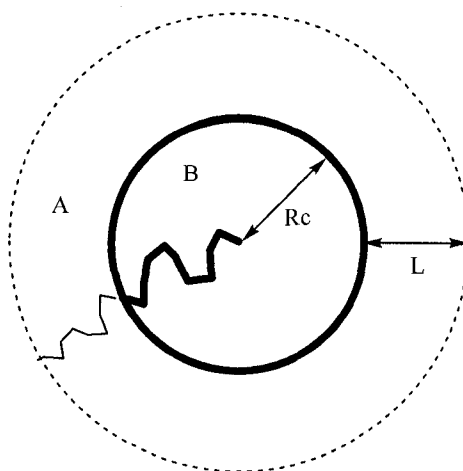


Figure I-26. Schematic representation of polymeric micelles formed by AB diblock copolymers.

Table I-1. Experimental techniques for micelle characterization.³⁴⁸

Techniques	Micelles characteristics
NMR	Chain dynamics
Dynamic light scattering (DLS)	R_h
Fluorescence spectroscopy	Chain dynamics, CMC
Transmission electron microscopy (TEM)	Shape, size of micelles
Viscometry	R_h , intrinsic viscosity
Size exclusion chromatography (SEC)	R_h , dynamics of micellar equilibrium, MW of micelles
Static light scattering (SLS)	Weight-averaged molecular weight, R_g
Small angle neutron scattering (SANS) and small angle X-ray scattering (SAXS)	Weight-averaged molecular weight, R_g , R_c
Ultracentrifugation	Micelle density, molecular weight (Z average)
Stop flow technique	Kinetics of micelle formation and dissociation

4.2.1 Nuclear magnetic resonance (NMR) spectroscopy

NMR spectroscopy is a quick and convenient method for monitoring the relative solvation of AB diblock copolymers in water (D_2O) and can be used as a qualitative indicator of self-assembly. Figure I-27 shows an example of the block copolymer of *N,N*-dimethyl(4-vinylbenzyl)amine (DMVBA) and *N,N*-dimethyl acrylamide (DMA).⁵⁰ As the PDMBVA block undergoes its hydrophilic-hydrophobic phase transition then the signals in the NMR spectrum associated with this species will both reduce in intensity and broaden as a result of drastically reduced chain mobility (i.e. desolvation). Provided no macroscopic precipitate is observed then such observations indicate supramolecular self-assembly in a fashion such that the hydrophobic portion is “shielded” from the aqueous environment. From this we infer micelle formation. The reversibility of micelle formation can likewise be conveniently monitored by simply adjusting conditions back to those in which the block copolymer is expected to be unimeric i.e. doubly hydrophilic.

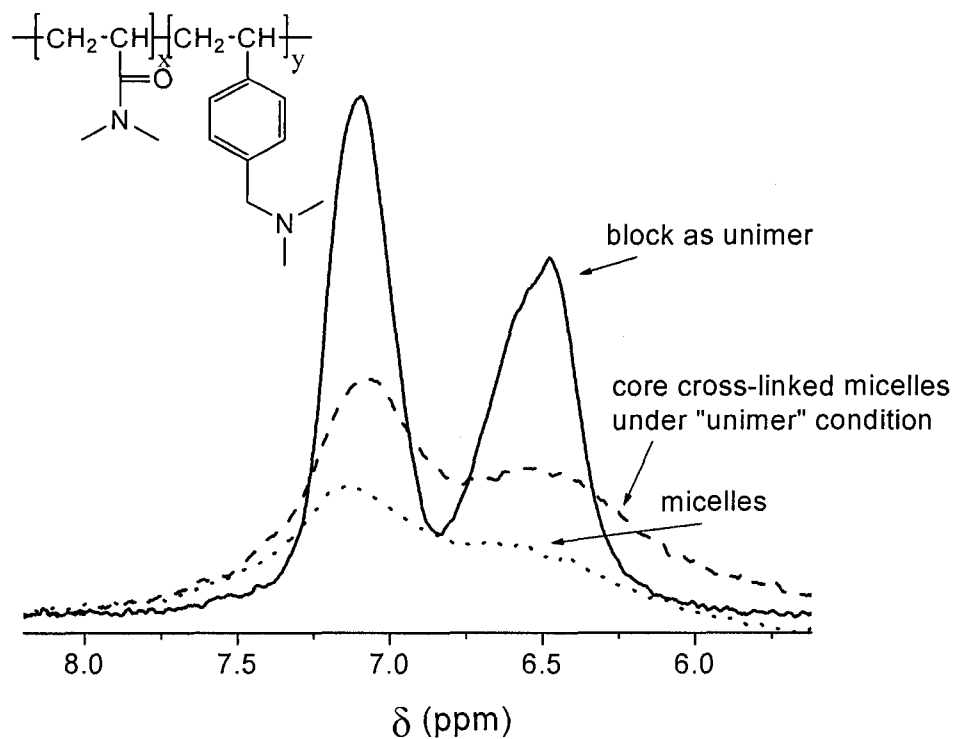


Figure I-27. Example of ^1H spectra of unimers, micelles and cross-linked micelles under 'unimer' condition.

Likewise, NMR spectroscopy can be employed to confirm successful core crosslinking. Employing the same protocol as above we find that if, after crosslinking, the aqueous conditions are adjusted to favor unimer formation that we do observe changes in the NMR spectrum. However the polymeric micelles cannot break apart due to the crosslinking. As such, while the core becomes hydrophilic, and certainly solvated to a certain extent, the chain mobility is still drastically reduced. As such we expect to observe an increase in intensity and narrowing of the signals associated with the core but not to the extent of the free unimer chains, see Figure I-27 as an example.

4.2.2 Dynamic light scattering (DLS)

DLS is employed as the primary tool to examine the aggregation and dissociation behavior of the block copolymers. In DLS we measure the time dependence of the intensity of scattered light from a small region of the solution. The fluctuations in the intensity of scattered light are related to the rate of diffusion of species in and out of the region being studied and data can be analyzed directly to give the diffusion coefficient of these species. Since the rate of diffusion is related to size, the diffusion coefficient is typically converted to the hydrodynamic radius (or Stoke radius) using the Stoke-Einstein equation:

$$R_h = kT/6\pi\eta D_0 \quad \text{Equation 13}$$

Where k is the Boltzmann constant, T is the absolute temperature, η is the viscosity of the solvent, and D is the diffusion coefficient.

When block copolymers exist as unimers in the solution, they will possess small hydrodynamic radii. A large increase in the hydrodynamic radius will be observed upon self-assembly. Likewise DLS can be used as an indicator for successful cross-linking. Since the block copolymers can no longer exist in the unimeric state, large hydrodynamic radii should still be observed even under conditions where unimer formation would be favored.

4.2.3 Fluorescence spectroscopy

The formation and dissociation of polymeric micelles can also be examined via

fluorescence spectroscopy employing probe molecules such as pyrene. In the pyrene fluorescence spectrum there are five distinct peaks labeled $I_1 \rightarrow I_5$. The intensity of the I_1 peak is sensitive to the polarity of its environment whereas I_3 is environmentally insensitive. As such, the ratio of I_1/I_3 is often used as an indicator of the polarity of the environment in which the pyrene is residing. A decrease in I_1/I_3 indicates movement from a high to a low polarity environment. The addition of pyrene to an aqueous solution of a block copolymer in its unimeric state will result in an I_1/I_3 value typical of pyrene alone in water. Upon micellization it is predicted that the pyrene will preferentially partition to the hydrophobic micellar core which will be verified by a drop in the I_1/I_3 ratio.

CHAPTER II

OBJECTIVES OF RESEARCH

The ability to synthesis (co)polymers in a controlled manner, i.e. with predetermined molecular weights, narrow molecular mass distributions, and with controllable topologies and architectures is becoming increasingly important as the demand for highly functional materials in specialty applications continues to grow. Classic living polymerization techniques, such as living anionic polymerization and group transfer polymerization, are limited in application due to either the restricted choice of monomer, or the exigent polymerization conditions. However, the recent discovery and development of the controlled/living free radical polymerization (CRP) methodologies including nitroxide mediated polymerization (NMP), atom transfer radical polymerization (ATRP), and reversible addition-fragmentation chain transfer (RAFT) polymerization, now facilitate the preparation of advanced materials from a wide range of functional monomers. Of these CRP processes, RAFT has proven itself to be, arguably, the technique of choice for the synthesis of well-defined water-soluble (co)polymers in either organic or aqueous media, due to its applicability to the widest range of monomers, its superior functional group tolerance, and its ease of execution.

An important family of water-soluble polymers are those which contain “triggerable” functional groups. Such polymers can be responsive to one or a combination of stimuli, including but not limited to, solution pH, temperature, salt concentration, shear stress, etc. They are termed “smart” polymers because they can undergo either conformational changes or phase transitions in response to the application of specific external stimulus. Of particular interest are AB diblock copolymers in which

at least one block is tunably hydrophilic/hydrophobic. Such materials, upon the application of a stimulus, can self-assemble to form polymeric micelles with the hydrophobic blocks in the core, stabilized by the hydrophilic blocks in the corona. Such processes are typically completely reversible, i.e. the polymeric micelles will dissociate into unimers upon the removal of the applied stimulus. Such materials have found a wide range of applications such as drug delivery and enhanced oil recovery.

The overall objective of this research project is to utilize RAFT as a synthetic method to prepare a variety of novel “smart” water-soluble AB diblock copolymers which would exhibit stimuli-responsive aqueous solution properties. In specific, the goals of this research include:

- 1) Design and synthesize novel trithiocarbonate CTA's that are water-soluble, and effective in mediating RAFT polymerization of acrylate, acrylamido, and styrenic-based monomers.
- 2) Design and synthesis of novel stimuli-responsive AB diblock polyelectrolytes.
- 3) Design and synthesis of novel stimuli-responsive AB diblock polyzwitterions.
- 4) Design and synthesis of novel doubly responsive AB diblock copolymers which can form both normal and inverse polymeric micelles.

CTA design and synthesis

The key to accomplishing successful RAFT polymerizations is appropriate choice of chain transfer agent (RAFT agent or CTA). Dithioesters are probably the most widely employed/versatile CTA's, however, the trithiocarbonates (TTC's) have been attracting an increasing amount of attention recently, partly due to their ease of synthesis and

purification, which is a distinct advantage compared to the synthesis of many other RAFT agents. And TTC's have proven to be especially useful for the controlled polymerization of styrenic, acrylate, and acrylamido monomer derivatives, and in some instances under extremely facile conditions. As such we designed and synthesized a series of functional TTC's, in which the substitution about the TTC functionality was systematically varied. The effectiveness of these TTC's was evaluated and compared in the polymerization of the model acrylic monomer *n*-butyl acrylate (nBA). Whether the overall degree of control is affected by CTA structure, i.e. the nature of the Z and R groups, was addressed.

Synthesis of polyampholytes

A special and complex family of water-soluble polymers are polyampholytes (PAMs), which contain both cationic and anionic residues located on different repeat units. The *direct* synthesis of polyampholytes, i.e. without resorting to either protecting group chemistry or post-polymerization modification, is known to be challenging and has only been successfully achieved on several occasions. We have attempted to make polyampholytes comprised of styrenic-based cationic phosphonium monomers (**M63** and **M106**) and 4-vinylbenzoic acid (VBZ, **M62**) via RAFT mediated by **CTA26** directly in aqueous media. First, the controlled nature of the homopolymerizations of the monomers was examined from both the kinetics and the experimentally determined molecular weights and PDI's. Statistical PAMs were prepared, with the molar ratio of **M63/M106** and **M62** varied. Block PAMs were prepared by employing poly**M63/M106** as the macro-CTA for the block copolymerization with **M62**. The successful synthesis of

polyampholytes was verified by FT-IR spectroscopy. The pH-responsive behavior of the block copolymer was studied by ^{13}C NMR spectroscopy.

Synthesis of polycations

Cationic polymers are useful materials with a lot of commercial application, such as cosmetics, antimicrobial formulations, water treatment, and paper processing. A series of new styrenic-based pH-responsive AB diblock copolymers comprised of a permanently positively charged, hydrophilic, 4-vinylbenzyltrimethylphosphonium chloride (**M63**) block and a tunably hydrophilic/hydrophobic *N,N*-dimethylbenzylvinylamine (**M59**) block were synthesized via RAFT directly in aqueous media under homogeneous conditions. The molar compositions of two blocks were varied. Since such materials were expected to undergo pH-induced supramolecular self-assembly in water, solution behavior was investigated by a combination of techniques, including ^1H NMR spectroscopy, dynamic light scattering (DLS), and fluorescence spectroscopy. The presence of reactive tertiary amine functionality of **M59** in the aggregate cores also facilitated a core cross-linking reaction by use of difunctional cross-linking agent that could effectively “lock” the copolymers in the self-assembled state, which can be confirmed by ^1H NMR spectroscopy and DLS analysis.

Synthesis of schizophrenic polymer

A less studied family of stimuli-responsive materials are AB diblock copolymers in which both building blocks are sensitive towards an applied stimulus – such materials have been termed “schizophrenic” by some researchers. A doubly responsive AB diblock

copolymer comprised of *N*-isopropylacrylamide (**M75**) with 4-vinylbenzoic acid (**M62**) was synthesized via RAFT by using **CTA26** as the mediating agent in DMF. The solution properties of this copolymer were studied by a combination of ¹H NMR and DLS by controlling the aqueous solution pH and temperature. Both normal and inverse micelles were expected to be formed in aqueous media.

CHAPTER III

THE SYNTHESIS AND EVALUATION OF NEW DICARBOXYLIC ACID FUNCTIONAL TRITHIOCARBONATES: THE RAFT SYNTHESIS OF TELECHELIC POLY(*N*-BUTYL ACRYLATE)S

Introduction

The ability to synthesize functional (co)polymers in a controlled manner, i.e. with predetermined molecular weights, composition, and chain end functionality, has become increasingly important in recent years as the demand for materials in specialty applications grows. Fortunately, today the polymer chemist has many tools available to achieve these goals. Of particular note is the discovery and development of the controlled/living free radical polymerization techniques. For example, stable free radical polymerization (SFRP), best exemplified by nitroxide-mediated systems (NMP),^{92,93} atom transfer radical polymerization (ATRP),⁹⁴⁻⁹⁸ reversible addition-fragmentation chain transfer (RAFT) polymerization,⁹⁹⁻¹⁰¹ tellurium-mediated radical polymerization (TERP),³³⁸ and quinone transfer radical polymerization (QTRP)³⁴¹ are all versatile techniques for the preparation of well-defined polymers in a controlled fashion, although both TERP and QTRP have not yet been widely evaluated. Of these techniques, RAFT is arguably the most versatile, at least with respect to monomer choice. For example, monomers that have historically proven difficult to control via SFRP or ATRP can be readily polymerized in a controlled fashion via RAFT. Pertinent examples include the facile polymerization of both charged^{57-59,124} and neutral^{57,210,246,299} (meth)acrylamido monomers as well as 'problematic' species such as vinyl esters.³⁴⁹

Key to accomplishing successful RAFT polymerizations is appropriate choice of RAFT mediating agent, commonly referred to as the RAFT chain transfer agent (CTA) or more simply, RAFT agent. An advantage of RAFT is the wide range of CTAs that can be readily prepared thus facilitating the fine-tuning of a given polymerization system. Indeed, many research groups have, and continue to, report the preparation and evaluation of new RAFT agents. All RAFT agents are thiocarbonylthio compounds derived from dithioesters,⁹⁹ dithiocarbamates,²⁰⁰ xanthates,¹⁹² or trithiocarbonates.²⁰¹ While the acronym RAFT encompasses all systems in which the above thiocarbonylthio compounds are employed as mediating agents, the acronym **MADIX** (**M**acromolecular **D**esign by **I**nterchange of **X**anthate) is also used for those polymerizations which specifically employ xanthates. These thiocarbonylthio compounds differ only in the nature of the so-called Z and R groups. As a result of these structural differences not all RAFT agents are effective mediators for all monomers. However, some general classes are more ‘universally’ applicable than others. For example, the dithioesters are probably the most widely employed/versatile RAFT agents, whereas the xanthates do not typically work well for ‘common’ monomer families but have, for example, proven to be particularly effective for the vinyl ester family including vinyl acetate³²³ and the sugar derivative 6-*O*-vinyladipoyl- β -D-glucopyranose.³⁴⁹ The trithiocarbonates (TTCs) represent one of the least studied of the RAFT agent family, but have been attracting an increasing amount of attention recently. This is due, in part, to their ease of synthesis and purification. This is a distinct advantage when compared to the synthesis of many other RAFT agents. TTCs have proven to be especially useful for the controlled polymerization of styrenic, acrylate, and acrylamido monomer derivatives, and in some

instances under extremely facile conditions. For example, Lima and co-workers recently reported the use of trithiocarbonates RAFT agents for the synthesis of a range of telechelic poly(*n*-butyl acrylates) employing previously reported RAFT agents.³⁵⁰

As part of our continuing studies on RAFT polymerization we have synthesized a series of new functional TTCs for the polymerization of acrylic monomers. We report in this chapter the design and synthesis of three new dicarboxylic acid functional TTCs in which we have systematically varied the substitution about the TTC functionality. We have evaluated these new TTCs alongside previously reported literature examples in the polymerization of the model acrylic monomer *n*-butyl acrylate (nBA). We show that some of these species are indeed highly effective for this particular monomer although, as expected, the overall degree of control is affected subtly by CTA structure, i.e. the nature of the *Z* and *R* groups.

Experimental part

Reagents were purchased from Aldrich Chemical Company at the highest available purity and used as received unless stated otherwise. *n*-Butyl acrylate (nBA) was passed over a column of basic alumina to remove inhibitor and stored in a refrigerator at 0 °C until needed. 2,2'-Azobis(isobutyronitrile) was recrystallized from methanol and stored in a refrigerator prior to use. 2-(1-Carboxy-1-methylethylsulfanyl thiocarbonylsulfanyl)-2-methylpropionic acid (**CTA22**) and 3-benzylsulfanyl thiocarbonylsulfanylpropionic acid (**CTA24**) were prepared according to literature procedures.^{202,335}

Synthesis of 3-(2-carboxyethylsulfanylthiocarbonylsulfanyl)propionic acid (CTA25)

3-Mercaptopropionic acid (10.6 g, 0.1 mol), distilled/deionized water (100 mL) and 50 wt % NaOH solution (16.0 g, 0.2 mol) was added to a 250 mL round bottomed flask equipped with magnetic stir bar. This mixture was stirred for 30 min prior to the dropwise addition of carbon disulfide (6.0 mL, 0.1 mol). The resulting yellow solution was stirred overnight. 3-Bromopropionic acid (15.3 g, 0.1 mol) was added dropwise to the yellow solution and the mixture stirred overnight. The reaction mixture was acidified by the addition of concentrated hydrochloric acid and the resulting precipitate was collected using a Bucher funnel and flask. The product was washed with deionized water and then dried *in vacuo* overnight. Yield: ca. 90 % ¹H NMR (d₆-DMSO) δ (ppm): 2.65 (t, -CH₂-COOH), 3.51 (t, -S-CH₂), 12.5 (s, -COOH). ¹³C NMR (d₆-DMSO) δ (ppm): 32.3 (-CH₂-COOH), 33.0 (-S-CH₂-), 173.0 (C=O), 224.9 (C=S). CHSO elemental microanalysis. Theoretical: C, 33.06 %; H, 3.96 %; O, 25.16 %; S, 37.82 %. Found: C, 33.16 %; H, 3.67%; O, 25.68 %; S, 37.49 %. Mp: 110.2 °C.

Synthesis of 2-(2-carboxyethylsulfanylthiocarbonylsulfanyl)propionic acid (CTA26)

The target compound was prepared in the same manner as **CTA25** except 2-bromopropionic acid was used in place of 3-bromopropionic acid. Yield: ca. 90 %. ¹H NMR (d₆-DMSO) δ (ppm): 1.55 (d, CH₃-CH), 2.74 (t, -CH₂-COOH), 3.59 (t, -CH₂-S-), 4.77 (quar, -S-CH-CH₃(COOH)). ¹³C NMR (d₆-DMSO) δ (ppm): 17.4 (CH₃-CH), 32.5 (CH₂-COOH), 32.9 (-CH₂-S-), 48.9 (-CH-COOH), 172.2 (COOH-CH-), 173.1 (COOH-CH₂-), 222.9 (C=S). CHSO elemental microanalysis. Theoretical: C, 33.06 %; H, 3.96

%; O, 25.16 %; S, 37.82 %. Found: C, 33.18 %; H, 3.75 %; O, 25.72 %; S, 37.35 %. Mp: 126.0 °C.

Synthesis of 2-(2-carboxyethylsulfanylthiocarbonylsulfanyl)-2-methylpropionic acid

(CTA27)

3-Mercaptopropionic acid (10.6 g, 0.1 mol), distilled/deionized water (100 mL) and 50 wt % NaOH solution (16.0 g, 0.2 mol) was added to a round bottom flask equipped with a magnetic stir bar. The solution was stirred for 30 min prior to the dropwise addition of carbon disulfide (6.0 mL, 0.1 mol). The resulting yellow solution was stirred at room temperature overnight. Chloroform (29.9 g, 0.25 mol) and acetone (16.8 g, 0.3 mol) were then added followed by the dropwise addition of 50 wt % NaOH solution (60.0 g, 0.75 mol). Also a small 'pinch' of tetrabutylammonium hydrogen sulfate (TBAHS) was added to aid in phase transfer. The mixture was stirred at room temperature overnight. The mixture was acidified with concentrated hydrochloric acid and the resulting precipitate isolated by filtration with a Buchner funnel and flask. The precipitated was washed with distilled/deionized water. The product was then dried *in vacuo* overnight. Yield: ca. 40 %. ¹H NMR (d₆-DMSO) δ (ppm): 1.59 (s, C(CH₃)₂), 2.62 (t, -CH₂-COOH), 3.43 (t, -CH₂-S), 12.7 (s, -COOH). ¹³C NMR (d₆-DMSO) δ (ppm): 25.5 (-C(CH₃)₂), 32.0 (-CH₂-S-), 35.0 (COOH-CH₂-), 57.1 (-S-C(CH₃)₂COOH), 173.0 (C=O), 173.6 (C=O), 222.1 (C=S). CHSO elemental microanalysis. Theoretical: C, 35.80 %; H, 4.51 %; O, 23.85 %; S, 35.84 %. Found: C, 36.52 %; H, 4.54 %; O, 25.82 %; S, 33.12 %. Mp: 179.5 °C.

*Homopolymerization of *n*-butyl acrylate under bulk conditions*

Below is a typical procedure for the homopolymerization of *n*-butyl acrylate under bulk conditions at 70 °C employing CTA26 as the RAFT agent:

n-Butyl acrylate (12.8 g, 0.1 mol), CTA26 (108 mg, 0.427 mmol) and AIBN (~4.0 mg, 2.1×10^{-2} mmol) was added to a 50 mL round bottom flask equipped with a magnetic stir bar. The mixture was stirred for at least 30 min to ensure complete dissolution of CTA26 and AIBN in the monomer. Aliquots (2.0 mL) were transferred to 10 different vials (10.0 mL capacity) which were then sealed with rubber septa. Each vial was purged with nitrogen for 15 min. The vials were then immersed in a pre-heated oil bath at 70 °C. Vials were removed at various time intervals and polymerization halted by immediate exposure to air and cooling with liquid nitrogen. The samples were analyzed using a combination of size exclusion chromatography (SEC) and NMR spectroscopy.

Block copolymerization

Below is a typical procedure for the block copolymerization of *n*BA under bulk conditions at 70 °C employing a poly(*n*-butyl acrylate) macro CTA derived from CTA26:

n-Butyl acrylate (6.4 g, 0.05 mol), macro-CTA (1.85 g, 7.12×10^{-2} mmol), and AIBN (~1.0 mg) was added to a 50.0 mL round-bottomed flask equipped with a magnetic stir bar. The mixture was purged with dry N₂ for approximately 20 min prior to being immersed in a pre-heated oil bath at 70 °C. The copolymerization was allowed to proceed for ~1 h prior to being terminated by exposure to air and quenching in liquid nitrogen.

Analysis tools

^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker 300 53 mm spectrometer in either deuterated chloroform (CDCl_3) or deuterated dimethylsulfoxide (d_6 -DMSO). CHSO elemental microanalyses were performed by Quantitative Technologies Inc. Polymer molecular weights, molecular weight distributions, and polydispersity indices were determined by SEC in *N,N*-dimethylformamide (DMF)/ NEt_3 at a flow rate of 1.0 mL min^{-1} and $40 \text{ }^\circ\text{C}$. The SEC system was comprised of a Waters 515 HPLC pump, Waters 2410 RI detector, column oven, and a PolymerLabs PLgel $5\mu\text{m}$ MIXED-C $300 \times 7.5 \text{ mm}$ column (linear molecular weight range: $200 - 2,000,000 \text{ g/mol}$). The column was calibrated with a series of narrow molecular weight distribution poly(methyl methacrylate) standards (PolymerLabs). Data were analyzed with the Waters Empower software package.

Results and Discussion

Trithiocarbonates (TTC's) are a family of compounds that are effective mediating agents for the controlled RAFT polymerization of certain monomer classes. In particular, TTC's are especially applicable to the controlled polymerization of styrenic, acrylic, and acrylamido derivatives.^{201,202,351-353} Recently, for example, we have been examining TTC's as RAFT agents for the controlled polymerization of acrylamide,²⁹⁹ *N*-isopropylacrylamide,²¹⁰ and other structurally similar monomers. As part of our continuing studies, we decided to extend our monomer pool and examine the RAFT polymerization of commercially important functional acrylic species. Several efficient TTC's, such as **CTA22-CTA24** (Figure III-1) have been reported in the literature.^{202,352}

However, to date there are no reports of the systematic evaluation of TTCs in which the nature of the substituents (Z and R groups) is varied. In these preliminary studies we designed and synthesized three new TTCs, namely **CTA25**, **CTA26**, and **CTA27** (Figure III-1) and compared them to the previously reported species **CTA22** and **CTA24**. This was motivated by the desire to i) conduct a fundamental study examining the systematic change in trithiocarbonate R-group structure, i.e. primary vs. secondary vs. tertiary alkyl species, ii) to prepare novel dicarboxylic acid functional TTCs capable of yielding α,ω -functional polymers, and iii) to prepare novel water-soluble RAFT agents (although this initial screening describes their effectiveness in polymerizations of a model hydrophobic acrylic monomer under bulk conditions).

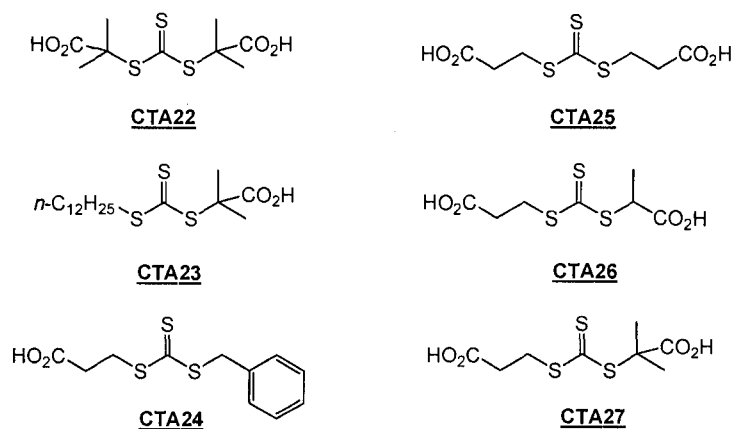


Figure III-1. Chemical structures of the trithiocarbonates evaluated for the RAFT polymerization of *n*-butyl acrylate.

