Design and Synthesis of Star Macromolecular Architectures with Degradable Functionality

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Abstract

Polymers with star shaped architectures represent an interesting class of macromolecule. Core cross-linked star (CCS) polymers in particular have shown potential for use in various fields of application including drug delivery, paint additives and membrane formation. The work presented in this thesis is directed towards investigating the synthesis of CCS polymers, looking at various ways of modifying the structural design to further expand the potential range of applications as well as develop a deeper understanding of this unique class of macromolecule. This was achieved through the incorporation of labile functional groups such that specific regions of the CCS polymer could be selectively targeted for degradation, thereby altering the structure and consequentially the properties in a controlled fashion.

The core/shell structure of CCS polymers allowed for a range of selectively degradable CCS polymers to be synthesized, where either the arms or the core could be selectively targeted for degradation. This was achieved by using a combination of Atom Transfer Radical Polymerization (ATRP) and Ring-Opening Polymerization (ROP) to incorporate acid-labile ester linkages into the CCS polymer structure. Subsequent hydrolysis of these bonds was shown to be an efficient and precise means for cleaving the targeted moieties without damaging the ‘non-degradable’ component of the star’s structure.

Synthesis of both ‘arm-degradable’ and ‘core-degradable’ CCS polymers was shown to be possible, with hydrolysis of these polymers effectively converting the star architecture into highly cross-linked core particles in the case of arm-degradable CCS or linear polymers in the case of core-degradable CCS. To achieve this, a novel method for generating CCS polymers via ROP based cross-linking of bislactone monomers was developed. This approach was subsequently applied to the synthesis of fully degradable CCS polymers, resulting in a polymerization which could be achieved in a one-pot process and thus eliminate the need for isolation and purification of the intermediate macroinitiator.

Factors affecting the extent of CCS polymer formation for these selectively degradable polymers were investigated. Experimental reaction conditions such as the arm molecular weight, the relative amount of cross-linker to macroinitiator and the overall reaction concentration were all shown to have significant influence. The
effectiveness of several cross-linkers was also examined, with the divinyl monomers ethylene glycol dimethacrylate (EGDMA) and divinylbenzene (DVB) being used to generate non-degradable cores and the bislactone monomers 4,4’-bioxepanyl-7,7’-dione (BOD) and 2,2-bis(e-caprolactone-4-yl)propane (BCP) being used to generate degradable core domains. A higher conversion of arms into CCS polymer was observed for the use of EGDMA compared to DVB, whilst BOD proved to be more efficient than BCP.

Side reactions involving star-star coupling and gelation of the CCS polymers generated via the ROP cross-linking approach were investigated. Hydroxyl impurities from adventitious water was found to be the main cause of star-star coupling during CCS formation, with carefully prepared anhydrous conditions being shown to effectively stop this coupling reaction. Issues of continued star-star coupling after precipitation leading to insolubility of the CCS polymers was also found to be a problem, with catalyst trapped within the core domain thought to be promoting coupling of the cores and decreasing the solubility. This problem of reduced shelf life was overcome by either storing the degradable CCS polymers at low temperature (≤2°C) or in the presence of a solvent such as tetrahydrofuran (THF), with both methods effectively stopping any further coupling reactions.

The versatility of these selectively degradable CCS polymers was subsequently investigated, with several different techniques for post-synthesis modification of the coronal structure being developed. A range of CCS polymers with miktoarm, block copolymer arm and mikto/block copolymer arm structures were generated and shown to be a viable means of manipulating properties such as the size, density and chemical composition of the CCS corona. Further functionalization to incorporate multiple pendent acetylene groups into the arms of the CCS polymer was also carried out. The increased functionality of this CCS polymer was demonstrated by attaching azide functionalized linear polystyrene via a copper (I) catalyzed cycloaddition reaction between the azide and acetylene groups. This resulted in a CCS polymer with ‘brush-like’ arm structures, the grafted segment of which could be liberated via hydrolysis of the polyester star structure to generate molecular brushes.
Declaration

This is to certify that

(i) this thesis comprises only my original work towards the PhD except where indicated in the Preface;
(ii) due acknowledgement has been made in the text to all other material used;
(iii) the thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

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Publications Obtained from this Thesis

**Refereed Journal Articles**

‘Degradable Core Cross-Linked Star Polymers via Ring-Opening Polymerization’


‘Synthesis of Core Cross-Linked Star Polymers with Adjustable Coronal Properties’

**Patents**

Qiao, G. G.; Connal, L. A.; Wiltshire, J. T. *Porous Polymeric Materials and Polymer Particles For Preparation Thereof*, International patent application

**Conference Proceedings**


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List of Abbreviations and Symbols

The following abbreviations and symbols are used throughout this thesis

AIBN  Azobisisobutyronitrile
ARGET Activators regenerated by electron transfer
ATRA Atom transfer radical addition
ATRP Atom transfer radical polymerization
BCP 2,2-Bis(ε-caprolactone-4-yl)propane
BHEMN 4,6-Bis(2-hydroxyethyl)-5,5-dimethylnonanedioic acid
BHEO 4,5-Bis(2-hydroxyethyl)octanedioic acid
BOD 4,4'-Bioxepanyl-7,7'-dione
bpy 2,2'-Bipyridine
CCS Core cross-linked star
CL ε-Caprolactone
CRP Controlled radical polymerization
Dₜ Hydrodynamic diameter
Da Dalton
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DLS Dynamic light scattering
DMF N, N-Dimethylformamide
DP Degree of polymerization
DVB Divinylbenzene
EGDMA Ethylene glycol dimethacrylate
EPR Enhanced permeability and retention
f Number of arms incorporated into CCS polymer
FDA Federal Drug Administration (USA)
FTIR Fourier transform infrared spectroscopy
GA Glycolic acid
GC Gas chromatography
GC-MS Gas chromatography – mass spectrometry
GPC Gel permeation chromatography
GTP Group transfer polymerization
IR  Infrared
LA  Lactic acid
LS  Light scattering
Mₐ  Number average molecular weight
Mₙ  Weight average molecular weight
MALLS  Multiangle laser light scattering
MMA  Methyl methacrylate
NMP  Nitroxide-mediated polymerization
NMR  Nuclear magnetic resonance
PCL  Poly(ε-caprolactone)
PD  Polydispersity
PEG  Poly(ethylene glycol)
PgMA  Propargyl methacrylate
PHEMA  Poly(2-hydroxyethyl methacrylate)
PMDETA  $N, N', N'', N'''$-Pentamethyldiethylenetriamine
PMMA  Poly(methyl methacrylate)
PPgMA  Poly(propargyl methacrylate)
PSt  Poly(styrene)
P(TMS-PgMA)  Poly((Trimethylsilyl)propargyl methacrylate)
RAFT  Reversible addition-fragmentation chain transfer
RI  Refractive index
ROP  Ring-opening polymerization
SD  Standard deviation
Sn(Oct)₂  Stannous octoate (stannous 2-ethylhexanoate)
St  Styrene
Tₘ  Glass transition temperature
TBAF  Tetra-$n$-butyl ammonium fluoride
TEMPO  2,2,6,6-Tetramethylpiperidinyloxy
THF  Tetrahydrofuran
TMS-PgMA  (Trimethylsilyl)propargyl methacrylate
WF  Weight fraction
°C  Degrees Celsius
$\chi_C$  Conversion of cross-linker
$\chi_A$  Conversion of macroinitiator into CCS polymer arms
Chapter 1 - Introduction

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1.1 Introduction
In the past decade, the field of polymer chemistry has undergone a revolution of sorts. Exciting new developments in controlled polymerization techniques have opened the doorway for the synthesis of a wide range of novel, well-defined polymeric architectures. Structures such as comb, brush and star shaped polymers are all now possible and represent only a small fraction of what has been shown to be possible. Recently, novel polymeric architectures such as these have become the focus of considerable attention due to a growing demand for highly functionalized, well-defined macromolecules for nanoscale applications, particularly in the electronic and biotechnology fields.

One particular class of macromolecule which has significant potential in terms of its academic and industrial importance is that of star polymers. In this thesis we will look at further developing the functionality of this class of polymer to increase its application potential. This chapter introduces several different approaches for synthesizing star polymers, looking at the synthesis route, the various polymerization techniques, and the resulting structure of the star polymer. In addition to this, the concept of functionalization will also be discussed.

1.2 Synthesis of Star Polymers
Star polymers represent an interesting class of macromolecule due to their unique three-dimensional architecture which is typified by a central core with radiating linear polymeric arms. The architectural makeup of this type of polymer generates some very interesting rheological properties such that star polymers can have a very high molecular weight (> 100,000 g/mol) but still possess a solubility and viscosity similar to linear or branched polymers of relatively low molecular weight. Properties such as these have led to a wide range of potential applications for CCS polymers, particularly in the areas of drug delivery, membrane formation, and paint additives.

In general, there are two methods for synthesizing star polymers which can be categorized as either following the ‘core first’ or the ‘arms first’ approach.
1.2.1 Core first approach

The ‘core first’ approach involves the use of a multifunctional initiator from which the arms of the star polymer are grown (Scheme 1.1). A variety of different controlled polymerization techniques have been successfully employed to synthesis star polymers via this route, including anionic polymerization,\textsuperscript{[8,9,10]} group transfer polymerization (GTP),\textsuperscript{[11]} nitroxide-mediated polymerization (NMP),\textsuperscript{[12,13]} atom transfer radical polymerization (ATRP),\textsuperscript{[14,15,16,17]} and reversible addition-fragmentation chain transfer (RAFT) polymerization.\textsuperscript{[18,19,20,21]}

\[
\text{Multifunctional Initiator} + M \xrightarrow{\text{Polymerization}} \text{Star Polymer}
\]

\textbf{Scheme 1.1:} Synthesis of star polymers via the ‘core first’ approach.

In order for this method to generate star polymers with uniform arm lengths and low molecular weight distributions, the multifunctional initiator has to fulfill several criteria. Firstly, all of the initiation sites must be equally reactive (i.e. 100% initiation efficiency) to ensure that each star polymer contains exactly the same number of arms. Furthermore, each initiation site must experience a similar rate of initiation, which has to be higher than that of the propagation rate, such that the degree of polymerization achieved for each arm is similar.

One of the drawbacks associated with the ‘core first’ approach is that the number of arms on the star polymer is limited to the initial functionality of the initiator. Consequently, star polymers generated via this method typically have small arm numbers (3-8) and relatively low molecular weight cores. In order to overcome this limitation, hyperbranched\textsuperscript{[22,23]} and dendritic\textsuperscript{[24,25,26]} polymers have been utilized as multifunctional macroinitiators to synthesize high molecular weight star polymers with many arms. Functionalized nanoparticles\textsuperscript{[27,28,29]} and poly(saccharides)\textsuperscript{[30,31]} have also been utilized for this purpose.
1.2.2 Arms first approach

Star polymers can also be generated via the ‘arms first’ approach as illustrated in Scheme 1.2. Here, living linear arms (macroinitiator) capable of further chain extension are initially synthesized. These terminally reactive linear polymer chains are subsequently used to initiate the polymerization of a cross-linkable monomer such that the active arm ends are coupled together to form star-shaped polymer with a cross-linked core. A variation of this technique involves the copolymerization of linear macromonomer with cross-linker using low molar mass initiators.\cite{32} Both these techniques result in star polymers where the initiating functionality is preserved within the core of the star polymer. This allows for a second type of arm to be grown out from the core to produce what is known as a miktoarm star polymer via the ‘in-out’ method.\cite{1,33,34,35} Other, more complex, architectures can also be generated such that star polymers with block copolymer arms\cite{36,37} or even dendron terminated arms\cite{36,38} can easily be synthesized. In this thesis, star polymers will be generated exclusively by the ‘arms first’ approach.

![Scheme 1.2: Synthesis of star polymers via the ‘arms first’ approach.](image)

Star polymers generated via the ‘arms first’ approach have a very unique three dimensional architecture, consisting of a highly cross-linked core domain surrounded by a number of radiating linear arms. The number of arms follows a statistical distribution and typically ranges from anywhere between 10 to 100 arms per star depending on the reaction conditions. The structure of these star polymers is very different to that of star polymers generated via the ‘core first’ approach and will hereafter be referred to as core cross-linked star (CCS) polymers to avoid ambiguity.
Traditionally, CCS polymers synthesized by the ‘arms first’ approach have made use of controlled polymerization techniques (Section 1.3). This allows for the generation of very high molecular weight CCS polymers, in excess of one million in some instances, whilst still maintaining very narrow polydispersities ($M_w/M_n < 1.2$). It also facilitates the incorporation of a high degree of functionalization as discussed in the next section.

### 1.2.3 Functionalization

The controlled polymerization techniques used to synthesize CCS polymers allow for the incorporation of a wide variety of different functional groups, ranging from hydrophilic groups such as hydroxyl, carboxylic acid and amine groups to click chemistry functionalities such as alkyne and azide groups. The unique three-dimensional architecture of CCS polymers allows for the incorporation of these functionalities within different regions of the CCS polymer such that the core, the arms, or the surface of the star can be selectively functionalized (Scheme 1.3). For example, the use of functionalized monomer during arm formation can lead to CCS polymers where each arm contains a vast number of functional groups, either incorporated into the backbone of the polymeric arms or attached as pendant functionalities.[39] Alternatively, end functionalized arms can be synthesized through the use of a functional initiator to yield CCS polymers where only the periphery of the star is functionalized.[40,41] The core domain can be functionalized in a similar fashion through use of functional cross-linkers or functional monovinyl comonomers during the core formation step.[42,43]
The ability to functionalize the arms is particularly important since the coronal domain significantly influences the physical properties displayed by the CCS polymer. Properties such as the crystallinity or hydrophilicity of a CCS polymer can easily be modified by changing the type of polymer used to generate the arms. For example, Connal et al.\textsuperscript{[5]} showed that the glass transition temperature ($T_g$) of CCS polymers could be decreased from 123°C to -122°C by simply changing the polymeric composition of the arms from poly(methyl methacrylate) to poly(dimethylsiloxane). The length and the number of arms, i.e. the size and density of the corona, also play a significant role in determining the properties of CCS polymers. A reduction in arm length has been shown to reduce the viscosity of CCS polymer solutions due to the structure becoming more compact and hence reducing the degree of entanglement experienced between adjacent star polymers.\textsuperscript{[44]}

1.3 Controlled/Living Polymerization
The term ‘controlled’ or ‘living’ polymerization refers to a chain growth polymerization reaction that propagates with minimal irreversible chain-transfer or
chain-termination reactions. This allows for a higher degree of control compared to conventional free radical polymerizations which are very difficult to control due to fast, irreversible termination of the growing radicals through combination and disproportionation reactions. In general, a living polymerization can be identified by the following characteristic properties:\[45\]

1) Living polymerizations proceed until all monomer is consumed and may continue growth if further monomer is added.

2) In a living polymerization the molecular weight increases linearly with conversion.

3) In a living polymerization the concentration of active species remains constant. i.e. A plot of $\ln([M]_0/[M]_i)$ vs time should be linear.

4) Living polymerizations provide narrow molecular weight distributions ($M_w/M_n < 1.2$).

5) Block copolymers can be prepared by sequential addition of monomers.

6) End groups are retained allowing end-functional polymers to be obtained in quantitative yield.

The first example of a living polymerization was demonstrated by Szwarc in 1956.\[46\] Since then a range of living polymerization systems have been developed including anionic,\[47,48\] ring-opening,\[49\] group transfer,\[50\] nitroxide-mediated radical polymerization (NMP),\[51,52,53,54,55\] atom transfer radical polymerization (ATRP),\[56,57\] and reversible addition-fragmentation chain transfer (RAFT) polymerization.\[58,59,60,61\]

The development of these controlled polymerization techniques has led to the generation of a range of complex macromolecules with well-defined architectures and narrow polydispersities. A prime example of this has been in the emergence of star polymers as discussed in Section 1.2.

1.3.1 Anionic Polymerization

The use of a living polymerization technique to synthesize CCS polymers was first reported by Rempp and co-workers\[62\] in 1969. Since then, many other groups have successfully used this technique to prepare CCS polymers\[63,64,65,66,67\] and indeed, in the early days, this was the most prevalent method.

The mechanism of living anionic polymerization typically involves the chain growth of vinyl monomers initiated by a strong base and anion. Early investigators used alkali metal initiators in NH$_3$ (liq.) but these were replaced by metal alkyls such as $n$-
butyllithium in the 1940’s.\cite{68} Scheme 1.4 shows the initiation step involving BuLi and the subsequent polymerization of vinyl monomer. For this polymerization to proceed, the substituent R group must possess an electron withdrawing group capable of stabilizing the propagating species. Examples of suitable electron withdrawing groups are esters (i.e. methyacrylate), cyano groups (i.e. acrylonitrile) and phenyl groups (i.e. styrene).

\[
\text{Bu Li}^+ + \text{R} \rightarrow \text{Bu}^{+} \text{H} \text{R}^+ \rightarrow \text{Bu}^{+} \text{H} \text{R} \rightarrow \text{Bu}^{+} \text{H} \text{R}^+ \rightarrow \text{Bu}^{+} \text{H} \text{R} \rightarrow \text{Bu}^{+} \text{H} \text{R}^+ \]

\textbf{Scheme 1.4:} General mechanism for anionic polymerization.

Unfortunately, this process requires very stringent reaction conditions and cannot be used in the presence of protic solvents such as water. In addition to this, the range of monomers which can be utilized is fairly limited as they must contain an appropriate electron withdrawing group to stabilize the propagating species. It has also been shown that the pendant vinyl bonds resulting from the anionic polymerization of divinyl monomers are 10 times less reactive in this approach, effectively limiting the extent of CCS formation by reducing the efficiency of the cross-linking reaction.\cite{69}

The use of living anionic polymerization to synthesize CCS polymers has subsequently been superseded by recent developments in controlled radical polymerization (CRP) techniques. The synthesis of highly functionalized macromolecules with precisely controlled architectures can now be achieved under less rigorous conditions and with more flexibility than previously required for anionic polymerizations.\cite{70,71,72}

1.3.2 Nitroxide-Mediated Polymerization (NMP)

The first example of a CRP technique used to prepare CCS polymers was reported by Solomon and coworkers\cite{73} in 1997 using nitroxide-mediated polymerization (NMP). Since then many other examples of CCS polymers prepared by NMP have been published in the literature.\cite{36,74,75,76,77}

The general mechanism for NMP is shown in Scheme 1.5. Here, an initiator such as azobisisobutyronitrile (AIBN) is fragmented at elevated temperatures to produce
radicals which are initially trapped at near diffusion rates by a nitroxide trapping agent, 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) in this case. The alkoxyamine produced then fragments, regenerating a carbon-centered radical which can react with monomer such as styrene. The nitroxide radical thus acts as a reversible radical mediator (i.e. reversibly terminates the propagating chain end without acting as a initiator itself), effectively reducing the overall concentration of propagating chains such that irreversible termination reactions are minimized resulting in a controlled, narrow polydisperse polymerization.

![Scheme 1.5: General mechanism for nitroxide-mediated polymerization.](image)

One of the major drawbacks associated with this class of controlled polymerization is that the persistent nitroxide radicals (TEMPO) are known to slowly and irreversibly abstract benzylic hydrogen atoms.\[^{78}\] This results in a loss of the controlling reaction partner and an increase in polydispersity. Another potential problem associated with NMP is related to the structural integrity of the synthesized polymers. It has been shown that the alkoxyamine chain ends undergo significant decomposition at elevated temperatures,\[^{54}\] a problem which effectively reduces the thermal stability of CCS polymers synthesized via this technique. This problem can be overcome by converting the alkoxyamine end-groups into more thermally stable moieties via reaction with
maleic anhydride,[79] however this involves an additional step which can be avoided through the use of alternative polymerization techniques.

1.3.3 Reversible Addition-Fragmentation Chain Transfer (RAFT) Polymerization

Another form of CRP that has been utilized to synthesize CCS polymers is that of reversible addition-fragmentation chain transfer (RAFT) polymerization.[80,81,82] The key to this process is the thiocarbonylthio RAFT agent which can reversibly activate the growing polymer chains to produce a living environment. A wide variety of molecules capable of acting as RAFT agents have now been reported, including a range of dithioesters, trithiocarbonates and xanthates.

The general mechanism for the addition-fragmentation equilibria experienced during RAFT polymerizations is shown in Scheme 1.6. In the early stages of the polymerization, a propagating radical (P_n•) is added to the RAFT agent (1) to form an intermediate radical (2). This is followed by fragmentation of (2) which gives rise to a polymeric thiocarbonylthio compound (3) and a new radical (R•). This new radical can then be reacted with monomer to form a new propagating radical (P_m•). A rapid equilibrium between the active propagating radicals (P_n• and P_m•) and the dormant polymeric thiocarbonylthio compound (3) provides an equal opportunity for all of the chains to grow evenly and therefore generate narrow polydisperse polymers.
One of the advantages of RAFT polymerization over the other forms of controlled polymerization lies in its versatility. The compatibility of RAFT with most monomer types and a wide range of reaction conditions\cite{58} make it a very powerful technique. However, the usefulness of RAFT in the synthesis of CCS polymers has been rather limited due to difficulties in obtaining stars with narrow polydispersities via this method.\cite{83} The use of RAFT polymerization also has the disadvantage that the thiocarbonylthio group is retained in the polymeric product, the presence of which results in a coloured polymer, typically pink.

1.3.4 Atom Transfer Radical Polymerization (ATRP)

In 1995, two important methods for controlled radical polymerization were published by the groups of Sawamoto\cite{84} and Matyjaszewski.\cite{85} Both were an extension of Atom Transfer Radical Addition (ATRA),\cite{86} a well-known method for the addition of an organic halide across an alkene double bond. They demonstrated that by using an excess of alkene monomer, the catalytic process for forming an alkane separated by
halide and initiator fragment continues to drive the reaction until all of the monomer is consumed. This process is commonly referred to as atom transfer radical polymerization (ATRP).

In the years since this technique was first reported, many other publications have followed which have demonstrated the versatility of ATRP in preparing a wide range of complex polymer architectures. ATRP has been extensively employed in the synthesis of CCS polymers\cite{87,88,89,90,91,92} and has proven to be the most efficient and popular technique for synthesis of this class of polymer. For this reason, ATRP will be one of the principle techniques utilized for the work presented in this thesis.

The general mechanism for ATRP is shown in Scheme 1.7. Initiation occurs as a result of a metal catalyst complex (M_{t}^{n}X_{m}L_{m}) reversibly abstracting a halogen from an initiator (R-X) to generate a radical species, while the metal complex is oxidized to M_{t}^{n+1}X_{n+1}L_{m}. The radical species can then react with monomer to produce a propagating radical (P_{n}\textbullet{}), which can either continue to react with monomer or return to a dormant yet ‘living’ species (P_{n-}\text{-}X). This type of polymerization is referred to as living since the polymer species P_{n}\text{-}X can be isolated, characterized and reinitiated to produce higher molecular weight polymer. Since the reaction equilibrium lies heavily in favour of the dormant species, the concentration of active P_{n}\textbullet{} radicals throughout the reaction is kept low and consequently little termination due to hydrogen abstraction or combination is observed. This, and the fact that the growing polymer radicals propagate at similar rates, leads to a controlled increase in molecular weight and results in a very narrow polydispersed polymer being produced.

\[
\text{Initiation} \quad R-X + M_{t}^{n}X_{n}L_{m} \rightarrow R\textbullet{} + M_{t}^{n+1}X_{n+1}L_{m}
\]

\[
\text{Propagation} \quad R\textbullet{} + \text{monomer} \rightarrow P_{n}\textbullet{}
\]

\[
P_{n}\textbullet{} + M_{t}^{n+1}X_{n+1}L_{m} \rightarrow P_{n}\text{-}X + M_{t}^{n}X_{n}L_{m}
\]

Scheme 1.7: General mechanism for atom transfer radical polymerization.
To better highlight this mechanism, a specific example involving the polymerization of styrene is shown in Scheme 1.8. In this case copper chloride catalyst is used to abstract a chlorine atom from tosyl chloride (TsCl), a typical ATRP initiator. This generates a tosyl radical which can subsequently react with styrene monomer to generate a growing polymer chain. Reversible capping of the radical allows the polymer to return to a dormant state, with the equilibrium of this reaction favouring the dormant species and thereby resulting in a controlled polymerization.

**Scheme 1.8:** Tosyl chloride initiated ATRP of styrene.

ATRP has widely been used for the polymerization of methacrylates, however, an extensive range of monomers, including most of those amenable to conventional radical polymerization, have been successfully polymerized via ATRP. The choice of monomer plays an important role in the degree of control that can be achieved via ATRP since every monomer possesses its own intrinsic radical propagation rate. Thus, for a specific monomer, the concentration of propagating radicals and the rate of radical deactivation need to be adjusted to maintain polymerization control. However, the equilibrium position for the overall reaction isn’t solely dependant on the monomer since it is also a catalytic system and can be adjusted by the amount and reactivity of the transition metal catalyst added.
The choice of catalyst for use in ATRP is very important since it determines the position of the atom transfer equilibrium and the dynamics of the exchange between the dormant and active species. The initial reports on ATRP made use of copper(I) and ruthenium(II) complexes. Since then, a wide range of transition metal complexes have been used as catalysts in ATRP, the most common being based on a copper(I) halide and nitrogen based ligands such as 2,2'-bipyridine (bpy) and $N,N',N''-N'''$-pentamethyldiethylenetriamine (PMDETA) (Figure 1.1). For the transition metal complex to be appropriate for use in ATRP it must have two readily accessible oxidation states and a good affinity for the particular halogen associated with the initiator.