Design Rationale

While **CTA22** and **CTA24** have proven to be effective RAFT agents, there are some drawbacks to each of these species, at least with respect to the research aims as outlined above. **CTA22**, while readily water-soluble, is symmetrically substituted about

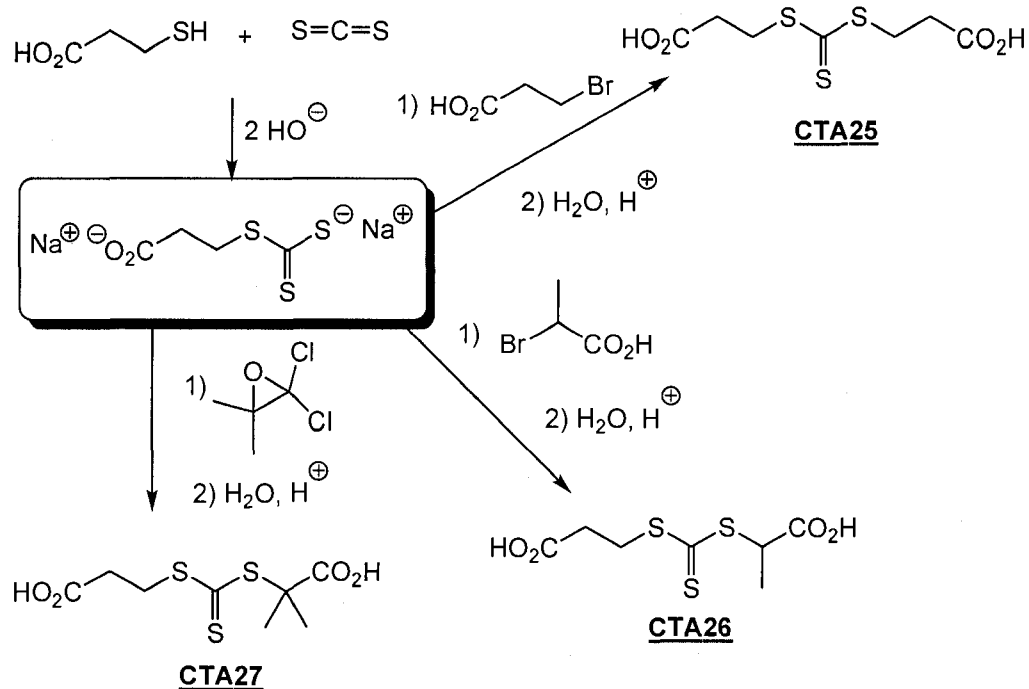
the TTC core (i.e. the Z and R groups are identical), and therefore acts as a difunctional RAFT agent with chain propagation occurring in both directions from the central TTC functional group. As such it offers a very convenient route to ABA triblock copolymers but is of limited use for the preparation of AB diblock copolymers unless one cleaves the trithiocarbonate functionality post-polymerization, i.e. includes an additional synthetic step. **CTA24** was designed to facilitate chain growth in only one direction. This is by virtue of the unsymmetrical nature of the substitution about the TTC core. In this instance we can consider the CO₂HCH₂CH₂S- species as the Z-group and the benzylic functionality as the R group. Fragmentation of **CTA24** is clearly favored in the direction that yields the more stable benzylic radical. While **CTA24** is an effective RAFT agent^{335,352} and is further highlighted here (vide infra), it does suffer from reduced aqueous solubility by virtue of the hydrophobic benzylic fragment. Additionally, it does not yield α,ω -dicarboxylic acid functional materials. These apparent ‘drawbacks’ for **CTA22** and **CTA24** do not make these ineffective RAFT agents; on the contrary, they merely do not meet the design criteria of being highly water-soluble and capable of yielding dicarboxylic acid telechelic AB diblock copolymers directly. **CTA25-CTA27** were designed specifically to address the issue of preparing such telechelic materials while simultaneously evaluating the effect of the nature of the ‘R’ group. In all instances the Z group can be considered to be the CO₂HCH₂CH₂-S- species, while the R group is varied from a primary (**CTA25**) to a secondary (**CTA26**) to a tertiary (**CTA27**) functional group. Since one important factor determining the overall effectiveness of RAFT agents is the ease of fragmentation of the R-group, we anticipate that, all other

things being equal, the effectiveness of CTA25-CTA27 should increase in the order CTA25 < CTA26 < CTA27.

Trithiocarbonate synthesis.

CTA22 and CTA24 were prepared according to literature procedures.^{202,335}

CTA25, CTA26, and CTA27 were synthesized according to Scheme III-1. Initially, the disodium salt of 3-dithiocarboxysulfanylpropionic acid was prepared from the reaction of the disodium salt of 3-mercaptopropionic acid with carbon disulfide. CTA25, CTA26, and CTA27 were then obtained from the reaction of the disodium salt of 3-dithiocarboxysulfanylpropionic acid with 3-bromopropionic acid, 2-bromopropionic acid and 2,2-dichloro-3,3-dimethyloxirane respectively. The use of the disodium salt of 3-dithiocarboxysulfanylpropionic acid as a nucleophilic reagent is particularly advantageous since it can be prepared on a large scale and is readily isolated and stored for extended periods. The structures of these novel TTCs were confirmed by a combination of NMR spectroscopy and elemental microanalysis.



Scheme III-1. The synthetic outline for the preparation of CTA25, CTA26, and CTA27.

Evaluation of trithiocarbonates in the polymerization of *n*-butyl acrylate.

Having prepared CTA22, CTA24, and CTA25-CTA27 their effectiveness as RAFT agents was compared using the model acrylic monomer *n*-butyl acrylate (nBA). In particular we were concerned with the effect of TTC structure, and the ratio of the initial TTC concentration to the initiator concentration ($[TTC]_0:[AIBN]_0$), on both the kinetic and number-average molecular weight (M_n) profiles. Table III-1 summarizes the experimental variables in this series of experiments.

Table III-1. Summary of $[\text{TTCl}]_0:[\text{I}]_0$, experimental molecular weights, polydispersity indices, and conversions for the trithiocarbonate-mediated homopolymerizations of *n*-butyl acrylate at 70 °C under bulk conditions.

CTA	$[\text{CTA}]^a:[\text{I}]^b=5:1$				$[\text{CTA}]^a:[\text{I}]^b=10:1$				$[\text{CTA}]^a:[\text{I}]^b=20:1$			
	% Conv ^c	M_n (g/mol) ^d	M_w/M_n ^d	% Conv ^c	M_n (g/mol) ^d	M_w/M_n ^d	% Conv ^c	M_n (g/mol) ^d	M_w/M_n ^d	% Conv ^c	M_n (g/mol) ^d	M_w/M_n ^d
<u>CTA22^e</u>	21	5,800	1.20	15	3,600	1.19	10	2,700	1.18			
	46	8,700	1.15	43	9,200	1.13	33	9,200	1.12			
	67	11,400	1.14	60	11,400	1.13	62	12,300	1.12			
<u>CTA24</u>	83	13,200	1.15	75	12,500	1.15	92	15,300	1.15			
	18	6,200	1.17	13	4,200	1.18	16	4,200	1.14			
	39	10,700	1.16	33	9,900	1.15	27	8,000	1.12			
<u>CTA25</u>	53	14,700	1.14	50	14,100	1.14	65	18,200	1.10			
	65	17,400	1.17	75	20,700	1.15	71	19,300	1.15			
$M_n=200,000\sim 300,000$ g/mol and $M_w/M_n=1.90\sim 2.10$												
<u>CTA26</u>	20	7,200	1.15	27	8,600	1.13	9	3,000	1.14			
	36	12,900	1.14	47	13,200	1.17	33	9,600	1.12			
	65	18,800	1.14	60	16,900	1.16	69	17,900	1.09			
<u>CTA27^e</u>	76	19,800	1.15	78	19,500	1.15	75	21,100	1.13			
	18	6,700	1.16	24	7,200	1.15	75	3,700	1.16			
	50	14,200	1.15	46	14,000	1.14	14	8,700	1.12			
	68	16,300	1.16	58	16,700	1.14	43	12,500	1.13			
	86	19,700	1.19	73	19,700	1.15	67	18,300	1.15			

a) $[\text{CTA}]$ = concentration of RAFT chain transfer agent

b) $[\text{I}]$ = concentration of initiator

c) As determined by $^1\text{H NMR}$ spectroscopy

- d) As determined by size exclusion chromatography in *N,N*-dimethylformamide at 40 °C. The system was calibrated with narrow molecular weight distribution poly(methyl methacrylate) standards
- e) 5 vol % *N,N*-dimethylformamide was added to aid in the dissolution of the TTC.

In the initial series of experiments, the five TTCs were evaluated at 70 °C and a $[\text{TTC}]_0:[\text{AIBN}]_0$ of 20:1. In all instances the target molecular weight at quantitative conversion was 30,000 g/mol ($[\text{nBA}]:[\text{TTC}] = 234$). Polymerizations were conducted under bulk conditions, although in the case of **CTA22** and **CTA27** a small amount (~5 vol %) of DMF was required to aid in the dissolution of the TTC. Figure III-2 shows the pseudo first order kinetic plots for the nBA homopolymerizations employing **CTA22** and **CTA24** (A), **CTA25-CTA27** (B), as well as the corresponding M_n and M_w/M_n vs. conversion plots (C and D).

For **CTA22** and **CTA24** the kinetic profiles are very similar with the slopes (i.e. the apparent rate constant, K_{app}) being essentially identical. For **CTA24** the linear fit passes through the origin whereas there appears to be a small induction period of ca. 5 min in the case of **CTA22**. Such induction periods are not uncommon in dithioester-mediated RAFT systems.^{42,58,124,236,246,253} In contrast, such induction periods are not typical of TTC-mediated systems and we ascribe the observed small induction period here to a small amount of residual oxygen. Regardless of the cause, given the close similarity of the kinetic profiles it is apparent that the main RAFT equilibrium is rapidly established. In the case of **CTA25-CTA27**, the kinetic profiles are also near-identical with all fits passing through the origin. Indeed, the kinetic profiles of the new TTCs as well as **CTA22** and **CTA24** are all similar indicating that from a purely kinetic standpoint all the RAFT agents perform equally well, at least under the initially screened conditions. The experimentally determined apparent first order dependence on monomer concentration is interesting since alkyl acrylates, under normal stationary free radical polymerization conditions, are well-known to deviate from this first-order dependence

with $[M]$ exponents in the range 1.4-1.8. Such deviations have been rationalized in terms of intramolecular chain transfer to polymer as recently discussed by Nikitin and Hutchinson.³⁵⁴ However, the kinetic plot is not expected to be sensitive to the occurrence of such chain transfer reactions.

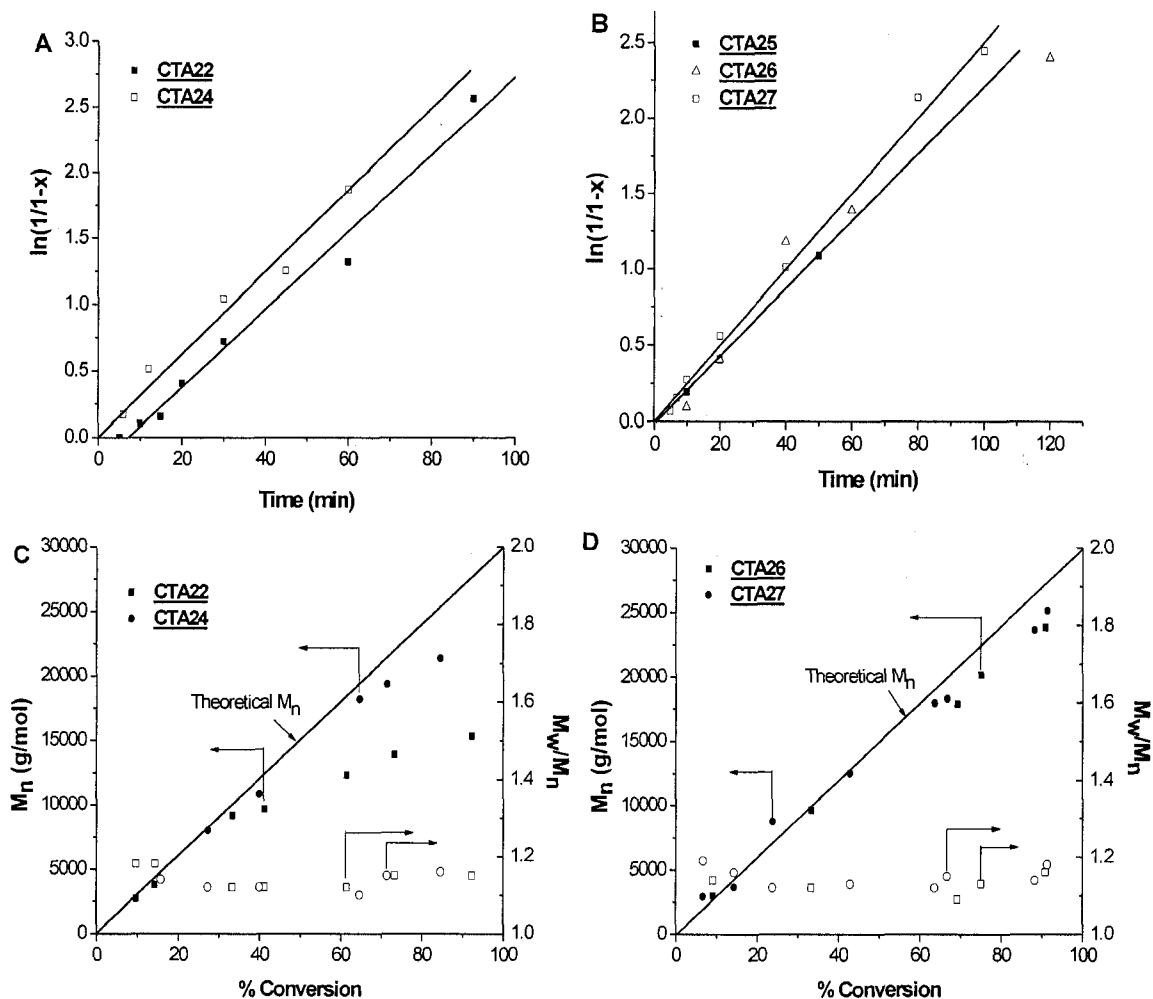


Figure III-2. The pseudo first order kinetics plots for CTA22, CTA24 (A) and CTA25-CTA27 (B) for *n*-butyl acrylate at 70 °C under bulk conditions with $[TTC]_0:[AIBN]_0 = 20:1$, and the corresponding M_n and M_w/M_n vs. conversion plots (C and D).

This near-uniformity in the kinetic profiles is not, however, equally manifest with respect to the molecular weight control in these polymerizations. In the case of CTA22

excellent agreement is observed between the theoretical and observed M_n up to ca. 30% conversion after which a significant deviation to lower M_n values is observed. This negative deviation occurs simultaneously with the appearance of a much higher molecular weight species which is clearly visualized in the SEC traces, see Figure III-3, this higher molecular weight species has a poly(methyl methacrylate) equivalent M_n of > 200,000 g/mol.

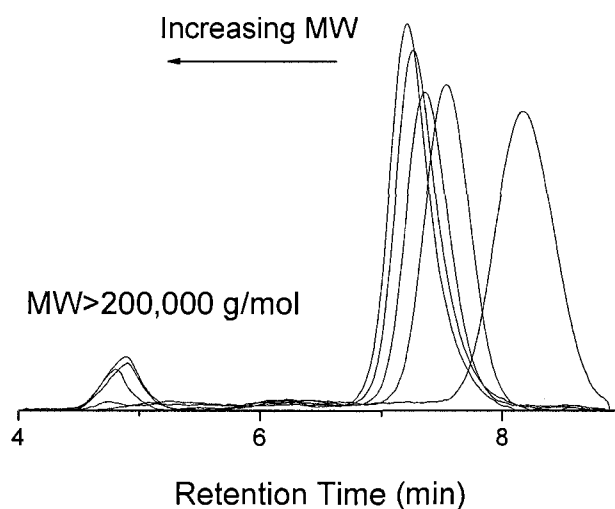


Figure III-3. SEC traces (RI signal) for the bulk homopolymerization of nBA at 70 °C with CTA22 with $[\text{CTA22}]_0:[\text{AIBN}]_0 = 20$.

Most previous studies involving the use of CTA22 in acrylate polymerizations have typically targeted very low molecular weights. For example, in their report of the use of CTA22 and CTA23 as mediators in acrylic polymerizations, Lai and coworkers reported experimentally determined molecular weights in the range of ~1,100 – 6,800 g/mol for monomers such as ethyl and butyl acrylates.²⁰² In the single example where a higher molecular weight ethyl acrylate homopolymer was targeted, molecular weight

control was lost and the resulting polydispersity index was 1.43. The lower than predicted molecular weights observed here for the main population of propagating chains can clearly be attributed to the presence of the higher molecular weight species. One possible explanation is that, upon reaching a critical degree of polymerization, the central trithiocarbonate core becomes so sterically hindered that the addition of a polymeric propagating chain across the C=S bond becomes difficult. Figure III-4 shows a schematic representation as well as a space-filling model of a polynBA 22-mer ($M_n \sim 2,800$ g/mol). The accessibility to the S atom of the central C=S bond apparently becomes somewhat reduced as the DP_n increases. However, the actual degree of hindrance is anticipated to be a function of adopted chain conformation which in turn is expected to be a function of monomer structure and polymerization conditions, i.e. bulk vs. solution. As such the critical chain length at which addition to the C=S bond by a polymeric macroradical starts to become difficult may well be highly system dependent. However, further studies in which a closer examination of the effect of targeted DP_n and the resulting overall control of molecular weight will be necessary to confirm this hypothesis.

However, as the accessibility to the TTC core drops, especially for higher molecular weight polymer chains, the free propagating chains have the ability to grow in an uncontrolled fashion to much higher-than-predicted molecular weights. Since the radical concentration (propagating chains in this case) is dictated by [AIBN] and since $[CTA22]_0:[AIBN]_0 = 20$ only a very small number of these high molecular weight species are present. Even so, only a few chains need propagate to high molecular weight to effect the observed molecular weight deviation for the main population of lower molecular weight chains. The CTA24-mediated polymerization did proceed with good

control over the molecular weight with the experimentally determined values being close to the theoretically expected values based on the fractional conversion. The evolution of M_n with conversion was linear with little/no deviation from the expected M_n values until higher conversions were attained. The minor deviations at these higher conversions may be due to the fact that the experimentally determined molecular weights are not absolute but are relative to poly(methyl methacrylate) standards. However, we cannot dismiss the possible occurrence of undesirable chain transfer reactions (either to monomer or polymer) as a possible cause for the observed deviation.³⁵⁵⁻³⁵⁷ Indeed, it is now well established that alkyl acrylates readily undergo both inter- and intramolecular chain transfer to polymer even at sub-ambient temperatures. The occurrence of such side-reactions is expected to manifest itself in the M_n vs. conversion plot as a negative deviation (lower apparent molecular weight).³⁵⁶ However, the generally good kinetic and molecular weight profiles observed for **CTA24** are consistent with previous reports detailing the use of this TTC in RAFT polymerizations. For both **CTA22** and **CTA24**, the polydispersities decrease with increasing conversion to final values in the range of ~ 1.10-1.20, well below the theoretical lower limit of 1.50 for a normal free radical polymerization and in the range typical for RAFT-prepared (co)polymers.

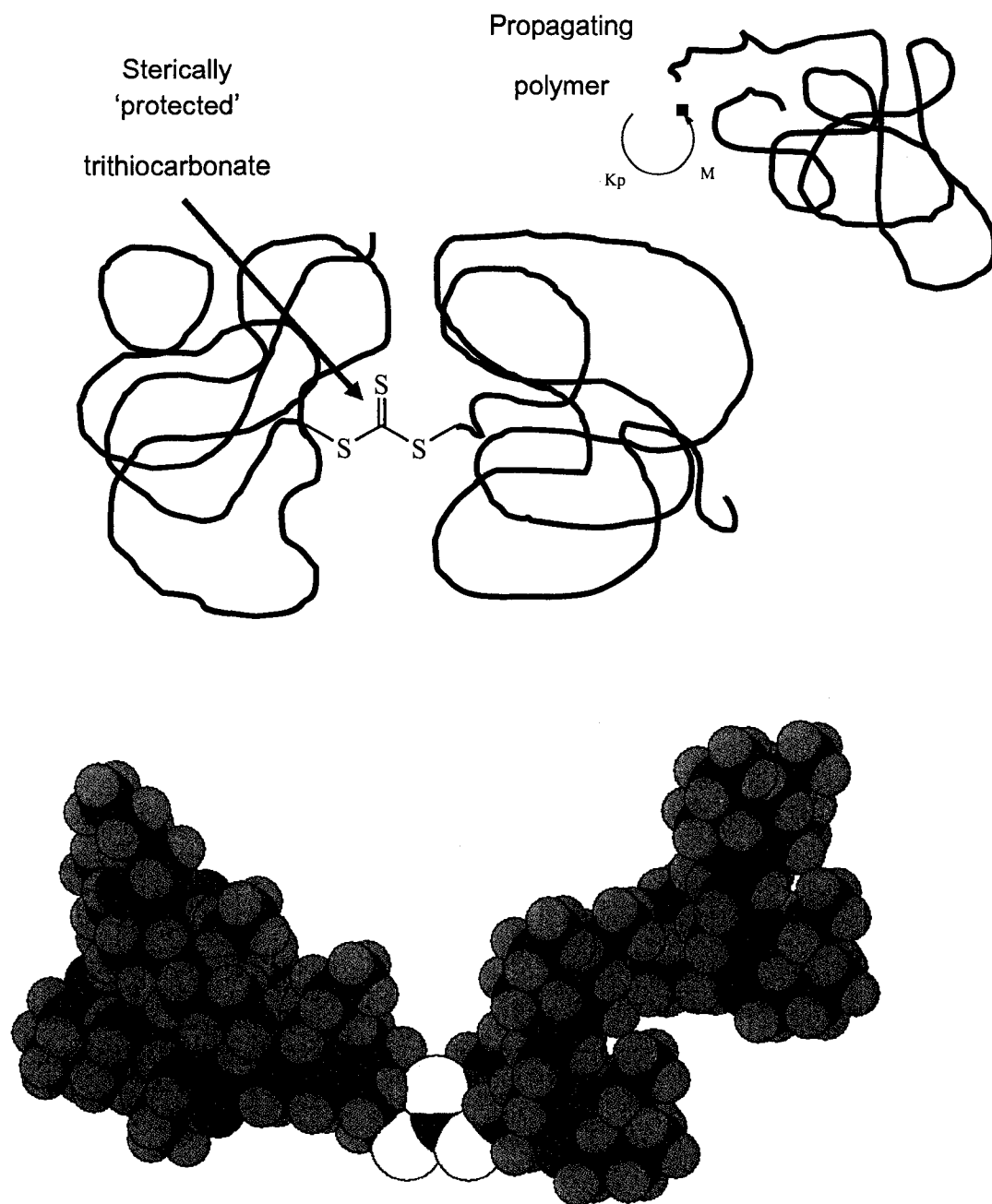


Figure III-4. Schematic representation and space filling model demonstrating the proposed steric shielding of the TTC core in CTA22-mediated polymerizations.

Figure III-2D shows the M_n and M_w/M_n vs. conversion profiles for **CTA26** and **CTA27**. The molecular weight data for **CTA25** is not included since no control was observed. Figure III-5 shows the SEC traces (RI signal) for the **CTA25**-mediated polymerization of nBA. The behavior of the nBA polymerization in the presence of **CTA25** is clearly much more complicated than in the case of the other TTCs. The resulting molecular weight distribution is complex with, at the very least, a trimodal distribution being observed. Additionally, we note that the retention times for all the species in the molecular weight distribution remain essentially constant with their concentration simply increasing with increasing conversion. This is a feature more closely associated with conventional free radical polymerization behavior.

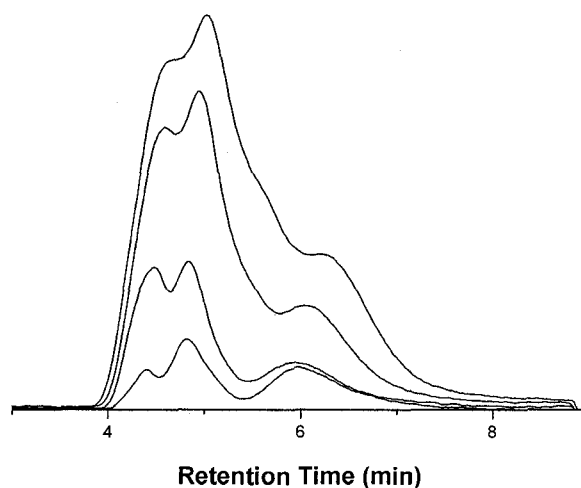
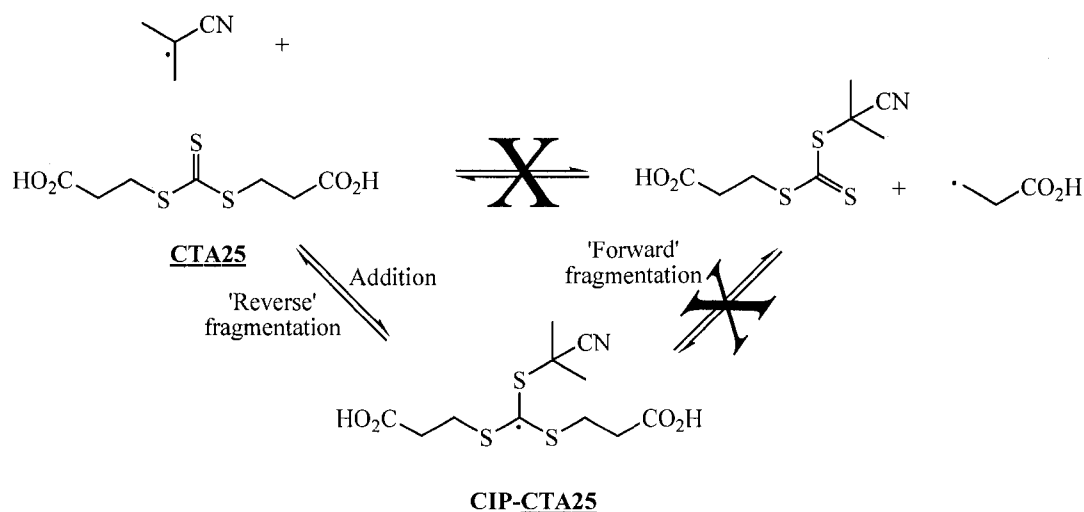


Figure III-5. SEC traces (RI signals) for the bulk homopolymerization of nBA at 70 °C with **CTA25** with $[\text{CTA25}]_0 : [\text{AIBN}]_0 = 20$.