![bpy PMDETA](image)

**Figure 1.1:** Chemical structure of common nitrogen based ligands used in ATRP.

Due to the relatively large amount of catalyst used in traditional ATRP, typically in the order of $0.1 - 1$ mol % relative to monomer, the polymers generated via this method contain a significant amount of residual metal complex. This is undesirable as the toxicity of these metal complexes may limit the polymer’s usefulness, particularly for applications in the biomedical field. Several efficient strategies for catalyst removal have been developed to combat this problem as highlighted in a recent review by Tsarevsky and Matyjaszewski. However, simply passing the polymer solution through a column filled with ion-exchange resin or absorbent such as alumina is sufficient to reduce the amount of residual catalyst to a level suitable for most applications.

Initiators used in ATRP are typically alkyl halides and the rate of polymerization is first order with respect to the concentration of the alkyl halide. To obtain well defined polymers with narrow molecular weight distributions the halide group, $X$, must rapidly and selectively migrate between the growing chain and the transition metal complex. Currently, the most popular halogens for use in ATRP have been chlorine and bromine since it has been found that they offer the best molecular weight
control. Some pseudo-halogen, such as thiocyanate, have also been used successfully.

The selection of reaction conditions for ATRP is dependant on many factors including the particular choice of monomer, catalyst and initiator. They can be carried out in bulk (without solvent) but, due to steric hindrance effects slowing the polymerization down, it is often preferred to use a solvent. Common solvents for ATRP include ketones (butanone, acetone), alcohols (2-propanol), aromatics (p-xylene, anisole) and even aqueous systems. The main determining factor for the choice of solvent, apart from solubility of the reaction mixture, is the effect that the solvent has on the catalyst. Issues such as catalyst poisoning, catalyst structural changes and solvent-assisted side reactions all need to be taken into consideration when choosing an appropriate solvent.

One of the main problems associated with ATRP, and for that matter all CRP processes, is that the propagating radicals are rapidly trapped by oxygen, resulting in termination of the polymerization. For this reason, all reaction mixtures must be rigorously deoxygenated. However, the recent development of ARGET (activators regenerated by electron transfer) ATRP by Matyjaszewski and coworkers has demonstrated that air can be consumed in ATRP systems by the addition of a sufficient amount of an appropriate reducing agent, such as tin(II) 2-ethylhexanoate. The general mechanism for ARGET ATRP is shown in Scheme 1.9. Here, the ATRP activator (Cu(I) species) is first rapidly oxidized by oxygen to the Cu(II) species, which is then reduced back to the Cu(I) state by a reducing agent, thereby regenerating the activator species. There is an initial induction period during which air is consumed, and eventually the polymerization starts, proceeding via the standard ATRP mechanism. The use of a very active copper catalyst and an excess of reducing agent which reacts slowly allows for a controlled polymerization that can be carried out in the presence of a limited amount of air (i.e. a sealed reaction vessel).
The use of ARGET ATRP to synthesize CCS polymers is an exciting prospect as it could potentially increase the commercial viability of this class of polymer. Unfortunately, due to the very recent nature of the discovery of this technique (published online December 2005), it was not utilized for the work presented in this thesis.

### 1.3.5 Ring Opening Polymerization (ROP)

Another form of controlled polymerization used extensively for the work presented in this thesis is ring-opening polymerization (ROP). ROP is a living polymerization technique which proceeds in a chain growth fashion by consecutively ‘opening’ cyclic monomers to form linear polymer.

The actual mechanism by which this type of polymerization proceeds is dependent on the catalyst system used. A number of different systems have been shown to successfully initiate ROP, with the two most common being based on the use of aluminium isopropoxide (Al(O’Pr)_3) or tin(II) 2-ethylhexanoate, commonly referred to as stannous octoate (Sn(Oct)_2), the structures of which are shown in Figure 1.2. Stannous octoate has the added benefit of being approved by the American Food and Drug Administration (FDA), making it particularly attractive for use in the synthesis of polymers for biomedical applications. In addition to this, Sn(Oct)_2 is relatively cheap, has low toxicity, good versatility and high efficiency, making it an ideal catalyst for industrial based ROP applications.
The mechanism of ring opening polymerization catalyzed with Sn(Oct)$_2$ has been the subject of much discussion. Despite several proposals$^{[101,102,103,104,105]}$ over a long period of time, the actual mechanism has only recently been elucidated. There is now sufficient experimental evidence to show that ROP catalyzed by Sn(Oct)$_2$ proceeds via a coordination-insertion type mechanism,$^{[100,106,107]}$ the details of which are shown in Scheme 1.10.

**Scheme 1.10:** Mechanism for Sn(Oct)$_2$ catalyzed ROP of ε-caprolactone.

Stannous octoate is not capable of initiating ROP by itself and needs to have at least one carboxylic ligand replaced by an alkoxide before it can act as an initiator. This is achieved by reacting Sn(Oct)$_2$ with two equivalents of an alcoholic co-initiator to
form an active stannous dialkoxide (A) (Scheme 1.10, Step 1). Addition of a cyclic monomer, in this case $\varepsilon$-caprolactone (B), results in coordination and insertion of the monomer into the stannous alkoxide bond which opens the ring structure. This generates a propagating species (C), which can either continue to react with cyclic monomer (Scheme 1.10, Step 2) or undergo reversible chain transfer between the stannous alkoxide moiety and a hydroxyl group (Scheme 1.10, Step 3); the hydroxyl group being either from unreacted initiator or another growing polymer chain end. This rapid exchange results in a dynamic equilibrium between the activated and deactivated chains ((C) and (D) respectively) resulting in a controlled polymerization with narrow polydispersed polymers.

Unlike most other forms of controlled polymerization, ROP is not a radical based technique and is consequently not sensitive to the presence of radical scavengers such as oxygen. This makes it a much easier reaction to handle since degassing is not required, making it particularly useful for polymerizations involving sequential monomer additions such as in the generation of block copolymers. ROP also has the benefit of allowing for easy manipulation of polymer end-group functionality by modifying the choice of alcoholic co-initiator used.

One potential drawback associated with ROP is its sensitivity to water which can deactivate the catalyst by forming a stannous alcohol derivative (RO–Sn–OH) which is more thermodynamically stable and therefore a less efficient initiator than the stannous dialkoxide derivative. Therefore, the presence of water impurities can act to reduce the concentration of desired active initiator and potentially result in polymer being formed without incorporation of the desired end group functionality.

1.4 Degradable Polymers

Controlled polymerization techniques, such as the ones previously described in this chapter, have facilitated the ability to synthesize polymers with a wide variety of different functional groups. Of particular interest is the incorporation of labile groups within a polymer to impart degradable functionality. In today’s world, the application of structurally stable polymers can in some instances be undesirable, a classic example being the environmental concerns associated with the disposal of plastic bags. High-tech applications for degradable polymers also exist, particularly in the biomedical field where biodegradable polymers are being used as tissue engineering...
The incorporation of degradable functionality can also be used to manipulate the physical properties of a polymer system. Careful control over the degree and type of degradable functionality incorporated means that properties such as the mechanical strength, crystallinity, glass transition temperature ($T_g$) and viscosity of a polymer system can all be altered via controlled degradation.

The incorporation of degradable functionality into polymers can be achieved through application of a variety of different labile groups, including esters, disulfides, amides and carbonates to name a few. Polyester based structures in particular have attracted significant attention due to their ease of degradation by hydrolysis of the ester linkages. One type of polyester which has proven to be quite useful is polycaprolactone (PCL) which can be synthesized in a controlled fashion via ROP of ε-caprolactone (Scheme 1.10). One of the advantages of PCL, particularly in terms of biomedical applications, is that it has been given FDA approval and is considered to be both biocompatible and biodegradable such that its degradation products are capable of being absorbed by the body with minimal tissue reaction.\textsuperscript{112}

There are two principle mechanisms by which polyesters such as PCL can be degraded, involving either chemical hydrolysis or enzymatic degradation. Of these, chemical hydrolysis is the more common technique, with the mechanism for hydrolytic cleavage of PCL being shown in Scheme 1.11. The polymer degrades via random scission of the ester linkages,\textsuperscript{113} breaking the polymer down into small hydroxy carboxylic acid units (6-hydroxyhexanoic acid).

\begin{center}
\textbf{Scheme 1.11:} Hydrolytic degradation of PCL.
\end{center}

1.5 Potential Applications for CCS Polymers

The unique three-dimensional architecture of CCS polymers generates some very interesting physical properties, particularly in terms of their rheological behavior. As a result of these properties, many potential areas of application have emerged, ranging from viscosity modifiers in paints\textsuperscript{7} to precursors for the formation of honeycomb
films.\textsuperscript{[4,5,6]} One particular area which has attracted a great deal of interest concerns the use of CCS polymers as potential drug delivery vehicles.\textsuperscript{[3]}

For a macromolecule to be suitable for drug delivery applications it should ideally possess a large core domain capable of solubilizing hydrophobic drug molecules and a hydrophilic corona which acts to stabilize the particle in aqueous media. Several polymeric architectures have already received significant attention in this area, with the majority of research focusing on the use of micelles\textsuperscript{[114,115,116]} and dendrimers\textsuperscript{[117,118]} as potential drug delivery devices. However, both these polymer architectures have significant drawbacks in terms of drug delivery applications, with the instability of micelles under shear (i.e. when injected into the bloodstream) and the arduous process of generating dendrimers of sufficient core size tending to limit their usefulness.

The ability to utilize a variety of controlled polymerization techniques means that we can now synthesize CCS polymers with low polydispersities and high functionality. Combining this with the capacity to easily tune the core/shell size, high loading capacities, and no inherent stability issues makes CCS polymers ideally suited for drug delivery applications. The low viscosity of these polymers is another advantage in term of drug delivery, allowing for higher concentrations of drug loaded particles to be injected and effectively minimize dosage requirements. Furthermore, the capacity to generate highly functionalized CCS polymers could be used to introduce targeting, imaging, and biocompatible functionalities. The attachment of targeting ligands to create drug delivery devices capable of recognizing disease affected sites (cancerous cells, tumours) has significant potential. Not only does this allow for more effective drug delivery but in combination with imaging functionalities could be used as a diagnostic tool to identify diseased tissue.

One important aspect of potential drug delivery systems lies in the ability to control the release kinetics of the drug from the delivery vehicle. The structural properties of CCS polymers play a significant role in influencing the diffusion rate of encapsulated molecules out from the core of the polymeric carrier. By tailoring the core/shell size ratio, overall hydrodynamic volume, arm density and the degree of amphiphilicity we can control the release kinetics. However, a more attractive method involves the incorporation of degradable functionality such that a higher degree of control can be exerted over the dynamics of drug release. The structure of CCS polymers is ideally suited for this purpose, with the ability to selectively incorporate degradable
functionality into either the arm or the core domain making it possible to tailor the degradability. The design of degradable stars which are pH-sensitive also opens the door for targeted drug release since various tissues and organs within the body exist within localized pH environments. Degradable drug delivery devices can also prevent unwanted bioaccumulation of the polymeric carriers by breaking them down into smaller molecules which can be excreted from the body.

It therefore stands to reason that there is a significant need for CCS polymers which can be degraded under mild conditions, an area which has typically been overlooked in the past. Consequently, this thesis aims to address this issue, looking at various ways of incorporating degradable functionality into the structure of CCS polymers to increase their application potential.

1.6 Scope of Thesis
This research aims to investigate the synthesis of CCS polymers, looking at various ways of modifying the structural design to further expand the potential range of applications as well as develop a deeper understanding of this unique class of macromolecule. More specifically, this will be achieved through the incorporation of labile functional groups such that specific regions of the CCS polymer can be selectively targeted for degradation, thereby altering the structure and consequentially the properties in a controlled fashion.

The first aspect of this study began with looking at the incorporation of a degradable functionality specifically into the arm domain, such that all of the arms could be completely degraded and therefore liberate the cross-linked core particles. Chapter 2 reports on the synthesis of such polymers, using poly(caprolactone) macroinitiators to incorporate acid-labile ester linkages into the arms. Effects of varying reaction conditions on the formation of these CCS polymers are studied along with the degradation products resulting from subsequent hydrolysis of the arms.

Chapter 3 then looks at the incorporation of degradable functionality into the core domain, developing a novel ROP cross-linking approach which utilizes bislactone cross-linkers to generate polyester-based cores. The degradation of this type of CCS polymer is examined, with the hydrolysis products being compared to the case where degradable methacrylate-based cross-linkers are used.

In Chapter 4, the techniques developed in the previous Chapters are combined to generate novel CCS polymer which is fully degradable. A one-pot approach utilizing
ROP is developed, with the effect of varying reaction conditions and the use of different bislactone cross-linkers being examined. The mechanism of star-star coupling is also investigated, with potential ways of minimizing this unwanted side-reaction being explored.

The versatility of these CCS polymers is investigated in Chapter 5, with several different techniques for post-synthesis modification of the coronal structure (size, density and chemical composition) being developed. CCS polymers with miktoarm, block copolymer arm and mikto/block copolymer arm structures are investigated and shown to be a viable means of manipulating the structure and the subsequent properties of the CCS polymer.

In the final experimental based chapter of this thesis, Chapter 6, a method for increasing the functionality of degradable CCS polymers is investigated, incorporating multiple pendent acetylene functional groups into the arms of the CCS polymer. The attachment of terminal azido functionalized linear polystyrene to the acetylene groups of this functionalized CCS polymer via ‘click chemistry’ was subsequently explored, generating a novel class of CCS polymer with a ‘brush-like’ arm structure.

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Chapter 2 - Synthesis of Arm-Degradable CCS Polymer

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2.1 Introduction

CCS polymers represent an interesting class of macromolecule due to their unique three-dimensional architecture and subsequent rheological properties as previously described in Chapter 1. The ability to incorporate a wide variety of different functional groups into the structure of this class of polymer has been exploited by many researchers; however, the incorporation of labile functionalities has been widely overlooked. This Chapter investigates a method for introducing degradable functionality into the arms of CCS polymers such that they can be selectively degraded. This will not only increase the potential area of application for CCS polymers but also allow for a more in-depth study of the core domain, which up until now has never been directly visualized.

In order to synthesize CCS polymers with degradable arms it is necessary to incorporate an appropriate labile functionality such that the arms can be selectively degraded without affecting the remaining CCS structure. The susceptibility of ester linkages towards hydrolytic cleavage makes the use of polyester-based arms particularly suited for this purpose. In this Chapter a method for synthesizing polyester-based macrorinitiators via ROP of ε-caprolactone is described. These macrorinitiators are then utilized to synthesize CCS polymers with degradable arms via the ‘arms first’ approach with the effect of several reaction parameters on the extent of CCS formation being investigated. The ability to selectively hydrolyze the arms of these CCS polymers will also be examined and the resulting degradation products fully characterized.
2.2 Results and Discussion

2.2.1 Synthesis of ATRP/ROP duel initiator

The ‘arms first’ approach for synthesizing CCS polymers, as outlined in Chapter 1, requires the use of an initiator which can polymerize monomer to form linear macroinitiator. This macroinitiator retains the initiating functionality of the original initiator and can be further used to polymerize a cross-linker, resulting in the formation of CCS polymer. Traditionally, the same mechanism of polymerization (i.e. ATRP, NMP or RAFT) employed to generate the macroinitiator is used in the cross-linking step such that only a monofunctional initiator is required (Scheme 2.1, (a)). However, for the synthesis of CCS polymer with degradable polyester arms and non-degradable cross-linked core, two different polymerization techniques, namely ATRP and ROP, have to be employed, requiring the use of a difunctional initiator as illustrated in pathway (b) of Scheme 2.1.

Scheme 2.1: Synthesis of CCS polymer using (a) monofunctional initiator and (b) difunctional initiator.

For this work the asymmetric difunctional initiator, 2-hydroxyethyl 2'-methyl-2'-bromopropionate ((I) in Scheme 2.2), was used since it has previously been shown to
be an efficient initiator for both the ATRP of vinyl monomers and the ROP of lactone-based monomers.\textsuperscript{[1]} The dual functionality of this initiator is generated by the presence of the alkyl bromide end-group, which is used to initiate ATRP reactions, and the hydroxyl end-group, which is used to initiate ROP reactions.

![Synthesis of 2-hydroxyethyl 2'-methyl-2'-bromopropionate](image)

**Scheme 2.2:** Synthesis of 2-hydroxyethyl 2'-methyl-2'-bromopropionate (1).

The synthesis of 2-hydroxyethyl 2'-methyl-2'-bromopropionate has previously been reported in the literature\textsuperscript{[1,2,3]} and involves the partial esterification of ethylene glycol with an acid halide as shown in Scheme 2.2. Synthesis was carried out in the presence of a large excess of ethylene glycol (at least 25 times) in an effort to minimize the formation of di(alkyl bromide) initiator resulting from the reaction of 2-bromoisobutyryl bromide with both hydroxyl groups of a single ethylene glycol molecule. Success of the reaction was confirmed by both \textsuperscript{1}H NMR spectroscopy and gas chromatography/mass spectroscopy (GC-MS) which showed that after isolation and purification, the purity of the final product was >99%.

### 2.2.2 Synthesis of degradable macroinitiator

The degradable macroinitiator synthesized for this work will be based on polycaprolactone (PCL), a polyester derived from the ring-opening polymerization of \(\varepsilon\)-caprolactone (CL) monomer. PCL was chosen in preference to several other polyesters since it has FDA approval and has been shown to be both biocompatible and biodegradable, a necessity for many biomedical applications. In addition to this, PCL can be synthesized via a controlled polymerization technique, ROP, meaning that well-defined structures with narrow polydispersities can be achieved.

The ring-opening polymerization of CL has been well documented in the literature, with most reactions typically utilizing either aluminium isopropoxide, Al(O\textsuperscript{iPr})\textsubscript{3}, or stannous octoate, Sn(Oct)\textsubscript{2}, as the catalyst. The more robust nature, in terms of tolerance towards impurities, and the fact that it has FDA approval resulted in Sn(Oct)\textsubscript{2} being the preferred catalyst of choice for this work. Investigations into the
mechanism of Sn(Oct)₂ catalyzed ROP have shown that it proceeds via a coordination-insertion type mechanism requiring the use of an alcoholic co-initiator (refer Section 1.3.5). As a direct result of this initiation mechanism, the optimal ratio of alcoholic co-initiator to catalyst, [ROH]/[Sn(Oct)₂], reported to lie between 1-2:1.⁴,⁵ Alcohol in excess of [ROH]/[Sn(Oct)₂] > 2 serves only to act as a chain transfer agent, generating more chains but never changing the overall concentration of active chain ends. The choice of reaction conditions also needs to be carefully considered as it has been reported that extended reaction times⁶ and elevated temperatures⁷ can lead to transesterification reactions, resulting in increased polydispersities.

Based on these considerations, degradable polycaprolactone macroinitiator (PCL-Br) was synthesized by polymerizing CL with Sn(Oct)₂ and 2-hydroxyethyl 2'-methyl-2'-bromopropionate ([ROH]/[Sn(Oct)₂] = 2) at 130°C for 24 hours before recovery by precipitation into cold methanol. The reaction scheme is shown below in Scheme 2.3.

![Scheme 2.3: Synthesis of degradable polycaprolactone macroinitiator.](image)

The yields obtained for this polymerization typically ranged between 74-87% with a variety of different molecular weight polymers being synthesized through variation of the amount of monomer added. The resultant PCL-Br macroinitiator was analyzed by ¹H NMR spectroscopy, with assignment of the repeat unit as well as the chain end-groups being shown in Figure 2.1. In addition to the assigned resonances, a multiplet at δ4.16 ppm can be observed. This resonance is believed to be associated with resonance g of the first polyester repeat unit, i.e. the polyester repeat unit closest to the alkyl bromide end-group.
2.2.2.1 Molecular weight determination

The theoretical molecular weight of the synthesized PCL-Br macroinitiator can be calculated from the initial concentration of monomer and alcoholic initiator, $[\text{CL}]_0$ and $[\text{ROH}]_0$ respectively, by using Equation 2.1.

$$\mu_{\text{theoretical}} = \frac{[\text{CL}]_0}{[\text{ROH}]_0} \mu_{\text{CL}} + \mu_{\text{ROH}} \quad \text{Eq. 2.1}$$

The actual molecular weight of these polymers can be determined by gel permeation chromatography (GPC), the principles of which are described in Chapter 8. This technique allows for the accurate determination of molecular weight based on number and weight averages ($M_n$ and $M_w$ respectively), which can subsequently be used to measure the polydispersity ($M_w/M_n$) of the system, giving an indication of the uniformity of the polymer chain lengths. In addition to this, the molecular weight can also be determined through NMR end-group analysis. This involves comparing the intensity of the $^1$H NMR signal corresponding to the polymer end group to the
intensity of a signal corresponding to the repeat unit in the polymer backbone. From the ratio of these intensities it is possible to calculate the degree of polymerization and hence the number average molecular weight. The accuracy of this technique is related to the molecular weight of the polymer, with clear visualization of the end-groups only being possible for relatively low molecular weight polymers. From Figure 2.1 it can be seen that resonances $a$ ($\delta 1.93$ ppm), $b$ ($\delta 4.27$ ppm) and $g'$ ($\delta 3.65$ ppm) all correspond to end-group functionalities of the PCL-Br macroinitiator which can be compared to a signal corresponding to the polyester repeat unit, resonance $c$ ($\delta 2.30$ ppm), to obtain the molecular weight of the synthesized polymer. A comparison of the molecular weight of several PCL-Br macroinitiators obtained via each of these techniques (end-group analysis, GPC and theoretical) is shown in Table 2.1.

Table 2.1: Comparison of PCL-Br molecular weight as determined via GPC and $^1$H NMR end-group analysis.

<table>
<thead>
<tr>
<th>Molecular Weight (g/mol)</th>
<th>Theoretical $^a$</th>
<th>GPC $^b$</th>
<th>NMR end-group $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M_n$</td>
<td>$M_w$</td>
<td>$a$</td>
</tr>
<tr>
<td>1,070</td>
<td>2,700</td>
<td>3,020</td>
<td>3,090</td>
</tr>
<tr>
<td>1,640</td>
<td>3,950</td>
<td>4,110</td>
<td>3,380</td>
</tr>
<tr>
<td>3,050</td>
<td>5,060</td>
<td>5,270</td>
<td>5,920</td>
</tr>
<tr>
<td>14,350</td>
<td>16,250</td>
<td>16,860</td>
<td>23,040</td>
</tr>
</tbody>
</table>

$a$ Theoretical molecular weight calculated from Eq. 2.1.

$b$ Molecular weight determined via GPC equipped with multiangle laser light scattering detector (MALLS) using a $dn/dc$ value of 0.079 for PCL in THF.

$c$ Molecular weight determined by comparing relative intensities of end group resonances ($a$, $b$, $g'$) to resonance $c$ (Figure 2.1).

From this data it can be seen that the molecular weights obtained from GPC analysis are slightly higher than those predicted by theory. This suggests that the initiation efficiency of 2-hydroxyethyl 2'-methyl-2'-bromopropionate towards ROP of CL is less than 100%. In order to calculate the initiation efficiency the monomer conversion must be known, however, since these reactions were performed in bulk (i.e. without solvent) the final reaction solution was extremely viscous, preventing accurate determination of the CL conversion. Due to the nature of bulk reactions, it also means that an assumption of similar monomer consumption across each of these reactions
cannot be made since, at high conversions, the higher molecular weight polymers are expected to have lower chain mobility due to viscosity and hence experience a slower rate of monomer consumption.

The molecular weight data determined via GPC in Table 1.2 shows that the polydispersity (PD = $M_w/M_n$) of these macroinitiators is relatively low (PD < 1.12), confirming that ROP of CL under these conditions results in a controlled polymerization. Comparison with the molecular weight data obtained via NMR end-group analysis shows that there is a good correlation between the GPC data and the molecular weight obtained by designating resonance $a$ as the end-group. This difference tends to increase when resonance $b$ is used for the end-group analysis and is even more pronounced for resonance $g'$. The reason for this is related to the number of protons associated with each end-group such that resonance $a$ has the strongest signal (6 H) compared to resonance $b$ (4 H) and resonance $g'$ (2 H). It can also be seen that as the molecular weight of the polymer increases, the error associated with the NMR end-group analysis also increases due to a reduction of the end-group signal intensity compared to that of the polymer backbone. Of these techniques, GPC is generally considered a more reliable and accurate method for determining molecular weight and as such all molecular weight data reported in this thesis has been obtained via GPC unless otherwise noted.

2.2.2.2 Livingness/ATRP compatibility

The synthesized PCL-Br macroinitiator contains an alkyl bromide end-group functionality, as confirmed by the presence of the methyl protons in the $^1$H NMR spectrum (Figure 2.1, resonance $a$), which is capable of initiating ATRP of vinyl monomers. It is this end-group functionality which will be utilized to cross-link the PCL-Br macroinitiators to form CCS polymer, however, it is possible that some of the polymer chains do not contain this functionality. The presence of any hydroxyl-containing impurities, such as adventitious water, during the polymerization of CL could potentially result in initiation from these impurities rather than the desired initiator, 2-hydroxyethyl 2'-methyl-2'-bromopropionate. This PCL would not contain the alkyl bromide functionality required to initiate ATRP and hence would not be able to participate in CCS formation. The ‘livingness’ of the PCL-Br macroinitiator was tested by chain extending the macroinitiator with methyl methacrylate (MMA) monomer under ATRP conditions as shown in Scheme 2.4.
Scheme 2.4: ATRP chain extension of PCL-Br macroinitiator with MMA to test livingness.

The chain extension of PCL-Br macroinitiator (M_n = 2700 g/mol, M_w/M_n = 1.12) resulted in a monomodal peak of PCL-b-PMMA block copolymer with low molecular weight distribution (M_n = 6900 g/mol, M_w/M_n = 1.09) as shown by the GPC traces in Figure 2.2. This confirms the high initiation efficiency of PCL-Br macroinitiator since there is no residual ‘dead polymer’ observed in the GPC trace, suggesting that the initiation of PCL chains by hydroxyl-containing impurities was negligible. The high initiation efficiency, narrow polydispersity and living nature of the PCL-Br chains make it an ideal macro-initiator for the synthesis of CCS polymer via the ‘arms first’ approach.

Figure 2.2: GPC traces of the ATRP chain extension of PCL-Br macroinitiator by MMA. ([PCL-Br] = [CuBr]/1.3 = [PMDETA]/1.3 = [MMA]/40 at 100˚C in 38.0 mL anisole)

2.2.2.3 Degradability

Since the PCL-Br macroinitiator will end up forming the arms of the CCS polymer, it is important that it can be hydrolyzed under controlled conditions without affecting
the non-degradable component of the CCS polymer, i.e. the core. In order to achieve this, a series of hydrolysis reactions were carried out using the previously synthesized PCL-\textit{b}-PMMA block copolymer to find suitable conditions for degrading the PCL segment without destroying the PMMA block. It was found this could be achieved in a reasonable time frame by heating the polymer sample at 60°C in an acidic solution (12 M HCl/H2O/THF = 1/3/40 volumetric ratio) for 24 hours. $^1$H NMR spectroscopic analysis of the residual hydrolyzed polymer (Figure 2.3 c)) showed it to be pure PMMA, as expected, with no residual resonances due to the aliphatic protons of the PCL chain.

![Figure 2.3: $^1$H NMR spectra of a) PCL-Br macroinitiator, b) PCL-\textit{b}-PMMA block copolymer and c) PMMA from the hydrolysis of PCL-\textit{b}-PMMA block copolymer.](image)

The molecular weight of the un-hydrolyzed PMMA, as determined by GPC (Figure 2.4), was 3900 g/mol which corresponds to the theoretical molecular weight of the PMMA segment of the PCL-\textit{b}-PMMA block copolymer (4200 g/mol). The combined $^1$H NMR and GPC results of the PCL-\textit{b}-PMMA block copolymer hydrolysis confirms that the PCL segment of a polymer can be completely degraded under the acidic conditions described without affecting non-degradable polymer segments such as PMMA.
Figure 2.4: GPC traces of the hydrolysis of PCL-b-PMMA block copolymer to liberate PMMA. (hydrolysis conditions: 40 mg PCL-b-PMMA in 4 mL acidic solution (12 M HCl/H₂O/THF = 1/3/40 volumetric ratio) heated at 60°C for 24h)

2.2.3 Synthesis of arm-degradable CCS polymers

The PCL-Br macroinitiator was used to synthesize arm-degradable CCS polymer by cross-linking the ATRP active chain ends with divinylbenzene (DVB) or ethylene glycol dimethacrylate (EGDMA) (Scheme 2.5). Both DVB and EGDMA were chosen to act as the cross-linking agent since both have been widely used in the ‘arms first’ approach to synthesizing non-degradable CCS polymers. The choice of cross-linker is also important since the core of the CCS polymer needs to be stable under the hydrolysis conditions used to degrade the PCL arms. This was shown to be true for both DVB and EGDMA based CCS polymers which were capable of producing stable core domains upon hydrolysis as described later in this chapter.

Scheme 2.5: Synthesis of arm-degradable CCS polymer using non-degradable cross-linkers divinylbenzene (DVB) and ethylene glycol dimethacrylate (EGDMA).
Due to the fact that CCS polymers have a more compact structure than corresponding linear polymers of the same molecular weight, GPC measurements using a mass-sensitive detector (e.g. RI detector) calibrated based on linear polymer standards will give an apparent molecular weight smaller than the true molecular weight. A more advanced and accurate technique to measure the molecular weight of CCS polymers uses light scattering techniques. For this reason a multiangle laser light scattering (MALLS) detector was used in conjunction with GPC to determine the absolute molecular weight of the CCS polymers reported in this thesis.

In addition to calculating the molecular weight of the synthesized CCS polymers it is also possible to determine the average number of linear polymeric arms ($f$) incorporated into the CCS polymer. This was achieved using the following equation:

$$f = \frac{W_{F_{arms}} \cdot M_{w,CCS}}{M_{w,arms}}$$  Eq 2.2

where the CCS molecular weight ($M_{w,CCS}$) and the molecular weight of the linear arms ($M_{w,arms}$) were determined by GPC-MALLS. The weight fraction of arms ($W_{F_{arms}}$) can be determined according to Equation 2.3 where the conversion of cross-linker ($\chi_C$) was determined by gas chromatography (GC) analysis and the conversion of arms ($\chi_A$) determined by GPC analysis.

$$W_{F_{arms}} = \frac{m(arms) \cdot \chi_A}{m(cross-linker) \cdot \chi_C + m(arms) \cdot \chi_A}$$  Eq 2.3

2.2.3.1 Optimization of reaction conditions

The large number of reaction variables and their complex relationship with one another means that the reaction conditions used to synthesize CCS polymers typically requires a certain degree of optimization. Factors such as the choice of solvent, catalyst system, reaction temperature, macroinitiator molecular weight, reactant ratios and concentration all play an important role in determining the extent of CCS formation. For this work, all ATRP cross-linking reactions were carried out using a CuBr/PMDETA catalyst system (1:1 molar ratio) in anisole at 100°C. Under these reaction conditions the solubility of the catalyst is high, allowing for a more
homogeneous reaction mixture and therefore improved control over the polymerization.\(^9\) Using these conditions as a basis, a series of arm-degradable CCS polymers were synthesized using either DVB or EGDMA cross-linker (Table 2.2 and 2.3 respectively) where several reaction variables were manipulated in order to optimize the polymerization.

**Table 2.2:** Synthesis of arm-degradable CCS polymer using PCL-Br macroinitiator and DVB cross-linker.

<table>
<thead>
<tr>
<th>Exp No.(^a)</th>
<th>(M_n) PCL-Br (g/mol)(^b)</th>
<th>PD PCL-Br(^b)</th>
<th>[PCL-Br] (mM)</th>
<th>[DVB]/[PCL-Br]</th>
<th>PCL-Br conv (%}(^c)</th>
<th>(M_n) (g/mol)(^b)</th>
<th>PD(^b)</th>
<th>(f)(^d)</th>
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\(^a\) All polymerizations were carried out at 100°C in anisole [PCL-Br] = [CuBr]/1.3 = [PMDETA]/1.3.  
\(^b\) Number average molecular weight (\(M_n\)) and polydispersity (PD) measured by GPC-MALLS.  
\(^c\) Percentage of incorporated linear PCL precursor into CCS polymer.  
\(^d\) Number of arms in CCS polymer, determined from Equation 2.2.

**Table 2.3:** Synthesis of arm-degradable CCS polymer using PCL-Br macroinitiator and EGDMA cross-linker.

<table>
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<th>Exp No.(^a)</th>
<th>(M_n) PCL-Br (g/mol)(^b)</th>
<th>PD PCL-Br(^b)</th>
<th>[PCL-Br] (mM)</th>
<th>[EGDMA]/[PCL-Br]</th>
<th>PCL conv (%}(^c)</th>
<th>(M_n) (g/mol)(^b)</th>
<th>PD(^b)</th>
<th>(f)(^d)</th>
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\(^a\) All polymerizations were carried out at 100°C in anisole [PCL-Br] = [CuBr]/1.3 = [PMDETA]/1.3.  
\(^b\) Number average molecular weight (\(M_n\)) and polydispersity (PD) measured by GPC-MALLS.
By examining the series of arm-degradable CCS polymers formed using the same PCL-Br macroinitiator \( (M_n = 2700 \text{ g/mol}, \frac{M_w}{M_n} = 1.12) \), it is possible to see the effect that the molar ratio of cross-linker to linear PCL-Br and the reaction concentration has on the extent of CCS formation for both DVB and EGDMA cross-linked polymers (Table 2.2 exp 1-6 and Table 2.3 exp 8-12 respectively). For both DVB and EGDMA based arm-degradable CCS polymers it was found that as the reaction concentration was increased, the conversion of macroinitiator into CCS polymer also increased up to a certain point after which gelation occurred. A similar trend was observed for increasing the relative amount of cross-linker, such that a maximum conversion was achieved followed by gelation of the reaction mixture. This gelation occurs as a result of star-star coupling interactions, where the CCS polymers are able to link together through the growing core domain to form an insoluble cross-linked network. This is due to the presence of unreacted vinyl bonds within the core of the CCS polymer resulting from the mechanism of CCS formation. The close proximity of these growing cores, either as a result of high concentration or large core size (i.e. high ratio of cross-linker to macroinitiator), can result in the propagating radical of one core reacting with the free vinyl group of another, resulting in star-star coupling which, if continued, can lead to gelation.

The trend of increasing conversion with concentration and relative ratio of cross-linker can be observed in the GPC traces for the series of reactions shown in Figure 2.5. The traces have two distinct peaks due to the incomplete conversion of macroinitiator into CCS polymer, with the high molecular weight CCS polymer eluting first (elution volume = 17-22 mL) followed by the unconverted linear macroinitiator (elution volume = 22-26 mL). These GPC traces have been normalized with respect to the unconverted macroinitiator peak to better show the relative conversion which, since a concentration detector (RI) was used, is proportional to the area under the curves. From these traces it can be seen that as the reaction concentration is increased (Figure 2.5 a)), the area under the CCS peak increases with respect to the unconverted macroinitiator, illustrating the fact that the conversion increases. A similar trend is observed when the relative amount of cross-linker is
increased (Figure 2.5 b)), resulting in a higher conversion of macroinitiator into CCS polymer.

![Figure 2.5: GPC traces of PCL arm-degradable CCS polymer formation for a) DVB cross-linker with variable reaction concentration (Table 2.2 exp 2-4); and b) EGDMA cross-linker with variable cross-linker amount (Table 2.3 exp 8-10).](image)

When DVB was used as the cross-linker, the highest conversion of arms into CCS polymer occurred at a cross-linker to macroinitiator molar ratio of 15:1 and an initial macroinitiator concentration of 40 mM (Table 2.2 exp 4). However, for the EGDMA cross-linked CCS polymer the optimal reaction conditions were found to occur at a cross-linker to macroinitiator molar ratio of 25:1 with an initial macroinitiator concentration of 5 mM (Table 2.3 exp 10). A comparison of these two systems shows that the DVB based CCS polymer requires a much higher concentration compared to the EGDMA based system (optimal conditions at 40 mM and 5 mM respectively). Conversion of arms into CCS polymer was also much less when DVB was used as the cross-linking agent as opposed to EGDMA (42% compared to 78%), suggesting that DVB is a less reactive cross-linker than EGDMA under these reaction conditions.

The molecular weight of the macroinitiator also plays an important role in the extent of CCS conversion. By using smaller molecular weight PCL-Br macroinitiator (M_n = 2,300 g/mol, M_w/M_n = 1.05) to form CCS polymer at the previously determined optimal conditions (Table 2.2 exp 7 and Table 2.3 exp 13) it was found that the arm
conversion could be increased from 42% to 57% for the DVB based CCS polymer and from 78% to 85% for the EGDMA based CCS polymer. These results are in accordance with the findings from earlier work done by our group\cite{10,11} and that of Matyjaszewski \textit{et al.}\cite{12} which showed that employing shorter arm lengths led to higher CCS polymer yields. This is believed to occur due to the shorter arms on the CCS polymer providing less steric hindrance and therefore favoring the incorporation of more arms into each star polymer. The reverse was also found to be true, such that when higher molecular weight PCL-Br macroinitiator was used, the yield of CCS polymer dropped dramatically. In fact, conversions greater than 10 % could not be achieved when PCL-Br macroinitiator with $M_n \sim 5,000$ g/mol was used and essentially no conversion was possible with molecular weights in excess of 10,000 g/mol under these reaction conditions. In order to achieve such CCS polymers, i.e. arm molecular weight $>10,000$ g/mol, using the degradable PCL-Br macroinitiator the reaction conditions would need to be re-optimized for that specific system.

In summary, the formation of arm-degradable CCS polymer was found to be dependent on several factors, particularly the choice of cross-linker, the macroinitiator molecular weight, the reaction concentration, and the relative amount of cross-linker added to the system. The use of lower molecular weight macroinitiators resulted in increased conversions, while EGDMA was found to be a more effective cross-linker than DVB. Optimal reaction conditions for star formation using EGDMA monomer was found to occur when $[\text{PCL-Br}] = [\text{EGDMA}]/25 = 5 \text{ mM}$, whereas for DVB the optimal conditions were $[\text{PCL-Br}] = [\text{DVB}]/15 = 40 \text{ mM}$.

2.2.3.2 \textit{Kinetic study of CCS formation}

A kinetic study of the formation of arm-degradable CCS polymer, using both EGDMA and DVB cross-linkers, was performed to better understand how these star polymers are formed and to further examine the effect that the choice of cross-linker has on the kinetics of the reaction. For this study, PCL-Br macroinitiator ($M_n = 2,750$ g/mol, $M_w/M_n = 1.10$) was reacted with DVB and EGDMA cross-linker under the optimal conditions reported in the previous section ($[\text{PCL-Br}] = [\text{CuBr}]/1.3 = [\text{PMDETA}]/1.3$ in anisole at 100°C; $[\text{PCL-Br}]_{\text{DVB}} = 40 \text{ mM}$, $[\text{PCL-Br}]_{\text{EGDMA}} = 5 \text{ mM}$). However, the same ratio of cross-linker to macroinitiator was used for both the DVB and EGDMA based reactions ($([\text{cross-linker}]/[\text{PCL-Br}] = 15$) such that the reactant ratios would be the same and hence generate comparable CCS polymers.
The experimental procedure for the kinetic study is analogous to the standard method of CCS synthesis with the exception that samples were taken during the course of the reaction. Since this technique requires that samples be extracted from the reaction mixture, care must be taken not to expose the system to oxygen which can act to inhibit the reaction. In this case, oxygen contamination was minimized by taking samples with an oven-dried syringe under an atmosphere of argon at positive pressure. The samples were subsequently quenched to stop further reaction and analyzed by GPC and GC-MS to obtain molecular weight and conversion data. The GPC traces of samples taken over an 8 hour period during the formation of CCS polymer using DVB and EGDMA cross-linker are shown in Figure 2.6.

**Figure 2.6**: GPC traces of arm-degradable CCS polymer formation over time using a) DVB and b) EGDMA cross-linker. ([PCL-Br] = [CuBr]/1.3 = [PMDETA]/1.3 = [cross-linker]/15 in anisole at 100°C; [PCL-Br]_{DVB} = 40 mM, [PCL-Br]_{EGDMA} = 5 mM)

The GPC traces in Figure 2.6 have been normalized with respect to the unconverted macroinitiator (elution volume = 27.5 mL) to better highlight the growth of CCS polymer. For the reaction series where DVB was used as the cross-linker (Figure 2.6 a)) it can be seen that after 2 hours of reaction a higher molecular weight shoulder peak has appeared (elution volume = 25 mL), becoming more defined as the reaction
proceeds. This shoulder peak represent polymer of an intermediate molecular weight (>30,000 g/mol) consisting only a few arms cross-linked together. Longer reaction times allow for these intermediate products will react further, linking together to form high molecular weight CCS polymers with many arms. The beginning of this process can be observed by the formation of an additional shoulder peak (elution volume = 23 mL) which, if allowed to react further, should eventually consume all of the intermediate product. Comparing this to the case where EGDMA is used as the cross-linker (Figure 2.6 b)), it appears that no intermediate product was formed. However, this is not the case and is simply due to the faster kinetics of the EGDMA based reaction, resulting in all of the intermediate product being consumed before the initial sampling at 2 hours. The extent of CCS formation over 8 hours is also much higher, highlighting the fact that EGDMA is much more reactive as a cross-linker under these conditions than DVB as previously discussed in Section 2.2.3.1. From the GPC traces it is also possible to see the formation of a small amount of very high molecular weight polymer (elution volume = 17.5 mL) believed to be a product of star-star coupling interactions.

The consumption of cross-linker and macroinitiator was also monitored during the kinetic study, the results of which are shown in Figure 2.7. These plots of conversion versus time further serve to emphasize difference in reactivity of these two cross-linkers, once again showing that EGDMA is much more reactive under these conditions. From Figure 2.7 a) it can be seen that the vast majority of EGDMA monomer has been consumed within the first 2 hours of reaction (85%) compared to DVB for which only 16% had been consumed. This will directly affect the rate of macroinitiator conversion since the number of arms capable of being incorporated into CCS polymer depends on the core size, a factor which is dictated by the extent of cross-linker conversion. This is in fact what is seen, with a similar trend being observed for both the rate of macroinitiator conversion and cross-linker conversion. However, it should be noted that for a given cross-linker conversion the extent of macroinitiator conversion appears to be higher for the DVB based reaction compared to the EGDMA based reaction. This would mean that the DVB based CCS polymer would have a larger number of arms and a smaller core when compared to the EGDMA based CCS polymer of a similar molecular weight.
Figure 2.7: Conversion of a) cross-linker and b) macroinitiator during kinetic study as measured by GC-MS and GPC respectively.

Using the previous data, it was possible to calculate the molecular weight of the CCS polymer and the number of arms incorporated as a function of time for both the EGDMA and the DVB based reactions, the results of which are shown in Figure 2.8. From these graphs it can be seen that the molecular weight of the EGDMA based CCS polymer increases much more rapidly than that of the DVB based polymer as expected. For both these reactions the molecular weight trend over time seems to mimic that of the number of arms. This makes sense since as the number of arms incorporated into the CCS polymer increases, so too does the overall molecular weight. The formation of the intermediate product for the DVB based polymerization, as previously discussed, can also clearly be seen, with low molecular weight low arm number product being present for the first 6 hours of the reaction. These results also provide confirmation that CCS polymers synthesized under these conditions having similar molecular weight would contain a higher number of arms for the DVB based polymer ($M_n = 135,000$ g/mol, $f = 30$) compared to the EGDMA based polymer ($M_n = 154,000$ g/mol, $f = 22$).
2.2.4 Degradation of CCS polymer arms

2.2.4.1 Core stability

By hydrolyzing the PCL arms of the arm-degradable CCS polymers previously synthesized, it is possible to directly analyze the liberated cross-linked core particles. However, this requires that the core domain be stable under the conditions used to hydrolyze the arms, such that only the arms are degraded leaving the core intact. The stability of the different core domains was analyzed by hydrolyzing PMMA arm analogs of the PCL/EGDMA and PCL/DVB CCS polymers. Since PMMA has already been shown to be stable under the hydrolysis conditions used to degrade PCL (Section 2.2.2.3), any change in molecular weight for the PMMA/EGDMA or PMMA/DVB CCS polymers must be due to degradation of the cross-linked core domain. GPC traces showing the effects of hydrolysis on the PMMA/EGDMA and PMMA/DVB CCS polymers are shown below in Figure 2.9.

**Figure 2.8:** Change in a) molecular weight and b) average arm number of CCS polymer synthesized during the kinetic study.
Figure 2.9: GPC traces of the hydrolysis of a) PMMA/EGDMA CCS polymer and b) PMMA/DVB CCS polymer. (hydrolysis conditions: 40 mg CCS polymer in 4 mL acidic solution (12 M HCl/H2O/THF = 1/3/40 volumetric ratio) heated at 60°C for 24h)

From Figure 2.9 it can clearly be seen that the hydrolysis conditions used in this experiment had no effect on the structural integrity of these CCS polymers, with the GPC traces before and after hydrolysis being exactly the same. The slight variation in molecular weights can be attributed to the inherent accuracy of the measurement technique and isn’t sufficient to indicate any degradation of the core domain. Of particular interest is the stability of the EGDMA core since it also contains ester linkages, inherited from the methacrylate end-groups of the EGDMA cross-linker. Therefore, under these reaction conditions the ester linkages within the PCL arms are capable of being hydrolyzed but not those within the EGDMA cross-linked core. This can potentially be explained by the mechanism involved in the acidic hydrolysis of ester bonds, a process which first requires protonation of the carboxylic oxygen atom in order to activate it toward nucleophilic attack by water.\[^{13}\] It has been shown that the stability of this carbonyl bond is greatly affected by its localized environment, with both acyl and alkyl substituents (i.e. R'CO₂R where R' = acyl and R = alkyl) having a significant influence on the rate of hydrolysis. The effect of these substituents can be quite complex, with sterics, resonance stabilization and polarity all playing a part.\[^{14,15}\] For this reason, it is theorized that the higher degree of
substitution at the α-carbon of poly(EGDMA) (Figure 2.10, α-carbon = *) compared to that of PCL is acting to stabilize the ester linkages within the core. This is supported by the findings of other research groups, where the esters bonds of similarly cross-linked structures based on EGDMA were found to very stable towards hydrolysis.\textsuperscript{[16,17,18,19]}

![Diagram](image.png)

**Figure 2.10:** Degree of substitution of the α-carbon (*) within the core compared to the arms.

We can use this information to predict the surface functionality of the hydrolyzed core particle, a factor which depends on the particular ester linkage that has been hydrolyzed to cleave the arms from the core (Scheme 2.6). If the ester linkage closest to the core, \(i\), can be hydrolyzed under the reaction conditions employed in this work then the liberated core particles would be carboxylic acid surface functionalized. Alternatively, if ester linkage \(i\) was stable then hydrolysis would occur at ester linkage \(ii\), resulting in a hydroxy surface functionalized core. The stabilizing effect of the substitutions observed in the EGDMA core tend to suggest that the dimethyl group in the PCL arms will stabilize ester linkage \(i\), resulting in the generation of hydroxyl groups rather than carboxylic acids at the surface of the hydrolyzed core. This was further supported by the fact that poly(2-hydroxyethyl methacrylate) (PHEMA), analogous to the hydroxy surface functionalized core, did not convert to the carboxylic acid derivative when subjected to the hydrolysis conditions used to degrade the PCL arms.
Scheme 2.6: Effect of hydrolyzing different ester linkages, i or ii, on the surface functionality of the resultant core particle.

2.2.4.2 Molecular weight analysis
Several different arm-degradable CCS polymers with varying arm length and core structure (DVB and EGDMA cross-linked) were hydrolyzed under acidic conditions to degrade the polycaprolactone arms and liberate the core. This system also has the added advantage that it doesn’t require fractionation to remove any unconverted PCL-Br macroinitiator since this will be degraded along with the PCL arms of the CCS polymer, leaving only the non-degradable core particles. GPC traces of the arm-degradable CCS polymers before and after hydrolysis are shown in Figure 2.11, with the corresponding molecular weights and polydispersities being listed in Table 2.4.
Figure 2.11: GPC traces of arm-degradable CCS polymer before and after hydrolysis; a) 2.3k PCL/DVB (Table 2.4 exp 1), b) 2.3k PCL/EGDMA (Table 2.4 exp 2) and c) 4.7k PCL/EGDMA (Table 2.4 exp 3).

Table 2.4: Molecular weight analysis of arm-degradable CCS polymers before and after hydrolysis.