The inability of **CTA25** to effectively mediate the polymerization of nBA is not surprising when one considers the nature of the intermediate radical formed from the

addition of either a primary (AIBN-derived) radical or oligomeric nBA radical to the C=S, see Scheme III-2.



Scheme III-2. Possible addition-fragmentation pathways for the **CTA25**-mediated polymerization of nBA using AIBN as the source of primary radicals.

The addition of a cyanoisopropyl (CIP) radical to **CTA25** will yield the intermediate radical labeled **CIP-CTA25**, Scheme III-2. As with any RAFT agent these addition steps are reversible. However, to function as effective mediating agents, fragmentation of the **CIP-CTA25** intermediate radical must be favored in the direction of the R group – indeed this is obviously a prerequisite for effective molecular weight control, i.e. there must be a fine balance between the forward and reverse rates of addition and fragmentation and the rates of reinitiation and propagation for effective control. However, in the case of **CTA25**, the desired ‘forward’ fragmentation will yield a *primary* alkyl radical, i.e. the $\text{CO}_2\text{HCH}_2\text{CH}_2\cdot$ radical species. A much lower energy fragmentation pathway exists, namely the ‘reverse’ fragmentation of **CIP-CTA25** to regenerate the *tertiary* CIP radical and **CTA25**. Clearly, of these two possible

fragmentation pathways, the undesirable ‘reverse’ fragmentation will be favored. As such, the cyanoisopropyl radical is most likely the species *primarily* responsible for chain initiation. While Scheme III-2 depicts an extreme case in which there is no forward fragmentation, given the complex resulting molecular weight distribution observed in Figure III-5, it seems likely that some chains are initiated as a result of the fragmentation in the preferred forward direction. A recent ab initio study by Coote and Radom³⁵⁹ describing the effect of alkyl substituents (Z' in $\text{CH}_3\text{SC}(\text{OZ}')\text{S}-\text{CH}_2\text{OCOCH}_3$) in the xanthate-mediated polymerization of vinyl acetate clearly demonstrated that fragmentation of intermediate radicals (at least for the series of xanthates evaluated) is not only a function of resulting radical stability but also of reactant/product stabilities and can, in certain instances, lead to an unexpected fragmentation pathway as a result of this balance. However, it still seems likely that the majority of chains are initiated by AIBN-derived primary radicals. Since the $[\text{AIBN}]$ is much lower than the $[\text{CTA25}]$, molecular weight control is also lost, Table III-1. This non-ideal RAFT behavior may be compounded by the fact that even after formation of nBA oligomers, addition of these radical species to **CTA25** yields a radical intermediate with x2 *primary* R groups and a *secondary* oligomeric nBA species, thus still favoring ‘reverse’ fragmentation, although not, most likely, to the same extent as in the case of an AIBN-derived primary radical. Indeed the degree of R-group fragmentation might be expected to increase as more primary radicals are converted to nBA oligomeric species. While the kinetic plot (Figure III-2B) for the **CTA25**-mediated homopolymerizations indicated pseudo-first order kinetics (a feature often cited as being indicative of a controlled/living polymerization³⁵⁹) this alone clearly does not confirm controlled polymerization, as is evident in the

molecular weight vs. conversion profile, but merely indicates a constant number of active species. Indeed, such pseudo-first order kinetic behavior is also expected in a conventional free radical polymerization under steady state conditions.³⁶⁰ All things considered, therefore, we would advise against the use of CTA25 in conjunction with AIBN as an effective CTA/initiator combination for the polymerization of nBA.

In contrast to CTA25, both CTA26 and CTA27 are very effective mediating agents (Figure III-2D) yielding homopolymers with both good molecular weight control and low polydispersities. Indeed, the ability of these two new TTCs to control the molecular weight is comparable, if not superior to that of CTA24. As with CTA24 the M_n vs. conversion plots are linear and show only small deviations from the theoretical M_n at $\geq 90\%$ conversion. Again, these small deviations could be due to the occurrence of undesirable inter or intramolecular chain transfer reactions to polymer as discussed above. The enhanced control observed in the case of CTA26 and CTA27 vs CTA25 is clearly related to the now favored 'forward' fragmentation of intermediate radicals, i.e. TTC activation, which is a direct result of the secondary and tertiary nature, and (meth)acrylate like structure, of the R groups in CTA26 and CTA27 respectively.

Effect of $[TTC]_0:[AIBN]_0$

Having demonstrated that both CTA26 and CTA27 have the ability to mediate nBA homopolymerizations at least as effectively as other previously reported TTCs we decided to examine the effect of $[TTC]_0:[AIBN]_0$ on the polymerization kinetics for these two species, see Table III-1. This ratio can often be a critical factor in determining the overall success of a RAFT polymerization at least with respect to control over the

molecular weight and molecular weight distribution. In the case of dithioesters a typical $[\text{CTA}]_0:[\text{I}]_0$ ratio is 5:1. Lower ratios, while often resulting in faster polymerizations may be less controlled, whereas higher ratios may afford better overall control but often at the expense of polymerization time.²⁴⁶

Figure III-6 shows the pseudo-first order kinetic plots for the homopolymerization of nBA at 70 °C and ratios of 10:1, and 5:1 for both **CTA26** (A) and **CTA27** (B). The plots in all instances are essentially linear with the best fits passing through the origin. As expected, in both instances the polymerizations proceed more quickly at lower $[\text{TTC}]_0:[\text{AIBN}]_0$ ratios. This is consistent with previous reports on the effect of $[\text{TTC}]_0:[\text{I}]_0$ for TTC-mediated polymerizations. For example, Convertine et al. recently described the room temperature polymerization of *N*-isopropylacrylamide employing **CTA23** in DMF and clearly demonstrated the kinetic effect of changing the ratio of **CTA23** to the azo initiator with lower ratios resulting in faster polymerizations.

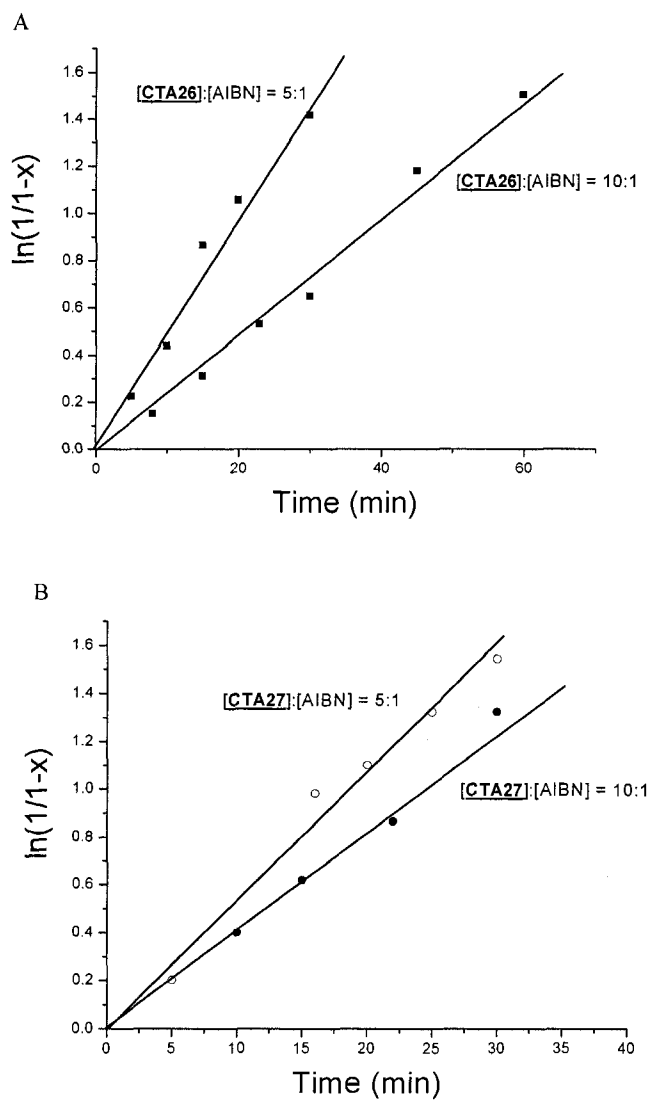


Figure III-6. Pseudo first order kinetic plots for the bulk homopolymerization of nBA at 70 °C employing CTA26 and CTA27 at $[TTC]_0:[AIBN]_0 = 5$ and 10.

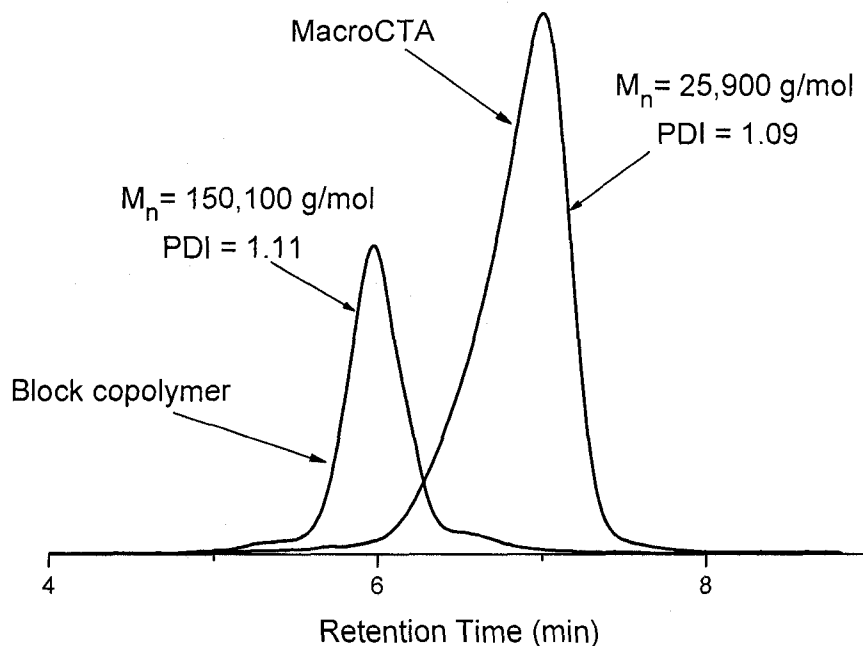


Figure III-7. SEC traces (RI signals) for a poly(*n*-butyl acrylate) homopolymer ($M_n = 25,900$ g/mol, $M_w/M_n = 1.09$) prepared with **CTA26** and the resulting nBA-nBA ‘block’ copolymer ($M_n = 150,100$ g/mol, $M_w/M_n = 1.11$).

Perhaps the most telling indicator of a controlled/“living” polymerization is the ability to prepare block copolymers by sequential monomer addition or by isolating the first block, purifying it, and then employing it as a macro-initiating species (or macroRAFT agent in this case) for the subsequent block copolymerization. As such, and to demonstrate the full utility of these new TTCs, we have conducted a self-blocking experiment, i.e. polymerized nBA from a polynBA homopolymer, employing a homopolymer derived from **CTA26** as the macroRAFT agent. Figure III-7 shows the SEC traces (RI signal) for the macro-RAFT agent as well as the resulting ‘block’ copolymer. The macro-RAFT agent has a M_n of $\sim 26,000$ g/mol and polydispersity index

of 1.09 with the resulting block copolymer having an experimentally determined M_n of ~150,000 g/mol and polydispersity index of 1.11. The SEC traces indicate extremely high reinitiation efficiency with the resulting block copolymer possessing an essentially symmetrical unimodal molecular weight distribution. There is some detectable presence of lower molecular weight species (small hump on the right of the main block copolymer peak) which we ascribe to macro-RAFT agent impurity, and there is likewise a small higher molecular weight impurity which is most likely a result of undesirable termination reactions. However, both are present in very small quantities relative to the main block copolymer species and thus we conclude that the overall blocking efficiency is very high.

Summary/Conclusions

Here we have reported the synthesis of three new trithiocarbonates (**CTA25**-**CTA27**) in which the nature of the substitution about the TTC functional group has been systematically varied. We have subsequently evaluated their effectiveness as mediating agents in the RAFT homo- and block polymerization of *n*-butyl acrylate. Both **CTA26** and **CTA27**, TTCs with potential secondary and tertiary alkyl leaving (R) groups, perform as well as previously reported TTCs and yield poly(*n*-butyl acrylate) homopolymers with good molecular weight control and low polydispersities. **CTA25** was shown to be ineffective by virtue of the proposed favored “reverse” fragmentation pathway as opposed to the required “forward” pathway required for effective molecular weight control. The use of **CTA22** as a mediating agent for the homopolymerization led to bimodal molecular weight distributions with a significantly high molecular weight impurity. We speculate that this arises due to a steric crowding effect of the central C=S

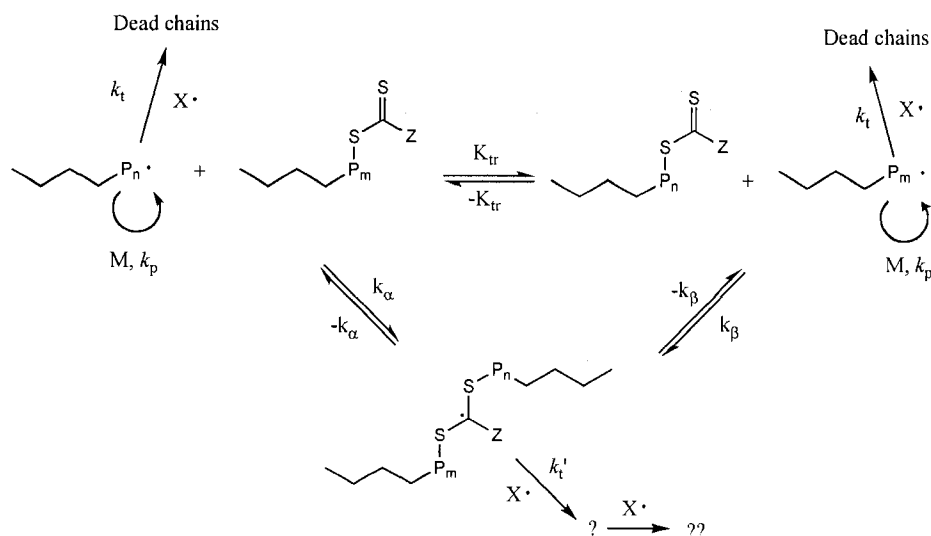
bond making the addition reaction difficult and resulting in some degree of uncontrolled polymerization. However, further experiments are required to prove/disprove this. The effect of $[TTC]_0:[AIBN]_0$ was determined for **CTA26** and **CTA27** and it was shown that the polymerizations were faster at the lower $[TTC]_0:[AIBN]_0$ ratios. Finally, we demonstrated the ability to form AB 'diblock' copolymers with nBA with high re-initiation efficiency employing a poly(*n*-butyl acrylate) macroRAFT agent. The synthesis of these new trithiocarbonates now allows the facile preparation of dicarboxylic acid telechelic poly(alkyl acrylates) under straightforward conditions. We are currently extending our studies to the preparation of more highly functional materials.

CHAPTER IV

RAFT POLYMERIZATION OF STYRENIC-BASED PHOSPHONIUM MONOMERS, AND A NEW FAMILY OF WELL-DEFINED STATISTICAL AND BLOCK POLYAMPHOLYTES

Introduction

The ability to prepare polymeric materials with controllable molecular characteristics has undergone significant advances in the past decade.³⁶¹ For example, since its disclosure in the open-literature in 1998 by researchers at CSIRO,^{99,223} reversible addition-fragmentation chain transfer (RAFT) radical polymerization, Scheme IV-1, has proven itself to be an extremely versatile synthetic technique that facilitates the controlled polymerization of a wide range of functional monomers under a broad range of experimental conditions.³⁶²⁻³⁶⁶ One particularly useful feature of RAFT relates to its application for the synthesis of water-soluble/dispersible (co)polymers (WSPs) under homogeneous conditions in either organic or directly in aqueous media.^{57,362,363} For example, RAFT has been successfully employed for the synthesis of (co)polymers based on the (meth)acrylamido,^{208,210,367-372} (meth)acrylic,^{257,370} and styrenic families^{50,61,370,373} of monomers containing neutral,^{50,208,210,246,253,257,368,374-377} anionic,^{58-61,372} cationic,^{61,255,373,378,379} and zwitterionic (betaine)^{122,124,298,370} hydrophilic functionality. Aside from the choice of monomeric substrate, a wide range of RAFT mediating agents^{199,213} (RAFT CTAs) have likewise been evaluated for the preparation of WSPs.³⁶² All of the major families of RAFT CTAs have been employed including derivatives of trithiocarbonates, dithioesters, xanthates, and dithiocarbamates.



Scheme IV-1. A simplified RAFT mechanism.

Within the family of WSPs cationic, or potentially cationic, materials are particularly interesting due to their varied aqueous solution properties and potential applications.³⁸⁰ To date, a wide range of cationic/amine-containing substrates from various monomer families have been polymerized via RAFT in both aqueous and non-aqueous media.³⁶² For example, one of the earliest reports outlining the controlled polymerization of amine/ammonium-containing substrates was by Mitsukami et al.⁶¹ who described the synthesis of AB diblock copolymers of *N,N*-dimethylbenzylvinylamine (DMBVA, **M59**) and the permanently cationic species (*ar*-vinylbenzyl)trimethylammonium chloride (VBZ, **M62**). More recently, Mitsukami and coworkers³⁷³ reported the synthesis of a series of the same styrenic-based amine/ammonium block copolymers⁶¹ and conducted detailed aqueous solution studies of these materials as a function of solution pH and clearly demonstrated the effect of copolymer composition and architecture (block vs. statistical structures) on the size of the pH-induced nano-sized supramolecular assemblies. Sumerlin et al.⁵⁰ reported the synthesis and aqueous solution

properties of pH-responsive copolymers comprised of *N,N*-dimethylacrylamide (**M74**) with DMBVA (**M59**) and likewise demonstrated the ability of such copolymers to undergo reversible pH-induced supramolecular self-assembly as well as the ability to form novel core-crosslinked polymer aggregates. Styrenic derivatives are not the only types of amine/ammonium monomers that have successfully polymerized in a controlled manner under RAFT conditions. (Meth)acrylamido and (meth)acrylate substrates, such as 2-(dimethylamino)ethyl methacrylate (DMAEMA, **M87**)³⁷⁹ and *N*-[3-(dimethylamino)propyl]-methacrylamide (**M105**) have also been successfully homo- and copolymerized in both aqueous and non-aqueous media. What is clear, however, is that all cationic monomers that have so far been polymerized via RAFT have contained tertiary *amine* and/or quaternary *ammonium* functional group(s).

A more specialized, and complex, family of ionic materials are polyampholytes (PAMs),^{67,81,103,381} which are polyelectrolytes that contain, or potentially contain, both cationic and anionic residues located on different repeat units, in contrast to the other major family of polyelectrolytes – the polybetaines.^{81,122,124,382} A review of the literature indicates that the cationic building block in all reported synthetic polyampholytes has, likewise, been either an amine or ammonium species while the anionic building block may be a carboxylate or sulfonate species for example. Synthetic examples of such materials have been known since the 1950's,⁸¹ but even today there are relatively few examples of controlled-structure statistical or block PAMs, and many of these are attainable only after recourse to either functional group protection/deprotection protocols or the post-polymerization modification of suitably functional precursor materials.^{81,383-}
³⁸⁵ The *direct* synthesis of polyampholytes, i.e. without resorting to either protecting

group chemistry or post-polymerization modification, has only been reported several times previously. Armes and co-workers⁷¹ described the nitroxide-mediated polymerization of sodium styrenesulfonate (**M61**) in an ethylene glycol/water mixture in which the resulting homopolymer was employed as a macroinitiator for the block copolymerization with various comonomers including 2-vinylpyridine (2VP, **M23**) and **M59** to yield the corresponding block PAMs. Polymerization yields were very low for the **M23** copolymerization but significantly better in the case of **M59** comonomer. More recently, Xin et al.³⁸⁶ reported the RAFT synthesis of AB diblock copolymers of **M87** with sodium acrylate (NaA). **M87** was polymerized first in the presence of cumyl dithiobenzoate with AIBN in anisole to yield homopolymers with well-controlled molecular masses and narrow molecular mass distributions. The poly**M87** homopolymers were then employed as macro RAFT agents for the block copolymerization with NaA directly in water. Block copolymer formation was confirmed via a combination of aqueous size exclusion chromatography, and NMR and FTIR spectroscopies. The aqueous solution properties of the resulting block polyampholytes were also briefly examined.

In light of these limited reports, especially with PAMs prepared in a direct fashion via CRP methods, we decided to examine the feasibility of employing RAFT as a synthetic technique for the direct synthesis of new examples of controlled-structure statistical and block PAMs. We report in this chapter our preliminary results concerning the homopolymerization of styrenic-based cationic *phosphonium* monomers (**M63** and **M106** in Figure IV-1) and 4-vinylbenzoic acid (VBZ, **M62** in Figure IV-1) in aqueous and non-aqueous media using an acid-functional, water-soluble trithiocarbonate CTA

whose synthesis were described in Chapter III.³⁸⁷ We demonstrate the controlled nature of the homopolymerizations of the monomeric substrates as evidenced from the experimentally determined molecular characteristics. Subsequently we show the ability to prepare statistical PAMs with kinetic characteristics different to those of the homopolymerizations of the cationic or **M62** monomers. Finally, we employ phosphonium macroCTAs for the block copolymerization with **M62** to yield the first examples of PAMs with a cationic *phosphonium* building block, and only the second example describing the direct synthesis of such materials via RAFT.

Experimental Part

All reagents were purchased from the Aldrich Chemical Company at the highest purity available and used as received unless stated otherwise. 2-(2-Carboxyethylsulfanyl thiocarbonylsulfanyl) propionic acid (**CTA26**) was prepared according to the method outlined in Chapter III.³⁸⁷ 2,2'-Azobis(2-methylpropionitrile) (AIBN) was recrystallized from methanol and stored in a freezer until needed. 4,4'-Azobis(4-cyanovaleric acid) (V-501) was purchased from Wako Chemicals, recrystallized from methanol and stored in a freezer until needed.

*Synthesis of 4-Vinylbenzyl(trimethylphosphonium) chloride (**M63**)*

To a 500 mL conical flask equipped with a magnetic stir bar was added 4-vinylbenzyl chloride (15.25 g, 0.1 mol) and 100 mL of trimethylphosphine solution (1.0 M in THF). The mixture was then stirred at room temperature for 3 days yielding a white

precipitate. The precipitate was collected by Buchner filtration, washed with THF and dried in vacuo overnight at room temperature. Yield: ca. 85 %.

Synthesis of 4-Vinylbenzyl(triphenylphosphonium) chloride (M106)

To a 500 mL conical flask equipped with a magnetic stir bar was added 4-vinylbenzyl chloride (15.25 g, 0.1 mol), triphenylphosphine (26.20 g, 0.1 mol) and benzene (100 mL). The mixture was then stirred at room temperature for 3 days yielding a white precipitate. The precipitate was collected by Buchner filtration, washed with acetone and dried in vacuo overnight at 40°C. Yield: ca. 80 %.

Synthesis of 4-vinylbenzoic acid (M62)

To a 500 mL round-bottomed flask equipped with a magnetic stir bar was added α -bromo-*p*-toluic acid (19.0 g, 0.088 mol), triphenylphosphine (26.2 g, 0.10 mol), and acetone (200 mL). The flask was then immersed in a preheated oil bath at 60°C and left to stir overnight. Subsequently, the resulting precipitate was isolated by Buchner filtration. To a 1L round-bottomed flask equipped with a magnetic stir bar was added the isolated solid along with formaldehyde (360 mL of a 37 wt% aqueous solution), distilled water (170 mL) and sodium hydroxide (28.0 g, 0.70 mol) dissolved in 170.0 mL of deionized water. The mixture was stirred vigorously for ca. 3 h after which the solution was filtered to remove the precipitated triphenylphosphine oxide. The filtrate was subsequently acidified with conc. HCl and the resulting precipitate isolated as the crude product by Buchner filtration. The crude product was washed with distilled water and subsequently dried in vacuo at room temperature overnight. Yield: 80 %.

Homopolymerization of 4-vinylbenzyl(trimethylphosphonium) chloride (M63)

To a 20.0 mL round bottomed flask equipped with a magnetic stir bar was added M63 (4.0 g, 1.751×10^{-2} mol), CTA26 (34.0 mg, 1.339×10^{-4} mol), V-501 (4.0 mg, 1.429×10^{-5} mol) (target $M_n = 30,000$, [CTA]:[I] = 10) and D₂O (8.0 g). The flask was immersed in an ice-bath and left to stir for ~ 1 h to ensure complete dissolution of all components. Subsequently the contents were split equally between eight small vials that were sealed with rubber septa. Each vial was then purged with N₂ for ca. 30 min while immersed in an ice-bath. After purging, all vials were immersed in a preheated oil bath at 80°C. Vials were removed from the oil-bath at regular time intervals and polymerization terminated via immediate exposure to air and quenching with liquid nitrogen.

Homopolymerization of 4-vinylbenzyl(triphenylphosphonium) chloride (M106)

4-Vinylbenzyl(triphenylphosphonium) chloride was homopolymerized according to the procedure described above for M63.

Homopolymerization of 4-vinylbenzoic acid (M62)

To a 20 mL round-bottomed flask equipped with a magnetic stir bar was added M62 (4.0 g, 2.70×10^{-2} mol), CTA26 (34.0 mg, 1.34×10^{-4} mol), AIBN (4.0 mg, 1.43×10^{-5} mol) (Target $M_n = 30,000$, [CTA]:[I] = 10, 50 wt %), and d₆-DMSO (8.0 g, 0.103 mmol). The flask was immersed in an ice-bath and left to stir for ~ 1 h to ensure complete dissolution of all species. Subsequently, the contents were split equally between eight small vials which were sealed with rubber septa. Each vial was then purged with N₂ for ca. 30 min while immersed in an ice-bath. After purging all vials were immersed in a

preheated oil bath at 80°C. Vials were removed at predetermined time intervals and terminated via immediate exposure to air and quenching with liquid nitrogen.

Statistical copolymerization of M62 and M63

To a 20.0 mL round-bottomed flask equipped with a magnetic stir bar was added M63 (0.607 g, 2.06×10^{-3} mol), M62 (0.393 g, 2.67×10^{-3} mol), CTA26 (8.0 mg, 3.15×10^{-5} mol), V-501 (1.0 mg, 3.57×10^{-6} mmol) (Target $M_n = 30,000$, [CTA]:[I] = 10, at 10 wt %), sodium carbonate (0.28 g, 2.67×10^{-3} mol), and D₂O (10.0 g, 0.50 mol). The flask was immersed in an ice-bath and left to stir for ~ 1 h to ensure complete dissolution. Subsequently the contents were split equally between eight small vials that were sealed with rubber septa. Each vial was then purged with N₂ for ca. 30 min while immersed in an ice-bath. After purging all vials were immersed in a preheated oil bath at 80°C. Vials were removed at predetermined time intervals and terminated via immediate exposure to air and quenching with liquid nitrogen.