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<th>Exp&lt;sup&gt;a&lt;/sup&gt;</th>
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<th>CCS Mn&lt;sub&gt;n&lt;/sub&gt; (g/mol)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>PD&lt;sup&gt;d&lt;/sup&gt;</th>
<th>f&lt;sup&gt;e&lt;/sup&gt;</th>
<th>Hydrolyzed CCS Mn&lt;sub&gt;n&lt;/sub&gt; (g/mol)&lt;sup&gt;d&lt;/sup&gt;</th>
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<sup>a</sup> Exp 1-3 correspond to Figure 2.11 a) - c) respectively.
<sup>b</sup> Type of cross-linker used to synthesize CCS polymer.
<sup>c</sup> Molecular weight of PCL-Br macroinitiator used to synthesize CCS polymer.
<sup>d</sup> Number average molecular weight (M<sub>n</sub>) and polydispersity (PD) measured by GPC-MALLS.
<sup>e</sup> Number of arms in CCS polymer, determined from Equation 2.2.
This GPC analysis clearly shows that the molecular weight of the CCS polymers is reduced upon hydrolysis, liberating cores with molecular weights ranging between 30 kDa and 230 kDa depending on the size of the original CCS polymer. The largest core molecular weight (232,300 g/mol) was recorded for the EGDMA based CCS polymer with the shortest arm length (2,300 g/mol). This was expected since these conditions (i.e. shorter arm lengths combined with EGDMA rather than DVB cross-linker) were previously shown to be more conducive to CCS formation, resulting in higher molecular weight polymers which subsequently have larger core domains. Figure 2.11 and Table 2.4 also show that the polydispersity of the CCS polymers increases upon hydrolysis of the arms. This is due to the nature of the cross-linking reaction used to generate the core, which, while still a controlled polymerization, proceeds in a random fashion and therefore results in an increased core polydispersity. Close examination of the GPC trace of the hydrolyzed DVB based CCS polymer (Figure 2.11 a)) reveals a lower molecular weight shoulder peak occurring at an elution volume of 28 mL. This is believed to correspond to the hydrolyzed product of macroinitiator which has undergone chain extension but has not been incorporated into CCS polymer, i.e. the intermediate molecular weight product identified during the kinetic study in Section 2.2.3.2. A similar low molecular weight peak is also observed for the hydrolyzed product of the 2.3 kDa PCL/EGDMA CCS polymer (Figure 2.11 b), 29 mL elution volume), however this peak is significantly reduced compared to the DVB based polymer due to the smaller amount of unconverted macroinitiator present prior to hydrolysis.

The hydrolyzed core particles isolated in this investigation displayed poor solubility, such that when they were taken out of solution, either by precipitation or solvent evaporation, the majority of the sample could not be resolubilized. This meant that the GPC analysis had to be carried out using a diluted reaction solution such that the core particles remained soluble. In addition to this, the dn/dc value of the cross-linked core particles is not known, requiring that an assumption of 100% mass recovery of the injected sample be made in order to calculate the molecular weight. Despite this, the experimentally determined molecular weights of the hydrolyzed core particles closely matched that predicted by theory as can be seen in Table 2.4.
2.2.4.3 Hydrodynamic size analysis

Dynamic light scattering (DLS) measurements of the CCS polymers listed in Table 2.4 were recorded before and after hydrolysis (Figure 2.12) in order to compare the diameter of the CCS polymer to that of the liberated core. From these traces it can clearly be seen that degradation of the CCS polymer arms results in a significant reduction in diameter. However, the magnitude of this size reduction is not solely due to the length of the removed arm since shrinkage of the exposed core will also occur as a result of the highly cross-linked core particles becoming less soluble upon removal of the arms. The average diameter of these CCS polymers before and after hydrolysis is shown in Table 2.5 with the results being reported as hydrodynamic diameters ($D_h$), a measurement which corresponds to the effective size of the polymer as determined by its diffusional properties.

**Figure 2.12:** DLS traces of arm-degradable CCS polymers before and after hydrolysis; a) 2.3k PCL/DVB (Table 2.5 exp 1), b) 2.3k PCL/EGDMA (Table 2.5 exp 2) and c) 4.7k PCL/EGDMA (Table 2.5 exp 3).

| exp$^a$ | core$^b$ | arm $M_n$ (g/mol)$^{c,d}$ | CCS | Hydrolyzed CCS |
|--------|---------|-------------------|======|----------------|
|        |         | $M_n$ (g/mol)$^d$ | $D_h$ (nm)$^e$ | SD (nm)$^f$ | $M_n$ (g/mol)$^d$ | $D_h$ (nm)$^e$ | SD (nm)$^f$ |
| 1      | DVB     | 2300              | 85200 | 9.5 | 2.6 | 30600 | 5.7 | 1.8 |
| 2      | EGDMA   | 2300              | 367100 | 46.8 | 8.1 | 232300 | 21.6 | 5.9 |
| 3      | EGDMA   | 4700              | 152300 | 17.3 | 3.3 | 91400 | 10.9 | 2.5 |

$^a$ Exp 1-3 corresponds to polymers in Table 2.4 exp 1-3 respectively.
The average diameter of the DVB and EGDMA CCS polymers, based on the number-average scattering intensity, was found to range between 9-47 nm which corresponds to previous findings for other non-degradable CCS polymers. After hydrolysis the diameter of the remaining polymer was found to have been reduced, yielding DVB and EGDMA cores with average diameters ranging between 5-22 nm (Table 2.5). For each of the CCS polymers analyzed here, the size of the corresponding hydrolyzed core is approximately half that of the original polymer. The effect of arm length and core type on the hydrodynamic diameter of these polymers appears to be fairly minimal, with the main determining factor being related to the polymer’s overall molecular weight as highlighted in Figure 2.13.

**Figure 2.13:** Hydrodynamic diameter of CCS polymers and core particles as a function of molecular weight.
2.3 Conclusions
A range of CCS polymers with degradable arm functionality were successfully synthesized via the ‘arms first’ approach by combining the controlled polymerization techniques of ATRP and ROP. Utilizing this method, degradable PCL arm CCS polymers were synthesized with both EGDMA and DVB cores. Various reaction parameters, especially the macroinitiator concentration and the molar ratio of cross-linker to macroinitiator, were studied in order to determine the optimal reaction conditions with EGDMA being found to yield higher conversion of arms into CCS polymer compared to DVB. The kinetics of this reaction were also investigated, confirming that EGDMA was indeed much more reactive as a cross-linker than DVB under these reaction conditions. Hydrolysis experiments showed that the PCL arms could be selectively degraded, liberating the highly cross-linked EGDMA and DVB cores which were further analyzed by GPC and DLS. The arms of the CCS polymers were shown to provide a significant solubilizing effect, with their removal resulting in the core becoming only sparingly soluble. Hydrolysis of the arms also resulted in an increase in the polydispersity, with the molecular weight of the core particles ranging between 40-220 kDa, closely matching that predicted by theory. The hydrodynamic diameter of the core particles was also measured and found to correspond to approximately half that of the original CCS polymers, with molecular weight being found to be the determining factor in relation to the size of these polymers.

2.4 References


# Chapter 3 - Synthesis of Core-Degradable CCS Polymer

## 3.1 Introduction

3.1.1 Existing methods for synthesizing core-degradable CCS polymers.

3.1.2 Bislactone approach for synthesizing core-degradable CCS polymers

## 3.2 Results and Discussion

3.2.1 Synthesis of 4,4'-bioxepanyl-7,7'-dione (BOD)

3.2.2 Synthesis of non-degradable macroinitiator

3.2.3 Synthesis of core-degradable CCS polymer

3.2.4 Degradation of CCS polymer core

## 3.3 Conclusions

## 3.4 References
3.1 Introduction
Following the successful synthesis of CCS polymers with selectively degradable arms, it was desired to further expand this area of investigation by incorporating degradable functionality into the core of CCS polymers. The ability to be able to control the degradability of the core domain represents an important development in broadening the potential range of applications for CCS polymers. One such example, as highlighted in our recent review on the topic,[1] lies in the field of potential drug delivery devices where small molecules encapsulated within CCS polymers could be released in a controlled fashion via degradation of the core domain. It also provides a valuable step towards the synthesis of fully degradable CCS polymers, an area which will be further explored in Chapter 4 of this thesis. In this Chapter a novel method for synthesizing core-degradable CCS polymers is developed based on the use of a bislactone cross-linker. The synthesis of this cross-linker and its subsequent use in generating CCS polymers will be investigated, with the ability to selectively hydrolyze the core domain being examined and the resulting degradation products fully characterized.

3.1.1 Existing methods for synthesizing core-degradable CCS polymers
Several different techniques have already been reported in the literature for incorporating degradable functionality into the core of CCS polymers, with the majority focusing on the use of modified dimethacrylate monomers as the degradable cross-linking component (Figure 3.1). For example, Ruckenstein and Zhang[2] synthesized core-degradable CCS polymer using ethylene glycol di(1-methacryloyloxy)ethyl ether (I) cross-linker. This allowed for the incorporation of acid-labile ester linkages which could easily be hydrolyzed to break apart the core structure of the CCS polymer. Long and coworkers[3] also used a similar approach showing that both dicumyl alcohol dimethacrylate (2) and 2,5-dimethyl-2,5-hexanediol dimethacrylate (3) cross-linkers could be used to incorporate acid-labile ester linkages into the core of CCS polymers. Each of these ester based cross-linkers was polymerized under living anionic conditions but the resultant polydispersities of the stars turned out to be quite broad. Issues of low conversion and small molecular weight were also experienced indicating that the bulky structure of these monomers reduced their efficiency as cross-linkers for CCS formation.
Figure 3.1: Methacrylate based cross-linkers which have been used to synthesize core-degradable CCS polymers.

Other degradable functionalities apart from ester linkages have also been incorporated into dimethacrylate based cross-linkers. An example of this is shown by the work of Patrickios and coworkers\cite{4,5,6} who, in addition to synthesizing degradable ester-based cross-linkers, also utilized acid-labile siloxane and acetal groups to synthesize dimethyldi(methacryloyloxy-1-ethoxy)silane (4) and di(methacryloyloxy-1-ethoxy)methane (5) cross-linker respectively. These degradable cross-linkers were subsequently polymerized using group transfer polymerization to yield CCS polymers with degradable cores. However, this technique also suffered from the bulky nature of the cross-linkers, yielding CCS polymers with broad polydispersities and, in the case of the siloxane cross-linker, low conversions. Another type of degradable cross-linker based on the incorporation of cleavable disulfide linkages, bis(2-methacryloyloxyethyl) disulfide (6), was synthesized by Matyjaszewski and coworkers.\cite{7} This degradable cross-linker was subsequently used to generate CCS polymers under ATRP conditions where the disulfide linkages within the core could be cleaved via use of a reducing agent. This technique allowed for high conversions but still suffered from broad polydispersities.

3.1.2 Bislactone approach for synthesizing core-degradable CCS polymers

For this work it was decided to develop an alternative route for synthesizing core-degradable CCS polymers involving the use of a bislactone cross-linker. The proposed method of synthesis in this case still follows the ‘arms first’ approach and is exactly the same as the previously described systems except that a cyclic based cross-linker replaces the use of divinyl based cross-linkers. This requires that the cross-linking step be performed under ROP conditions, with the macroinitiator arms being
hydroxyl end-functionalized so they can initiate polymerization of the bislactone cross-linker. Since ROP is a controlled polymerization technique the polydispersity of stars produced via this method should be comparable to that of CCS polymers generated via other controlled polymerization techniques. The use of lactone based cross-linkers allows for the synthesis of CCS polymers with polyester-based cores which can subsequently be degraded via hydrolysis of the incorporated ester linkages, resulting in a core-degradable CCS polymer.
3.2 Results and Discussion

3.2.1 Synthesis of 4,4′-bioxepanyl-7,7′-dione (BOD)
To synthesize core-degradable CCS polymer a hydrolysable monomer must be employed as the cross-linking agent. For this work the bislactone 4,4′-bioxepanyl-7,7′-dione (BOD) was chosen as the degradable cross-linker due to its structural similarity to ε-caprolactone, with BOD consisting of two caprolactone rings bridged at the 4 position (Scheme 3.1). BOD has also been shown to display similar reactivity to CL, with the synthesis of several degradable cross-linked networks being reported in the literature.[8,9] By using BOD to cross-link linear macroinitiator under ROP conditions the resultant CCS polymer will possess a degradable polyester core, the structure of which is essentially that of cross-linked polycaprolactone and as such is expected to exhibit biocompatible and biodegradable properties similar to that of PCL.

![Scheme 3.1: Synthesis of 4,4′-bioxepanyl-7,7′-dione (BOD).](image)

The synthesis of BOD cross-linker was achieved though the Baeyer-Villiger oxidation of 4,4′-bicyclohexanone as shown in Scheme 3.1. This reaction was attempted using two different oxidizing agents, m-chloroperoxybenzoic acid and a hydrogen peroxide/formic acid mixture, with both reactions generating the desired bislactone product as confirmed by 1H NMR spectroscopy. The hydrogen peroxide based reaction was performed using a crystalline adduct of urea and hydrogen peroxide which can be handled without danger, thereby avoiding the use of highly concentrated
hydrogen peroxide solutions. The yield of these two reactions varied significantly, with the \( m \)-chloroperoxybenzoic acid mediated reaction producing a yield in excess of 96% compared to that of only 60% for the hydrogen peroxide/formic acid route. GC-MS analysis of the isolated reaction products (Figure 3.2) showed that any unreacted 4,4'-bicyclohexanone had been successfully removed, however, a small amount of an intermediate product (Mw = 210) was observed in the products of both reactions, 7.0% and 1.4% for the \( m \)-chloroperoxybenzoic acid and hydrogen peroxide/formic acid reactions respectively. This intermediate product corresponds to 4,4'-bicyclohexanone where only one of the cyclic ketone groups has been oxidized, resulting in a monolactone with no capacity to act as a cross-linker.

**Figure 3.2:** GC traces of the synthesis of BOD cross-linker a) before reaction, b) after reaction using \( m \)-chloroperoxybenzoic acid, and c) after reaction using hydrogen peroxide/formic acid.

The presence of this intermediate monolactone product should not act to inhibit the cross-linking reaction used to form the CCS polymer core; instead it will behave similar to CL monomer, undergoing ROP to act as ‘spacer’ rather than cross-linker. However, while this monolactone should not prevent the formation of core-degradable CCS polymer, it will decrease the active amount of cross-linker present. For this reason it was decided to use the higher purity BOD from the hydrogen peroxide/formic acid based reaction to synthesize the subsequent CCS polymers.
3.2.2 Synthesis of non-degradable macroinitiator

In order to synthesize core-degradable CCS polymer using BOD, it is necessary that the macroinitiator arms be hydroxyl end-functionalized such that they can initiate ROP of the bislactone cross-linker. In addition to this, the CCS polymer arms are required to be able to withstand the hydrolysis conditions used to degrade the core, meaning that the macroinitiator must be synthesized from a suitable non-degradable polymer such as poly(methyl methacrylate) (PMMA) or poly(styrene) (PSt). For this reason the dual ATRP/ROP initiator 2-hydroxyethyl 2'-methyl-2'-bromopropionate, previously used for the synthesis of arm-degradable CCS polymer in Chapter 2, was employed to generate a suitable macroinitiator for the synthesis of core-degradable CCS polymer (Scheme 3.2).

![Scheme 3.2: Synthesis of non-degradable PMMA-OH and PSt-OH macroinitiators.](image)

From the work presented in Chapter 2 of this thesis it was shown that 2-hydroxyethyl 2'-methyl-2'-bromopropionate was capable of initiating ROP of the CL monomer, with the subsequent PCL-Br macroinitiator being an efficient initiator for the ATRP of MMA. However, when 2-hydroxyethyl 2'-methyl-2'-bromopropionate was used to initiate ATRP of MMA it was found that polymers with broad polydispersities ($M_n = 23,100$ g/mol, $M_w/M_n = 1.51$) were generated. Styrene (St) monomer was also polymerized using this initiator in an attempt to achieve narrower polydispersities, with the reactions conditions being summarized in Table 3.1 and the corresponding GPC traces being shown in Figure 3.3.
Table 3.1: Conditions used to synthesize non-degradable macroinitiators.

<table>
<thead>
<tr>
<th>Macroinitiator&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Monomer</th>
<th>Ligand&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Temp (°C)</th>
<th>(M_n) (g/mol)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>PD&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMMA-OH</td>
<td>MMA</td>
<td>PMDETA</td>
<td>100</td>
<td>23,100</td>
<td>1.51</td>
</tr>
<tr>
<td>PSt-OH 10k</td>
<td>St</td>
<td>bpy</td>
<td>80</td>
<td>10,700</td>
<td>1.09</td>
</tr>
<tr>
<td>PSt-OH 7k</td>
<td>St</td>
<td>PMDETA</td>
<td>80</td>
<td>7,700</td>
<td>1.03</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were performed with \([I] = [CuBr] = [M]/60\) in bulk, where \(I\) = 2-hydroxyethyl 2'-methyl-2'-bromopropionate and \(M\) = monomer.

<sup>b</sup> Ratio of ligands: \([CuBr] = [PMDETA] = [bpy]/3\).

<sup>c</sup> Number average molecular weight (\(M_n\)) and polydispersity (PD) measured by GPC-MALLS.

Figure 3.3: GPC traces of non-degradable macroinitiators synthesized using 2-hydroxyethyl 2'-methyl-2'-bromopropionate. (Conditions as per Table 3.1)

As can be seen from Table 3.1 and Figure 3.3 narrower polydispersities were achieved when 2-hydroxyethyl 2'-methyl-2'-bromopropionate was used to polymerize St as opposed to MMA. However, for the PSt-OH 7k macroinitiator there is a small higher molecular weight shoulder peak present in the GPC trace, thought to be due to either termination products or polymer initiated from contaminant di(alkyl bromide) functional initiator (refer to earlier discussions in Section 2.2.1). If this shoulder peak is in fact due to the presence of a small amount of contaminant initiator, then all of the polymerizations should display a similar shoulder peak, a feature which is not apparent in the GPC trace of the PSt-OH 10k macroinitiator. For this reason the PSt-OH 10k macroinitiator was selected to be used in the subsequent reactions to generate core-degradable CCS polymer.
3.2.3 Synthesis of core-degradable CCS polymer

Core-degradable CCS polymer was synthesized by polymerizing BOD cross-linker with PST-OH 10k macroinitiator in toluene at 110°C ([PSt-OH] = 0.02 M = [BOD]/10 = [Sn(Oct)2]/0.5). The conditions for this reaction were based on the optimal reaction conditions found for the synthesis of fully degradable CCS polymers as discussed in Chapter 4. Since the cross-linking reaction proceeds via ROP and is not affected by the presence of oxygen, it means that less stringent sampling procedures than those previously described for the sampling of ATRP reactions can be employed, making the reaction much easier to monitor. In this particular case the reaction was monitored by GPC and GC-MS with the corresponding results being shown in Figures 3.4 and 3.5 respectively.

**Figure 3.4:** GPC traces monitoring the synthesis of core-degradable CCS polymer over time followed by fractionation. ([PSt-OH] = 0.02 M = [BOD]/10 = [Sn(Oct)2]/0.5 in toluene at 110°C)
Figure 3.5: Conversion of BOD monomer during the synthesis of core-degradable CCS polymer as determined via GC-MS analysis.

From the GPC traces in Figure 3.4 it can be seen that there is a gradual evolution in molecular weight, with approximately 55% of the linear PSt-OH macroinitiator having been converted into CCS polymer after 48h. The reaction was stopped at this point and fractionally precipitated to remove any unconverted arms, yielding pure CCS polymer with a $M_n$ of 214,800 g/mol and a low polydispersity ($M_w/M_n = 1.18$). From the GC-MS results it was found that 87% of the BOD monomer had been consumed within the first 48h, resulting in an average of 13.6 arms being incorporated into the final CCS polymer as calculated by Equation 2.2. DLS measurements were also performed on the fractionated CCS polymer revealing an average hydrodynamic diameter of 14.2 nm in THF, a size which corresponds to other CCS polymers cross-linked using divinyl monomers.

These results show that the ring-opening polymerization of bislactone monomers is a viable technique for synthesizing CCS polymers with polyester based cores. However, the issue of whether or not these CCS polymers can truly be classified as ‘core-degradable’ still remains to be seen, a claim which is investigated in the next section of this thesis.

3.2.4 Degradation of CCS polymer core

The use of lactone based cross-linkers to synthesize CCS polymers generates a polyester core domain which can be completely degraded into small monomeric units and therefore release the original polymeric arms. This process is illustrated in Figure
3.6 with degradation of the BOD cross-linked core resulting in the generation of monomeric 4,5-bis(2-hydroxyethyl)octanedioic acid (BHEO). This is completely different to the case where methacrylate based cross-linkers are used to synthesize core-degradable CCS polymers (refer Section 3.1.1) which when degraded will break apart to yield linear arms that have been chain extended (Figure 3.6). The reason for this lies in the location of the degradable linkage, which for lactone-based cores is situated in the backbone of the cross-linked chains whereas for methacrylate-based cores it is located in the bridging unit between the cross-linked chains.

**Figure 3.6:** Difference in core structure of core-degradable CCS polymers synthesized with BOD compared to degradable methacrylate cross-linkers (1) – (6) (refer Figure 3.1).

Hydrolysis of the PST/BOD core-degradable CCS polymer was performed under acidic conditions previously found to hydrolyze PCL ester linkages without affecting PMMA or PST polymer chains. The hydrolysis product was isolated by precipitation and analyzed via GPC (Figure 3.7). The GPC traces confirmed that all of the original CCS polymer had been completely degraded to yield lower molecular weight product which matched that of the original linear PST arms (Mn = 10,700 g/mol, M_w/M_n = 1.09). This was further confirmed by ^1^H NMR spectroscopy which showed the hydrolysis product to be consistent with that of the original linear PST-OH macroinitiator.
Figure 3.7: GPC traces of PSt-OH macroinitiator, core-degradable CCS polymer, and the product from its subsequent hydrolysis.

From these results it can clearly be seen that the BOD cross-linked CCS polymer can indeed be classified as ‘core-degradable’, providing an important step towards the synthesis of fully degradable CCS polymers, a topic which is addressed in the following Chapter.
3.3 Conclusions

In this Chapter an alternative pathway for the synthesis of core-degradable CCS polymers was investigated. This process focused on the use of bislactone monomers to form the degradable cross-linked core as opposed to the labile methacrylate based cross-linkers which have previously been used for this purpose. In order to achieve this the monomer 4,4'-bioxepanyl-7,7'-dione (BOD), a bislactone resembling two caprolactone rings bridged at the 4 position, was synthesized via the oxidation of a cyclic diketone. The use of several different oxidizing agents was examined, with a hydrogen peroxide/formic acid mixture being found to produce the highest purity BOD, such that the amount of intermediate monolactone product present was minimized. The duel initiator 2-hydroxyethyl 2'-methyl-2'-bromopropionate was used to synthesize macroinitiator capable of initiating ROP of the BOD cross-linker, with the St based macroinitiators having lower polydispersities than those synthesized from MMA. PST-OH macroinitiator (Mn = 10,700 g/mol, Mn/Mw = 1.09) was subsequently used to initiate the polymerization of BOD cross-linker, resulting in the formation of core-degradable CCS polymer (Mn = 214,800 g/mol, Mn/Mw = 1.18) with an average of 13.6 arms per star. Hydrolysis of this CCS polymer resulted in degradation of the core and full recovery of the original linear PST arms, showing that this new methodology is a viable pathway for the synthesis of core-degradable CCS polymers.

3.4 References

Chapter 4 - Synthesis of Fully Degradable CCS Polymer

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4.1 Introduction

The next obvious step in the evolution of degradable CCS polymers involves the incorporation of degradable functionality into both the arm and the core domain in order to achieve fully degradable CCS polymers. There are several ways this can be achieved but perhaps of greatest interest is the combination of previously described techniques to synthesize CCS polymers via ring-opening polymerization of cyclic esters. This method allows for the synthesis of CCS polymers with polyester-based structures (both arm and core moieties) which can therefore be degraded under controlled conditions via hydrolysis of the ester linkages within the polymer. The ability to completely degrade these CCS polymers into small monomeric units could prove invaluable for many potential areas of application, particularly in their use as templating devices for the synthesis of nanoporous materials.

The proposed method of synthesis in this case involves the ROP of CL monomer to generate linear PCL macroinitiator capable of initiating further ROP reactions. This is followed by the addition of a bislactone monomer to the reaction mixture, resulting in cross-linking of the arms and formation of completely polyester-based CCS polymer. This method differs from the previously described techniques for synthesizing arm-degradable and core-degradable CCS polymers since only one form of controlled polymerization (ROP) is required as opposed to a combination of ROP and ATRP. Consequentially, the synthesis of fully degradable CCS polymers can be carried out in a two-step one-pot process without the need for isolation and purification of the intermediate macroinitiator product.

This Chapter examines this novel ROP-based method for synthesizing fully degradable CCS polymer, comparing the use of two different bislactone cross-linkers and exploring the effects of various reaction conditions on the yield of CCS polymer. The degradability of these CCS polymers was subsequently examined, with the hydrolysis products being analyzed via $^1$H NMR spectroscopy. The long term stability of these polymers was also investigated along with the phenomenon of star-star coupling.
4.2 Results and Discussion

4.2.1 One-pot synthesis

The proposed method for synthesizing fully degradable CCS polymers, as previously outline in Section 4.1, requires the use of two consecutive ROP reactions, one to synthesize the PCL arms followed by another to cross-link these arms and thus form CCS polymer (Scheme 4.1). In this case an alcoholic initiator, butanol (BuOH), is being used to synthesize the hydroxyl functional PCL macroinitiator. Subsequent cross-linking of the PCL macroinitiator is achieved via the addition of a bislactone monomer, BOD, resulting in the formation of CCS polymer which can easily be degraded via hydrolysis of the ester linkages within the arms and the core.

![Scheme 4.1: One-pot, two-step synthesis of fully degradable CCS polymers.](image)

One particular advantage of this synthesis route is that unlike other forms of controlled polymerizations, such as ATRP, ROP is not a radical based technique and is consequently not sensitive to the presence of radical scavengers such as oxygen. This makes it a much easier reaction to handle and allows for the process to be carried out as a one-pot synthesis where cross-linker can be directly added to the system after arm formation without any need for isolation or purification of the intermediate products. The robust nature of the ROP reaction and its amenability toward one-pot synthesis makes this method of synthesizing CCS polymers particularly attractive, especially in terms of large scale synthesis for commercial applications.
4.2.1.1 Solvent compatibility

One of the issues associated with one-pot synthesis of CCS polymers is that the reaction conditions should be the same for the arm formation step as employed for the core formation step, ideally only requiring the addition of cross-linker to the reaction solution. This approach is problematic since the PCL macroinitiators previously reported in this thesis have all been synthesized using bulk reaction conditions, i.e. in the absence of solvent, the most common technique for this type of polymerization. While this works well for the synthesis of arms, the same conditions can’t be used for the cross-linking reaction as the steric hindrance effects induced by the bulk reaction conditions would likely result in an uneven distribution of cross-linking monomer, with the heterogeneous reaction conditions leading to a loss of polymerization control and potential gelation. In addition, the final bulk reaction solution for the PCL macroinitiator will almost certainly contain a small amount of unreacted CL monomer, the presence of which could result in its incorporation during the core formation step, acting as unwanted ‘spacer’ monomer.

To avoid these problems and achieve a homogeneous reaction mixture it is necessary to use an appropriate solvent system, several of which were investigated for this work. From the range of solvents which have been successfully employed for the ring-opening polymerization of lactones catalyzed by Sn(Oct)$_2$ the most commonly reported examples tend to involve the use of either THF$^{[1]}$ or toluene$^{[2]}$ as an appropriate solvent. The main difference between the two solvent systems is the limitation to reaction temperature that they impose due to their boiling points, with THF being capable of achieving reaction temperatures of up to 65°C while toluene can extend this limit up to 110°C. This is a very important limitation since it was found that the kinetics of the ring-opening polymerization of CL depend greatly on the reaction temperature as highlighted in Figure 4.1.
Figure 4.1: Effect of temperature on monomer conversion during the synthesis of linear PCL ([Sn(Oct)$_2$] = [BuOH]/2 = [CL]/104 in toluene, [CL]$_0$ = 1M).

Figure 4.1 shows the consumption of monomer as a function of time for the ROP of CL monomer at several different reaction temperatures. As expected these polymerizations show living characteristics, with the linear plot of ln([CL]$_0$/[CL]) vs. time confirming a constant concentration of the active species.$^{[3]}$ More significantly, the rate of polymerization (defined as $r_p = -d[CL]/([CL]dt) = (1/t)\ln([CL]_0/[CL])$) is seen to increase dramatically with reaction temperature, such that the polymerization carried out at 110°C was 5 times faster than that at 80°C and over 50 times faster than that at 65°C. These polymerizations were all conducted in toluene, however when THF at 65°C was used the rate of polymerization was found to be very similar to that of toluene at 65°C, showing that the rate of polymerization is more dependent on the overall reaction temperature than the choice of solvent itself. Therefore, to achieve fast polymerization times a high reaction temperature is required, however if the reaction temperature is too high then this can conversely result in unwanted transesterification reactions.$^{[4]}$

For the ROP reactions performed in this work it was found that toluene provided a suitable polymerization solvent, with a reaction temperature of 110°C being high enough to achieve high conversions within a reasonable time frame whilst still being low enough to avoid significant transesterification reactions. The low miscibility of toluene with water is also quite useful for ROP reactions, effectively minimizing the amount of water impurities present. This is important as water is known to reduce the rate of Sn(Oct)$_2$ catalyzed ROP$^{[5]}$ as well as being capable of acting as an initiator.
itself, a consequence which can lead to star-star coupling reactions as described in Section 4.2.4.

4.2.1.2 Synthesis of fully degradable CCS polymers

The one-pot synthesis of fully degradable CCS polymer was carried out in two separate steps as indicated in Scheme 4.1. In the first step, \( n \)-butanol ([BuOH] = 19.2 mM) was used to initiate the ring-opening polymerization of \( \varepsilon \)-caprolactone ([CL] = 1 M) in toluene at 110°C using stannous 2-ethylhexanoate ([Sn(Oct)\(_2\)]/[BuOH] = 0.5) as the catalyst. BuOH was chosen as the alcoholic initiator as its boiling point of 117°C is higher than the reaction temperature of 110°C and thus is not distilled from the reaction vessel. Sampling of the reaction solution showed that after 24 hours the conversion of CL was > 99%, yielding hydroxy functional PCL macroinitiator with a number-average molecular weight of 5,300 g/mol and low polydispersity (\( M_w/M_n = 1.07 \)).

On completion of the first step (CL conversion >99%, 24h) the bislactone 4,4'-bioxepanyl-7,7'-dione (BOD), discussed previously in Section 3.2.1, was added to the reaction solution ([BOD]/[PCL] = 10). BOD was used as the cross-linking monomer due to its structural similarity to CL such that the core of the star polymer would chemically resemble the PCL arms only with bridges linking between the pentylene moieties. The conversion of the BOD monomer during the second stage of the reaction was monitored by GC-MS which showed that after 16 hours 86% of the BOD monomer had been consumed. The formation of CCS polymer over time was monitored by gel permeation chromatography equipped with a multi-angle laser light scattering detector (GPC-MALLS) (Figure 4.2) with the final trace at 16 hours showing that approximately 85% of the linear arms (27 mL elution volume) had been converted to yield CCS polymer (22 mL elution volume). A small fraction (approx. 3%) of high molecular weight polymer (\( M_n = 1.50 \times 10^6 \) g/mol, 17 mL elution volume) was also observed, believed to be a result of star-star coupling interactions initiated by the presence of water impurities during the initial PCL synthesis, a topic which is more comprehensibly discussed in Section 4.2.4 of this thesis. Fractionation of the final reaction solution yielded pure CCS polymer with a number-average molecular weight of 362,000 g/mol with approximately 43 arms per star. The polydispersity of the fractionated CCS polymer was also quite low (\( M_w/M_n = 1.13 \)),
showing that the ROP cross-linking step proceeded in a controlled fashion as expected.

**Figure 4.2:** GPC traces of fully degradable CCS polymer synthesis ([CL] = 1M, [Sn(Oct)₂] = [BuOH]/2 = [CL]/104 in toluene at 110°C) after addition of BOD cross-linker ([BOD]/[PCL] = 10) along with final fractionated sample.

One of the potential problems associated with this reaction system involves the method of cross-linker addition. The BOD cross-linking monomer, which exists as a white powdery solid, is only sparingly soluble in toluene at room temperature. However, when heated to 110°C, i.e. the reaction temperature, toluene is capable of completely solubilizing BOD, albeit rather slowly. This creates a problem since when the cross-linking monomer is added to the reaction solution it take awhile to dissolve, resulting in a temporarily inhomogeneous reaction mixture which is not ideal for CCS formation. One potential way of overcoming this problem involved dissolving the BOD monomer in toluene prior to its addition to the reaction solution. Unfortunately this proved to be rather impractical due to the fact that the toluene had to be heated to high temperatures which subsequently had to be maintained during the transfer process in order to avoid BOD precipitating from solution. Alternatively, BOD can be pre-solubilized in dichloromethane, an extremely good solvent for BOD, and slowly added to the toluene reaction solution at 110°C. While a small amount of BOD does
precipitate from solution upon addition, creating a slightly cloudy reaction mixture, it does disperse the cross-linking monomer a lot more effectively than if it was added directly as a solid. In addition to this, the low boiling point of dichloromethane (41°C) results in it boiling off almost instantaneously without affecting the overall temperature of the reaction solution. Consequently, the dichloromethane method of cross-linker addition was used for all subsequent one-pot syntheses of CCS polymer requiring the use of blislactone monomers in the cross-linking step.

4.2.1.3 Hydrolysis and characterization

From the previous results it can be seen that it is possible to generate CCS polymer which is entirely polyester based with PCL arms and BOD cross-linked core. In Chapters 2 and 3 of this thesis we have previously shown that the PCL arms of a CCS polymer can be selectively degraded under acidic conditions as can the BOD cross-linked core domain, breaking the structure down into small-chain acids (Scheme 4.2). Since the core and the arms in this case are essentially the same polymer, the degradation rates are expected to be similar. This means that the PCL/BOD CCS polymers should break down rapidly, with hydrolysis of the arm and core domains occurring simultaneously via a random chain scission mechanism. This is a very useful property for potential templating applications; however, there may be other instances where the rate of degradation between the arms and the core is required to be different, particularly in the area of potential drug delivery devices where a difference in degradation rates could be used to control the kinetics of drug release. While this area is not addressed in this thesis, it could easily be achieved through the use of various cyclic esters, such as lactic acid (LA) or glycolic acid (GA), to generate a range of arms with different degradation rates to that of the BOD cross-linked core.
To quantitatively examine the degradation of these PCL/BOD CCS polymers, hydrolysis experiments were conducted in deuterated solvents (THF-d₈ and D₂O) and analyzed via ¹H NMR spectroscopy. As can be seen from Scheme 4.2, there are two major degradation products resulting from the hydrolysis of fully degradable CCS polymer, 6-hydroxyhexanoic acid from degradation of the PCL arms and 4,5-bis-(2-hydroxyethyl)octanedioic acid (BHEO) from degradation of the BOD cross-linked core. Due to the structural similarity of these degradation products, with BHEO being equivalent to two 6-hydroxyhexanoic acid units linked together at the 4 position, it was impossible to distinguish between them in the ¹H NMR spectra. It should also be noted that ¹H NMR spectroscopy of the CCS polymer cannot be used to detect the BOD core structure, due in part to the structural similarity between the core and the arms but mainly because of the reduced segmental mobility of the core domain. This problem is common to all CCS polymers where the reduced segmental mobility of the highly cross-linked core domain results in a broadening of the characteristic resonances of the core such that they disappear into the baseline.¹⁶,⁷,⁸,⁹ However, this is not really an issue for the proposed ¹H NMR spectroscopic analysis since it was possible to see the difference between the PCL structure of the CCS polymer and the resulting degradation products, thereby allowing quantification of the hydrolysis reaction.
Comparison of the $^1$H NMR spectra before and after hydrolysis (Figure 4.3) revealed that the triplet at $\delta$3.99 ppm corresponding to e-CH$_2$ in the PCL backbone is greatly reduced after hydrolysis and is complimented by the appearance of the triplet at $\delta$3.46 ppm corresponding to $\epsilon$-CH$_2$ in the degradation product. In addition, the resonance at $\delta$1.58 ppm corresponding to d-CH$_2$ of the CCS polymer initially overlapped with the b-CH$_2$ resonance but after hydrolysis it was removed and replaced by the $\delta$-CH$_2$ resonance of the degradation product ($\delta$1.47 ppm). The disappearance of the d-CH$_2$ and e-CH$_2$ resonances in the CCS polymer and the appearance of the $\delta$-CH$_2$ and $\epsilon$-CH$_2$ resonances in the degradation product show that hydrolysis has occurred, the extent of which can be calculated by comparing the integral of the e-CH$_2$ resonance before and after hydrolysis. For the hydrolysis shown in Figure 4.3 the percentage of hydrolyzed ester bonds was calculated to be approximately 97%.

**Figure 4.3:** $^1$H NMR spectra of fully degradable CCS polymer taken a) before, and b) after 24h of hydrolysis (60°C, THF-d$_8$:D$_2$O = 13.3:1, 0.272 M HCl).

Since the core segment is indistinguishable from the arms in both the pre-degradation and post-degradation samples when analyzed by $^1$H NMR spectroscopy, further
analysis was required to confirm that the core had indeed been degraded and that the inability to detect it wasn’t due to the reduced segmental mobility of the core. Attempts to precipitate the hydrolysis reaction solution showed that polymeric components were not present, a fact further confirmed by GPC measurements. This, combined with the successful recovery of PST arms from the hydrolysis of PST/BOD CCS as reported in Chapter 3, indicates that the BOD core had indeed been degraded into small BHEO units, confirming that the PCL/BOD CCS polymer is fully degradable.

4.2.2 Factors effecting CCS conversion
The fully degradable CCS polymer described in the previous Section was synthesized based on the optimal reaction conditions as determined from a series of experiments in which several reaction variables were manipulated (Table 4.1). The optimal reaction conditions were determined to occur when the conversion of PCL arms into CCS polymer was high and a high molecular weight for the CCS polymer could be achieved in a relatively short time (Table 4.1, exp. 1).

**Table 4.1:** Effect of reaction conditions on the synthesis of fully degradable PCL/BOD CCS polymers.

<table>
<thead>
<tr>
<th>Exp.</th>
<th>[CL] (M)</th>
<th>M&lt;sub&gt;n&lt;/sub&gt; PCL (g/mol)&lt;sup&gt;b,c&lt;/sup&gt;</th>
<th>[BOD]/[PCL]</th>
<th>Arm conv. (%)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>BOD conv. (%)&lt;sup&gt;e&lt;/sup&gt;</th>
<th>M&lt;sub&gt;n&lt;/sub&gt; CCS (g/mol)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>PD&lt;sup&gt;c&lt;/sup&gt;</th>
<th>f&lt;sup&gt;f&lt;/sup&gt;</th>
<th>t (h)&lt;sup&gt;g&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>6,000</td>
<td>10</td>
<td>85</td>
<td>86</td>
<td>362,000</td>
<td>1.13</td>
<td>43</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>6,000</td>
<td>10</td>
<td>80</td>
<td>87</td>
<td>353,000</td>
<td>1.14</td>
<td>33</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>6,000</td>
<td>5</td>
<td>60</td>
<td>-&lt;sup&gt;h&lt;/sup&gt;</td>
<td>54,000</td>
<td>1.12</td>
<td>9&lt;sup&gt;i&lt;/sup&gt;</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>6,000</td>
<td>5</td>
<td>46</td>
<td>-&lt;sup&gt;h&lt;/sup&gt;</td>
<td>182,000</td>
<td>1.16</td>
<td>24&lt;sup&gt;i&lt;/sup&gt;</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
<td>12,000</td>
<td>10</td>
<td>67</td>
<td>90</td>
<td>455,000</td>
<td>1.22</td>
<td>30</td>
<td>46</td>
</tr>
</tbody>
</table>

<sup>a</sup> All polymerizations were carried out at 110°C in toluene; exp 1-4: [Sn(Oct)<sub>2</sub>] = [BuOH]/2 = [CL]/104, exp 5: [Sn(Oct)<sub>2</sub>] = [BuOH]/2 = [CL]/350.

<sup>b</sup> Approximate molecular weight (M<sub>n</sub>) when CL conversion >99%.

<sup>c</sup> Number average molecular weight (M<sub>n</sub>) and polydispersity (PD) measured by GPC-MALLS.

<sup>d</sup> Percentage incorporation of linear PCL precursor into CCS polymer.

<sup>e</sup> Determined by GC-MS analysis.

<sup>f</sup> Number of arms in CCS polymer (f) determined from Equation 2.2.

<sup>g</sup> Polymerization time after addition of BOD monomer.

<sup>h</sup> Measurements were not taken as concentration was too low to accurately measure.
In Section 2.2.3.1 of this thesis we saw the effect that simple variations in the reaction conditions can have on the extent of CCS formation for the case where ATRP is used to generate the cross-linked core domain; however it is uncertain whether these results can be directly related to the synthesis of fully degradable CCS polymers where the cross-linking step is performed under ROP conditions. We have already seen how significant the effect of temperature is on the rate of polymerization for ROP reactions (Section 4.2.1.1), now we wish to look at the effect of factors such as concentration, reactant ratios, and macroinitiator molecular weight. By analyzing the data in Table 4.1 it is possible to gain a deeper understanding of how these reaction variables influence the formation of CCS polymer synthesized via ROP cross-linking.

4.2.2.1 Concentration
The effect that the overall reaction concentration has on the extent of CCS formation can be seen by comparing exp 1 and 2 and exp 3 and 4 where the only variable that has been modified is the concentration. In both these cases it was seen that when the concentration of the reaction solution was increased the conversion of PCL macroinitiator into CCS polymer tended to decrease, changing from 85% to 80% between exp 1 and 2 and from 60% to 46% between exp 3 and 4. While the effect of doubling the concentration only results in a minor decrease in conversion for both these examples, it does appear contrary to the case for ATRP cross-linking where an increase in concentration generally leads to higher conversions. This is not too difficult to comprehend since the two mechanisms of CCS formation are completely different, one relying on radical based reactions and the other involving a coordination-insertion mechanism. It therefore stands to reason that variations in reaction concentration could have a completely different effect on the extent of CCS formation achieved via these separate mechanisms.

4.2.2.2 Cross-linker ratio
From Table 4.1 it is also possible to see the effect that the amount of BOD cross-linker added to the system has on the extent of CCS formation. By comparing exp 1 and 3 and exp 2 and 4 it can be seen that a decrease in the relative amount of cross-linker reduces the conversion of PCL arms into CCS polymer whilst also leading to
increased polymerization times to yield high molecular weight polymers. From these results it can be seen that the relative amount of cross-linker is halved, the effect this has on the extent of CCS formation is fairly significant, changing from 85% to 60% between exp 1 and 3 and from 80% to 46% between exp 2 and 4. A similar effect was observed during the synthesis of ATRP cross-linked CCS polymers (Section 2.2.3.1), a result which makes sense since as the amount of cross-linker is reduced the core size becomes restricted reducing the amount of arms which can be incorporated, a scenario which is independent of the cross-linking mechanism. In addition to this it was also observed that for an increase in the relative amount of cross-linker added to the system, the amount of very high molecular weight polymer formed during the ROP cross-linking reaction also increased. This contaminant product is believed to be a result of star-star coupling interactions, the occurrence of which increases as the core size expands (due to higher cross-linker ratios) allowing for more interaction between the cores of growing stars.

4.2.2.3 Arm Length

The final reaction variable which was examined was the molecular weight of the PCL macroinitiator, a factor which directly translates to the arm length of the resulting CCS polymer. It has been well documented in the literature,\textsuperscript{[9,10,11]} and further confirmed by the results presented in Chapter 2 of this thesis, that for ATRP cross-linked CCS polymers the arm length can significantly effect the extent of CCS formation, with shorter arms generally resulting in higher CCS polymer yields. A similar trend was observed for the case of ROP cross-linking, with comparison between exp 2 and 5 of Table 4.1 showing that an increase in arm length (6kDa to 12kDa) resulted in a decrease in the extent of CCS polymer conversion (80% to 67%). This effect is believed to occur due to less steric hindrance being provided by the shorter arms of the CCS polymer therefore allowing for the incorporation of more arms into each star polymer. It was also observed that a longer polymerization time was required to achieve significant conversion when the higher molecular weight PCL macroinitiator was used, a result which supports the assumption of increased steric hindrance.
4.2.3 Comparison of alternative bislactone cross-linkers

In addition to using BOD monomer, it was decided to investigate the potential for using other bislactone monomers as the cross-linking component for the synthesis of fully degradable CCS polymer. Of particular interest was the bislactone 2,2-bis(ε-caprolactone-4-yl)propane (BCP).

4.2.3.1 Synthesis of 2,2-bis(ε-caprolactone-4-yl)propane (BCP)

Like BOD, BCP is capable of acting as a cross-linking component under ROP conditions with its use being previously reported in the synthesis of degradable cross-linked networks.[12] Structurally it is very similar to BOD, except that the bridging unit between the ε-caprolactone rings in BCP consists of a methylated quaternary carbon (Scheme 4.3). This extended bridging unit provides BCP with greater structural flexibility in comparison to BOD, a property which may elicit some interesting properties when used to synthesize CCS polymers.

The synthesis of BCP cross-linker was achieved through the Baeyer-Villiger oxidation of 2,2-bis(4-oxocyclohexyl)propane as shown in Scheme 4.3. This reaction was performed using the conditions which had previously been found to be the most efficient for synthesizing BOD monomer (Section 3.2.1), with a hydrogen peroxide/formic acid mixture acting as the oxidizing agent. The reaction product was isolated and purified with 1H NMR spectroscopy confirming that the desired
bislactone product has been synthesized. The yield of this reaction was quite high (83%) with GC-MS analysis of the isolated reaction product (Figure 4.4) showing that any unreacted diketone, 2,2-bis(4-oxocyclohexyl)propane, had been successfully removed. A small amount (3.8%) of an intermediate product (Mw = 252) was observed in the reaction product corresponding to 2,2-bis(4-oxocyclohexyl)propane where only one of the cyclic ketone groups has been oxidized. A similar intermediate monolactone product was observed during the synthesis of BOD monomer, with its presence not affecting the cross-linking reaction during CCS formation where it has the potential to act as a ‘spacer’ molecule. For this reason it was decided that further purification of the BCP monomer was not necessary.

![Figure 4.4: GC traces of the synthesis of BCP cross-linker a) before and b) after reaction.](image)

4.2.3.2 CCS formation

The BCP cross-linker was polymerized under the optimal reaction conditions previously described to synthesize BOD cross-linked CCS polymer (Section 4.2.1.2) with BOD being directly replaced by BCP. The reaction was conducted as a two-step one-pot process where BCP was added directly to the reaction solution once conversion of the CL monomer was >99% (24h, M_n (PCL) = 5,100 g/mol). After 48 hours of reaction 83% of the BCP monomer had been consumed but the conversion of arms into CCS polymer was only 41%. The resultant CCS polymer generated was calculated to have a number average molecular weight of 335,800 g/mol (M_w/M_n = 1.27) with an average of 34.4 arms. The results of this polymerization and that of the
equivalent BOD reaction are summarized in Table 4.2 with the corresponding GPC traces being shown in Figure 4.5.

Table 4.2: Comparison of fully degradable CCS polymers synthesized using different bislactone cross-linkers.a

<table>
<thead>
<tr>
<th>cross-linker</th>
<th>Mₐ PCL (g/mol)b</th>
<th>arm conv. (%)c</th>
<th>cross-linker conv. (%)d</th>
<th>Mₐ CCS (g/mol)b</th>
<th>PDb</th>
<th>fₑ</th>
<th>t (h)f</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOD</td>
<td>5,300</td>
<td>85</td>
<td>86</td>
<td>362,000</td>
<td>1.13</td>
<td>43</td>
<td>16</td>
</tr>
<tr>
<td>BCP</td>
<td>5,100</td>
<td>41</td>
<td>83</td>
<td>335,800</td>
<td>1.27</td>
<td>34</td>
<td>48</td>
</tr>
</tbody>
</table>

a All polymerizations were carried out at 110°C in toluene; [CL] = 1M, [Sn(Oct)₂] = [BuOH]/2 = [CL]/104, [cross-linker]/[PCL] =10.
b Number average molecular weight (Mₐ) and polydispersity (PD) measured by GPC-MALLS.
c Percentage incorporation of linear PCL precursor into CCS polymer.
d Determined by GC-MS analysis.
e Number of arms in CCS polymer (fₑ) determined from Equation 2.2.
f Polymerization time after addition of bislactone cross-linker.

Figure 4.5: a) GPC traces of fully degradable CCS polymers and precursor PCL arms and b) cross-linker conversion during CCS synthesis (samples correspond to data in Table 4.2).

A comparison of the two fully degradable CCS polymers synthesized under the same reaction conditions shows that similar molecular weight CCS polymer (Figure 4.5 a) elution volume = 22 mL) is generated in both instances, Mₐ = 362,000 g/mol for the BOD based CCS compared to 335,800 g/mol for the BCP based CCS (Table 4.2). However, the reaction time to reach similar cross-linker conversion (83-86%) took 3
times longer for the BCP reaction (Figure 4.5 b)) with the resultant conversion of arms into CCS polymer also being significantly reduced, less than half that achieved for the BOD based reaction. These results suggest that the BCP cross-linker is less reactive towards the formation of CCS polymer than BOD cross-linker under these reaction conditions, possibly due to the bulky methyl groups creating steric hindrance issues which making it harder to generate the dense core region during the cross-linking step. The GPC traces of the two fully degradable CCS polymers (Figure 4.5 a)) also reveal that in addition to the synthesis of CCS polymer (elution volume = 22 mL) the generation of very high molecular weight polymer (1-2 million Da) also occurred (elution volume ~ 17 mL). This high molecular weight polymer is believed to be a product of star-star coupling and is more prevalent in the BCP cross-linked reaction due to the longer reaction time required for CCS formation resulting in an increased probability of star-star coupling interactions occurring.

4.2.3.3 Hydrolysis

In Section 4.2.1.3 of this thesis it was shown that PCL/BOD based CCS polymer can be completely degraded by hydrolyzing the ester bonds within the polymer to generate small-chain acids. Similar results are expected for the hydrolysis of PCL/BCP based CCS polymer with the major degradation products being shown in Scheme 4.4.