Block copolymerization of M63 and M62

To a 50.0 mL round bottomed flask equipped with a magnetic stir-bar was added M63 (2.0 g, 8.76×10^{-3} mol), CTA26 (17.0 mg, 6.70×10^{-5} mol), V-501 (4.0 mg, 1.43×10^{-5} mol) (target $M_n = 30,000$, [CTA]:[I] = 5, at 50 wt %), and distilled water (4.0 g). The mixture was stirred while being purged with nitrogen for ca. 1 h after which it was immersed in a pre-heated oil bath at 80 °C. After 40 min the polymerization was stopped by immediate exposure to air and quenching in liquid nitrogen. The mixture was subsequently dialyzed against distilled water for 2 days with daily changes of water.

Following this, the macro CTA was isolated via lyophilization. To a 100 mL round-bottomed flask equipped with a magnetic stir-bar were added the macro CTA (1.2 g, 5.25×10^{-3} mol), **M62** (0.39 g, 2.63×10^{-3} mol), sodium carbonate (0.279 g, 2.63×10^{-3} mol), V-501 (2.0 mg, 7.14×10^{-6} mol), and D₂O (4.0 g, 0.2 mol). The mixture was then stirred for 1 h while submersed in an ice-bath to ensure complete dissolution. Following this, the solution was transferred to five separate vials; each vial was capped with a rubber septum and then purged with nitrogen for ca. 30 min while immersed in an ice-bath. All vials were then immersed in a pre-heated oil bath at 80 °C. Vials were removed from the oil bath at various time intervals and the polymerization terminated via immediate exposure to air and immersion in liquid nitrogen. The copolymer solution was then dialyzed against deionized water for 2 days prior to being isolated by lyophilization.

*Block copolymerization of **M62** and **M106***

Block copolymers of **M62** and **M106** was prepared in an identical fashion to that described above for the **M62/M63** block copolymer.

*Methylation of poly**M62** homopolymers*

To a 250 mL round bottomed flask equipped with a magnetic stir bar was added poly**M62** (0.5 g, 3.38×10^{-3} mol), sodium carbonate (0.5 g, 4.72×10^{-3} mol), methyl iodide (0.973 g, 1.00×10^{-2} mol), and DMF (30.0 mL). The mixture was subsequently stirred overnight at 50°C. After cooling to room temperature distilled water (200 mL) was added to the reaction flask and the resulting precipitate isolated by Buchner filtration. The precipitate was washed with additional distilled water and then dried in vacuo.

Characterization techniques

^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker 300 53 mm spectrometer in appropriate deuterated solvents or solvent mixtures. FTIR spectra were recorded on a Thermo Nicolet Nexus 470 FTIR spectrometer equipped with a Smart Orbit. Polymer molecular masses, molecular mass distributions, and polydispersity indices were determined by aqueous size exclusion chromatography (ASEC) in 0.1 M Na_2SO_4 /1 vol % acetic acid flow rate of 0.20 mL min^{-1} at ambient temperature. The system was comprised of a Viscotek VE1122 pump, Viscotek VE3580 RI detector, Viscotek T60 dual viscosity/right angle laser light scattering detector, a CATSEC 1000 7μ (50 x 4.6 mm) guard column followed by a series of two CATSEC columns (CATSEC 1000 7μ 250 x 4.6 mm + 100 5μ 250 x 4.6 mm) with a theoretical linear molecular mass range of 200 – 2,000,000 g/mol. The dn/dc for the homopolymers derived from **M63** was determined to be 0.150. Data were analyzed with the Omnisecc Interactive GPC software package. Organic SEC was conducted on a Waters system comprised of a Waters 515 HPLC pump, Waters 2487 Dual λ absorbance detector, Waters 2410 RI detector with a PolymerLabs PLgel 5 μm MIXED-C column, in THF stabilized with BHT at a flow rate of 0.5 ml/min. The column was calibrated with a series of narrow molecular mass distribution poly(methyl methacrylate) standards.

Results and Discussion

One of the most remarkable features of RAFT is its broad applicability with respect to the general monomer classes that are capable of being polymerized in a controlled manner coupled with its tolerance to a wide range of functional groups.

Indeed, the controlled polymerization of monomers bearing anionic, cationic, zwitterionic, and neutral functionality from various monomer families can, and has, been readily achieved in both organic and aqueous environments under both homogeneous and heterogeneous conditions. Interestingly, of all the functional materials which have so far been prepared via RAFT, little attention has been paid to the preparation of zwitterionic materials, and especially to PAMs.⁸¹ Indeed, while synthetic examples of PAMs have been known for over 50 years there are, even today, few reports describing the preparation of well-defined, controlled structure PAMs with, for example, block architectures prepared by any polymerization technique. Given the high monomer/functional group tolerance of RAFT, one might expect it to be the ideal technique to facilitate the direct synthesis of PAMs without recourse to protection/deprotection protocols or post-polymerization modification reactions. Currently there is only one report in the open literature detailing the *direct* synthesis of PAMs via RAFT.³⁸⁶ In light of the sparse literature detailing the RAFT synthesis of PAMs we decided to explore the possibility of preparing a wholly new family of such materials, namely PAMs in which the cationic building block is a permanently charged *phosphonium* species. Currently, phosphonium-based PAMs are unknown, and, to the best of our knowledge, an evaluation of the polymerization of phosphonium monomers, by any controlled radical polymerization technique has not been conducted. Given this, we decided to prepare two examples of styrenic-based phosphonium monomers and evaluate their homopolymerization characteristics under RAFT conditions with the carboxylic acid-functional trithiocarbonate chain transfer agent (**CTA26**) directly in aqueous media.

4-Vinylbenzyl(trimethylphosphonium) chloride (**M63**) and 4-vinylbenzyl(triphenyl-phosphonium) chloride (**M106**), Figure IV-1, were prepared from the reaction of 4-vinylbenzyl chloride and trimethylphosphine or triphenylphosphine respectively in high yields. 4-Vinylbenzoic acid (**M62**) was prepared via a Wittig reaction as detailed above. We reported the synthesis of **CTA26** in Chapter III.³⁸⁸

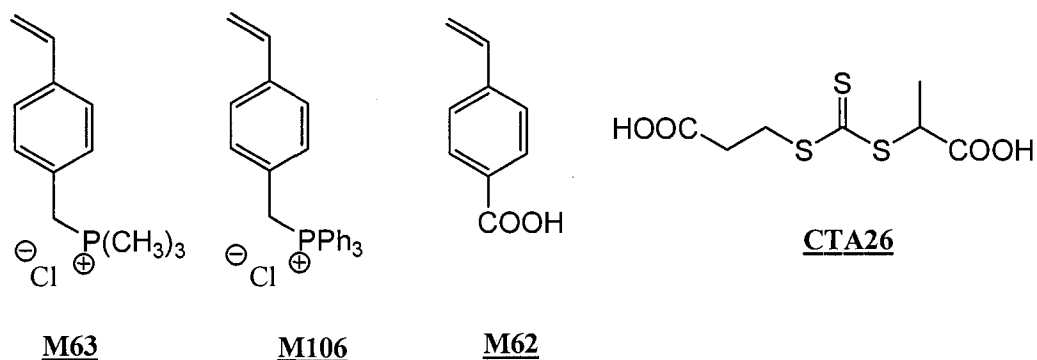


Figure IV-1. Chemical structures of monomers and RAFT chain transfer agent used in these studies.

Given that the RAFT polymerization of phosphonium substrates has not been previously reported, we first examined the homopolymerization characteristics of both **M63** and **M106** with **CTA26** under homogeneous conditions in aqueous media to ensure the substrates could be polymerized in a controlled fashion.

Figure IV-2 shows the pseudo-first order rate plots for the homopolymerization of **M63** and **M106** conducted in D_2O at 50 wt% monomer, 80°C , and at two different values of $[\text{CTA26}]:[\text{V-501}]$ (the monomer conversion were determined using ^1H NMR spectroscopy). It is evident that in both cases the plots are essentially linear. It should be noted that in the case of RAFT polymerizations this only indicates that the polymerization is operating under steady-state conditions. However, the fact that the

linearity is observed up to high conversions does indicate the effective suppression of the Trommsdorff effect. In the case of **M63** (Figure IV-2A) the homopolymerizations proceed rapidly with, for example, 83 % conversion being reached in 60 min for $[\text{CTA26}]:[\text{V-501}] = 5$. There is no evidence of an induction period, which can be observed for certain RAFT CTA/monomer combinations, and is particularly apparent in certain dithioester-mediated RAFT polymerizations,²²⁴ but which is less common/absent in the case of trithiocarbonate-mediated systems. From the kinetic plots we can readily determined the apparent rate constant of propagation, $k_{\text{app}} = k_p[\text{R}\cdot]$, where k_p is the rate constant of propagation and $[\text{R}\cdot]$ is the radical concentration. For these homopolymerizations, k_{app} is equal to 1.8 and 1.1 h⁻¹ in the case of **M63** for $[\text{CTA26}]:[\text{V-501}] = 5$ and 10 respectively. Additionally, the effect of $[\text{CTA26}]:[\text{V-501}]$ is as expected with the higher ratio of reagents resulting in slower overall rate of polymerization which is consistent with previous reports on the effect of $[\text{CTA}]:[\text{I}]$.²²³

M63 homopolymers were analyzed by aqueous size exclusion chromatography (ASEC) to determine their molecular masses (MMs) and molecular mass distributions (MMDs). As a representative example, Figure IV-3 shows the ASEC traces (RI signal) for aliquots withdrawn from an **M63** homopolymerization conducted at 80°C, 50 wt% monomer, and with $[\text{CTA26}]:[\text{V-501}] = 10$. In all instances the experimentally determined chromatograms are unimodal, symmetric, and narrow ($M_w/M_n \leq 1.10$) with no visible evidence of either high or low molecular mass impurities. Additionally, the systematic shift to lower retention times with increasing conversion is consistent with a controlled polymerization.

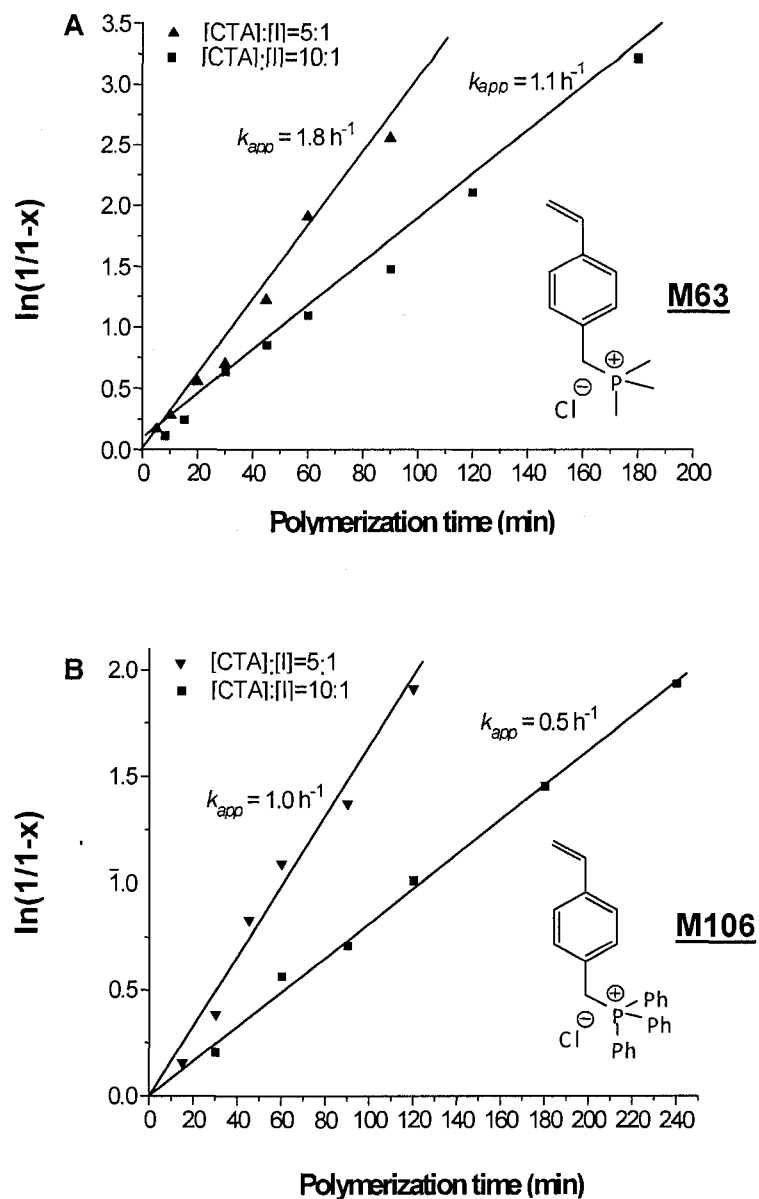


Figure IV-2. Pseudo first-order kinetic plots for the homopolymerization of **M63** and **M106** at 50 wt% monomer in aqueous media with **CTA26** at two different ratios of **[CTA26]:[V-501]**.

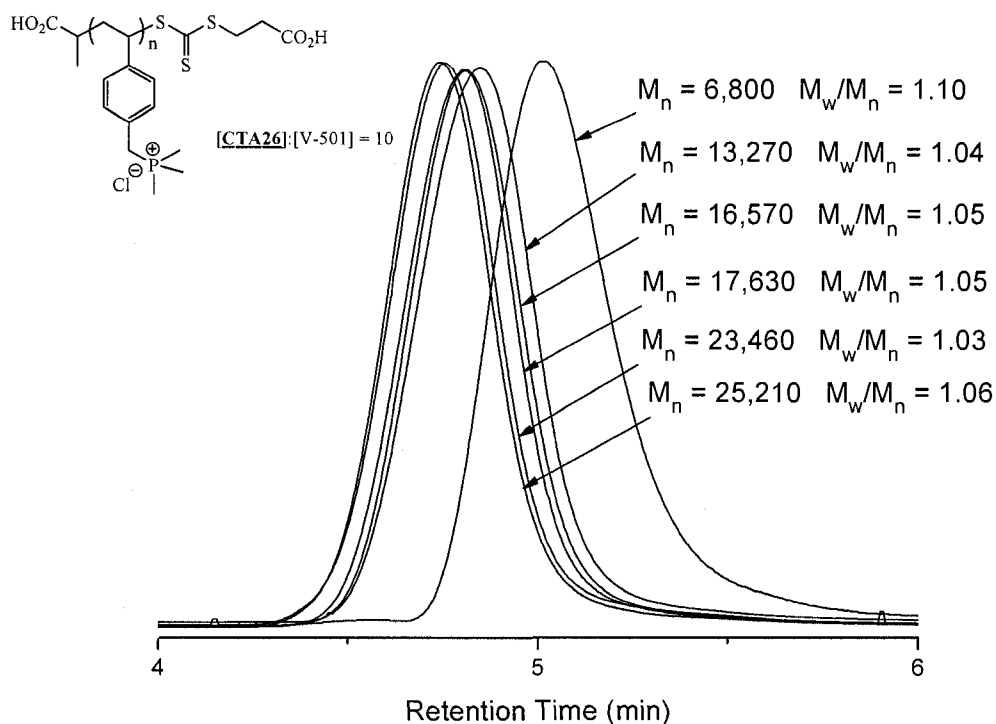


Figure IV-3. Aqueous size exclusion chromatographic traces (RI signal) for the homopolymerization of **M63** in aqueous media at 10 wt% monomer demonstrating the evolution of molecular mass as a function of conversion.

While both the kinetic and ASEC results suggest a controlled polymerization, perhaps a better indicator is the plot of number-average molecular mass (M_n) vs. conversion. Figure IV-4 shows a composite M_n vs. conversion plot for two homopolymerizations of **M63** at $[CTA26]:[V-501] = 5$ and 10 along with the evolution of M_w/M_n for target molecular masses at quantitative conversion of 30,000. In both instances the evolution of MM is linear, passes through the origin, and is in extremely close agreement with the theoretical value at all given fractional conversions. Such linearity is entirely consistent with a controlled polymerization. Additionally, in both

instances the resulting polydispersities (M_w/M_n) are very low with measured values \leq 1.10.

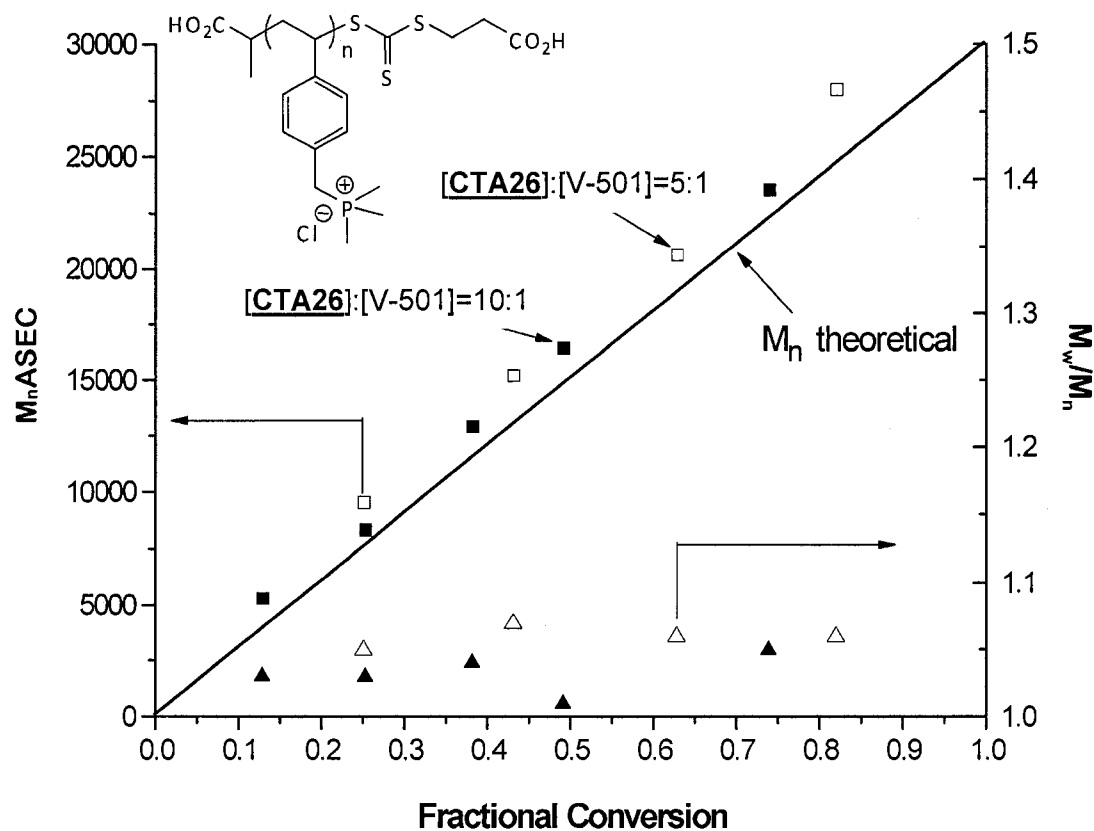


Figure IV-4. Plots of M_n ASEC and M_w/M_n vs. conversion for a homopolymerization of **M63** at [CTA26]:[V-501] = 5:1 and 10:1.

Having established that the homopolymerization of **M63** proceeds in a controlled fashion we next conducted similar experiments for **M106**. Figure IV-2B shows the pseudo-first order kinetic plots for the homopolymerization of **M106** under identical conditions to those reported above for **M63**. A direct comparison of **M63** with **M106** indicates that **M63** polymerizes faster than **M106** under identical conditions at both [CTA26]:[V-501] ratios. For example, **M63** reaches ca. 84% conversion after 100 min

whereas **M106** reaches ca. 55 % conversion after the same period of time for $[\text{CTA26}]:[\text{V-501}] = 10$. While **M106** polymerizes at a slower rate than **M63**, presumably due to its enhanced steric bulk, the kinetic plots are, however, linear to high conversion and exhibit the same general trends as **M63**. Unfortunately, the subsequent determination of the molecular mass and molecular mass distribution could not be accomplished for the **M106** homopolymers due to the very limited solubility of the materials in the ASEC eluent at room temperature.

While **M62** has been both homo- and co-polymerized previously via RAFT^{61,370} it has not been polymerized under conditions mediated by a trithiocarbonate-based RAFT CTA, and as such we felt it prudent to additionally examine the homopolymerization of **M62** as described above for **M63** and **M106**. Kinetic evaluations for the homopolymerization of **M62** were conducted in DMSO since an initial polymerization in water yielded a homopolymer with an experimentally determined M_n significantly higher than the theoretical ($M_{n,\text{expt}} = 93,300$ and $M_w/M_n = 1.36$, whereas $M_{n,\text{theory}} = 21,000$). The only difference between the **M63/M106** and **M62** homopolymerizations in water was the need for added base to aid in the dissolution of **M62**. While a weak base was employed in a stoichiometric amount based on **M62** we cannot dismiss the possible occurrence of loss of **CTA26** via base hydrolysis. Indeed, dithioesters have been demonstrated to be susceptible to base hydrolysis and are, in fact, more stable under acidic conditions.²⁵⁶ Figure IV-5 shows the pseudo-first order rate plots for the homopolymerization of **M62** with $[\text{CTA26}]:[\text{V-501}] = 5$ and 10, at 50 wt% monomer and 80°C. Consistent with the use of **CTA26** as a mediating agent in the **M63** and **M106** homopolymerizations, **M62** exhibits linear pseudo-first order kinetics. In the case of **M62**, k_{app} at the two different

ratios of **CTA26**/V-501 are 1.3 and 0.75 h⁻¹ respectively. As such, **M62** also appears to polymerize at a slower rate than **M63**, although polymerizes faster than **M106**. However, direct apparent rate comparisons are difficult given the different solvent conditions.

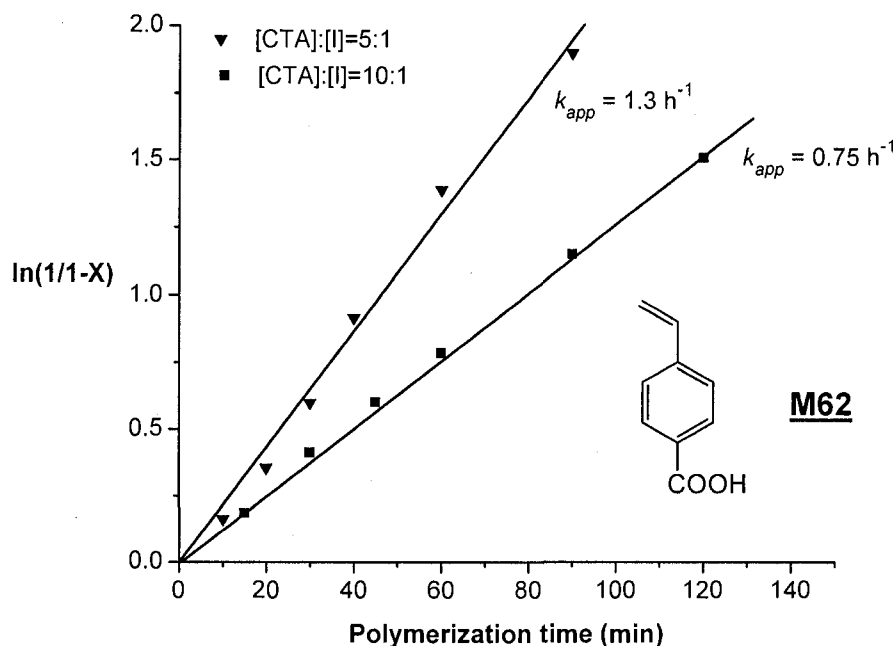


Figure IV-5. Pseudo first-order kinetic plot for the homopolymerization of **M62** at 50 wt% monomer in DMSO with **CTA26** at two different ratios of [**CTA26**]:[V-501].

The determination of the molecular mass and molecular mass distribution for **M62** homopolymers also could not be achieved directly via ASEC since our instrument was configured specifically for the analysis of cationic polymers. Under such ASEC eluent conditions the **M62** homopolymers are protonated and thus hydrophobic and as such cannot be analyzed. However, in contrast to the **M106** homopolymers, **M62** homopolymers can be chemically modified to facilitate their analysis via organic SEC. Poly**M62** can be readily methylated using CH₃I in DMF to yield the methyl carboxylic ester derivative that is readily soluble in THF. While not ideal, since post-polymerization

chemical modification of a (co)polymer rarely results in quantitative derivatization, it can be accomplished to an extent that facilitates analysis via SEC in THF. For example, Figure IV-6 shows the experimentally measured SEC traces (RI signal) for methylated polyM62 samples from the previously described homopolymerization. Gratifyingly, the chromatograms are unimodal and symmetric indicating a high level of esterification as well as demonstrating the controlled nature of the original M62 homopolymerization.

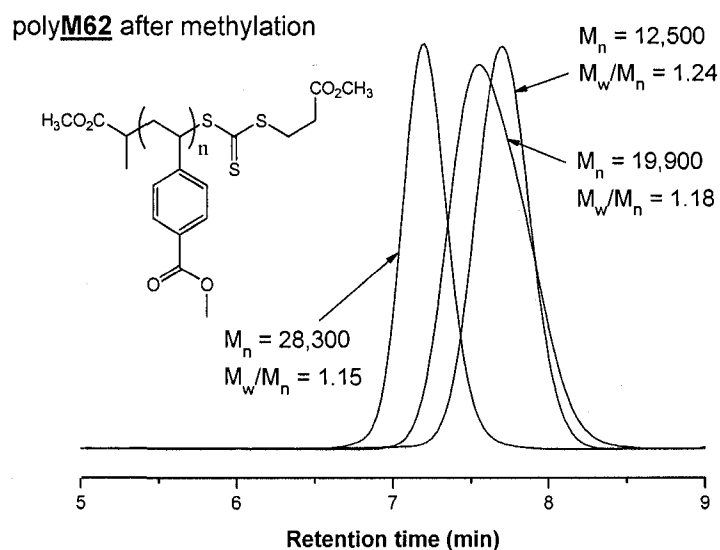


Figure IV-6. Size exclusion chromatographic traces (RI signal) for the homopolymerization of M62, after methylation with CH_3I , recorded in THF. With the molecular mass and molecular mass distribution values readily available.

With the MM and MMD values readily available it is possible to examine the evolution of M_n and MMD as a function of conversion. Figure IV-7 shows the plot of M_n , as determined by SEC with THF as the eluent, vs. conversion with the theoretical M_n line adjusted to take account of the increase in MM assuming quantitative methylation. We see that the evolution of MM is linear and agrees almost perfectly with the theoretical

value at a given fractional conversion. Additionally, the polydispersity index decreases with increasing conversion with M_w/M_n falling from 1.24 to 1.15. Given these observations we can conclude that the homopolymerization of **M62** under these conditions with **CTA26** is likewise controlled.

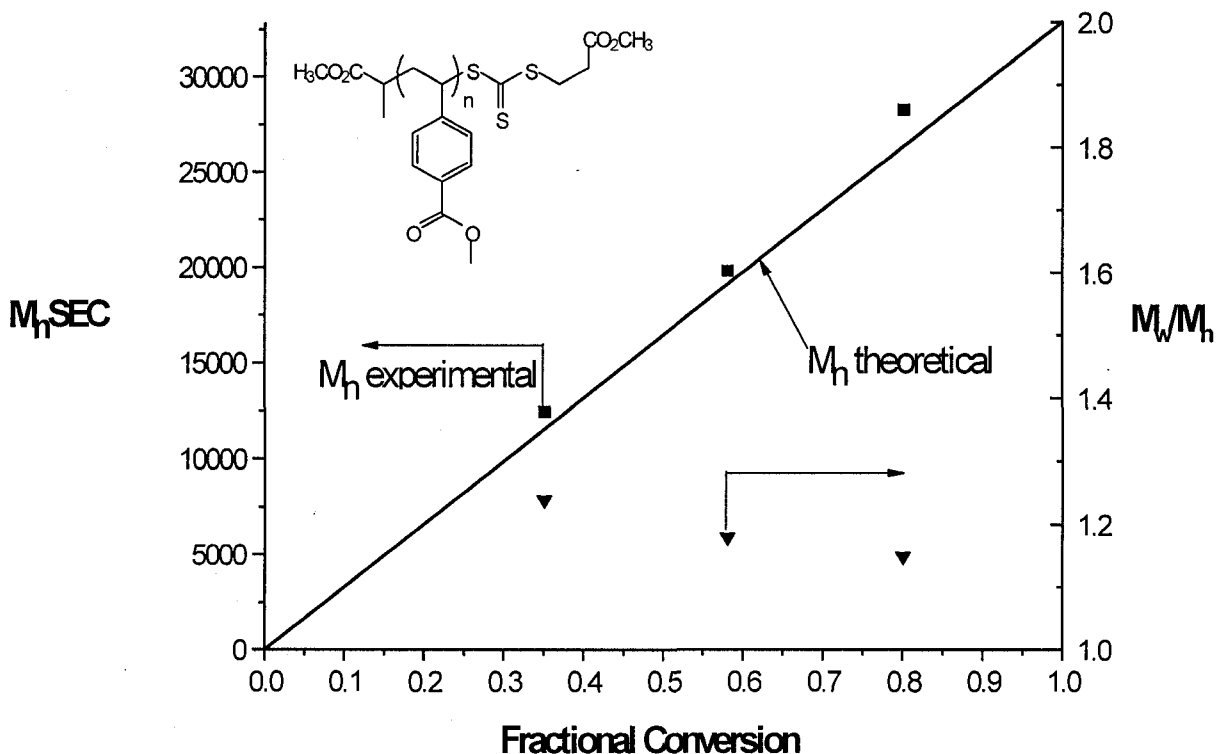


Figure IV-7. Plots of M_n SEC and M_w/M_n vs. conversion for a homopolymerization of **M62** as determined in THF after methylation of the precursor **M62** polymer.

Having established that **M63**, **M106** and **M62** polymerize in a controlled fashion with **CTA26** directly in water or DMSO we next examined the ability to prepare statistical and block copolymers of **M63/M106** with **M62** with the aim of directly synthesizing a new family of well-defined polyampholytic materials. Initially we focused on the statistical copolymerization of **M63** with **M62** at molar ratios of 1:1, 1:3, and 3:1. Copolymerizations were conducted directly in aqueous media at 10 wt% monomer, 80°C

and with $[\text{CTA26}]:[\text{V-501}] = 5$ and 10 in the presence of an equimolar concentration of sodium carbonate, based on M62, to aid in its dissolution. Copolymerizations were conducted at 10 rather than 50 wt% due to solubility issues – the M63/M62 combination for example was not homogeneous at 50 wt% monomer. An evaluation of the pseudo first order kinetic plots shows that in the case of the $1:1$ copolymerization of M63 and M62, Figure IV-8A, the general trends are the same as those observed for the homopolymerizations, namely linear plots which pass through the origin with a clear, and expected, effect of $[\text{CTA26}]:[\text{V-501}]$. However, the statistical copolymerization is significantly faster than any of the homopolymerizations even though the $[\text{M}]$ was only 10 wt% compared to the 50 wt% in the case of the homopolymerization experiments. For example, in the case of the copolymerization at $[\text{CTA26}]:[\text{V-501}] = 5$, 82% conversion is achieved in 30 min compared with M63 and M62 homopolymerizations which reached 60 and 48% conversion respectively after a similar time period even though the $[\text{M}]$ was five times greater. The calculated k_{app} values for the M63/M62 copolymerizations are 3.4 and 1.8 h^{-1} for the $[\text{CTA26}]:[\text{V-501}] = 5$ and 10 respectively. One possible cause for this difference between the M63, M106, M62 homo- and M63/M62 copolymerizations can be attributed to the possible occurrence of ion-pairing. Even though each monomer has an associated counterion it is possible that there exists, in solution, M63/M62 ion-pairs. Indeed, such species are well known and there is often, but not always, a tendency towards alternation in the resulting structure since the ion-pair may polymerize as a discrete “dimeric” species. Such monomer pairing, or dimerization, and the corresponding enhancement in polymerization rate is well documented for monomers

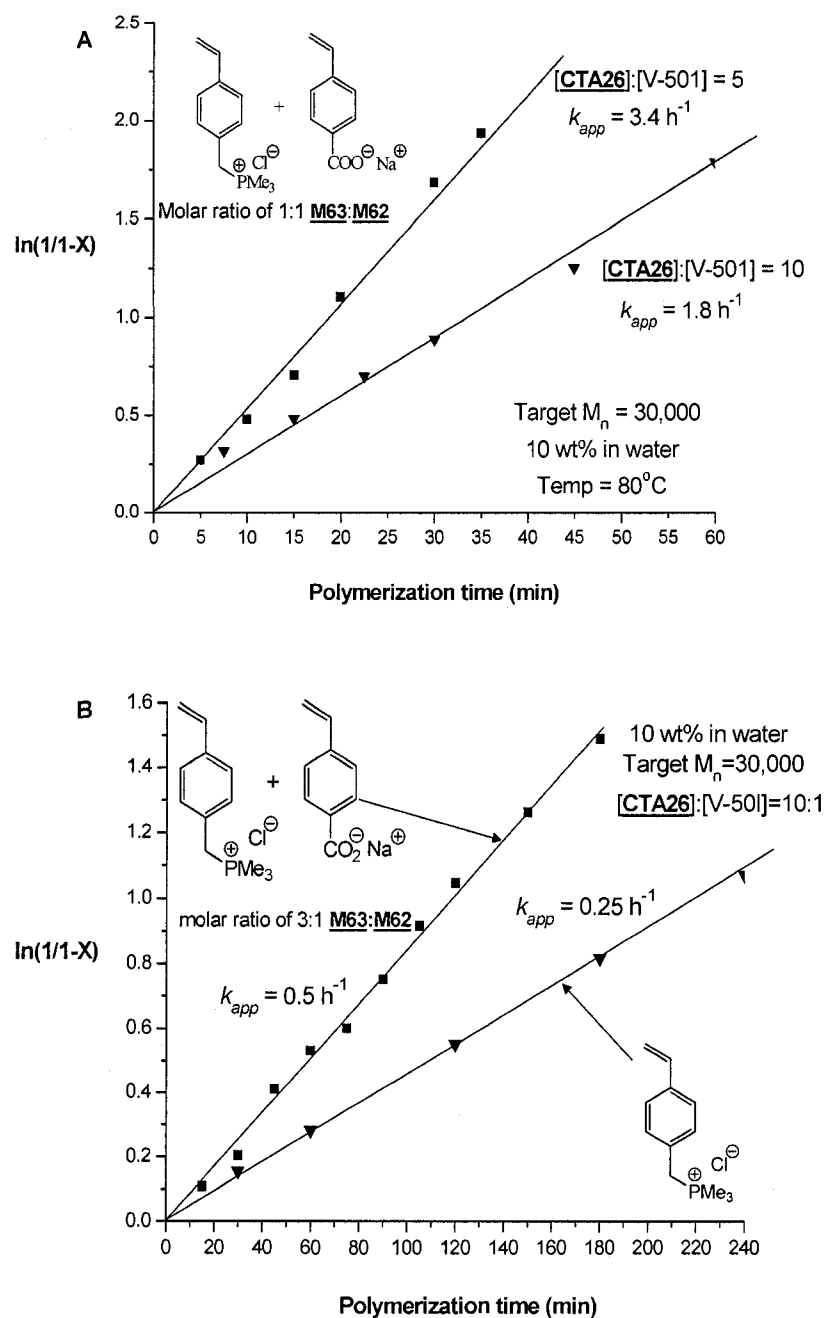
capable of forming, for example, hydrogen-bonded monomer pairs such as those that exist between (meth)acrylic acid, or 2-(hydroxyethyl) (meth)acrylate.³⁸⁹

To further demonstrate this kinetic difference, Figure IV-8B shows the pseudo first order rate plots of an **M63** homopolymerization and an **M63/M62** (3:1 molar ratio) statistical copolymerization performed under identical conditions, i.e. at 10 wt% monomer with **[CTA26]:[V-501] = 10**. The copolymerization proceeds at approximately twice the rate of the analogous homopolymerization of **M63** with $k_{app} \approx 0.5 \text{ h}^{-1}$ for the copolymerization and 0.25 h^{-1} for the **M63** homopolymerization. Interestingly however, the 3:1 statistical copolymerization proceeds at a significantly slower rate than the analogous 1:1 statistical copolymerization ($k_{app} = 1.8 \text{ h}^{-1}$ and 0.5 h^{-1} respectively). Assuming monomer pairing is responsible for the enhanced rate of polymerization this is not surprising since in the 3:1 copolymerization there will exist a combination of monomer pairs and free **M63**. As a consequence the overall rate of polymerization would be predicted to be intermediate the **M63** homopolymerization and the equimolar, i.e. 1:1, **M63/M62** copolymerization that is the case.

Having successfully prepared novel phosphonium-based statistical PAMs we next evaluated the possibility of preparing the corresponding block PAMs. Block copolymers were prepared using either **M63** or **M106** homopolymers as macro CTAs for the subsequent polymerization of **M62**. In the same manner as described above, the kinetic profiles for the block copolymerizations were evaluated. Figure IV-9 shows the pseudo first order rate plots for two separate block polymerizations. Figure IV-9A shows the kinetic profile for the block PAM prepared using an **M106** macro CTA at 10 wt%, and 80°C. The plot is clearly linear with a k_{app} of 0.5 h^{-1} . Similarly, Figure IV-9B shows the

rate plot for the block copolymerization of M62 employing an M63 macro CTA which has a measured k_{app} of 0.6 h^{-1} . The near identical k_{app} values is not surprising since in the case of the block copolymerizations, employing either M63 or M106 macro CTAs under the same conditions, still leads to what amounts to a simple M62 ‘homopolymerization’.

Unfortunately, determining the molecular masses and molecular mass distributions for polyampholytic copolymers, with either statistical or block architectures, via SEC, is extremely problematic especially for materials such as these where one building block has a pH-dependent aqueous solubility. The insolubility of M62 residues at low pH does not facilitate analyses under those conditions used for the permanently cationic M63 or M106 homopolymers. Similarly, it is not possible to easily modify M63 or M106 residues to facilitate analysis by organic SEC.



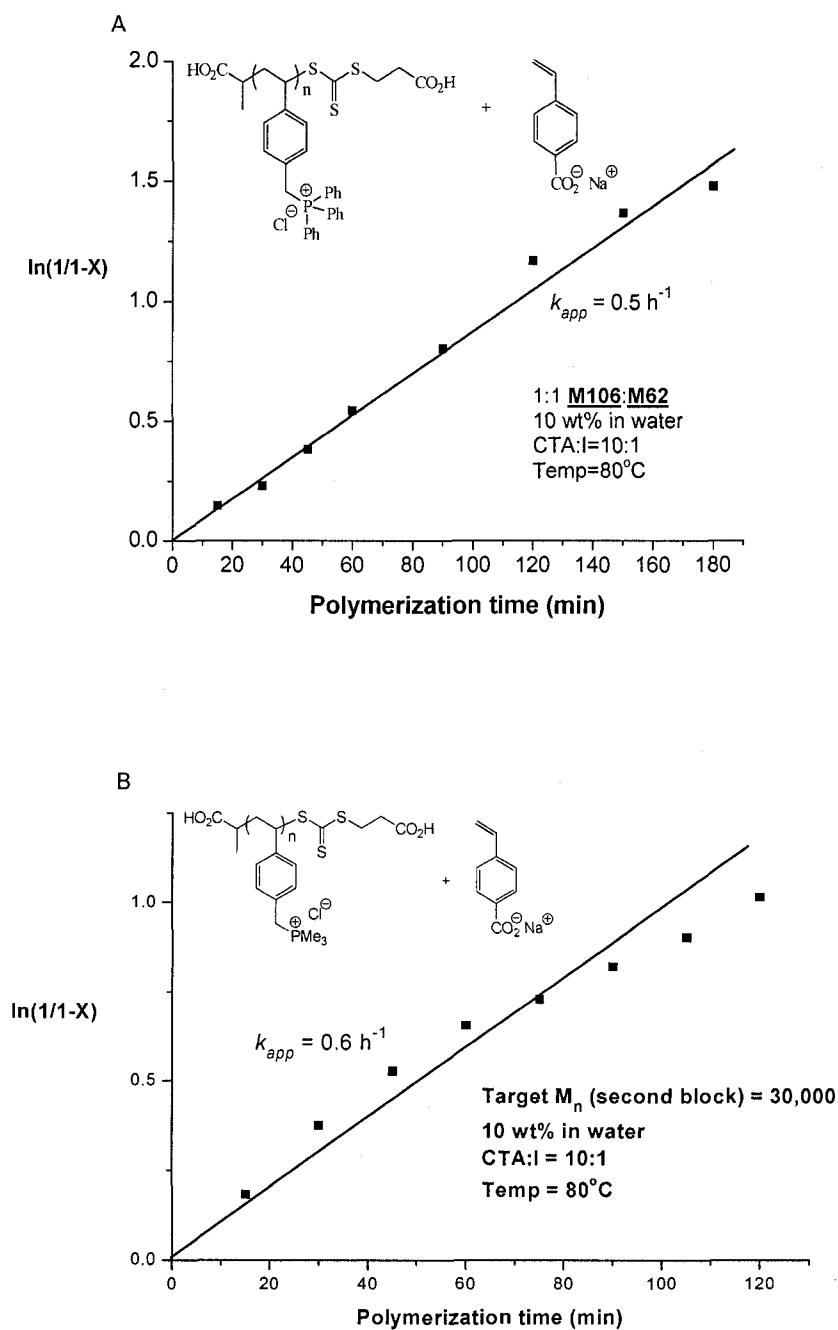


Figure IV-9. Pseudo first-order kinetic plots for (A) the block copolymerization of **M62** employing a poly**M106** macro CTA at a target molar ratio of 1:1 at 10 wt% in water with $[\text{CTA26}]:[\text{V-501}] = 10$, and (B) the block copolymerization of **M62** employing a poly**M63** macro CTA at a target molar ratio of 1:1 at 10 wt% in water with $[\text{CTA26}]:[\text{V-501}] = 10$.

Given the inherent difficulty in analyzing the polyampholytic materials via either organic or aqueous SEC, FTIR spectra were recorded for the **M63**, **M106**, and **M62** homopolymers as well as examples of statistical and block copolymers to demonstrate, qualitatively, the successful formation of these new polyampholytic materials. Figure IV-10 shows the FTIR spectra of an **M63** and **M62** homopolymer (A and B) as well as examples of the statistical (C) and block (D) PAMs. Consider first IV-10A – a poly**M63** homopolymer. The key absorptions here are those centered at ca. 3350, 3000-2900, 1700, 1450-1350, and 950 cm^{-1} , which can be attributed to –OH, aromatic C-H, aromatic combination and overtones bands, PCH_2 - and -PCH_3 (1450-1350 cm^{-1}), and -PCH_3 (950 cm^{-1}), although the PCH_2 - and PCH_3 (1450-1350 cm^{-1}) overlap with various absorptions associated with carboxylic acid dimers/carboxylate anions which may also be present as end-groups. The key absorption for diagnostic purposes is the strong -PCH_3 absorption at 950 cm^{-1} that will clearly be associated only with the **M63** residues. Figure IV-10B shows the spectrum for a poly**M62** homopolymer. Similarly, key absorptions include the broad –OH band centered at ca. 3400 cm^{-1} , with a weak aromatic C-H next to it at ~ 3000 cm^{-1} , and the triplet of strong bands at ca. 1650-1400 cm^{-1} which are attributed to the symmetric and asymmetric bands associated with the carboxylate functionality and also the C-O-H in-plane bend. It is this grouping of three bands which will serve as the key diagnostic feature associated with the **M62** residues. Figures C and D represent examples of **M63-M62** statistical and block polyampholytes respectively. Since we are unable to distinguish architecture from the spectra we would anticipate that the FTIR spectra of these two materials be essentially identical, which appears to be the case. Gratifyingly, in both instances we can clearly identify those ‘unique’ absorptions associated with the

individual M63 and M62 species such as the distinctive -PCH₃ band at ca. 950 cm⁻¹ confirming the presence of M63 and the triplet of bands from ca. 1650-1400 cm⁻¹ associated with M62. The presence of absorption bands associated with the M63 and M62 residues in IV-10C/D thus qualitatively confirms successful synthesis of both the novel statistical and block PAMs.

It should be noted that the presence of the thiocarbonyl end-groups is difficult to confirm via FTIR spectroscopy since the characteristic C-S and C=S absorptions are both weak and can be variable (C-S), occur in the fingerprint region, and overlap with other more intense absorptions including the C-O stretch for example.

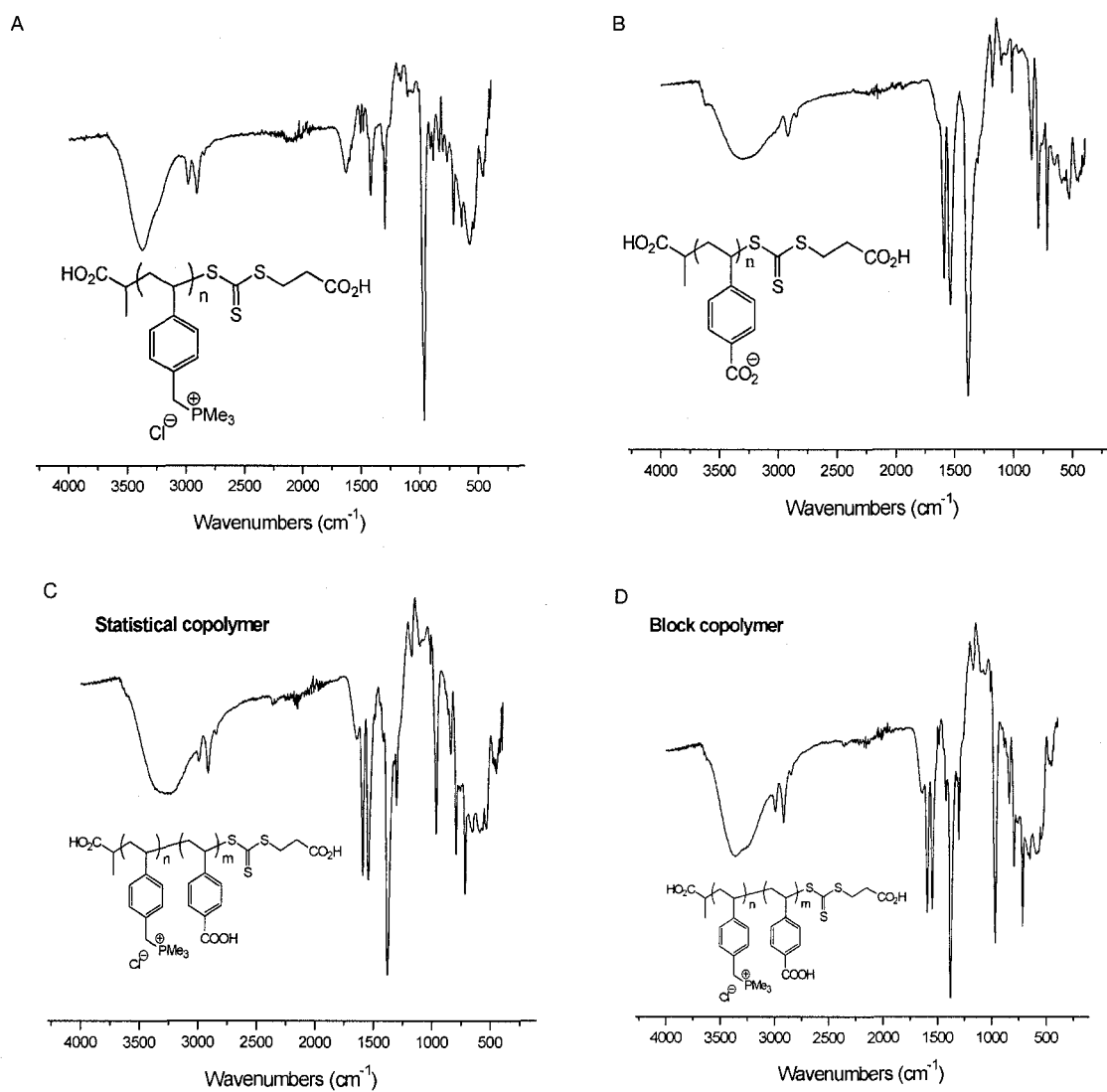


Figure IV-10. FTIR spectra of (A) a poly**M63** homopolymer, (B) a poly**M62** homopolymer, (C) a poly(**M63-M62**) statistical copolymer, and (D) a poly(**M63-M62**) block copolymer.

While **M63** and **M106** are permanently charged, **M62** has a readily accessible pK_a and is thus easily reversibly ionized. Also, **M62** is an example of a “smart” building block in the sense that in the free acid form it is hydrophobic whereas in the ionized state it is hydrophilic. Such readily tunable hydrophilicity/hydrophobicity can be exploited in

the preparation of stimulus-induced nanosized self-assemblies in aqueous media. Indeed, **M62** has been previously employed in such a capacity.^{62,72} While we have not, at this time, conducted a thorough evaluation of the aqueous solution properties of these new PAMs we have performed some preliminary NMR spectroscopic experiments. NMR spectroscopy, and especially ¹H NMR spectroscopy, has proven to be a very powerful and useful tool for evaluating the relative solvation of component building blocks of “smart” copolymers in aqueous solution as a function of applied stimulus, including (but not limited to) changes in pH, temperature, and salt concentration. Unfortunately, ¹H NMR spectroscopy proved to be of little use for these styrenic-based copolymers since there are no distinct resonances associated with the **M62** block which can be conveniently monitored with changes in the solution pH. As such we examined the ¹³C NMR spectra. However, this is also problematic given its lower sensitivity and problems associated with being able to prepare an aqueous solution of a copolymer at a sufficiently high concentration to facilitate straightforward analysis. Figure IV-11 shows the ¹³C NMR spectra of an **M62/M63** block copolymer (molar ratio 1:1) recorded at pH 10.0 (A) and pH 2.0 (B) plotted between $\delta = 200$ and 100 ppm. Two points are worth noting. Firstly, the C=O resonance associated with the carboxylate is clearly evident in spectrum A at ca. δ 175 ppm under conditions of high pH when we would expect the **M62** residues to be ionized and hence hydrophilic and solvated. In contrast, at pH 2.0 (B), when the **M62** residues are fully protonated, the resonance associated with the C=O are completely absent. Additionally, changing the solution pH from 10.0 to 2.0 results in a broadening of the resonances associated with the aromatic carbons. Both of these features are entirely consistent with a hydrophilic-to-hydrophobic phase transition association with the **M62**

residues, and given the block structure it is reasonable to assume that this results in self-assembly yielding nanosized polymer aggregates such as micelles.

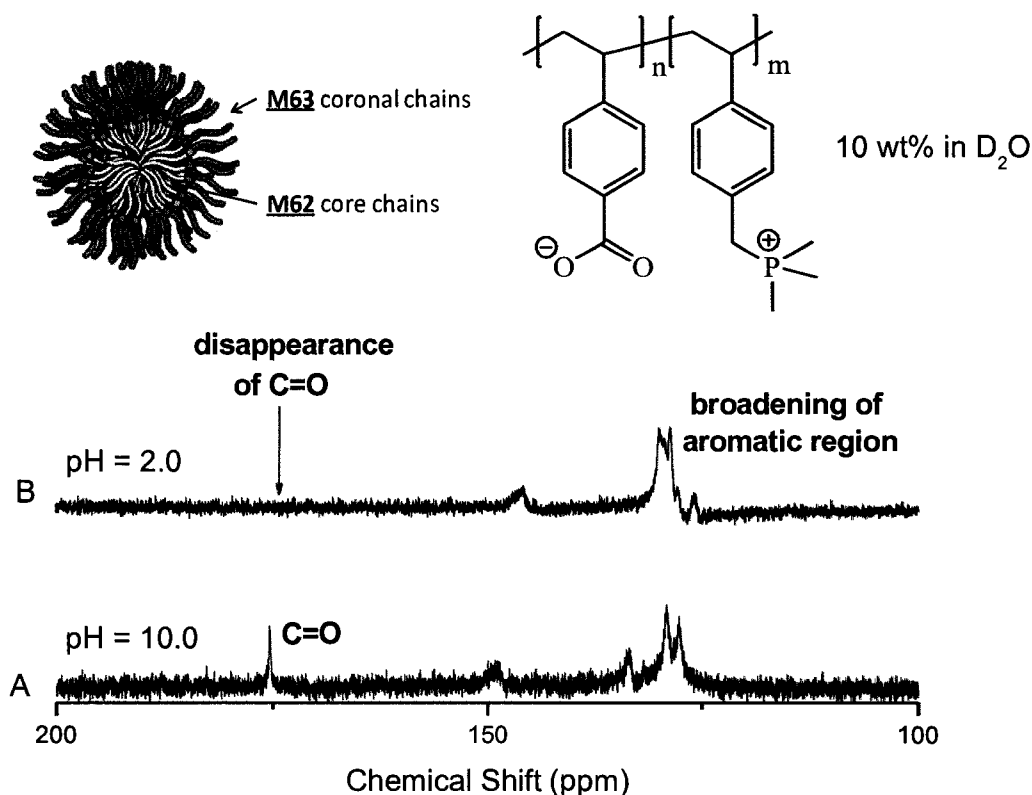


Figure IV-11. ^{13}C NMR spectrum of a 1:1 molar ratio AB diblock copolymer of **M63** with **M62** recorded in water at pH = 10.0 (A) and pH = 2.0 (B).

Summary and Conclusions

Herein we have described the first example of the controlled, aqueous radical polymerization of phosphonium, styrenic-based monomers by RAFT, indeed by any controlled-radical technique, employing a water-soluble trithiocarbonate that we described in Chapter III. We have shown that the characteristics of the **M63** and **M106** homopolymerizations are entirely consistent with them proceeding in a controlled fashion

as judged from the experimentally determined molecular characteristics of the resulting homopolymers. Additionally, **M62** was also shown to polymerize in a controlled fashion in DMSO. Statistical copolymerization of **M63** with **M62** was readily achieved in water at 10 wt% monomer yielding the first examples of statistical PAMs with a cationic phosphonium building block. Also, the use of either poly**M63** or poly**M106** macro CTAs allowed for the subsequent block copolymerization of **M62** to yield the first examples of block PAMs with a phosphonium building block and only the second example in which block PAMs have been prepared *directly* by RAFT and one of only a handful of examples in which materials have been prepared without the need for either protection/deprotection chemistries or post-polymerization modification. The successful formation of the statistical and block PAMs was proven qualitatively by FTIR spectroscopy. Finally, we demonstrated the pH-responsive nature of one of the AB diblock PAMs using ^{13}C NMR spectroscopy.