![Scheme 4.4: Major degradation products resulting from the hydrolysis of PCL/BCP CCS polymer.](image-url)
The degradation of PCL/BCP CCS polymer was quantitatively monitored by conducting the hydrolysis experiment in deuterated solvents (THF-d\textsubscript{8} and D\textsubscript{2}O) and analyzing the reaction solution over time via $^1$H NMR spectroscopy (Figure 4.6). A comparison of the $^1$H NMR spectra before and after hydrolysis revealed that the triplet at $\delta$4.02 ppm corresponding to e-CH\textsubscript{2} in the polyester backbone of the CCS polymer was greatly reduced after hydrolysis and complemented by the appearance of the triplet at $\delta$3.50 ppm corresponding to $\varepsilon$-CH\textsubscript{2} of the hydrolyzed ester. The extent of hydrolysis can be calculated by comparing the integrals of e-CH\textsubscript{2} before and after hydrolysis which revealed that for the BCP/PCL based CCS polymer approximately 97\% of the ester linkages had been hydrolyzed back to their monomeric constituents.

![Figure 4.6](image)

Figure 4.6: $^1$H NMR spectra of PCL/BCP CCS polymer taken a) before and b) after 24 h of hydrolysis (60°C, CD\textsubscript{3}COCD\textsubscript{3}:D\textsubscript{2}O (13.3:1), 0.272 M HCl), * = bridging methyl groups from BCP cross-linker.

When BOD is used to synthesize fully degradable CCS polymer $^1$H NMR spectroscopy of the star cannot be used to detect the BOD core structure due to the
reduced segmental mobility of the core, a problem which results in a broadening of
the characteristic resonances due to the core such that they disappear into the baseline.
However, when BCP is used as the cross-linker the two methyl groups in the bridging
unit between the lactone rings are flexible enough and of a high enough intensity that
they can be detected by $^1$H NMR spectroscopy (Figure 4.6 a): * $\delta$0.80 ppm) even
though significant broadening is still observed. For the $^1$H NMR spectra of the
hydrolyzed product the resonance due to the bridging methyl groups becomes stronger
and sharper (Figure 4.6 b): * $\delta$0.76 ppm) as it is no longer bound within the rigid core
structure but instead exists as a small-chain hydrolysis product, 4,6-bis(2-
hydroxyethyl)-5,5-dimethylnonanedioic acid (BHEMN in Scheme 4.4), resembling
two 6-hydroxyhexanoic acid units bridged at the 4 position by a methylated
quaternary carbon. The other characteristic resonances of BHEMN are obscured by
the resonances associated with the hydrolysis product of the linear arms due to their
structural similarity.

4.2.4 Star-star coupling reactions
One of the major issues associated with the synthesis of CCS polymers is the
occurrence of star-star coupling interactions, a problem which results in a broadening
of the polydispersity and can eventually lead to gelation if allowed to proceed too far.
These coupling interactions occur during the core formation step and is inherent to all
CCS syntheses regardless of the cross-linking mechanism, be it ATRP, ROP or any
other form of controlled polymerization used to synthesize CCS polymers. While star-
star coupling can occur during both ATRP and ROP cross-linking, the actual
mechanism by which it occurs is quite different. For the case of ATRP cross-linking it
is well known that the star-star coupling reaction occurs between the cores of two
growing stars as illustrated in Figure 4.7. This reaction can proceed via two different
pathways, either by an active radical in one core polymerizing an unreacted vinyl
bond in the other or by a radical-radical termination reaction between the two growing
cores. As discussed in Chapter 2 of this thesis this type of coupling reaction requires a
close proximity of the growing core, generally brought about by highly concentrated
reaction mixtures and large core sizes (i.e. excessive cross-linker added to system).
Figure 4.7: Core-core interactions during CCS formation facilitated by ATRP and ROP cross-linking resulting in star-star coupling.

A similar mechanism for star-star coupling is observed during the formation of CCS polymers via ROP cross-linking (Figure 4.7). Here the core-core linking occurs as a result of an active hydroxyl group within one core initiating the polymerization of an unreacted pendant lactone within the other. Due to the mechanism of ring-opening polymerization there is no linking through radical-radical termination reactions commonly associated with the CRP methods for synthesizing CCS polymers, however the ROP cross-linking reaction can potentially suffer from another form of star-star coupling involving arm-core interactions as shown in Figure 4.8. This type of reaction occurs when hydroxyl impurities such as water or diols are present in the reaction solution, with their presence resulting in macroinitiator which is active at both ends. For the case of PCL/BOD CCS polymer, if any adventitious water is present in the reaction solution it can potentially act as an initiator, resulting in PCL macroinitiator where one end is hydroxy functionalized but the other consists of a carboxylic acid group. This macroinitiator would then be incorporated into a CCS polymer with the carboxylic acid group being located at the periphery of the star. A subsequent condensation reaction between this carboxylic acid group and a hydroxyl group from the core of another star would result in star-star coupling, with the high reaction temperatures employed during the ROP cross-linking reaction facilitating this condensation reaction. For the case of diol initiated macroinitiator, the star-star coupling reaction proceeds in a similar fashion, however this time the periphery of the CCS polymer would possess a hydroxyl group capable of initiating ROP of an unreacted pendant lactone within the core of another star and thereby linking the two
stars. While this is a possibility it is unlikely that any contaminant diol would be present in the reaction mixture, with atmospheric water contamination being a more likely source for this type of star-star coupling reaction.

**Figure 4.8:** Arm-core interactions resulting in star-star coupling during ROP CCS formation due to the presence of water or diol contaminants.

In an effort to minimize the amount of star-star coupling reactions during the formation of fully degradable CCS polymer, an attempt was made to perform the reaction under extremely anhydrous conditions. In this case the synthesis was performed as two separate reactions, i.e. not a one-pot synthesis, as this allowed for isolation and purification of the intermediate macroinitiator product. In order to remove all traces of water from the reaction, rigorous purification of all reagents and solvent was required. This was achieved by distilling everything just prior to use with the aid of a drying agent (either CaH₂ or Na metal) and transferring it to a flame-dried reaction vessel under high purity argon. The reaction was carried out under a continuous flow of argon with a CaCl₂ drying tube attached to the condenser to eliminate atmospheric moisture.

The results of this extensive purification can be seen in the GPC traces of the synthesized CCS polymers (Figure 4.9). Trace a) of Figure 4.9 was based on the use of PCL macroinitiator synthesized under the rigorous conditions previously described, showing no evidence of higher molecular weight star-star coupling product. The same batch of PCL macroinitiator was then used to repeat this reaction (Figure 4.9 b)) which again showed no star-star coupling reactions had occurred, confirming that the high purity reaction conditions effectively stopped the formation of water initiated
PCL chains. To prove this was the case and not simply a result of the two step reaction allowing for isolation and purification of the PCL macroinitiator, a third reaction was performed, except that this time the PCL macroinitiator was synthesized under less rigorous reaction conditions (Figure 4.9 c). The corresponding GPC trace for this reaction clearly shows the formation of a higher molecular weight product due to star-star coupling, confirming that it was the actual batch of PCL macroinitiator used and not the two step reaction process which eliminated the star-star coupling reaction.

![Diagram showing GPC traces for CCS polymer synthesis.

Figure 4.9: GPC traces of fully degradable CCS polymer synthesized using a) & b) highly purified PCL macroinitiator [reaction b) is a repeat of reaction a) using same PCL macroinitiator], and c) standard PCL macroinitiator.

4.2.5 Shelf life
An interesting problem involving the stability of these fully degradable CCS polymers was noticed when samples that had been stored for a prolonged period were reanalyzed. The solubility of these polymers was found to decrease over time with GPC analysis showing an increase in the amount of high molecular weight polymer associated with the product of star-star coupling (Figure 4.10). This phenomenon was observed for all CCS polymers produced via the ring-opening polymerization of a bislactone, both BOD and BCP, with fractionation to remove any star-star coupling product as well as any unreacted macroinitiator not stopping the process. Even rigorous purification of the CCS polymer involving filtering through alumina columns and multiple precipitations didn’t appear to help. One possible explanation for this is
the presence of Sn(Oct)$_2$ catalyst which has become trapped within the core of the precipitated CCS polymer. If this is the case then the cores could still potentially be active toward ROP, albeit rather slowly due to the absence of high temperature, resulting in star-star coupling reactions. This would also explain why this type of behavior is not observed for CCS polymers formed using CRP methods, with precipitation being an effective means for stopping radical-based polymerizations.

**Figure 4.10:** GPC traces of precipitated PCL/BOD CCS polymer stored under different conditions for 38 days; a) original polymer, b) low temp (<2°C) storage, c) room temp (25°C) storage, d) vacuum (5 mm Hg) storage in desiccator, e) THF (20 mg/mL) storage.

In an attempt to prolong the shelf life of these ROP cross-linked CCS polymers, several different methods of storage were investigated looking at the effects of temperature, oxygen, isolation method and solvents. Figure 4.10 shows the GPC traces related to this investigation with both refractive index (RI, represented by a solid line ——) and light scattering (LS, represented by a dashed line ----) responses being shown. By comparing the original GPC trace of the precipitated CCS polymer (Figure 4.10 a)) to those obtained after 38 days of storage (Figure 4.10 b) to e)) it is
possible to see what effect has been had on the amount of additional star-star coupling, with the LS traces more clearly showing this effect due to the increased scattering potential of the higher molecular weight product. From these traces it can be seen that after 38 days the amount of star-star coupling increased for the samples which were stored at room temperature and under vacuum in a desiccator (Figure 4.10, traces c) and d) respectively), with these samples eventually becoming completely insoluble after 4 months of similar storage. However, the sample which was stored in the fridge (Figure 4.10 b)) showed almost no change even after 4 months, indicating that the low temperature was sufficient to halt any further star-star coupling reactions. Perhaps of greater significance was the result obtained from the storage of precipitated CCS polymer in a solvent, tetrahydrofuran (THF) (Figure 4.10 e)). In this case the high molecular weight product due to star-star coupling disappeared completely, with resampling after 4 months showing similar results. The ability of this storage method to prevent star-star coupling can be explained by the fact that the solvent disperses the CCS polymers, preventing the cores of adjacent stars from remaining in close proximity for extended periods such that the probability of ROP induced coupling at this temperature is minimal. As for the disappearance of the preexisting star-star coupling product, it is thought to eventually become insoluble and precipitate from solution such that it can no longer be detected by GPC analysis. Unfortunately the existence of this insoluble polymer cannot be confirmed due to the relatively small amount. Either way, these results clearly show that the shelf life of these fully degradable CCS polymers can be extended either by storing them at reduced temperatures (<2°C) or in the presence of a solvent such as THF.

The effect of non-solvent used during precipitation was also investigated since it was thought that the use of a hydroxyl containing solvent, i.e. methanol, may be promoting further ROP reactions. This was tested by precipitating CCS polymer into hexane and storing it under the previously described conditions, with similar results between methanol and hexane suggesting that the precipitation solvent was not a factor in the stability issue. Other methods of storage not involving precipitation were also examined, with CCS polymer left in the reaction solution (i.e. no isolation) as well as a sample isolated by solvent evaporation both becoming insoluble after 38 days of storage at room temperature. This makes sense if the coupling reaction is being facilitated by the presence of Sn(Oct)$_2$ since neither of these storage methods resulted in the removal of the catalyst. It also explains why these two samples experienced an
accelerated insolubility compared to the precipitated samples discussed previously, with precipitation removing the majority of Sn(Oct)$_2$ such that only a small amount remains trapped within the CCS polymer and therefore reducing the rate of star-star coupling.
4.3 Conclusions

In summary, this Chapter has shown that ring-opening polymerization can be applied to the synthesis of fully degradable CCS polymers. Similar to non-degradable CCS polymer synthesis via the ‘arms first’ approach utilizing CRP techniques, these degradable CCS polymers were shown to possess high molecular weight and narrow polydispersities. The use of ring-opening polymerization techniques allowed for the reaction to be carried out as a one-pot process thus eliminating the need for isolation and purification of the intermediate macroinitiator product. The manipulation of several reaction parameters, particularly concentration, arm length and the molar ratio of cross-linker to macroinitiator, was investigated in order to determine their effect on the extent of CCS formation, with the results generally mimicking those found for the case of ATRP mediated CCS formation. The effectiveness of two bislactone cross-linkers, BOD and BCP, was also examined with a higher conversion of arms into CCS polymer being achieved when BOD was used compared to BCP, possibly due to the added steric bulk of the BCP monomer making formation of the dense core region unfavorable. Both BOD and BCP based CCS polymers were shown to be fully degradable with $^1$H NMR spectroscopy confirming that >97% of the ester linkages had been hydrolyzed, converting the high molecular weight CCS polymers into small-chain acid units. The phenomenon of star-star coupling was also investigated, with hydroxyl impurities such as water being found to be the main cause of star-star coupling for ROP based reactions. Issues of continued star-star coupling after precipitation of the CCS polymers was also found to be a problem, with the presence of Sn(Oct)$_2$ catalyst trapped within the core domain thought to be promoting coupling reactions between the cores and decreasing the polymer’s solubility. This problem of reduced shelf life was shown to be overcome by either storing the fully degradable CCS polymers at low temperature (<2°C) or in the presence of a solvent such as THF, with both methods effectively stopping any further coupling reactions.

4.4 References


Chapter 5 - Modification of CCS Polymer Corona

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5.1 Introduction
One of the defining properties of CCS polymers is that their structure can be divided into two distinct regions, that of the cross-linked core and that of the arms or corona. The coronal domain is of particular importance since its structural makeup can significantly influence the physical properties displayed by the CCS polymer. Properties such as the crystallinity and hydrophilicity of a CCS polymer can easily be modified by changing the type of polymer used to generate the arms. For example, Connal et al.\textsuperscript{[1]} showed that the glass transition temperature ($T_g$) of CCS polymers could be decreased by over 200$^\circ$C simply by changing the polymeric composition of the arms from poly(methyl methacrylate) ($T_g = 123^\circ$C) to poly(dimethylsiloxane) ($T_g = -122^\circ$C), whereas such an effect was not observed when changing the polymeric composition of the core domain. Other examples of similarly dramatic physical property changes induced via manipulation of the coronal structure have also been reported, with conversion of the poly($\text{tert}$-butyl acrylate) arms of a CCS polymer into poly(acrylic acid) arms, via cleavage of the $\text{tert}$-butyl groups, being shown to change the CCS polymer from hydrophobic to hydrophilic.\textsuperscript{[2,3]} The length and the number of arms, i.e. the size and density of the corona, also play a significant role in determining the properties of CCS polymers. For example, a reduction in arm length has been shown to reduce the viscosity of CCS polymer solutions, a result of the CCS polymers becoming more compact in structure and therefore reducing the degree of entanglement experienced between adjacent star polymers.\textsuperscript{[4]} Therefore, in order to achieve a greater degree of control over the physical properties displayed by CCS polymers we have to be able to control the coronal properties.

In this Chapter we explore the synthesis of a range of CCS polymers with adjustable coronal properties such that it is possible to manipulate the size, density and chemical composition of the CCS corona post-synthesis. This is achieved by utilizing the techniques developed in the previous Chapters such that CCS polymers with heterogeneous coronal structures can be synthesized. Several different approaches for synthesizing miktoarm CCS polymers, block copolymer arm CCS polymers and combinations thereof are investigated, with specific focus being paid to the incorporation of partially degradable functionality into the coronal domain. These highly functional CCS polymers are then subjected to post-synthesis modification involving either hydrolysis or extension of the coronal domain, with the corresponding effect on the CCS structure being fully analyzed.
5.2 Results and Discussion

5.2.1 Miktoarm CCS polymers

The term miktoarm (from the Greek word miktos, meaning mixed) is used to refer to star polymers consisting of chemically different arms. In the past decade considerable effort has been made toward synthesizing this class of star polymer as it was realized that their unique structure was capable of exhibiting some very interesting properties.\[5\] They also provide a unique means for controlling the coronal makeup of CCS polymers, particularly when a mixture of degradable and non-degradable arms are used such that one type of arm can be selectively removed, thereby altering the coronal structure and the subsequent properties of the CCS polymer.

The synthesis of miktoarm CCS polymers can in general be accomplished using two separate methods, the ‘in-out’ approach and the ‘simultaneous cross-linking’ approach. Both these mechanisms will be used here to synthesize partially arm-degradable CCS polymer, with the advantages and disadvantages of each approach being discussed in detail.

5.2.1.1 In-out method

The most commonly reported method for synthesizing miktoarm CCS polymers has traditionally been the ‘in-out’ approach.\[6,7,8\] It was first reported by Funke\[9,10\] and then extended and improved by Rempp,\[11,12,13\] with the basic principle being shown below in Scheme 5.1. Here, regular CCS polymer is firstly synthesized via the ‘arms first’ approach using terminally reactive linear polymer chains to initiate the polymerization of a cross-linkable monomer such that the active arm ends are coupled together. Since the initiating functionality of the macroinitiators is preserved within the core of the CCS polymer it is possible to use then to grow a second type of arm out from the core and hence generate miktoarm CCS polymer.

![Scheme 5.1: Synthesis of miktoarm CCS polymer via the ‘in-out’ approach.](image)}
In order to synthesize miktoarm CCS polymers for which the coronal structure can be manipulated post-synthesis, it is required that a mixture of degradable and non-degradable arms be used. From the work presented earlier in this thesis it has been shown that the ester linkages within PCL can easily be hydrolyzed under conditions which won’t affect the structural integrity of non-degradable polymers such as PMMA. For this reason it was decided to synthesize miktoarm CCS polymers with PCL as the degradable arm component and PMMA as the non-degradable arm component. The order in which these arms can be attached to the miktoarm CCS polymer, either as primary arm during initial CCS formation or secondary arm grown out from the core, is determined by the mechanism of ‘in-out’ formation. As can be seen from Scheme 5.1, the initiating functionality which is used to cross-link the primary arms is the same that is used to grow the secondary arms out from the core. Since the core domain in this case will be formed by cross-linking non-degradable EGDMA under ATRP conditions, it is also required that the secondary arms be grown via ATRP. This restricts the non-degradable PMMA to being the secondary arms, meaning that the initial step requires the synthesis of PCL/EGDMA CCS polymer analogous to the arm-degradable CCS polymers discussed in Chapter 2. This proposed approach for synthesizing partially degradable miktoarm CCS polymer is outlined in Scheme 5.2.

Scheme 5.2: Synthesis of partially degradable miktoarm CCS polymer via the ‘in-out’ approach and subsequent hydrolysis.
The first step of this reaction involved the use of a duel ATRP/ROP initiator, 2-hydroxyethyl 2’-methyl-2’-bromopropionate, to initiate the polymerization of CL monomer under ROP conditions and thereby generate PCL-Br macroinitiator ($M_n = 4,600 \text{ g/mol}, M_w/M_n = 1.11$). The terminal alkyl bromine group of the PCL-Br macroinitiator was then used to initiate the polymerization of EGDMA monomer under ATRP conditions to form the required CCS polymer, with the corresponding GPC traces being shown in Figure 5.1. The reaction conditions used here were similar to those reported to achieve optimal conversion in Chapter 2, however the GPC traces revealed that the conversion of arms into CCS polymer in this case was significantly reduced, decreasing from 85% to 60%. This can be attributed to the use of higher molecular weight arms, 4.6 kDa compared to 2.3 kDa, a factor which tends to reduce CCS conversion as previously discussed in Chapter 2. This unconverted macroinitiator can potentially act as an alternative initiation source during the subsequent synthesis of miktoarm CCS polymer, resulting in the generation of contaminant linear PCL-PMMA polymer. For this reason the PCL/EGDMA CCS polymer was fractionated to yield pure star polymer with a molecular weight of $M_n = 152,300 \text{ g/mol} (M_w/M_n = 1.18)$ and an average of 18.7 arms per star (Table 5.1, entry 1A).

![Figure 5.1: GPC traces of the formation of PCL/EGDMA CCS polymer. (\([\text{PCL-Br]} = 7.5 \text{ mM} = [\text{CuBr}]/1.3 = [\text{PMDETA}]/1.3 = [\text{EGDMA}]/15\) in anisole at 100°C)](image-url)
Table 5.1: Synthesis of miktoarm CCS polymer via the ‘in-out’ approach with adjustable coronal properties.

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>$M_n$ (g/mol)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>PD&lt;sup&gt;c&lt;/sup&gt;</th>
<th>arm $M_n$ (g/mol)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>$D_h$ (nm)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>SD (nm)&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>152,300</td>
<td>1.18</td>
<td>4,600</td>
<td>15.3</td>
<td>2.9</td>
</tr>
<tr>
<td>1B</td>
<td>277,900</td>
<td>1.33</td>
<td>mixed</td>
<td>24.8</td>
<td>7.1</td>
</tr>
<tr>
<td>1C</td>
<td>205,700</td>
<td>1.26</td>
<td>6,700</td>
<td>14.0</td>
<td>3.1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Sample reference numbers refer to Scheme 5.2, reaction conditions as defined in text.

<sup>b</sup> Number average molecular weight ($M_n$) and polydispersity (PD) measured by GPC-MALLS.

<sup>c</sup> Average number of arms in CCS polymer ($\phi$) determined by Equation 2.2.

<sup>d</sup> Average hydrodynamic diameter ($D_h$) in THF measured by dynamic light scattering.

<sup>e</sup> Standard deviation (SD) of polymer’s hydrodynamic diameter.

<sup>f</sup> Theoretical values based on 100% initiation efficiency of the secondary extension reaction.

In the second step of this reaction the previously synthesized PCL/EGDMA CCS polymer was used as macroinitiator to grow PMMA arms out from the core, thereby generating the required miktoarm CCS polymer (Table 5.1, entry 1B). One of the drawbacks of this reaction is its susceptibility toward gelation. This occurs because the propagating radicals are located at the outer ends of the growing secondary arms, the close proximity of which increases the probability of radical-radical termination reactions between the stars which can eventually lead to gelation. In order to avoid this, the reaction had to be closely monitored and not allowed to attain high monomer conversion. In this particular case the reaction was stopped after 9 hours, with GPC analysis (Figure 5.2) showing the generation of a higher molecular weight polymer being representative of the miktoarm CCS polymer ($M_n = 277,900$ g/mol, $M_w/M_n = 1.33$). <sup>1</sup>H NMR spectroscopic analysis of this isolated polymer confirmed that PMMA had been incorporated into the CCS polymer, with a comparison of the relative integral areas showing that the molar ratio of MMA to CL was approximately 2.4:1. This equates to a molecular weight of 325,300 g/mol for the miktoarm CCS polymer as determined by NMR spectroscopy.
One of the drawbacks of the ‘in-out’ approach for synthesizing miktoarm CCS polymers is the unknown efficiency of the chain extension reaction to generate the secondary arms. If the initiation efficiency of this reaction is 100% then each macroinitiator incorporated into the CCS polymer should result in the generation of an additional secondary arm, theoretically doubling the number of arms which were incorporated into the initial CCS polymer. Realistically this is not the case, with the high cross-linking density of the core and the steric hindrance created by the arms effectively reducing the accessibility to these initiation sites and lowering the efficiency of this reaction.\textsuperscript{[8,14]} This unknown initiation efficiency means that the number and molecular weight of the secondary arms in the subsequent miktoarm CCS polymer cannot be accurately determined, with the molecular weight data only showing the extent to which the secondary monomer was polymerized and not how it was distributed within the polymer. For example, a miktoarm CCS polymer of a given molecular weight would have half as many secondary arms if the initiation efficiency were 50% as opposed to 100%, with the corresponding molecular weight of these arms being twice that predicted by theory. Even though the initiation efficiency is not known in this case it is expected to be quite low, with several papers\textsuperscript{[8,14]} showing that the initiation efficiency of this type of reaction can vary between 5-50% with typical values being more in the range of 20%.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure5_2.png}
\caption{GPC traces of the formation of PCL/PMMA miktoarm CCS polymer via the ‘in-out’ approach and subsequent hydrolysis to remove the PCL arms (corresponding data in Table 5.1).}
\end{figure}
The synthesized miktoarm CCS polymer was subsequently hydrolyzed in order to remove the PCL arms, thereby reducing the arm density and changing the chemical composition of the corona. GPC traces of this reaction (Figure 5.2) showed that the molecular weight of the miktoarm CCS polymer was reduced upon hydrolysis, yielding CCS polymer with only PMMA arms (confirmed by $^1$H NMR spectroscopy) and a number-average molecular weight of 205,700 g/mol ($M_w/M_n = 1.26$) (Table 5.1, entry 1C). This corresponds very closely to the theoretical molecular weight of the hydrolyzed product ($M_n, \text{theory} = 195,733$ g/mol), however the number and molecular weight of the PMMA arms attached to this CCS polymer is still unknown. If an assumption of 100% initiation efficiency is made then it can be calculated that there would be an average of 18.7 arms per star, each with a molecular weight of 6,700 g/mol. A more realistic estimate of 20% initiation efficiency would result in an average of 3.7 arms attached to the core, each with a molecular weight of approximately 33,900 g/mol. The increased polydispersity of this hydrolysis product ($M_w/M_n = 1.26$) also tends to suggest that the distribution of arms between the individual stars is quite varied, with some stars having significantly more arms than the average value and some having significantly less. While the distribution of arm number may be broad, the molecular weight of the arms should all still be very similar due to the controlled nature of the polymerization technique use to grow the secondary arms out from the core.