CHAPTER V

RAFT SYNTHESIS AND AQUEOUS SOLUTION PROPERTIES OF PH-RESPONSIVE AB DIBLOCK STYRENIC-BASED COPOLYMERS OF 4-VINYLBENZYLTRIMETHYLPHOSPHONIUM CHLORIDE WITH *N,N*-DIMETHYLBENZYL VINYLAMINE

Introduction

The ability to synthesize (co)polymers in a controlled manner, i.e. with predetermined molecular characteristics such as the molecular mass (MM), narrow molecular mass distributions (MMD), and with controllable topologies and architectures is becoming increasingly important as the demand for highly functional materials in specialty applications continues to grow. Of the currently available approaches, the controlled/living free radical polymerization (CRP) methodologies including atom transfer radical polymerization (ATRP), stable free radical polymerization, best exemplified by nitroxide-mediated polymerization (NMP), and reversible addition-fragmentation chain transfer (RAFT) radical polymerization,^{99,100,223,389,390} have developed into a powerful set of synthetic techniques that now facilitate the preparation of advanced materials, many of which, were unattainable only a decade ago. Of these three CRP processes, RAFT has proven itself to be, arguably, the technique of choice for the synthesis of well-defined water-soluble (co)polymers in either organic³⁹⁰ or aqueous media.^{57,123,362} This is due to its applicability to the widest range of monomers, its superior functional group tolerance, and its ease of execution. These characteristics alone make RAFT an extremely versatile synthetic tool for the preparation of materials with, for example, predictable stimuli-responsive aqueous solution properties. A recent review clearly highlights many of these features.³⁶² Indeed, in recent years many research groups

have been exploring the synthesis and properties of new stimuli-responsive, or “smart”, copolymers prepared via a variety of polymerization techniques. Examples of applied stimuli to which (co)polymers may respond include, changes in aqueous solution pH, temperature, electrolyte concentration, and light.³⁹¹ The physical manifestation of the response to an applied stimulus can be varied and may include a simple conformational change (chain expansion or contraction for example), a macroscopic phase transition (precipitation or dissolution), or self-assembly to form, for example, micelles or higher ordered structures.³⁹¹

Cationic polymers are interesting materials for various reasons and have found commercial application in cosmetics, antimicrobial formulations, water treatment, and paper processing to name but a few. RAFT has been successfully employed for the preparation of both amine^{50,61,99,259,379,392} and ammonium-based^{61,392,393} copolymers utilizing substrates from all the major, common monomer families including (meth)acrylic, (meth)acrylamido, and styrenic derivatives. Many of these monomers have been polymerized as one specific building block in ‘smart’ materials that are capable of undergoing stimulus-induced self-assembly.^{123,362,394} Amine/ammonium functional groups are not the only species capable of bearing a formal positive charge, with other cationic groups including sulfonium, phosphonium, and oxonium species. Of these, the phosphonium substrates are of comparable stability to ammonium substrates and can be readily prepared via straightforward S_N reactions between appropriate phosphines and alkyl halides, as described in Chapter IV. While AB diblock copolymers with two cationic/potentially cationic building blocks have been previously prepared, they have to date been composed of monomers with amine/ammonium functional groups.^{61,392} For

example, the research group of Armes has reported extensively on the synthesis and aqueous solution properties of such materials prepared via group transfer and atom transfer radical polymerization methodologies.^{12,19,346,395-397} To the best of our knowledge bis-cationic block copolymers built from inherently different cationic/potentially cationic functional groups have never before been reported.

In this chapter we describe the RAFT synthesis and aqueous solution properties of new styrenic-based, pH-responsive, “smart” AB diblock copolymers comprised of a permanently positively charged, hydrophilic block of 4-vinylbenzyltrimethylphosphonium chloride (TMP, **M63**) with a tunably hydrophilic/hydrophobic *N,N*-dimethylbenzylvinylamine (DMBVA, **M59**) block. These represent the first examples of “mixed” cationic copolymers prepared by any technique. We demonstrate that these materials can be conveniently synthesized via trithiocarbonate-mediated RAFT polymerization directly in aqueous media under homogeneous conditions. Such materials are shown to undergo pH-induced self-assembly in water yielding nano-sized aggregates consistent with the well-documented hydrophilic-to-hydrophobic phase transition behavior associated with the DMBVA building block. Finally, we show that the presence of reactive tertiary amine functionality in the aggregate cores facilitates a core cross-linking reaction that effectively “locks” the copolymers in the aggregated state.

Experimental Part

All reagents were purchased from the Aldrich Chemical Company at the highest available purity and used as received unless stated otherwise. 4-

Vinylbenzyltrimethylphosphonium chloride (**M63**) was prepared from the reaction between 4-vinylbenzyl chloride and trimethylphosphine as described in Chapter IV.²⁸⁷ 4,4'-Azobis(4-cyanovaleric acid) (V-501) was purchased from Wako Chemicals, recrystallized from methanol and stored in a freezer until needed. 3-((1-Carboxyethylthio)carbonothioylthio)propanoic acid (**CTA26**) was prepared as outlined in Chapter III.³⁸⁷ (2-[4-(2-Hydroxyethyl)-1-piperazine]ethanesulfonic acid) (HEPES) was purchased from Fisher Scientific.

*Homopolymerization of **M63***

Below is a typical procedure for the homopolymerization of **M63**:

To a 20 mL vial equipped with a magnetic stir-bar was added **M63** (3.0 g, 1.32×10^{-2} mol), **CTA26** (25.0 mg, 1×10^{-4} mol), V-501 (6.0 mg, 2.14×10^{-5} mol), and 6.0 g distilled water (Target $M_n = 30,000$ g/mol, [CTA]:[I]=5:1, at 50 wt%). The mixture was subsequently purged with nitrogen, with stirring, for ca. 1 h after which it was immersed in a pre-heated oil bath at 80°C. After 40 min the polymerization was stopped by immediate exposure to air and quenching in liquid nitrogen. The polymerization mixture was subsequently dialyzed against distilled water for 2 days with change of water twice per day. Following this, the macro CTA was isolated via lyophilization using a Labconco Freeze Dry System/Freezone 4.5.

*Block copolymerization of **M63** with DMVBA(**M59**)*

Below is a typical procedure for the preparation of a poly(**M63**-*block*-**M59**) copolymer with a molar ratio of **M63**:**M59** = 1:1.

To a 25 mL round-bottomed flask equipped with a magnetic stir-bar were added the polyM63 homopolymer (0.5 g, 2.19×10^{-3} mol), M59 (0.35 g, 2.20×10^{-3} mol), 10 mL pH 4 buffer solution (sodium acetate/acetic acid, 6.0 M, prepared in advance), and V-501 (2.0 mg, 7.14×10^{-6} mol). The mixture was stirred while being purged with dry nitrogen for ca. 1 h before it was immersed in a pre-heated oil bath at 80 °C. After 1 h the polymerization was stopped by immediate exposure to air and quenching in liquid nitrogen. The mixture was dialyzed against slightly acidic distilled water for 2 days with change of water twice daily. Following this, the copolymer was isolated via lyophilization using a Labconco Freeze Dry System/Freezone 4.5.

Micelle core cross-linking reaction

Polymeric micelles with a hydrophilic M63 corona and a hydrophobic M59 core were core-cross-linked with 1,4-bis(bromomethyl)benzene as follows: 1,4-bis(bromomethyl)benzene (7.0 mg, 2.57×10^{-5} mol, 10 mol % based on M59 residues) was added to a poly(M63-*block*-M59) (M63:M59=1:1) solution (0.1 g copolymer in 10 mL deionized water). The pH of the solution was then adjusted to ca. 12.0 to facilitate self-assembly. The solution was subsequently stirred overnight at 50 °C. Following this, the solution was cooled to room temperature and dialyzed against slightly acidic distilled water for 2 days with the water being changed twice daily. The core-cross-linked aggregates were isolated by lyophilization using a Labconco Freeze Dry System/Freezone 4.5.

General characterization techniques

^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker 300 53 mm spectrometer in appropriate deuterated solvents or deuterated solvent mixtures. Polymer molecular masses (MM), molecular mass distributions (MMD), and polydispersity indices (M_w/M_n) were determined by aqueous size exclusion chromatography (ASEC) in 0.1 M Na_2SO_4 /1 vol % acetic acid at a flow rate of 0.20 ml/min at ambient temperature. The system was comprised of a Viscotek VE1122 pump, Viscotek VE3580 RI detector, a CATSEC 1000 7μ (50 x 4.6 mm) guard column followed by a series of two CATSEC ASEC columns (CATSEC 1000 7μ 250 x 4.6 mm + 100 5μ 250 x 4.6 mm) with a theoretical linear MM range of 200 – 2,000,000 g/mol. The system was calibrated with a series of narrow MMD poly(ethylene oxide) standards (M_n range of standards 620 – 460,000). Data were analyzed with the OmniseC Interactive SEC software package.

Fluorescence spectroscopy

Pyrene sequestration experiments were performed in 2.0 ml of 10 mM HEPES buffer with 100 μM pyrene and 0.5 $\mu\text{g/ml}$ polymer. The pH was adjusted from 4 to 13.5 via the addition of 1.0 M NaOH or HCl solution. Fluorescence was measured with an ISS K2 fluorometer (Champaign, IL) equipped with a xenon lamp and microprocessor-controlled photomultiplier. Measurements were made in 1 cm x 1 cm quartz cuvettes, with 1 mm slits on both excitation and emission monochromators. The excitation wavelength was 345 nm; the monomer fluorescence was read at 396 nm and that of excimer at 475 nm.

Dynamic light scattering

Dynamic light scattering (DLS) studies of the copolymers at concentrations of 1 wt% in an aqueous 0.1 M NaCl solution were conducted using a Malvern Instruments Zetasizer Nano ZS instrument equipped with a 4 mW He-Ne laser operating at $\lambda = 633$ nm, an avalanche photodiode detector with high quantum efficiency, and an ALV/LSE-5003 multiple tau digital correlator electronics system. The data were collected and processed using the Dispersion Technology Software V4.20.

Results and Discussion

Copolymer synthesis

The target **M63-M59** AB diblock copolymers were prepared from functional styrenic monomers via RAFT directly in aqueous media at 80°C with the water-soluble azo initiator, V-501, and a trithiocarbonate chain transfer agent (**CTA26**), Figure V-1, whose synthesis we described in Chapter III.³⁸⁷

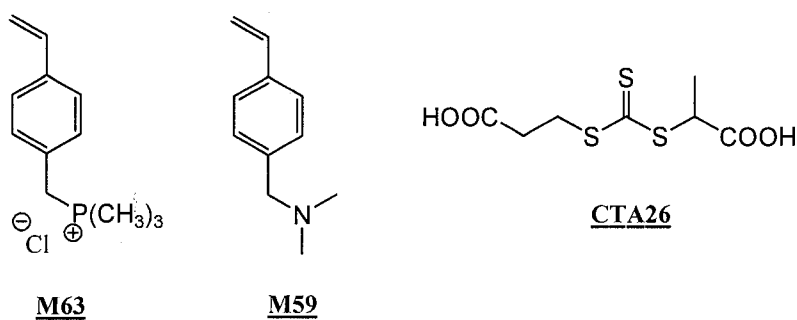


Figure V-1. Chemical structures of monomers and RAFT CTA used in these studies.

M106 was chosen as a building block given its permanently hydrophilic nature coupled with the fact that we demonstrated in Chapter IV that it polymerizes in a

controlled fashion via RAFT in water with CTA26.²⁸⁷ M59 was chosen as the comonomer due to its well-documented stimuli-responsive properties.^{50,61,392} Specifically, M59 is a pH-responsive species which is hydrophilic when protonated but hydrophobic when deprotonated. For block copolymer syntheses a M63 macroCTA was used in all instances. We did not evaluate the reverse sequence, i.e. employing a M59 macroCTA for the polymerization of M63, although such an approach is not expected to be problematic given that both monomers are styrenic derivatives. The molecular characteristics of the polyM63 macroCTA employed for the copolymer syntheses described herein are summarized in Table V-1 (first entry).

Table V-1. Summary of the molecular masses, polydispersity indices, compositions and hydrodynamic properties of the M63 homopolymer and M63-M59 AB diblock copolymers.

Sample	M_n , theory	M_n , expt ^a	M_w , expt ^a	M_w/M_n ^a	Theoretical composition	Observed composition ^b	D_h ^c (nm), pH 2	D_h ^c (nm), pH 12
<u>P</u> <u>M63</u> macroCTA	20,800	11,480	13,450	1.17	-	-	-	-
<u>P</u> (<u>M63-b-M59</u>)	31,530	18,930	26,120	1.38	50:50	55:45	6.0	20.0
<u>P</u> (<u>M63-b-M59</u>)	28,280	15,340	21,500	1.40	66:34	63:37	4.0	24.0
<u>P</u> (<u>M63-b-M59</u>)	23,750	12,870	17,040	1.32	75:25	79:21	3.0	30.0

a As determined by aqueous size exclusion chromatography, calibrated with narrow molecular mass poly(ethylene oxide) standards

b As determined by NMR spectroscopy

c As determined by dynamic light scattering

The experimentally determined M_n is significantly lower than the theoretical M_n ($M_{n,theory} = 20,800$ vs $M_{n,expt} = 11,480$). Such a discrepancy is almost certainly due to the fact that the aqueous size exclusion chromatography (ASEC) system was calibrated with linear, narrow molecular mass distribution poly(ethylene oxide) standards which are clearly poor equivalents for the cationic, styrenic-based **M63** homopolymer. However, the measured polydispersity index is low with an experimentally determined $M_w/M_n = 1.17$, which is entirely consistent with (co)polymers prepared via RAFT in aqueous media.³⁶² Kinetic studies for the homopolymerization of **M63** and **M59** were not conducted since we reported in Chapter IV a detailed description of the kinetic features for the homopolymerization of TMP in water with **CTA26**.²⁸⁷ Likewise, as noted above, the RAFT (co)polymerization characteristics of **M59** are well documented.^{50,61,392}

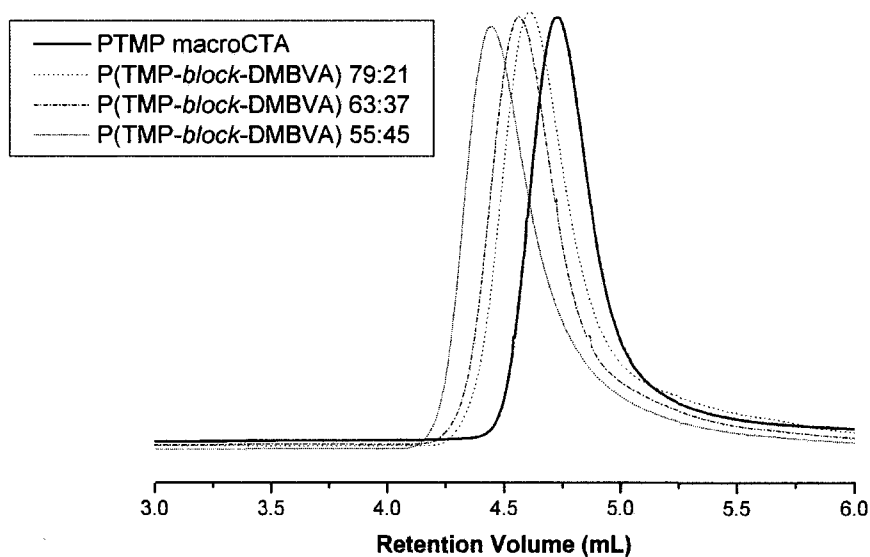


Figure V-2. ASEC traces for a **M63** (TMP) homopolymer employed as a RAFT macro-CTA along with the **M63-M59** (TMP-DMBVA) AB diblock copolymers.

Figure V-2 shows the ASEC traces (RI signal) of the polyM63 homopolymer employed as the macroCTA along with the chromatograms for the three AB diblock copolymers with M59. The clear shift to lower retention volume, relative to the M63 homopolymer, coupled with the unimodal, near-symmetric nature of the copolymer traces indicates a high blocking efficiency and the successful formation of well-defined AB diblock copolymers. The molecular masses and molecular mass distributions for the AB diblock copolymers are listed in Table V-1. The experimentally determined M_n values do not agree with the theoretical values for the same reason noted above for the M63 homopolymer. However, and as expected, the M_n values fall as we move from the 55:45 to the 63:37 to the 79:21 M63:M59 copolymers. Since the same M63 macroCTA was employed in all block syntheses, the theoretical M_n will fall moving from the equimolar to the M63-rich copolymers. The measured polydispersity indices increase in all instances for the block copolymers relative to the M63 macroCTA, with M_w/M_n values for the AB diblock copolymers between 1.32-1.40. Such values are also consistent for AB diblock copolymers prepared by RAFT. The block copolymer compositions were determined using ^1H NMR spectroscopy, Table V-1, and are close to the targeted values. Having successfully prepared the target AB diblock copolymers we proceeded to evaluate their aqueous solution properties with an emphasis on the anticipated reversible, pH-induced self-assembly.

Aqueous solution properties

The M63-M59 AB diblock copolymers were hypothesized to exhibit interesting aqueous solution properties by virtue of the fact that while the M63 residues are

permanently hydrophilic, the solubility of the **M59** residues is sensitive to the aqueous solution pH.^{50,392} The presence of such a “smart” component in AB diblock copolymers offers a convenient route for preparing nanosized aggregates such as polymeric micelles and higher ordered structures.^{398,399} Additionally, since the solubility properties of such “smart” building blocks are reversible, the formation of nanosized assemblies is likewise expected to be reversible.

The self-assembly properties of the **M63-M59** copolymers were examined as a function of solution pH employing NMR and fluorescence spectroscopies and dynamic light scattering. Figure V-3 shows a series of ¹H NMR spectra, recorded in D₂O, at two different pH's for the 55:45 **M63-M59** diblock copolymer along with the ¹H NMR spectrum of the **M63** homopolymer used as a macro CTA. In the case of the **M63** homopolymer, A', we clearly see the resonances associated with the key functional groups. The signals associated with the three methyl groups are evident at $\delta \sim 1.5$ ppm (labeled A) while the benzylic hydrogen's and aromatic hydrogen's are clearly visible at $\delta \sim 3.4$ and ca. 6.1-7.0 ppm respectively. B' shows the ¹H NMR spectrum of the **M63-M59** block copolymer at pH 2 – solution conditions in which both blocks are hydrophilic and thus the copolymer is expected to exist as single molecularly dissolved chains or unimers.³⁹⁹ Indeed, under these conditions we clearly observe the resonances associated with both the **M63** and **M59** building blocks. Specifically, in addition to those resonances observed in A' associated with **M63** we see signals at ca. δ 2.5 ppm (D) and ca. 4.1 ppm (E) which are associated with the dimethylamino hydrogen's and the methylene hydrogen's bound directly to the dimethylamino group respectively. C' shows the ¹H NMR spectrum of the same copolymer solution with the pH adjusted to 10.0 via the

addition of NaOD. Under these conditions the tertiary amine residues of **M59** are deprotonated and the **M59** block becomes hydrophobic.

Consistent with the anticipated hydrophilic-to-hydrophobic phase transition, the resonances associated with the **M59** residues completely disappear. This indicates dehydration and significantly reduced mobility of the **M59** block. Interestingly, we also observe some decrease in the intensity of the resonances associated with the **M63** residues, which likewise suggests some degree of dehydration under these conditions, although no macroscopic precipitate is observed. This indicates that the **M63** block is still sufficiently solvated/hydrophilic to facilitate the self-assembly process. While such NMR experiments do not prove the formation of polymeric self-assemblies such as spherical micelles, such nanosized structures can be reasonably expected given the block-nature of the materials being investigated, and the documented ‘smart’ properties of the **M59** component.

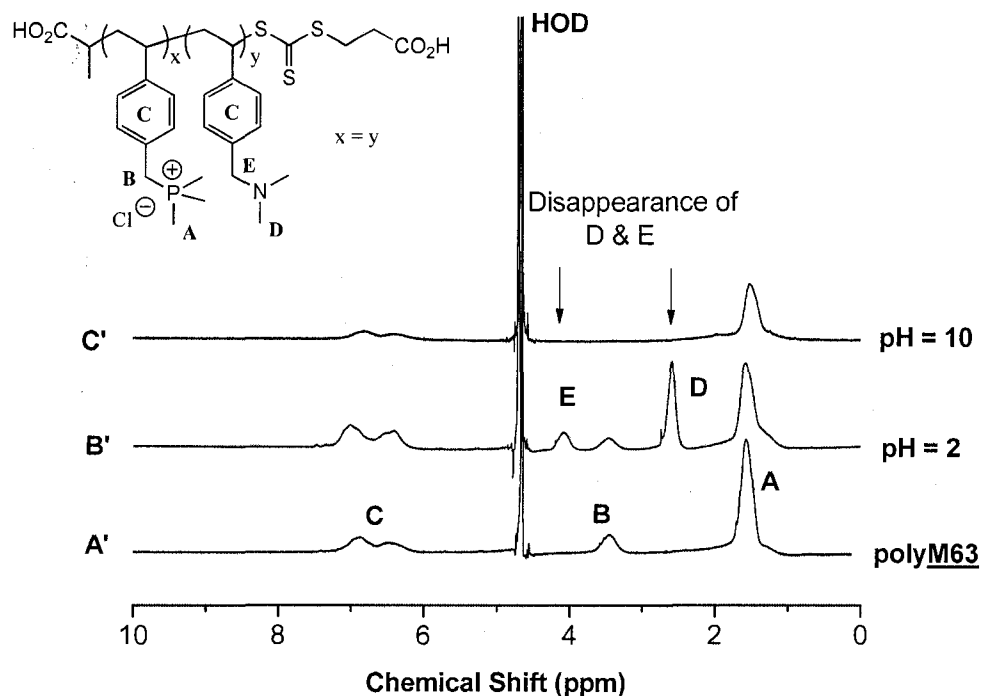


Figure V-3. ^1H NMR spectra, recorded in D_2O of a polyM63 homopolymers (A'), a poly(M63-block-M59) copolymer at pH 2 (B') and the same AB diblock copolymer at pH 10 (C').

A more quantitative picture of self-assembly can be obtained from DLS experiments. DLS is a fast and convenient technique facilitating the determination of the hydrodynamic properties of (co)polymers in both the unimeric and self-assembled states. Each of the M63-M59 block copolymers were analyzed by DLS as 1 wt% solutions (in 0.1 M NaCl) at both high and low pH. At low pH, i.e. under those conditions where the block copolymers are anticipated to exist as unimers, the experimentally determined hydrodynamic diameters (D_h) ranged from 3.0-6.0 nm, Table V-1. Such D_h values are entirely consistent with single, molecularly dissolved polymer chains with similar molecular masses.⁵⁹ Likewise, we see that as the average degree of polymerization for the M63-M59 diblock copolymers falls the D_h value of the unimers also falls. Upon raising

the pH to 12, DLS indicates that the AB diblock copolymers do undergo a self-assembly process yielding aggregates with measured D_h values in the range 20-30 nm, Table V-1. In all instances these larger species are the only species present. Since the three AB diblock copolymers have a constant **M63** block length these observed differences in D_h values in the self-assembled state are a clear indication of the effect of the **M59** block length. What is clear is that as the molecular masses of the AB diblock copolymers fall, i.e. moving from the 55:45 \rightarrow 63:37 \rightarrow 79:21 copolymers, the D_h values increase. These differences in D_h are therefore most likely due to differences in the aggregation number (N_{agg}), or the average number of copolymer chains per aggregate.

The tunably hydrophilic/hydrophobic nature of the **M59** building block suggests that the formation of such nanosized self-assemblies should be completely reversible. Figure V-4 shows the vol% distributions, determined via DLS, for the 63:37 **M63-M59** block copolymer at pH 2, pH 12, and then back to pH 2. It is clear that the self-assembly process is completely reversible with initial D_h sizes consistent with unimers (ca. 4.0 nm) whereas the D_h value at pH 12 is ca. 20 nm. Reducing the solution pH back to 2 results in the complete disassembly of the aggregates and a return to the unimeric state. Indeed there is no discernible difference between the unimer size distributions after the cycling of the solution pH.

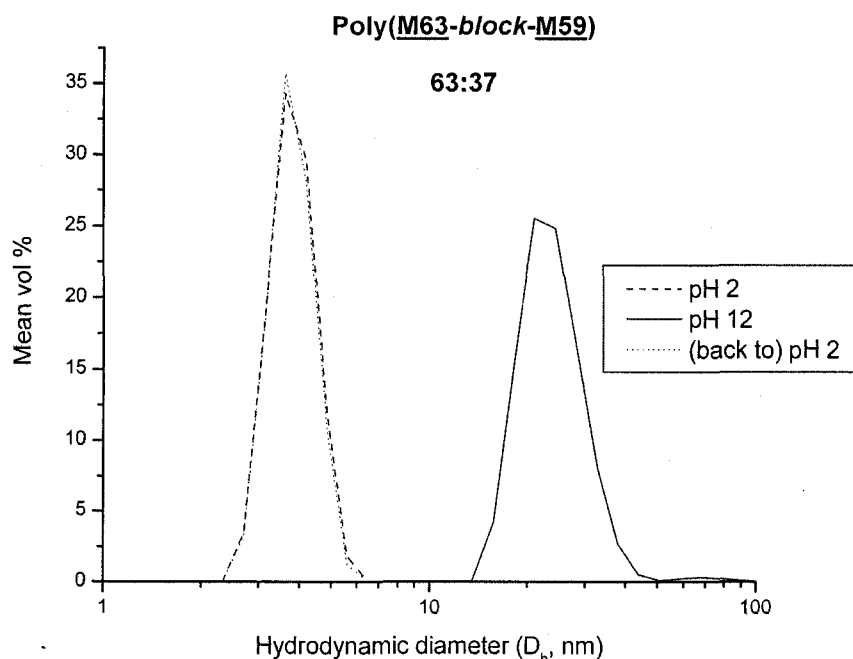


Figure V-4. Experimentally determined hydrodynamic size distributions for a **M63-M59** block copolymer of molar composition 2:1 at high and low pH values.

A complementary technique to both NMR spectroscopy and DLS is fluorescence spectroscopy (FS). As a technique it is useful for monitoring the sequestration abilities of polymeric self-assemblies, and in the case of these pH responsive copolymers it can be used to determine the critical pH at which the self-assembly process occurs. FS experiments were conducted using pyrene as a probe molecule. When the hydrophobic polymeric blocks collapse into micelles pyrene is sequestered and concentrated in their interior which leads to an increased rate of excimer formation.⁴⁰⁰ Indeed, we see in Figure V-5 that when the solution pH is gradually increased from 4.0 to 13.5 the excimer fluorescence at around 475 nm dramatically increases. Additionally, such behavior is completely reversible: when the pH of the sample was brought back down to 1 (the dotted line in Figure V-5), the spectrum closely resembled the initial one, taken at pH 4.