Dynamic light scattering (DLS) measurements were used to monitor the change in hydrodynamic diameter ($D_h$) of this series of CCS polymers over the course of these transformations (PCL CCS to PCL/PMMA miktoarm CCS to PMMA CCS), with the DLS traces being shown in Figure 5.3 and the corresponding data in Table 5.1. From these results it can clearly be seen that the modification of the coronal domain has a significant effect on the hydrodynamic size of the CCS polymer. By using the ‘in-out’ approach to graft additional arms to the CCS core it was observed that the average $D_h$ increased from 15.3 nm up to 24.8 nm. Since this type of measurement equates the size of the polymer to a hard sphere with equivalent hydrodynamic properties, this is in no means an indication of the length of the secondary arms. In fact the $D_h$ will be effected by a number of factors which include the packing density of the arms, arm molecular weight, and the interaction potential with the solvent (THF in this case). Hydrolysis of the miktoarm CCS polymer was also seen to have an effect, with the
average $D_h$ decreasing from 24.8 nm down to 14.0 nm, a size similar to that of the original CCS polymer.

![DLS traces of the formation of PCL/PMMA miktoarm CCS polymer via the ‘in-out’ approach and subsequent hydrolysis to remove the PCL arms.](image)

**Figure 5.3:** DLS traces of the formation of PCL/PMMA miktoarm CCS polymer via the ‘in-out’ approach and subsequent hydrolysis to remove the PCL arms.

(Corresponding data in Table 5.1)

### 5.2.1.2 Simultaneous cross-linking method

An alternative method for synthesizing miktoarm CCS polymers is via the ‘simultaneous cross-linking’ approach. The general mechanism for this technique is shown in Scheme 5.3 and involves the cross-linking of two different types of polymeric macroinitiator (macroinitiators A and B) simultaneously. For this approach to work successfully it is required that the reactivity of the two different types of macroinitiator be similar such that the resultant CCS polymers contain a mixture of both polyA and polyB arms, i.e. miktoarm CCS polymers. If this is not the case and one type of macroinitiator is much more reactive than the other then the resulting product would be a mixture of homoarm CCS polymers. This technique is not just limited to the use of two different types of arms either, theoretically any number of chemically different macroinitiators can be cross-linked simultaneously to generate miktoarm CCS polymers with multiple arm types, a feat which cannot be achieved via the ‘in-out’ approach. Other advantages that this method has over the previously discussed ‘in-out’ approach include a greater control over the architectural makeup of...
the miktoarm CCS polymers. The fact that the molecular weight of the macroinitiators is known means that the problem of unknown secondary arm length/number experienced as part of the ‘in-out’ approach is not an issue, with the resulting structure of the miktoarm CCS polymers being more accurately defined in this case. Furthermore, the number of secondary arms is no longer limited by the low initiation efficiency associated with the growth of arms out from the core during the ‘in-out’ approach, meaning that more control can be exerted over the ratio of different arms incorporated into the miktoarm CCS polymers.

Scheme 5.3: Synthesis of miktoarm CCS polymer via the ‘simultaneous cross-linking’ approach.

In order to synthesize partially degradable miktoarm CCS polymer similar to that generated via the ‘in-out’ approach, it was proposed to simultaneously cross-link PCL and PMMA based macroinitiators as illustrated in Scheme 5.4. The degradable PCL based macroinitiator was synthesized in a similar fashion to that used in the ‘in-out’ approach, with 2-hydroxyethyl 2'-methyl-2'-bromopropionate being used to initiate ROP of CL monomer and thereby generate PCL-Br macroinitiator (M_n = 2,300 g/mol, M_w/M_n = 1.05) capable of initiating further ATRP reactions. Ideally, the same initiator should be used to generate the non-degradable PMMA based macroinitiator as was used to synthesize the PCL-Br macroinitiator, such that the reactivity of the macroinitiators in the subsequent cross-linking reaction would be similar. Unfortunately, as discussed in Section 3.2.2 of this thesis, the use of 2-hydroxyethyl 2'-methyl-2'-bromopropionate to initiate the polymerization of MMA resulted in polymers with very broad polydispersities (M_w/M_n > 1.5). For this reason tosyl chloride was used to initiate the polymerization of MMA under ATRP conditions, a well established reaction in the literature, with the resulting PMMA-Cl macroinitiator
having a number-average molecular weight of 7,500 g/mol and narrow polydispersity (Mw/Mn = 1.08).

Scheme 5.4: Synthesis of partially degradable miktoarm CCS polymer via the ‘simultaneous cross-linking’ approach and subsequent hydrolysis.

A one to one molar ratio of the PCL-Br and PMMA-Cl macroinitiators was subsequently cross-linked with EGDMA monomer under ATRP conditions. GPC traces of this reaction (Figure 5.4) clearly show the generation of a higher molecular weight product, with approximately 28% of the combined macroinitiator being converted into CCS polymer. This polymer was subsequently fractionated to remove the unconverted macroinitiator and yield pure CCS polymer with a number average molecular weight of 559,600 g/mol and a reasonably narrow polydispersity (Mw/Mn = 1.24) (Table 5.2, entry 2A). The presence of both PCL and PMMA in this fractionated CCS polymer was confirmed by 1H NMR spectroscopic analysis which, in conjunction with the monomodal peak detected by GPC, suggests that this polymer is indeed a miktoarm CCS and not a mixture of homoarm CCS polymers.
Figure 5.4: GPC traces of the formation of PCL/PMMA miktoarm CCS polymer via the ‘simultaneous cross-linking’ approach and subsequent hydrolysis to remove the PCL arms (corresponding data in Table 5.2).

Table 5.2: Synthesis of miktoarm CCS polymer with adjustable coronal properties via the ‘simultaneous cross-linking’ approach.

<table>
<thead>
<tr>
<th>entry</th>
<th>(M_n) (g/mol)</th>
<th>PD</th>
<th>(f)</th>
<th>arm (M_n) (g/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2A</td>
<td>559,600</td>
<td>1.24</td>
<td>53.1</td>
<td>2,300 (72%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7,500 (28%)</td>
</tr>
<tr>
<td>2B</td>
<td>460,800</td>
<td>1.36</td>
<td>14.8</td>
<td>7,500</td>
</tr>
</tbody>
</table>

\(a\) Sample reference numbers refer to Scheme 5.4, reaction conditions as defined in text.

\(b\) Number average molecular weight (\(M_n\)) and polydispersity (PD) measured by GPC-MALLS.

\(c\) Average number of arms in CCS polymer (\(f\)) determined by Equation 2.2.

Since the molecular weight of the PCL-Br and PMMA-Cl macroinitiators were different it is expected that their reactivity will also be different, resulting in miktoarm CCS polymer with a higher ratio of one type of arm compared to the other. \(^1\)H NMR spectroscopy was used to determine the relative amount of PCL and PMMA arms incorporated into the miktoarm CCS polymer (Figure 5.5) by comparing the integral of \(a\) (\(CH_2\)COO from PCL unit) to \(h\) (OCH\(_3\) from PMMA unit). Using this technique the molar ratio of PCL to PMMA was determined to be 2.6:1, showing that the smaller PCL arms (\(M_n = 2,300\) g/mol) were more readily incorporated into the miktoarm CCS polymer than the larger PMMA arms (\(M_n = 7,500\) g/mol). From this
data it was possible to calculate the average number of arms \((f)\) incorporated into the CCS polymer as being 53.1 (14.8 PMMA and 38.3 PCL arms).

![Figure 5.5: 1H NMR spectrum of PCL/PMMA miktoarm CCS polymer (Table 5.2, entry 2A).]

The miktoarm CCS polymer reported here can be classified as partially arm-degradable since one type of arm, the PCL component, can be selectively degraded to produce CCS polymer with a reduced number of arms. By hydrolyzing this partially arm-degradable CCS polymer we can change the chemical makeup of the coronal domain and hence modify the properties displayed by the CCS polymer. In addition to this, the hydrolyzed CCS polymer would potentially have a very different physical structure to that of standard CCS polymer since the number of arms would be much less compared to CCS polymer of a similar arm molecular weight. The actual hydrolysis of this partially degradable miktoarm CCS polymer was monitored by GPC which showed a reduction in molecular weight after hydrolysis (Figure 5.4) such that the resultant CCS polymer had a \(M_n\) of 460,800 g/mol and a polydispersity of 1.36 (Table 5.2, entry 2B). 1H NMR spectroscopy of the hydrolyzed polymer confirmed that all of the PCL arms had been removed to yield pure PMMA arm CCS polymer. Since the number and molecular weight of the degradable PCL arms in the miktoarm CCS polymer are known, the theoretical molecular weight of the CCS polymer after hydrolysis can be calculated. For the miktoarm CCS polymer reported here the
theoretical $M_n$ after hydrolysis was calculated to be 472,500 g/mol which is in accordance with that measured by GPC-MALLS (460,800 g/mol).

5.2.2 Block copolymer arm CCS polymers

In addition to miktoarm CCS polymers, the synthesis of other more complex architectures have also been shown to be possible such that CCS polymers with block copolymer arms\textsuperscript{[15,16,17]} and even dendron terminated arms\textsuperscript{[15,18]} have been reported in the literature. Of particular interest for its ability to modify the coronal properties is the use of block copolymer arms, with addition or removal of the outer block segment essentially changing the chemical makeup at the periphery of the star. This is important since it is the outer layer of the corona which controls many of the CCS polymer properties, particularly in terms of its interaction potential with other molecules.

The use of block copolymer arms also provides a means for changing the arm length of CCS polymers via post-synthesis modification reactions without affecting the arm number. This is quite useful since one of the consequences of synthesizing CCS polymers via the ‘arms first’ approach is that the number of arms incorporated into the star polymer is strongly dependent on the molecular weight of the macroinitiator (i.e. the arm length). It has been shown that as the length of the arm is reduced the number of arms incorporated into the CCS polymer tends to increase.\textsuperscript{[19,20,21]} This is an important relationship as it essentially controls the structure of the CCS polymer, allowing for the synthesis of stars with either many short arms or few long arms. It also has a direct effect on the rheological properties of CCS polymers, with the incorporation of a high number of arms generating a more compact coronal structure such that the degree of entanglement experienced between adjacent star polymers, i.e. the viscosity, is reduced.\textsuperscript{[4]}

The following work presented in this Chapter looks at several techniques for manipulating the coronal structure of CCS polymers through the use of block copolymer arms. This includes incorporating degradable functionality into the arms such that the outer coronal layer can be selectively removed, as well as synthesizing periphery functionalized CCS polymers capable of initiating further polymerization to extend the corona.
5.2.2.1 *Block copolymer method*

The use of block copolymers to synthesize CCS polymer with modifiable coronal structure was achieved according to Scheme 5.5. In this case the arms of the CCS polymer are comprised of semi-degradable poly(ε-caprolactone)-*b*-poly(methyl methacrylate) (PCL-*b*-PMMA) block copolymers, the PCL component of which can be selectively hydrolyzed to remove the outer coronal layer of the CCS polymer and therefore decrease the arm length.

**Scheme 5.5:** Synthesis of degradable block copolymer CCS and subsequent hydrolysis.

In order to synthesize such CCS polymer it was firstly required that a suitable macroinitiator be generated. This was achieved by using the difunctional initiator 2-hydroxyethyl 2'-methyl-2'-bromopropionate to synthesize PCL-*b*-PMMA-Br macroinitiator such that the degradable PCL component was situated at the non-active end of the macroinitiator. The hydroxyl functionality of this initiator was firstly used to initiate the ring-opening polymerization of CL monomer in the presence of Sn(Oct)₂ as catalyst. The resultant linear HO-PCL-Br polymer (Mₙ = 4,600 g/mol, Mᵥ/Mₙ = 1.11) retained the alkyl halide functionality of the initiator which was subsequently used to initiate the polymerization of MMA under ATRP conditions with CuBr/PMDETA as catalyst. Even though this is a controlled/living polymerization, it has been shown that prolonged reaction times leading to nearly
complete monomer conversion can induce a loss of end-group functionality.\[22\] For this reason the reaction was not allowed to go to high conversion, being stopped after 53% of the MMA had been consumed in order to preserve the alkyl bromide end-group functionality required for the subsequent ATRP cross-linking reaction to generate the CCS polymer. The resultant PCL-\textit{b}-PMMA-Br block copolymer (M\textsubscript{n} = 8,300 g/mol, M\textsubscript{w}/M\textsubscript{n} = 1.07) showed good initiation efficiency, with GPC analysis showing that all of the HO-PCL-Br macroinitiator underwent chain extension (Figure 5.6). The composition of the block copolymer was confirmed by \textsuperscript{1}H NMR spectroscopy with the molar fraction of MMA being determined by integration to be F\textsubscript{MMA} = 0.44. This value equates to an overall molecular weight of 7,624 g/mol which corresponds quite nicely to that determined via GCP analysis (8,300 g/mol).

![Figure 5.6: GPC traces of degradable block copolymer CCS synthesis and subsequent hydrolysis to remove the outer PCL coronal layer (corresponding data in Table 5.3).](image)

Ethylene glycol dimethacrylate (EGDMA) monomer was subsequently used to cross-link the ATRP active end group of the PCL-\textit{b}-PMMA-Br macroinitiator to synthesize CCS polymer with semi-degradable block copolymer arms. The extent of CCS formation was limited (10% conversion of arms into CCS polymer) and as such was fractionated to remove any unconverted macroinitiator and yield pure CCS polymer. GPC-MALLS was used to measure the absolute molecular weight (M\textsubscript{n} = 226,200 g/mol) and the polydispersity (M\textsubscript{w}/M\textsubscript{n} = 1.18) of the fractionated CCS polymer (Table 5.3, entry 3A) with the average number of arms being calculated as 7.2 per star. The
low conversion of this reaction and the corresponding low number of arms per star is a result of the relatively high molecular weight of the macroinitiator. It is possible that higher conversions could have been achieved by manipulating the reaction conditions to better suit the use of a larger macroinitiator but this was deemed unnecessary as the fractionation procedure was able to isolate a sufficient amount of the pure block copolymer CCS polymer for subsequent analysis.

Table 5.3: Synthesis of block copolymer arm CCS with adjustable coronal properties.

<table>
<thead>
<tr>
<th>entry</th>
<th>Mn (g/mol)</th>
<th>PD</th>
<th>( f^c )</th>
<th>arm Mn (g/mol)</th>
<th>Dh (nm)</th>
<th>SD (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3A</td>
<td>226,200</td>
<td>1.18</td>
<td>7.2</td>
<td>8,300</td>
<td>23.3</td>
<td>6.6</td>
</tr>
<tr>
<td>3B</td>
<td>207,100</td>
<td>1.26</td>
<td>7.2</td>
<td>3,910</td>
<td>18.6</td>
<td>4.3</td>
</tr>
</tbody>
</table>

*a Sample reference numbers refer to Scheme 5.5, reaction conditions as defined in text.
b Number average molecular weight (M_n) and polydispersity (PD) measured by GPC-MALLS.
c Average number of arms in CCS polymer (\( f \)) calculated using Equation 2.2.
d Average hydrodynamic diameter (D_h) in THF measured by dynamic light scattering.
e Standard deviation (SD) of polymer’s hydrodynamic diameter.

One of the unique properties of this novel CCS polymer lies in the ability to manipulate the size of the corona and hence alter the overall dimensions of the CCS polymer. This is made possible due to the presence of the degradable PCL block in the outer coronal layer of the star which essentially surrounds a non-degradable CCS polymer with PMMA arms and EGDMA cross-linked core. Removal of the PCL coronal layer was achieved through the use of acidic conditions which have previously been shown to be capable of hydrolyzing PCL without affecting the PMMA/EGDMA structure of the CCS polymer. GPC traces of the hydrolyzed CCS polymer (Figure 5.6) showed a reduction in molecular weight such that the resultant CCS polymer had a M_n of 207,100 g/mol and a polydispersity of 1.26 (Table 5.3, entry 3B). \(^1\)H NMR spectroscopic analysis of the hydrolyzed polymer confirmed that all of the PCL had been removed to yield CCS polymer with PMMA arms. Since the number of arms remains the same (\( f = 7.2 \)) and the molecular weight of the degradable PCL arm segment is known (M_n = 4,390 g/mol) it is possible to calculate the theoretical molecular weight of the CCS polymer after hydrolysis. For the block copolymer CCS reported here, the theoretical M_n after hydrolysis was calculated to be
194,600 g/mol which is in agreement with that measured by GPC-MALLS (207,100 g/mol).

Dynamic light scattering was used to measure the hydrodynamic diameter of the PCL-$b$-PMMA arm CCS polymer before and after hydrolysis (Figure 5.7). It was found that as the length of the arms was reduced from 8,300 g/mol to 3,910 g/mol, the hydrodynamic diameter also decreased (23.3 nm to 18.6 nm). The technique of using semi-degradable block copolymers to synthesize CCS polymer not only allows for precise control of the arm length through manipulation of the ratio of degradable to non-degradable polymer in the macroinitiator, but it also allows for the modification of coronal properties. For example, the CCS polymer reported here initially has surface properties characteristic of PCL which, though simple hydrolysis, can be modified to display properties characteristic of PMMA. By employing a range of different degradable and non-degradable monomers to synthesize the block copolymer arms, the potential to control properties such as the hydrophilicity or the crystallinity of the CCS corona is increased.

![Figure 5.7: DLS traces of degradable block copolymer CCS before and after hydrolysis (corresponding data in Table 5.3).](image-url)
5.2.2.2 **ROP chain extension method**

An alternative way of utilizing block copolymers to modify the coronal structure of CCS polymers is to add a polymer segment to the arms once the CCS polymer has been synthesized. Post-synthesis modifications such as this can be used to increase the length of the CCS polymer arms whilst also changing the coronal properties if the secondary polymer is different to that of the original arms. Such an approach can be achieved in various ways, one of which involves chain extension of the arms out from the surface of the CCS polymer. This technique requires that the arms be end-functionalized with an appropriate functionality capable of initiating polymerization but not being active towards the cross-linking reaction during CCS formation. Rather than protecting the initiating functionality or attempting to functionalize the arms after star formation it is much easier to incorporate two different initiating functionalities which can be utilized independently of one another. For this particular work it decided to make use of ATRP and ROP since the initiating functionalities of these two controlled polymerization techniques are compatible, with ATRP being tolerant of the presence of hydroxyl groups and ROP being tolerant of the presence of alkyl halide groups. Utilizing this technique it was possible to synthesize surface functionalized CCS polymer, the corona of which could be chain extended via ROP to modify the structure as shown in Scheme 5.6.

**Scheme 5.6:** Synthesis of hydroxyl surface functionalized CCS polymer capable of initiating ROP chain extension.
In order to achieve this, 2-hydroxyethyl 2'-methyl-2'-bromopropionate was used to initiate the polymerization of styrene under ATRP conditions to generate a difunctional macroinitiator (HO-PSt-Br) \( (M_n = 7,700 \text{ g/mol}, M_w/M_n = 1.03) \). The resultant structure of this polystyrene macroinitiator is such that it contains an alkyl bromide group at one end capable of initiating ATRP reactions and a hydroxyl functionality at the other end capable of initiating ROP reactions. This HO-PSt-Br macroinitiator was subsequently cross-linked through the ATRP active end-group with EGDMA, generating CCS polymer with hydroxyl terminated arms (Scheme 5.6). Any unconverted macroinitiator was removed via fractional precipitation to yield pure CCS polymer with a number average molecular weight of 265,700 g/mol \( (M_w/M_n = 1.16) \) and an average of 20.2 arms (Table 5.4, entry 4A).

### Table 5.4: Synthesis of ROP surface functionalized CCS polymer with adjustable coronal properties.

<table>
<thead>
<tr>
<th>entry</th>
<th>( M_n ) (g/mol)</th>
<th>PD</th>
<th>( f )</th>
<th>arm ( M_n ) (g/mol)</th>
<th>( D_h ) (nm)</th>
<th>SD (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4A</td>
<td>265,700</td>
<td>1.16</td>
<td>20.2</td>
<td>7,700</td>
<td>11.7</td>
<td>3.2</td>
</tr>
<tr>
<td>4B</td>
<td>544,400</td>
<td>1.25</td>
<td>20.2</td>
<td>21,400(^f)</td>
<td>23.7</td>
<td>7.4</td>
</tr>
<tr>
<td>4C</td>
<td>277,800</td>
<td>1.21</td>
<td>20.2</td>
<td>7,700</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\( ^a \) Sample reference numbers refer to Scheme 5.6, reaction conditions as defined in text.

\( ^b \) Number average molecular weight (\( M_n \)) and polydispersity (PD) measured by GPC-MALLS.

\( ^c \) Average number of arms in CCS polymer (\( f \)) calculated using Equation 2.2.

\( ^d \) Average hydrodynamic diameter (\( D_h \)) in THF measured by dynamic light scattering.

\( ^e \) Standard deviation (SD) of polymer’s hydrodynamic diameter.

\( ^f \) Theoretical molecular weight of arm based on 100% initiation efficiency of the extension reaction.

The hydroxyl end-functionalized arms of this CCS polymer were subsequently used to initiate ring-opening polymerization of \( \varepsilon \)-caprolactone to increase the arm length. GPC results (Figure 5.8) confirmed that chain extension of the arms occurred, generating CCS polymer with a number average molecular weight of 544,400 g/mol and a polydispersity of 1.25 (Table 5.4, entry 4B). The average extension of each arm was calculated to be 120 caprolactone units per arm, resulting in an increased arm molecular weight from 7,700 g/mol up to 21,400 g/mol. The calculated molecular weight of the extended arm is based on the assumption that the initiation efficiency of
the ROP chain extension reaction from the surface of the functionalized star is 100%. Unfortunately the initiation efficiency in this case cannot be directly measured but is likely to be less than 100% as later demonstrated for the case of ATRP initiated surface extension. This reduced initiation efficiency means that fewer arms would undergo chain extension, with the molecular weight of the extended arms being greater than predicted by theory. The reaction to extend the arms of the CCS polymer also resulted in a small amount of low molecular weight polymer being formed (Figure 5.8, Extended CCS (4B) 24-27 mL elution volume). This was due to the presence of linear macrorinitiator which wasn’t completely removed during the fractionation step, with the hydroxyl end-groups of the residual macrorinitiator being capable of initiating ROP such that a small amount of linear diblock copolymer was formed during the surface extension reaction.

**Figure 5.8:** GPC traces of the synthesis of surface functional CCS polymer chain extended by ROP and subsequent hydrolysis to remove the outer PCL coronal layer (corresponding data in Table 5.4).

The change in hydrodynamic diameter of this surface functionalized CCS polymer as a result of ROP chain extension was monitored by DLS (Figure 5.9). It was found that as the arm length of the CCS polymer increased in molecular weight from 7,700 g/mol to a theoretical value of 21,400 g/mol, the corresponding hydrodynamic
diameter also increased, changing from an average of 11.7 nm up to 23.7 nm. Another advantage of increasing the CCS polymer arm length via a post-synthesis chain extension reaction is that it provides a simplistic route for the synthesis of CCS polymers with a large number of high molecular weight arms. Traditionally this type of CCS polymer has been difficult to synthesize by the ‘arms first’ approach due to the fact that the number of arms incorporated into the star polymer is strongly dependent on the molecular weight of the macroinitiator (i.e. the arm length) as previously discussed in Section 5.2.2. This relationship can be controlled to a certain extent through the manipulation of reaction conditions; however, this is not an easy task due to the large number of reaction variables and the complex nature of their relationship to the structure of the CCS polymer. Therefore, a more attractive route for synthesizing CCS polymers with many high molecular weight arms would be to synthesize CCS polymer using low molecular weight macroinitiator to achieve high arm incorporation and then chain extending the arms to increase their molecular weight.

Figure 5.9: DLS traces of hydroxyl surface functionalized CCS polymer before and after ROP chain extension (Table 5.4, entry 4A and 4B).
Another advantage of this technique lies in the use of caprolactone as the chain extension monomer, with the subsequent degradability allowing for recovery of the original CCS polymer. This is possible since the extended PCL segment can easily be removed by hydrolysis without affecting the PST/EGDMA structure of the original CCS polymer. Experimental results showed this to be the case with hydrolysis of the chain extended CCS yielding a polymer with a molecular weight close to that of the original polymer (277,800 g/mol compared to 265,700 g/mol) (Figure 5.8 and Table 5.4, entry 4C). There was however a slight increase in the polydispersity of the star (1.16 to 1.21), with a very minor shoulder peak being detected in the GPC trace of the hydrolysis product (Figure 5.8, Hydrolyzed CCS; 19 mL elution volume). 1H NMR spectroscopic analysis confirmed that all of the PCL had been removed after hydrolysis, suggesting that the increased polydispersity was possibly due to the coupling of a small fraction of the stars, through termination of the preserved ATRP initiating functionalities within the core, facilitated by the high reaction temperature used for ROP chain extension.

\[ \text{5.2.2.3 ATRP chain extension method} \]

By utilizing similar principles to those employed in the synthesis of surface functionalized CCS polymer capable of initiating ROP, it is possible to generate CCS polymers capable of initiating other types of polymerization. Of particular interest is the incorporation of ATRP initiating functionalities such that the potential range of monomers which can be utilized is substantially increased. This would also lead to an increased ability to modify the physical properties of these CCS polymers, with many of the properties being directly related to the nature of the polymer present in the corona. In order to synthesize CCS polymers capable of initiating ATRP from the periphery of the arms, the following reaction pathway was proposed (Scheme 5.7).
Scheme 5.7: Synthesis of alkyl bromide surface functionalized CCS polymer capable of initiating ATRP chain extension.