These results are entirely consistent with those obtained by both NMR spectroscopy and DLS and the proposed self-assembly process in which aggregates with a hydrophobic M59 core are formed.

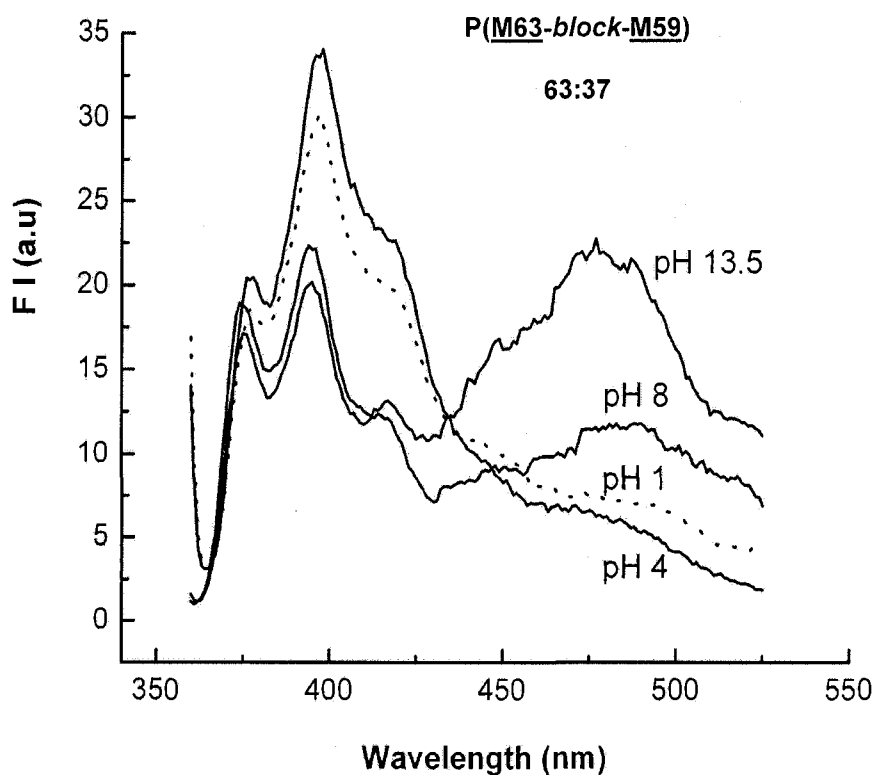


Figure V-5. Fluorescence spectra of pyrene in the presence of the M63-M59 2:1 block copolymer at various pH values. The pH was raised from 4 to 13.5 in the same cuvette.

The spectrum labeled pH 1 (dotted line) was obtained with the same sample after lowering pH from 13.5 to 1. The increased noise in the spectra at high pH is caused by increased light scattering from the formed micelles.

Synthesis of core cross-linked micelles

Many polymeric-based micelles are dynamic structures in the sense that there is continual exchange between unimers and those copolymer chains forming part of the micellar assembly, especially for those species in which the core-forming block has a low T_g . Additionally, complete disassembly occurs at concentrations below the critical

aggregation concentration (CAC). For certain applications, such as drug delivery for example, it might be desirable to maintain the self-assembled state even at concentrations below the CAC to prevent “burst” (uncontrolled) release of a therapeutic payload. Such “locked” structures can be obtained in several ways including covalent cross-linking of the core or the coronal shell,⁴⁰¹ and by electrostatic complexation.^{378,402} Covalent cross-linking, either in the core or corona, requires the presence of appropriate reactive functional groups capable of undergoing reactions post-self-assembly. Of these two approaches shell cross-linking has been evaluated widely, especially by Wooley and coworkers,^{343,403-407} who pioneered the approach, as well as by Armes et al.^{346,395,397} Covalent crosslinking of the aggregate core has been less widely evaluated.⁵⁰ In the case of the **M63-M59** diblock copolymers, the core-shell aggregates formed at high pH contain the **M59** residues in the core with tertiary amine functional groups that are available for post-assembly modification.

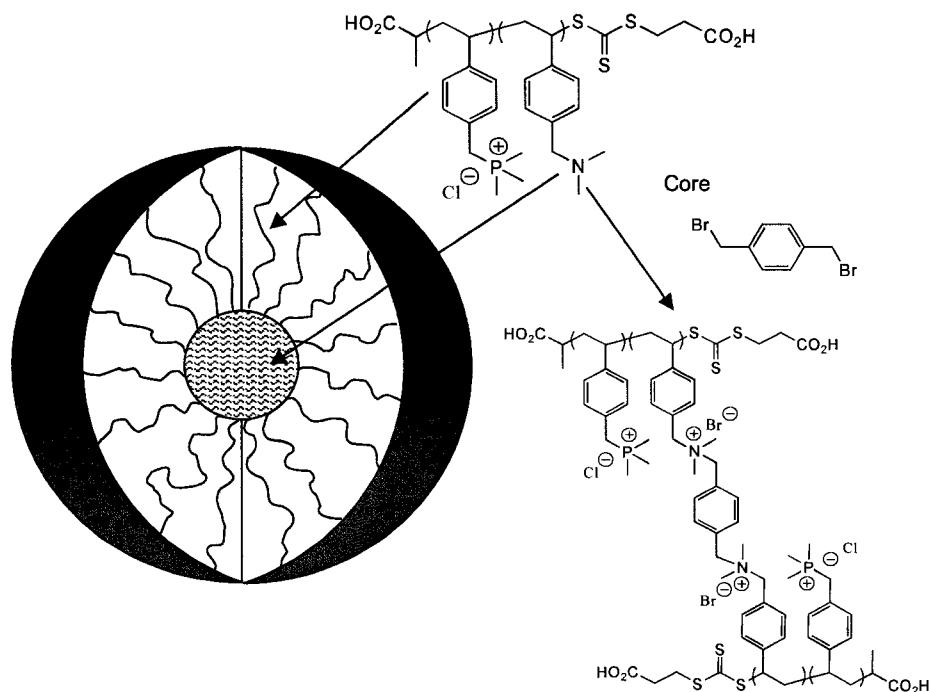


Figure V-6. Core-crosslinking via the reaction of the hydrophobic **M59** residues with 1,4-bis(bromomethyl)benzene.

Given the availability of the tertiary amine residues in the core we examined the ability to prepare such core-crosslinked aggregates by reaction with 1,4-bis(bromomethyl)benzene (BBMB), Figure V-6. The hydrophobic nature of BBMB suggests it would preferentially partition into the hydrophobic core of the polymeric assemblies when added to an aqueous solution of such nanosized aggregates. Once in the core it was anticipated that BBMB would react with the tertiary amine functional groups via a simple quaternization reaction. Given the dual functionality in BBMB such reactions, which can occur both inter- and intramolecularly, would result in core crosslinking. As such, BBMB was added to a micellar solution of the **M63-M59** block copolymers and allowed to react for 12 h at 70 °C. After core crosslinking, the micelle solutions were examined by ^1H NMR spectroscopy and DLS. Figure V-7 shows a series

of ^1H NMR spectra for the 55:45 M63-M59 AB diblock copolymer at pH 2 (B) prior to core cross-linking, and pH 12 (A) and pH 2 (C) after core crosslinking.

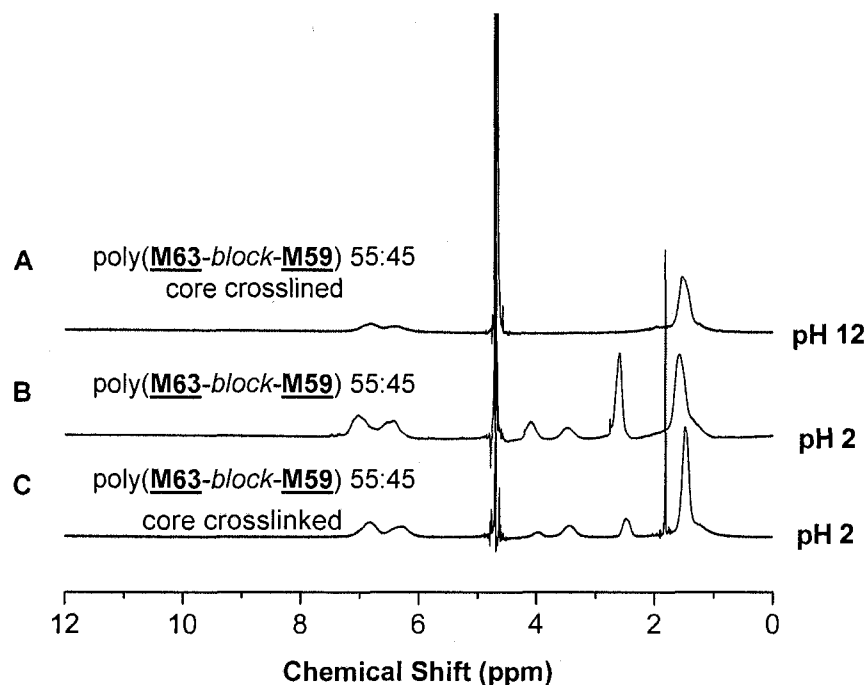


Figure V-7. ^1H NMR spectra, recorded in D_2O , of the 55:45 M63:M59 AB diblock copolymer at pH 12 after core crosslinking (A), at pH prior to core crosslinking (B), and at pH 2 after core crosslinking (C).

Figure V-7B shows the M63-M59 block copolymer at pH 2. Consistent with Figure V-3, resonance bands associated with both blocks are clearly visible and, indeed, the block copolymer is expected to exist as unimers under such aqueous solution conditions. The core crosslinking reaction must be performed at elevated pH to ensure that the M63-M59 block copolymer exists in the self-assembled state. The NMR spectrum of the 55:45 M63-M59 block copolymer at pH 12 after core crosslinking is shown in Figure V-7A. As expected, the spectrum looks identical to a non-core crosslinked system with those resonance bands associated with the M63 block being the

only ones visible. The spectrum of the core-crosslinked aggregates at pH 2.0 is shown in V-7C. At this pH the *non-core*-crosslinked aggregates disassemble to the unimeric state, and a spectrum identical to that in B would be expected. However, after core-crosslinking the aggregates are effectively locked and cannot disassemble. As such, while the core is now effectively hydrophilic there is still a significant reduced mobility associated with the **M59** block. While resonance bands associated with the **M59** residues are visible (the core is now hydrated to a certain extent) we see that the intensity of the **M59** bands, most clearly evident from the resonance associated with the dimethylamino protons at $\delta \sim 2.4$ ppm, is significantly reduced relative to the bands associated with **M106-M109** unimers in 52B.

Further verification of successful core crosslinking can be obtained from DLS. Figure V-8 shows the experimentally determined aggregate size distributions, measured at pH 2 and pH 12, for the same **M63-block-M59** copolymer after core crosslinking. At both pH values the aggregate size distribution is narrow and unimodal. At pH 12 aggregate sizes of ca. 29.1 nm were observed. This value is higher than the non-core cross-linked species at the same pH and may be due to a partial hydration of the core due to the presence of hydrophilic, permanently cationic residues. However, and in contrast to the non-core crosslinked aggregates, lowering the solution pH to 2.0 results in a further *increase* in the aggregate size to ca. 33.9 nm. Since core crosslinking effectively locks the aggregate structure lowering of the solution pH does not result in the disassembly of the polymeric aggregate back to unimers as discussed above. However, under such conditions the non-quaternized tertiary amine residues in the aggregate core can become protonated and thus hydrophilic and therefore solvated. Therefore this increase in size

can be attributed to the influx of water into the cross-linked aggregate core, resulting in core swelling and therefore an increase in aggregate size.

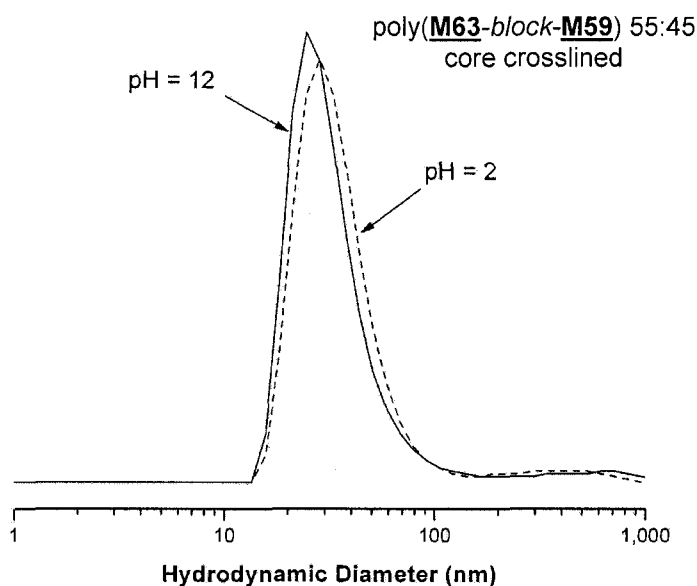


Figure V-8. Aggregate size distributions for the 55:45 M63-M59 AB diblock copolymer after core crosslinking at pH 12 and pH 2.

Summary/Conclusions

We have described herein the RAFT synthesis and aqueous solution properties of AB diblock copolymers of 4-vinylbenzyltrimethylphosphonium chloride (M63) with *N,N*-dimethylbenzylvinylamine (M59). The block copolymers were prepared directly in aqueous media using a water-soluble trithiocarbonate and the water-soluble azo initiator V-501. The pH-dependent aqueous solution properties of the M63-M59 block copolymers were evaluated using a combination of NMR and fluorescence spectroscopies, and dynamic light scattering. The AB diblock copolymers were shown to undergo pH-induced self-assembly, presumably forming core-shell polymeric micelle-

like structures, with the **M59** block forming the hydrophobic aggregate core at high pH, stabilized by the hydrophilic **M63** corona. Such aggregation was also shown to be completely reversible as judged by both DLS and fluorescence spectroscopy. Finally, we demonstrated, via NMR spectroscopy and DLS, the ability to effectively lock the aggregate structures via the reaction of the tertiary amine residues of the **M59** block in the core with a difunctional quaternizing agent bis(bromomethyl)benzene.

CHAPTER VI

A DOUBLY RESPONSIVE AB DIBLOCK COPOLYMER: RAFT SYNTHESIS AND AQUEOUS SOLUTION PROPERTIES OF POLY(*N*-ISOPROPYLACRYLAMIDE-*BLOCK*-4-VINYLBENZOIC ACID)

Introduction

Since its open disclosure on the literature,⁹⁹ reversible addition-fragmentation chain transfer (RAFT) radical polymerization has developed into a powerful synthetic tool, enabling the synthesis of hitherto unattainable (co)polymers under a broad range of experimental conditions, in a controlled manner, i.e. with predetermined molecular characteristics such as molecular mass.^{224,362,364,365,408} One of the benefits of RAFT as a synthetic tool has, undoubtedly, been the fact that it readily facilitates the preparation of new stimuli-responsive water-soluble polymers directly in either aqueous or organic media.^{57,362} Indeed, there are now many examples of such (co)polymers, prepared via RAFT, including materials responsive towards changes in solution pH,^{61,287,392} electrolyte concentration,¹²² and temperature.^{368,378,409,410} Such materials, including AB diblock and ABC triblock copolymers, are capable of undergoing supramolecular self-assembly in response to such stimuli to yield nanosized aggregates including multimeric micelles and higher order structures such as vesicles.^{399,411}

The majority of studies regarding stimuli-responsive copolymers have focused on AB diblock copolymers in which one block is permanently hydrophilic while the second is tunably hydrophilic/hydrophobic. For example, Armes et al. have reported extensively on such materials prepared by group transfer polymerization, living cationic polymerization, and atom transfer radical polymerization.^{7,12,412,413} A less studied family

of stimuli-responsive materials are AB diblock copolymers in which both building blocks are sensitive towards an applied stimulus – such materials have been termed “schizophrenic” by some researchers.^{342,396,414-416} While such materials are beginning to attract increasing interest,^{417,418} to date, very few examples of such materials have been prepared via RAFT.¹²¹

In this chapter we describe the synthesis and solution properties of a doubly responsive AB diblock copolymer of N-isopropylacrylamide (NIPAM, **M75**) with 4-vinylbenzoic acid (**M62**). We demonstrate that such materials can be readily prepared in a controlled fashion via trithiocarbonate-mediated RAFT and that both normal and inverse micelles can be formed directly, and reversibly, in aqueous media simply by controlling the aqueous solution pH and temperature.

Experimental Part

All chemicals were purchased from the Aldrich Chemical Company at the highest available purity and used as received unless stated otherwise. *N*-Isopropylacrylamide (**M75**) was recrystallized from methanol. 4-Vinylbenzoic acid (**M62**) was prepared via a Wittig reaction as described in Chapter IV.²⁸⁷ 2-(2-Carboxyethylsulfanyl thiocarbonylsulfanyl) propionic acid (**CTA26**) was prepared as outlined in Chapter III.³⁸⁷ 2,2'-Azobis(2-methylpropionitrile) (AIBN, Wako Chemicals) was recrystallized from methanol and stored in a freezer until needed.

Homopolymerization of NIPAM (M75)

Note: the experimental prep below refers to the synthesis of a polyM75 macroCTA. In the case of the kinetic studies, separate vials containing monomer, solvent, CTA, and initiator were prepared, purged with nitrogen, and immersed in a pre-heated oil bath at 60°C. Vials were removed at predetermined time intervals and analyzed using a combination of ¹H NMR spectroscopy and size exclusion chromatography.

To a scintillation vial (20.0 mL capacity) equipped with a magnetic stirbar was added M75 (2.0 g, 1.77×10^{-2} mol), CTA26 (16.9 mg, 6.65×10^{-2} mmol), AIBN (1.09 mg, 6.67×10^{-3} mmol) and DMF (4.0 g). The vial was sealed with a rubber septum and then stirred for 30 min to facilitate complete dissolution of all components. The solution was subsequently purged with nitrogen for 20 min. The vial was then immersed in a preheated oil bath set at 80°C. The polymerization was left for 60 min after which it was quenched by exposure to air and immediate immersion in liquid nitrogen. The resulting polyM75 homopolymer was purified by dialysis for 2 days with water change twice per day. The purified homopolymer was subsequently isolated by lyophilization.

Block copolymerization of PolyM75 with M62

To a scintillation vial (20.0 mL) capacity was added the polyM75 macroCTA (0.5 g, 4.42×10^{-3} mol), M62 (0.654 g, 4.42×10^{-3} mol), AIBN (1.0 mg, 6×10^{-3} mmol) and DMF (2.3 g). The vial was sealed with a rubber septum and then stirred for 30 min to facilitate complete dissolution of all components. The solution was subsequently purged with nitrogen for 20 min. The vial was then immersed in a preheated oil bath set at 60°C. The polymerization was left for 60 min after which it was quenched by exposure to air

and immediate immersion in liquid nitrogen. The resulting poly(M75-*block*-M62) copolymer was purified by dialysis in slightly basic water for 2 days with water change twice per day. The purified block copolymer was subsequently isolated by lyophilization.

Methylation of M62 residues

The carboxylic acid functional groups on the M62 residues were methylated using CH₃I according to the procedure as described in Chapter IV.

General characterization techniques

¹H NMR spectra were recorded on a Bruker 300 53 mm spectrometer in appropriate deuterated solvents. Size exclusion chromatography (SEC) was performed on a Waters system comprised of a Waters 515 HPLC pump, Waters 2487 Dual λ absorbance detector, Waters 2410 RI detector equipped with a PolymerLabs PLgel 5 μ m MIXED-C column in DMF/LiBr (0.1 M) at flow rate of 1.0 ml/min. The column was calibrated with a series of narrow molecular mass distribution poly(methyl methacrylate) standards.

Dynamic light scattering (DLS) experiments were conducted at concentrations of 1 wt% in aqueous 0.1 M NaCl solution using a Malvern Instruments Zetasizer Nano ZS instrument equipped with a 4 mW He-Ne laser operating at $\lambda = 633$ nm, an avalanche photodiode detector with high quantum efficiency, and an ALV/LSE-5003 multiple tau digital correlator electronics system. The data were collected and processed using the Dispersion Technology Software V4.20.

Results and Discussion

As a technique, RAFT facilitates the synthesis of a broad range of materials with advanced properties including those that are sensitive to environmental changes. Indeed there are now many literature examples of such copolymers with the majority representing species in which one block is permanently hydrophilic while the second is tunably hydrophilic/hydrophobic. A generally less well-studied group of materials are those in which both blocks, in an AB diblock copolymer, are sensitive to an applied stimulus. While examples of such doubly-responsive copolymers have been previously prepared via RAFT the full scope of the technique has not been brought to bear in synthesizing such materials. Given this we decided to examine the feasibility of preparing an example of a new doubly responsive AB diblock copolymer composed of N-isopropylacrylamide (**M75**) and 4-vinylbenzoic acid (**M62**), Figure VI-1.

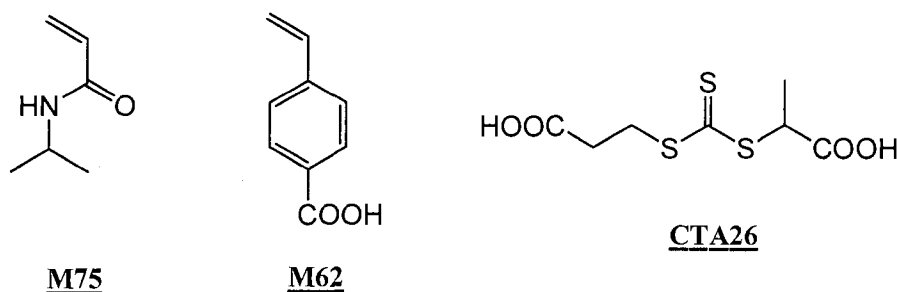


Figure VI-1. Chemical structures of monomers and RAFT chain transfer agent used in these studies.

M75 was chosen because of its well known and readily accessible lower critical solution temperature (LCST) of ca. 32°C, whereas **M62** was selected given its well-

documented pH-dependent aqueous solubility – it is readily water soluble when in the carboxylate form but completely hydrophobic when in the free acid form (as shown).

The RAFT homopolymerization of **M75** was conducted in DMF with AIBN as the source of primary radicals in the presence of **CTA26**. This is a RAFT agent that we demonstrated in Chapters III-V to be effective for the polymerization of both hydrophilic and hydrophobic substrates.^{287,387} **M75** was polymerized first since we have previously shown that when preparing block copolymers of an acrylamido substrate with a styrenic comonomer that better control is observed, in terms of block efficiency, when an acrylamido macroCTA is employed.⁵⁰ While **M75** has been polymerized by RAFT with a wide range of RAFT agents, including trithiocarbonates,³⁶² it has not been polymerized previously with **CTA26**. As such, and to verify control, we first conducted a series of experiments to demonstrate the controlled nature of the **M75** homopolymerization.

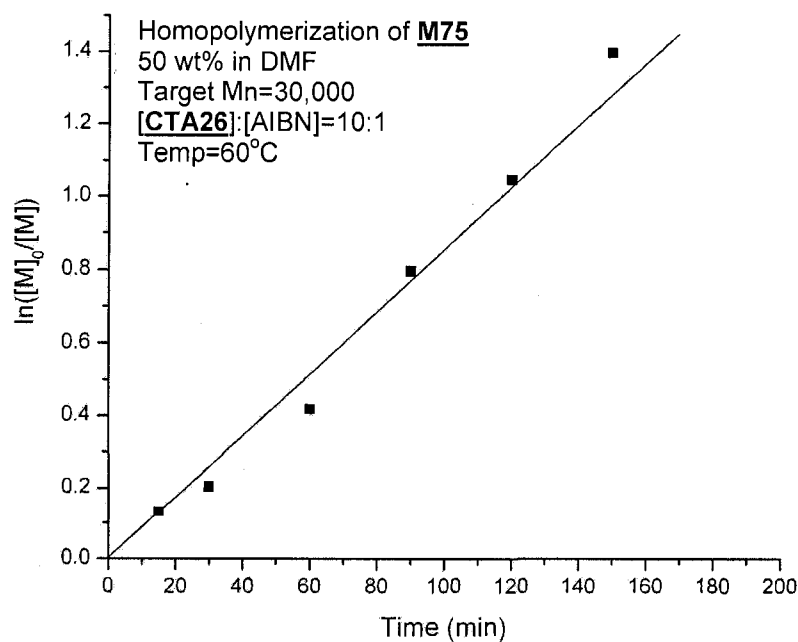


Figure VI-2. Pseudo first order kinetic plot for the homopolymerization of **M75** at 50wt% in DMF, 60°C, [CTA]:[I] = 10:1, for a target M_n of 30,000.

Figure VI-2 shows a representative example of a pseudo first-order kinetic plot for the homopolymerization of **M75** with **CTA26** in DMF at 60°C. Consistent with the majority of RAFT polymerizations, the homopolymerization of **M75** exhibits a first order dependence in monomer with no evidence of an induction period – a feature that may be observed for certain dithioester/monomer combinations but that is commonly absent from trithiocarbonate-mediated systems.³⁸⁷ Figure VI-3 shows representative SEC traces (RI signal) for aliquots withdrawn from the homopolymerization of **M75**.

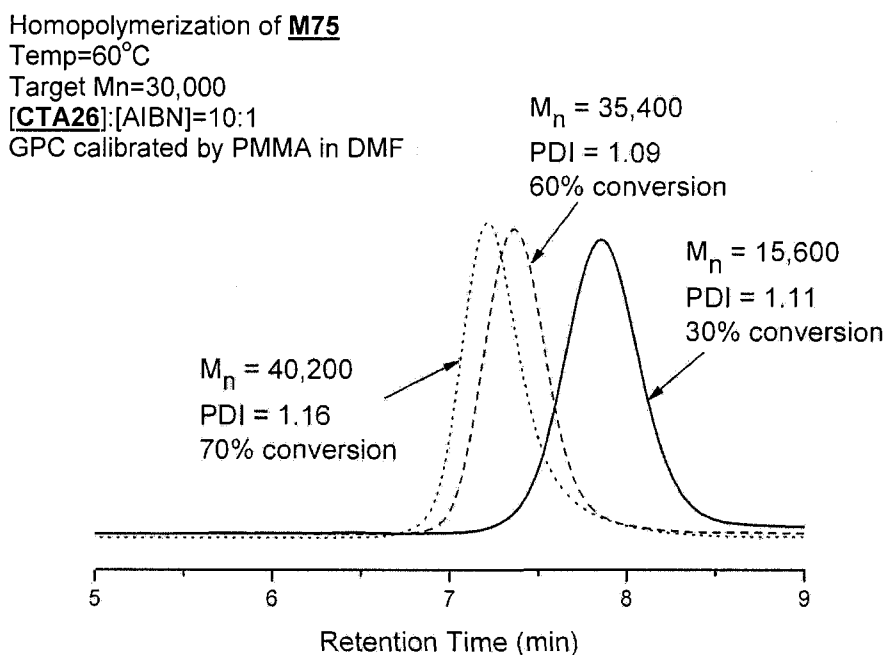


Figure VI-3. Size exclusion chromatographic traces (RI signal), measured in DMF/LiBr for aliquots withdrawn from the **M75** homopolymerization.

Consistent with a controlled polymerization we observe a systematic shift to lower retention time with increasing conversion with the chromatographic traces being unimodal and narrow with the measured polydispersity indices lying in the range $M_w/M_n = 1.09-1.16$. A better indicator, however, of the controlled nature is the M_n vs. conversion plot that should, ideally, be linear and pass through the origin. Figure VI-4 shows the evolution of M_n with conversion for the **M75** homopolymerization. We see that the plot is linear and does pass through the origin. However, the experimentally determined M_n values do not agree with the theoretical values. This discrepancy is almost certainly due to the fact that the SEC instrument was calibrated with narrow molecular mass poly(methyl methacrylate) standards which may be poor equivalents for poly**M75**.

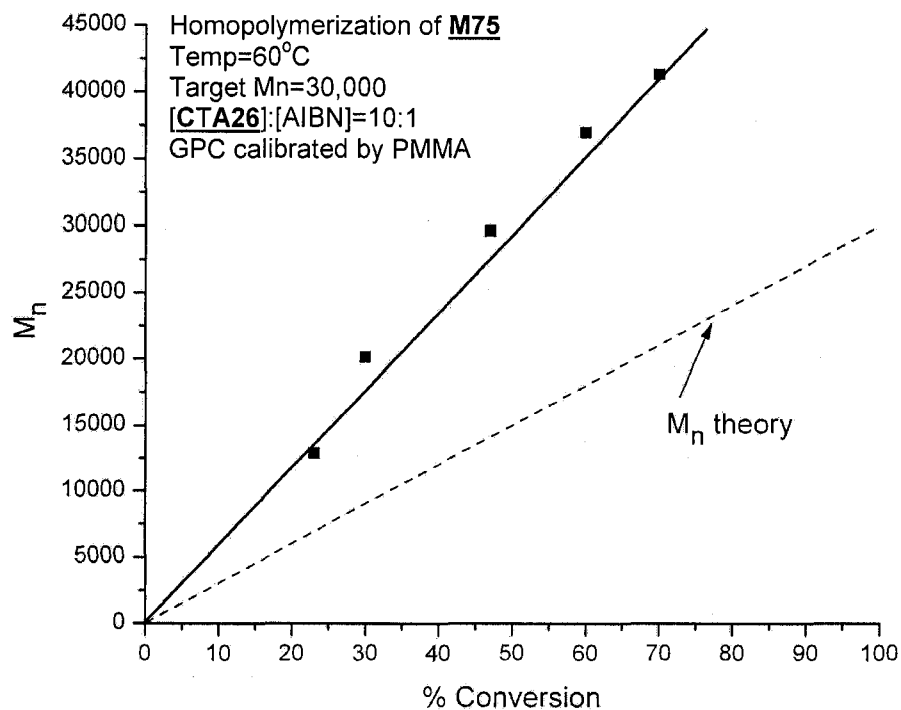


Figure VI-4. The M_n vs. conversion plot for the homopolymerization of **M75** with **CTA26** at 50 wt% in DMF with [CTA]:[I] = 10.

Having demonstrated that M75 polymerizes in an apparently controlled manner in the presence of CTA26 we next proceeded to prepare a block copolymer with M62. A new M75 macroCTA was prepared which was used in the subsequent polymerization with M62. The block copolymerization was conducted in DMF at 60°C. A block copolymer with a 50:50 molar composition was targeted. The actual composition, as determined by ¹H NMR spectroscopy, was shown to be 52:48. The symmetric composition was intentionally targeted since such molar ratios are best suited for materials with the anticipated doubly responsive properties. The most convenient method for verifying successful block formation is SEC analysis. Even though the synthesis of the M75-M62 block copolymer was conducted in DMF, the same solvent as employed as eluent for SEC analysis, we decided to methylate the acid residues on M62 to minimize any unfavorable interactions between these polar residues and the non-polar column packing material. Methylation was accomplished by treating the M75-M62 block copolymer with CH₃I according to the method outlined in Chapter IV.²⁸⁷ Figure VI-5 shows the SEC traces (RI signal) of the polyM75 macroCTA and the resulting methylated M75-M62-CH₃ AB diblock copolymer. A clear shift of the entire distribution to lower retention time is consistent with a high blocking efficiency and therefore successful block copolymer formation. Additionally, the polydispersity index of the resulting block copolymer is low, with $M_w/M_n = 1.07$.

Having successfully prepared a M75-M62 AB diblock copolymer we next proceeded to evaluate its aqueous solution properties. M75 is a well documented stimuli-responsive building block that is sensitive to changes in the temperature of aqueous solutions of the (co)polymer. Indeed, polyM75 has a well-established lower critical

solution temperature (LCST) of 32°C.³⁶⁸ In a similar manner, **M62** is also an established “smart” building block, but rather than being sensitive to changes in temperature it is tunably hydrophilic/hydrophobic as a function of solution pH.^{61,287} Specifically, at low pH, when the acid residues are protonated, **M62** is hydrophobic, whereas at pH values where the acid residues are ionized **M62** is hydrophilic. As such, it was anticipated that the **M75-M62** AB diblock copolymer would be capable of forming both normal and inverse nanosized multimeric aggregates in the same aqueous media simply by controlling the solution pH and temperature.

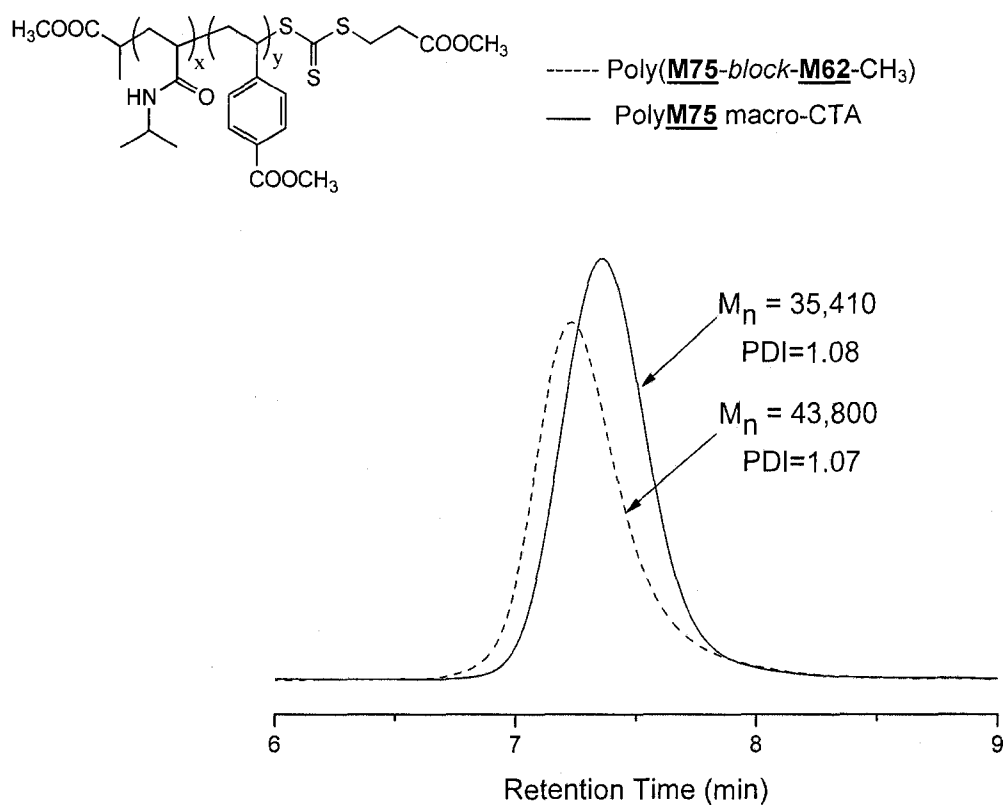


Figure VI-5. Size exclusion chromatographic traces (RI signals) for a **M75** macroCTA (solid line) and a methylated **M75-M62** AB diblock copolymer (dashed line) coupled with the measured M_n and PDI values.

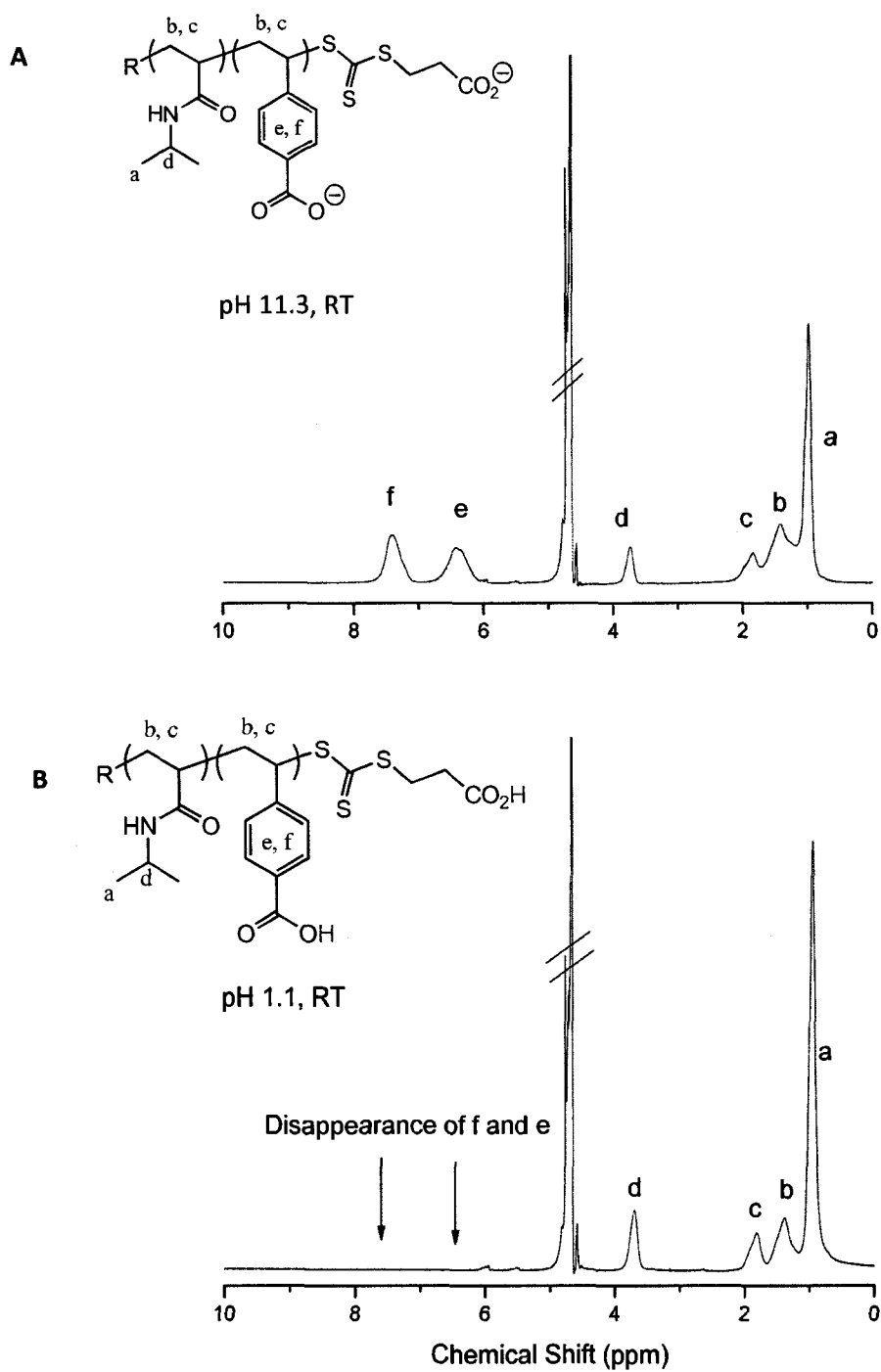


Figure VI-6. ^1H NMR spectra of the poly(**M75**-*block*-**M62**) copolymer at pH 11.3 and RT (A), and the same AB diblock copolymer at pH 1.1 and RT (B).

Figure VI-6 shows the ^1H NMR spectra of the M75-M62 AB diblock copolymer at pH values of 11.3 (A) and 1.1 (B) at room temperature. At pH 11.3, both building blocks are hydrophilic – the M75 being pH insensitive and the M62 block being fully ionized. As such, both building blocks are expected to be fully solvated. This is confirmed in Figure VI-6A where the signals associated with both monomers are clearly evident. In contrast, lowering the solution pH to 1.1 yields a very different spectrum, Figure VI-6B. The most striking difference is the complete disappearance of the signals labeled e and f associated with the aromatic hydrogens of the M62 building block. Under these conditions these signals are completely absent. Additionally, the resonances labeled a, b, and c vary in their relative intensities given the hydrophilic-to-hydrophobic transition of the M62 block. The essentially complete disappearance of the e, f signals indicates complete dehydration of these residues. Such changes are consistent with the formation of polymeric self-assemblies such as micelles, in which the non-solvated M62 block forms a hydrophobic core stabilized by the hydrophilic M75 block. While these NMR experiments do not prove the formation of such aggregates, it is not unreasonable to assume their formation given the block nature of the copolymer. Figure VI-7 shows the same block copolymer at elevated pH, conditions in which the M62 block is ionized and thus hydrophilic, but at 40°C, a temperature above the LCST of the M75 block and conditions under which the M75 species should be significantly dehydrated. Such a scenario appears to be consistent with the spectrum in Figure VI-7. Those resonances associated with the M62 block, and especially e and f, are clearly visible. On the other hand, the signals associated with M75, while not completely absent, are significantly reduced in intensity relative to the M62 signals (Figure VI-6A). For example, the signal

labeled d at $\delta \sim 3.9$ ppm, associated with the methine H of the isopropyl group in **M75** is drastically reduced relative to e and f.

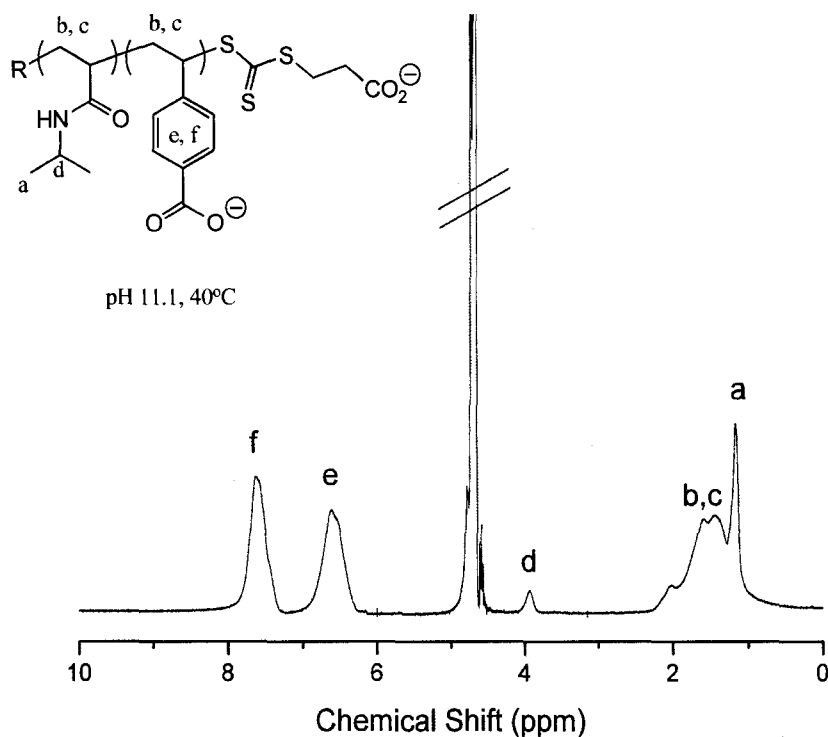
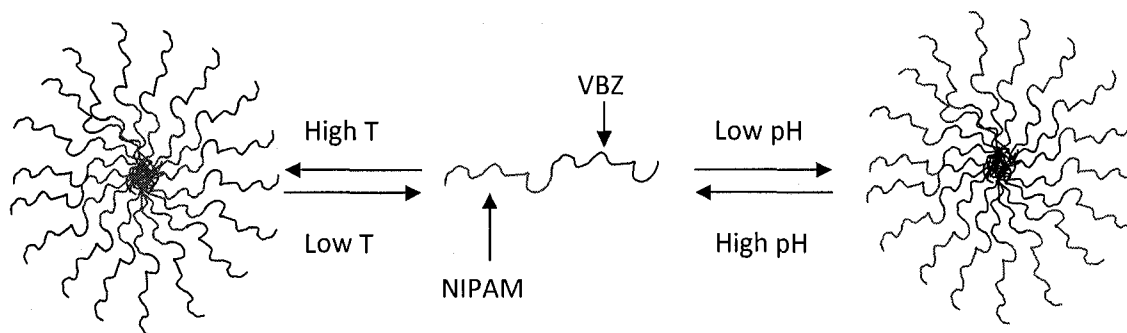


Figure VI-7. ^1H NMR spectrum of the poly(**M75**-*block*-**M62**) copolymer at pH 11.1 and 40°C.

The results presented in Figures VI-6 and VI-7 are consistent with the ability of the **M75-M62** AB diblock copolymer being able to form both normal and inverse micelles in the same aqueous solution simply by adjusting either the solution pH or temperature. This process is represented schematically in Scheme VI-1.



Scheme VI-1. Proposed formation of normal and inverse micelles in aqueous media for a M75-M62 AB diblock copolymer.

A more quantitative picture of this self-assembly process can be obtained from dynamic light scattering (DLS) experiments. Figures VI-8 and VI-9 show the hydrodynamic size distributions for the M75-M62 block copolymer at constant temperature but high and low pH, Figure VI-8, and at constant pH, but variable temperature, Figure VI-9. At 25°C and pH 12, Figures VI-8 and VI-9, the M75-M62 block copolymer is anticipated to exist as single molecularly dissolved copolymer chains, or unimers. Indeed, under these conditions average sizes in the range 14.8-15.8 nm are observed. Clearly these values should be identical since it is the same copolymer under the same conditions, however, the difference of only 1.0 nm is not significant. Lowering the solution pH to 2.0 results in the formation of aggregates with a measured D_h of 66.7 nm. There exists only a single population of aggregates with no evidence of larger, or smaller, including unimer, species. Under these conditions, the M75 block becomes hydrophobic and thus aggregates with the M62 block in the core, stabilized by the hydrophilic M75 block are expected. Moving from the unimeric state to the self-assembled state by raising the solution temperature while at elevated pH results in the formation of species with a measured D_h of 51.0 nm, Figure VI-9.

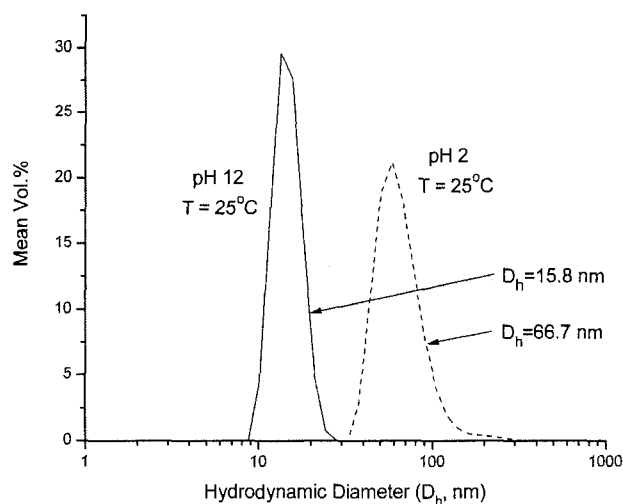


Figure VI-8. Hydrodynamic size distributions for the poly(M75-*block*-M62) AB diblock copolymer at ambient temperature and pH values of 12 and 2.

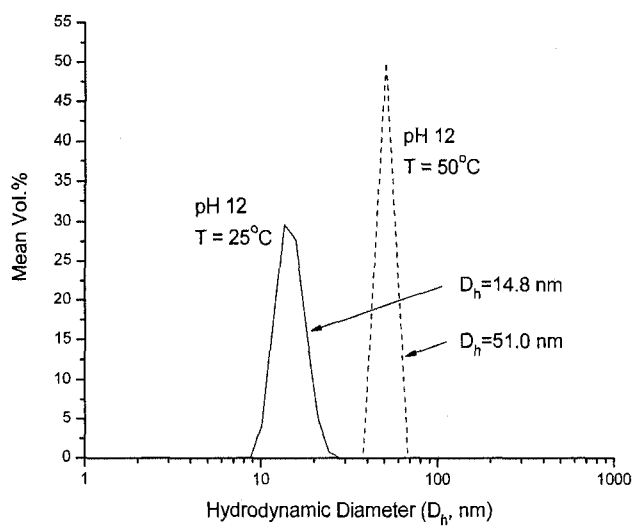


Figure VI-9. Hydrodynamic size distribution for the poly(M75-*block*-M62) AB diblock copolymer at pH 12 and $T = 25$ and 50°C

Summary and Conclusions

We have described herein the synthesis and aqueous solution properties of a near equimolar composition poly(*N*-isopropylacrylamide-*block*-4-vinylbenzoic acid) (poly(**M75**-*block*-**M62**)) copolymer. **M75** was homopolymerized in a controlled manner in DMF with a trithiocarbonate RAFT chain transfer agent (**CTA26**) to yield a well-defined macro-CTA that was subsequently employed for the block copolymer synthesis. Based on size exclusion chromatographic analysis, blocking efficiency was quantitative. The ability of such **M75**-**M62** block copolymers to undergo supramolecular self assembly to yield both normal and inverse nanosized micelles in the same aqueous environment was demonstrated using a combination of NMR spectroscopy and dynamic light scattering.

CHAPTER VII

CONCLUSIONS AND FUTURE WORK

Three new trithiocarbonates (CTA25-CTA27), along with three literature reported trithiocarbonates (CTA22-CTA24), were synthesized, in which the nature of the substitution about the TTC functional group has been systematically varied. Their effectiveness as mediating agents has been compared in the RAFT homo- and block polymerization of *n*-butyl acrylate (nBA). Both CTA26 and CTA27 perform as well as previously reported TTCs and yield poly(*n*-butyl acrylate) homopolymers with good molecular weight control and low polydispersities. CTA25 was shown to be ineffective as expected because of the proposed favored “reverse” fragmentation pathway as opposed to the required “forward” pathway for effective molecular weight control. The effect of [CTA]₀: [AIBN]₀ was determined for CTA26 and CTA27 and it was shown that the polymerizations were faster at the lower [CTA]₀: [AIBN]₀ ratios. Finally, we demonstrated the ability to form AB ‘diblock’ copolymers with nBA with high re-initiation efficiency employing CTA26 derived poly(nBA) as the macro-CTA.

CTA26 has been utilized in the subsequent synthesis of homo and copolymers via RAFT. The polymerizations of M63 and M106 represent the first example of the controlled, aqueous radical polymerization of phosphonium, styrenic-based monomers by RAFT, or by any controlled-radical technique. Additionally, M62 was also shown to polymerize in a controlled fashion in DMSO. Statistical copolymerization of M63 with M62 was readily achieved in water at 10 wt% monomer yielding the first examples of statistical polyampholytes with a cationic phosphonium building block. Also, the use of either polyM63 or polyM106 macro CTAs allowed for the subsequent block copolymerization

of **M62** to yield the first examples of block polyampholytes with a phosphonium building block and only the second example of block polyampholytes prepared *directly* by RAFT, without the need for either protection/deprotection chemistries or post-polymerization modification. The successful formation of the statistical and block PAMs was proven qualitatively by FTIR spectroscopy. The pH-responsive nature of poly(**M63-block-M62**) was confirmed by using ^{13}C NMR spectroscopy.

Poly**M63** was also used as macro-CTA in the polymerization of *N,N*-dimethylbenzylvinylamine (**M59**). A series of block copolymers with varied molar compositions were prepared directly in aqueous media. The pH-dependent aqueous solution properties of the **M63-M59** block copolymers were evaluated using a combination of NMR and fluorescence spectroscopies, and dynamic light scattering. The AB diblock copolymers were shown to undergo pH-induced self-assembly with the **M59** block forming the hydrophobic aggregate core at high pH, stabilized by the hydrophilic **M63** corona. Such aggregation was also shown to be completely reversible as judged by both DLS and fluorescence spectroscopy. Finally, we demonstrated the ability to effectively lock the aggregate structures via the reaction of the tertiary amine residues of the **M59** block in the core with a difunctional quaternizing agent bis(bromomethyl)benzene.

Finally, a doubly responsive block copolymer comprised of **M75** and **M62** with nearly equimolar composition was synthesized. **M75** was homopolymerized in a controlled manner in DMF mediated by **CTA26** to yield a well-defined macro-CTA that was subsequently employed for the block copolymer synthesis with **M62**. The blocking efficiency was quantitative based on size exclusion chromatography (SEC) analysis. The

ability of such M75-M62 block copolymers to undergo supramolecular self-assembly to yield both normal and inverse nanosized micelles in the same aqueous environment was demonstrated using a combination of NMR spectroscopy and dynamic light scattering.

Future work

CTA synthesis and evaluation

The key to successful RAFT polymerization is the appropriate choice of CTA according to specific type of monomer. Most of the effective CTA's are still not commercially available today and the synthesis and purification of CTA sometimes can be time-consuming. In our research, we utilized CTA26 for most polymerizations and it proved to be effective in controlling the polymerization of a variety of monomers. However, it may be less effective for methacrylate or methacrylamido monomers considering that the leaving group of CTA26 is secondary in contrast to the tertiary methacrylate/methacrylamido derived propagating radicals. Another novel diacid trithiocarbonate we synthesized, CTA27, may be a good candidate CTA when methacrylate/methacrylamido based polymers need to be prepared. However, further proof/evaluation will be needed.

Synthesis of polybetaines by polymerizing betaine monomers directly in aqueous solution

Polybetaines represents another important family of polyelectrolytes. They have a wide range of applications such as sewage treatment, flocculation, coagulation, drilling fluids, enhanced oil recovery, frictional drag reduction, and pharmaceuticals etc. For

example, phosphobetaines exhibit good bio/hemocompatibility and have found applications as coatings for medical devices such as catheters or arterial stents as well as materials for contact lens application. This is attributed to their biomimetic characteristics, i.e. their structural and chemical similarity to naturally occurring phospholipids.

Direct synthesis of well-defined polybetaines has always been challenging due to the unique solution properties of polybetaines, such as poor solubility in water due to the intra- and inter-chain interactions between cationic and anionic functional groups. Polybetaines are typically prepared by the direct polymerization of the betaine monomers in aqueous salt solution. Most living polymerization methods are not suitable for synthesis of polybetaines as they are not well suited for homogeneous media. In contrast, RAFT offers great potential for the controlled polymerization of betaine monomers. For example, DMBVA (**M59**) can be reacted with suitable sultones or lactones to yield the corresponding sulfo- or carboxybetaine monomers. These betaine monomers can be polymerized via RAFT in salt solution utilizing **CTA26** as the mediating agent. And they can also be copolymerized with permanently hydrophilic monomers such as TMP (**M63**) to get AB diblock copolymers, which would exhibit salt-responsive solution properties by virtue of the betaine block.

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