As illustrated in Scheme 5.7, the terminal hydroxyl group of linear HO-PCL-Br macroinitiator (M<sub>n</sub> = 4,600 g/mol, M<sub>w</sub>/M<sub>n</sub> = 1.11) was used to initiate ring-opening polymerization of the bislactone cross-linker 4,4′-bioxepanyl-7,7′-dione (BOD). This resulted in the generation of fully degradable CCS polymers similar to that reported in Chapter 3 of this thesis, with the exception that this time the surface of the CCS polymer is functionalized with ATRP initiating sites. GPC analysis (Figure 5.10) of the reaction product revealed that ~68% of the linear HO-PCL-Br macroinitiator was converted into CCS polymer, with subsequent fractionation yielding pure CCS polymer (M<sub>n</sub> = 179,400 g/mol, M<sub>w</sub>/M<sub>n</sub> = 1.15) (Table 5.5, entry 5A). The average number of arms incorporated into the CCS polymer was calculated to be 26.8, each of which is end functionalized with an alkyl bromide group capable of initiating further ATRP reactions.
Figure 5.10: GPC traces of the synthesis of surface functional CCS polymer chain extended by ATRP and subsequent hydrolysis to recover the extension product (corresponding data in Table 5.5).

Table 5.5: Synthesis of ATRP surface functionalized CCS polymer with adjustable coronal properties.

<table>
<thead>
<tr>
<th>entry</th>
<th>$M_n$ (g/mol)</th>
<th>PD</th>
<th>$f^c$</th>
<th>arm $M_n$ (g/mol)</th>
<th>$D_h$ (nm)</th>
<th>SD (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5A</td>
<td>179,400</td>
<td>1.15</td>
<td>26.8</td>
<td>4,600</td>
<td>18.8</td>
<td>3.7</td>
</tr>
<tr>
<td>5B</td>
<td>618,500</td>
<td>1.24</td>
<td>26.8</td>
<td>21,000$^f$</td>
<td>25.0</td>
<td>4.3</td>
</tr>
<tr>
<td>5C</td>
<td>159,000</td>
<td>1.29</td>
<td>N/A</td>
<td>N/A</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Sample reference numbers refer to Scheme 5.7, reaction conditions as defined in text.

$^b$ Number average molecular weight ($M_n$) and polydispersity (PD) measured by GPC-MALLS.

$^c$ Average number of arms in CCS polymer ($f$) calculated using Equation 2.2.

$^d$ Average hydrodynamic diameter ($D_h$) in THF measured by dynamic light scattering.

$^e$ Standard deviation (SD) of polymer’s hydrodynamic diameter.

$^f$ Theoretical molecular weight of arm based on 100% initiation efficiency of the extension reaction.

The alkyl bromide surface functionalized CCS polymer was subsequently used to initiate ATRP of methyl methacrylate monomer in the presence of CuBr/PMDETA...
catalyst. GPC traces of the reaction product (Figure 5.10) showed a shift to a higher molecular weight product, indicating that chain extension of the CCS polymer arms occurred. The number average molecular weight of the chain extended CCS polymer was determined by GPC-MALLS to be 618,500 g/mol ($M_w/M_n = 1.24$) (Table 5.5, entry 5B). Assuming that all of the arms were involved in the extension reaction then the average extension per arm can be calculated as 16,400 g/mol, resulting in an increased arm molecular weight from 4,600 g/mol up to a theoretical value of 21,000 g/mol. The extension reaction was closely monitored such that the polymerization could be stopped before the onset of gelation. The high local concentration of active initiating sites within the surface functional star polymer increases the probability of radical-radical termination reactions occurring. These termination reactions can take place either intra- or intermolecularly resulting in the coupling of arms within individual star polymers or between that of neighboring stars (star-star coupling) which can lead to gelation. The use of a controlled polymerization technique such as ATRP acts to minimize the concentration of growing radicals present at any given moment and effectively suppresses these termination reactions. However, as the extension reaction proceeds to higher conversions these coupling reactions start to become more prevalent due to the reduced amount of available monomer, eventually leading to gelation of the reaction system.

The use of lactone-based polymers to synthesize the initial alkyl bromide surface functionalized CCS polymer (PCL arms and BOD core) means that the original star polymer can be completely hydrolyzed. This allows for recovery of the extension product since the PMMA chains extended from the arms are non-degradable and as such can be liberated via hydrolysis of the extended CCS polymer (Scheme 5.7). This was found to be the case with hydrolysis of the ATRP chain extended CCS polymer yielding pure PMMA polymer as confirmed by $^1$H NMR spectroscopy. The molecular weight of this extension product ($M_n = 159,000$ g/mol, $M_w/M_n = 1.29$) (Table 5.5, entry 5C) was a lot larger than predicted by theory for 100% initiation efficiency of the arms (16,400 g/mol). Using this information it is possible to calculate that the actual initiation efficiency of the arms during the ATRP chain extension reaction was only 10%. Consequently, the structure of the ATRP chain extended CCS polymer isn’t that of a star polymer with a uniform layer of short PMMA chains attached to the end of each arm. A more realistic representation would be that of a star polymer with long PMMA chains attached to only a few of the preexisting PCL arms (Scheme 5.8).
Scheme 5.8: Effect of reduced initiation efficiency during chain extension from surface functionalized CCS polymer.

The structural difference brought about through a reduction in initiation efficiency would have a significant effect on the solution properties of the chain extended CCS polymer. For example, CCS polymer with an evenly distributed short polymeric layer added to the periphery of the star (i.e. 100% initiation efficiency) would be expected to have a significantly lower viscosity than that of a CCS polymer having only a few long polymer chains attached to the corona (i.e. 10% initiation efficiency). The reason for this is that the long polymer chains attached to the surface of the low initiation efficiency star would have a higher potential to interact with other CCS polymers and become entangled, essentially converting the compact low viscosity structure of the star into a pseudo high molecular weight linear polymer with increased viscosity.

This reaction was repeated several times in an attempt to improve the initiation efficiency of the arms, looking at variables such as reaction concentration, type of secondary monomer used (MMA and St), and even CCS polymers with differing number of arms. In each of these cases the initiation efficiency remained low, with analysis of the cleaved extension product revealing efficiencies of between approximately 3% and 16%. The low initiation efficiency of these ATRP chain extension reactions could be due to the loss of functionality of some of the initiating sites located at the periphery of the CCS polymer. The occurrence of radical termination reactions during either star formation or extension of the arms could
potentially destroy the initiating functionality of some of the arms and hence reduce the calculated efficiency. In addition to this, the accessibility of these initiation sites may be limited due to the compact nature of the CCS polymer and the potential for the initiating sites to be embedded within the corona of the star polymer rather than being situated at the periphery. Similar issues have been reported for the synthesis of molecular brushes[23] and miktoarm star polymers[14] where it has been found that the highly congested nature of the multifunctional macroinitiators resulted in reduced initiation efficiencies due to limited accessibility. Although the initiation efficiency of the ROP-based CCS extension reaction presented in Section 5.2.2.2 of this thesis could not be determined, it is expected to be higher than that of the ATRP-based extension reaction. This is due to the fact that ROP proceeds via a coordination-insertion mechanism rather than radical propagation as in the case of ATRP. This eliminates the potential loss of functionality due to radical termination reactions and therefore results in potentially higher initiation efficiencies. Evidence of this can be seen by the fact that gelation problems were not observed for the ROP-based chain extension, whereas the ATRP-based extension gelled at high conversions due to radical-radical termination reactions. Despite this, the ROP-based extension reaction is still expected to experience steric hindrance effects similar to that of the ATRP-based extension reaction and consequently will still have an initiation efficiency of less than 100%.

The hydrodynamic size of the surface functional CCS polymer before and after ATRP chain extension was monitored via DLS (Figure 5.11). It was found that as the molecular weight of the CCS polymer increased due to the extension of 10% of the arms with high molecular with PMMA chains (M_n = 159,000 g/mol) the hydrodynamic diameter of the corresponding CCS polymer also increased, changing from an average of 18.8 nm up to 25.0 nm. This result shows that even though the initiation efficiency of the arms was quite low it was still possible to significantly increase the hydrodynamic size of the CCS polymer. This is an important result since it shows that even the extension of only a few arms is still sufficient to appreciably alter the coronal properties of a CCS polymer and therefore modify its solution behavior.
5.2.3 Miktoarm/block copolymer arm CCS polymer
So far we have looked at manipulating the coronal structure of CCS polymer through the use of either miktoarm or block copolymer arm morphologies. A third type of architecture is also possible, where the previous two methods can be combined to generate CCS polymers with a combination of mikto and block copolymer arms. One of the consequences of using the ‘arms first’ approach to synthesize star polymers is that the initiating functionality of the linear macrorinitiator is preserved within the core of the CCS polymer. It has been well established that this embedded functionality can be used to grow a second type of arm out from the core to synthesize miktoarm star polymers via the ‘in-out’ approach, Section 5.2.1.1. However, if the functional groups located at the periphery of the CCS polymer arms are modified to match that of the preserved initiating sites within the core then the resultant CCS polymer would be capable of initiating polymerization from both the core and the arms simultaneously (Scheme 5.9). This allows for not only manipulation of the size of the CCS corona but also the packing density of arms within the corona.

Figure 5.11: DLS traces of alkyl bromide surface functionalized CCS polymer before and after ATRP chain extension (Table 5.5, entry 5A and 5B).
Scheme 5.9: Synthesis of alkyl bromide core/surface functionalized CCS polymer capable of simultaneously initiating ATRP chain extension from the core and the arms.

To achieve this, CCS polymer capable of initiating ATRP from the core was firstly synthesized by cross-linking HO-PCL-Br macroinitiator (Mₙ = 4,600 g/mol, Mₚ/Mₙ = 1.11) with EGDMA under ATRP reaction conditions (Scheme 5.9). GPC analysis of the reaction product (Figure 5.12) revealed that ~60% of the linear HO-PCL-Br macroinitiator had been converted into CCS polymer which was subsequently fractionated to yield pure CCS polymer (Mₙ = 152,300 g/mol, Mₚ/Mₙ = 1.18) with an average of 18.7 arms per star (Table 5.6, entry 6A).
**Figure 5.12:** GPC traces of the synthesis of core/surface functional CCS polymer chain extended by ATRP and subsequent hydrolysis (corresponding data in Table 5.6).

**Table 5.6:** Synthesis of ATRP core/surface functionalized CCS polymer with adjustable coronal properties.

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>$M_n$ (g/mol)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>PD&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Arm $M_n$ (g/mol)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>$D_h$&lt;sup&gt;d&lt;/sup&gt; (nm)</th>
<th>SD (nm)&lt;sup&gt;e&lt;/sup&gt;</th>
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<tr>
<td>6A</td>
<td>152,300</td>
<td>1.18</td>
<td>4,600</td>
<td>15.3</td>
<td>2.9</td>
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<tr>
<td>6B</td>
<td>514,600</td>
<td>1.29</td>
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<td>-&lt;sup&gt;f&lt;/sup&gt;</td>
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</tr>
<tr>
<td>6C</td>
<td>373,400</td>
<td>1.21</td>
<td>-&lt;sup&gt;f&lt;/sup&gt;</td>
<td>-&lt;sup&gt;f&lt;/sup&gt;</td>
<td>14.2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Sample reference numbers refer to Scheme 5.9, reaction conditions as defined in text.

<sup>b</sup> Number average molecular weight ($M_n$) and polydispersity (PD) measured by GPC-MALLS.

<sup>c</sup> Average number of arms in CCS polymer ($f$) calculated using Equation 2.2.

<sup>d</sup> Average hydrodynamic diameter ($D_h$) in THF measured by dynamic light scattering.

<sup>e</sup> Standard deviation (SD) of polymer’s hydrodynamic diameter.

<sup>f</sup> Values could not be determined due to unknown efficiency of core/surface extension reaction.

The structure of this CCS polymer is such that each arm is end functionalized with a hydroxyl group whereas the core contains an equivalent amount of alkyl bromide groups capable of initiating ATRP. By reacting this CCS polymer with an excess of 2-bromoisobutrylbromide, the terminal hydroxyl groups were converted into ATRP.
initiating functionalities similar to the alkyl bromide groups preserved within the core. 

$^1$H NMR spectroscopic analysis of the reaction product (Figure 5.13) confirmed the incorporation of additional ATRP initiating sites, with a resonance corresponding to the methyl groups of the attached 2-bromoisobutyryl functionality (OCO(CH$_3$)$_2$Br, 1.91 ppm) appearing after functionalization. Unfortunately, accurate integration proved impossible due to an overlap with a preexisting resonance, meaning that quantitative determination of the extent of reaction could not be achieved. However, it was also noticed that the resonance corresponding to the methylene protons adjacent to the terminal hydroxyl group (CH$_2$CH$_2$OH, 3.62 ppm) was not evident upon functionalization, indicating that all of the arms had been successfully end-capped with ATRP initiating groups.

![Figure 5.13: $^1$H NMR spectra of a) alkyl bromide core functionalized CCS polymer and b) alkyl bromide core/surface functionalized CCS polymer.](image)

This core/surface functionalized CCS polymer was subsequently used to initiate ATRP of methyl methacrylate monomer to extend the preexisting arms whilst simultaneously growing secondary arms out from the core (Scheme 5.9). GPC traces
of the reaction product (Figure 5.12) showed a shift to a higher molecular weight product ($M_n = 514,600$ g/mol, $M_w/M_n = 1.29$) (Table 5.6, entry 6B) indicating that chain extension of the CCS polymer occurred. In addition to the extended CCS product, a lower molecular weight peak ($M_n = 80,600$ g/mol, $M_w/M_n = 1.08$) was also observed (Figure 5.12, Extended CCS (6B) 22-25 mL elution volume) representing linear PMMA chains generated by the presence of a contaminant capable of initiating ATRP. The source of this contaminant is most likely due to the presence of linear macroinitiator which wasn’t completely removed by the fractionation step. Although this unconverted macroinitiator is considered to be “dead”, it is reactivated during functionalization of the CCS polymer surface where hydroxyl groups are converted into active ATRP initiating sites. The presence of this linear macroinitiator can be observed in the GPC trace of the fractionated CCS polymer as a low molecular weight shoulder peak attributing to ~10% of the total peak area (Figure 5.12, Fractionated CCS (6A) 24-27 mL elution volume). Even though this peak only accounts for ~10% of the area, it is actually based on a mass percentage and consequently, when relative molecular weights are taken into account, is actually found to account for ~80% on a molar basis. As seen earlier, the initiation efficiency of this linear macroinitiator is close to 100% for ATRP initiated chain extension whereas the congested structure of the CCS polymer tends to have a significantly reduced initiation efficiency. The reduced initiation efficiency of the star polymer and the presence of a large molar excess of linear macroinitiator means that the majority of the mass added through the chain extension reaction will be associated with the contaminant macroinitiator. Therefore, while the same amount of contaminant is still present (i.e. ~80 mole %) it will appear to have increased substantially on a mass basis due to the uneven distribution of monomer during chain extension. And in fact this is exactly what is observed in the GPC trace of the chain extension product, with the contaminant peak now attributing for approximately 50% of the total peak area.

The use of PCL macroinitiator to synthesize core/surface functionalized CCS polymer means that the chain extended star polymer can be degraded to a certain extent (Scheme 5.9). Hydrolysis of the extended CCS polymer resulted in degradation of the PCL arms and subsequent cleavage of the linear PMMA chains which had been extended from the arms. In addition to this, the EGDMA cross-linked core with PMMA arms, grown out from the core as a result of core initiated chain extension, was also liberated. GPC analysis of the hydrolysis reaction clearly shows the chain
extended core product (Figure 5.12, Hydrolyzed CCS (6C) 20-22 mL elution volume) which was determined to have a molecular weight of 373,400 g/mol ($M_w/M_n = 1.21$) (Table 5.6, entry 6C). The secondary peak in the GPC trace of the hydrolysis reaction (Figure 5.12, Hydrolyzed CCS (6C) 22-25 mL elution volume) can be attributed to the linear PMMA chains generated from chain extension of the contaminant macroinitiator. Since the degradable component of the PCL-$b$-PMMA contaminant is relatively small (4,390 g/mol), the contaminant peak appears to be unchanged after hydrolysis having a molecular weight of approximately 76,200 g/mol. Unfortunately this contaminant peak obscures the cleaved arm extension product generated from hydrolysis of the extended CCS polymer, making it impossible to accurately determine the length of the extended arms and therefore the initiation efficiency of the arms.

The additional molecular weight added through chain extension of the core/surface functionalized CCS polymer was calculated to be 362,300 g/mol. Of this additional mass it is possible to calculate how much was added through chain extension initiated from the arms as opposed to the core. By subtracting the molecular weight of the core (theoretical $M_n = 70,133$ g/mol) from that of the chain extended core product (6C) (373,400 g/mol), the molecular weight contribution from core initiated extension was calculated to be 303,267 g/mol. This accounts for 83.7% of the total extended mass, with the other 16.3% (59,033 g/mol) being attributed to chain extension initiated from the arms. If it is assumed that the rate of polymerization from the different initiation sites (i.e. core, arm, and contaminant macroinitiator) is the same, then the molecular weight of the hydrolyzed contaminant product (76,200 g/mol) should be representative of the polymer chains extended from the core and the arms. Based on this assumption the theoretical initiation efficiency of the core and the arms of the functionalized CCS polymer can be calculated as being 21% and 4% respectively. This shows that in this case chain extension from the core occurred much more easily than from the arms, a counterintuitive result as it is expected that the initiation sites at the core would be more sterically hindered than those at the end of the arms. One potential explanation for this is that the high concentration of propagating radicals at the surface of the CCS polymer resulted in a higher rate of radical termination between the initiating groups of the arms as opposed to the more protected initiating sites within the core. The fact that rapid gelation of the reaction mixture was also a problem is further evidence that this was indeed the case.
The effect of ATRP chain extension on the hydrodynamic diameter of the alkyl bromide core/surface functionalized CCS polymer was studied via DLS (Figure 5.14). It was found that as the molecular weight of the CCS polymer increased from 152,300 g/mol to 514,600 g/mol the corresponding hydrodynamic diameter also increased, changing from an average of 15.3 nm up to 36.9 nm. As discussed earlier in this Section, the extended CCS polymer can be hydrolyzed to remove the PMMA-\textit{b}-PCL arms and generate modified CCS polymer with PMMA arms that have been grown out from the core. The hydrodynamic diameter of this modified star polymer was found to be similar to that of the original CCS polymer having an average diameter of 14.2 nm. The effect of these core extended arms can be seen by comparing the diameter of this modified CCS polymer to that of the core with no arms attached. Generation of the naked core was achieved by hydrolyzing the original core/surface functionalized CCS polymer (6A) to remove the PCL arms and liberate the EGDMA cross-linked core. The hydrodynamic diameter of this naked core was determined to be 9.4 nm showing that the core extended arms add an extra 4.8 nm to the overall hydrodynamic size of the CCS polymer.

\textbf{Figure 5.14:} DLS traces of alkyl bromide core/surface functionalized CCS polymer (1), ATRP chain extended CCS (2), hydrolyzed CCS (3), and naked core (4) generated from the hydrolysis of the original core/surface functional CCS polymer (Table 5.6, entries 6A-6C).
5.3 Conclusions

The synthesis of functionalized CCS polymers which can be structurally modified post-synthesis was shown to be an efficient method for manipulating properties such as the size, density and chemical composition of the CCS corona. Several different methods for achieving such polymers were investigated, focusing on the use of miktoarm and block copolymer arm structures to incorporate chemical heterogeneity into the coronal domain. Miktoarm CCS polymer with a mixture of degradable and non-degradable arms were synthesized by both the ‘in-out’ and ‘simultaneous cross-linking’ approaches, with subsequent hydrolysis being shown to selectively remove one arm type and thereby reduce the overall number of arms. Of these two approaches the ‘simultaneous cross-linking’ method proved to be a more versatile technique, allowing for greater control over the ratio of different arms as well as their molecular weight. The use of block copolymers was also studied such that novel CCS polymer with a degradable outer coronal layer of PCL was synthesized using semi-degradable PCL-\(b\)-PMMA arms. Hydrolysis of the PCL layer was found to effectively reduce the arm length of the CCS polymer and consequently reduce the overall hydrodynamic size of the polymer. The opposite effect was observed for the case of surface functionalized CCS polymer which was shown to be capable of initiating both ROP and ATRP type reactions from the periphery of the arms. Chain extension of this type of CCS polymer resulted in increased arm lengths and hydrodynamic diameters even though initiation efficiencies were found to be adversely affected by the sterically hindered structure of the CCS polymer. The synthesis of a third class of CCS polymer capable of simultaneously initiating polymerization from the core and the periphery of the arms was also investigated. Chain extension of this core/surface functionalized CCS polymer under ATRP reaction conditions was shown not only to increase the length of the preexisting arms but also to increase the number of arms. This resulted in an increased hydrodynamic diameter with the better protected initiating sites within the core being found to undergo a higher degree of initiation than the functionalized arms.
5.4 References

Chapter 6 – Increasing CCS Polymer Functionality

6.1 Introduction

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6.3 Conclusions

6.4 References
6.1 Introduction

In the previous Chapters it has been shown that by incorporating ester linkages into the structural design of CCS polymers, it is possible to generate a range of selectively degradable star polymers. Furthermore, by manipulating the preserved functionality within the core or at the periphery of the arms, it was shown that the properties of these CCS polymers could be controlled to a certain extent, especially in terms of hydrodynamic size and coronal chemical composition. However, for greater application potential it is desired to increase the functionality of these degradable CCS polymers, a feat which is made possible by incorporating functional groups along the length of the arms rather than just at the periphery. This allows for a significant increase in the number of functional groups present within the CCS polymer, thereby facilitating a greater potential for tailoring the physical and chemical properties towards specific applications.

One particular class of functional group which has recently been receiving significant attention are those which allow for coupling via ‘click chemistry’, a term coined by Sharpless et al.\cite{1} to cover a group of ‘spring loaded’ reactions which exhibit high specificity, near quantitative yields and compatibility with a broad range of functional groups. Of particular interest is the Huisgen 1,3-dipolar cycloaddition reaction between azides and alkynes,\cite{2,3} one of the most popular forms of ‘click chemistry’ (Scheme 6.1). The uncatalyzed version of this reaction requires the use of elevated temperatures for prolonged periods and typically results in a mixture of 1,4- and 1,5-regioisomers. However, the addition of a copper(I) catalyst dramatically improves the regioselectivity to afford the 1,4-regioisomer exclusively and increases the reaction rate up to $10^7$ times,\cite{4} eliminating the need for elevated temperatures. The mechanism for this copper(I) catalyzed cycloaddition reaction involves the formation of a copper(I) acetylide species which subsequently complexes with an azide to form a 1,2,3-triazole. For a more in-depth discussion of this mechanism refer to the recent review by Bock et al.\cite{5}
Scheme 6.1: Example of 1,3-cycloaddition of an azide and terminal alkyne to give a 1,2,3-triazole. Thermal cycloaddition is non-regiospecific whereas the copper(I)-catalyzed reaction is 1,4-regioselective.

The copper(I) catalyzed version of this reaction is quite versatile and provides an efficient means for coupling a wide range of molecules in a regiospecific fashion under relatively mild reaction conditions, making it ideally suited for the direct functionalization of polymers. By incorporating acetylene or azido functional groups into polymers, it makes it possible to attach any number of different compounds as long as they contain the appropriate complementary functionality. A vast range of functionalized polymers have been synthesized via this technique, with ‘click chemistry’ also finding application in the synthesis of block copolymers, graft polymers, dendrimers, star polymers and even bioconjugates. ‘Click chemistry’ is also particularly useful for the functionalization of aliphatic polyesters such as the degradable CCS polymers reported here, as unlike the typical acidic or basic conditions required for many conventional organic transformations, the mild nature of click chemistry allows for functionalization without any degradation of the polyester structure.

In this Chapter we explore the possibility of utilizing ‘click chemistry’ to increase the functionality of degradable CCS polymers by incorporating acetylene groups into the arms. More specifically, it is proposed to synthesize fully degradable PCL/BOD CCS polymer having block copolymer arms where the peripheral block consists of multiple pendent acetylene groups. To demonstrate the increased functionality of these CCS
polymers, terminal azido functionalized linear polymers will be attached via 1,3-cycloaddition to the pendent acetylene functionalities, thereby generating CCS polymers with ‘brush-like’ arm structures and a degradable inner domain.
6.2 Results and Discussion

6.2.1 Terminal azido functional polymers

As described in Section 6.1, it is desired to synthesize a degradable CCS polymer with acetylene functionality incorporated into the arms. To demonstrate the increased functionality of this type of CCS polymer, it is planned to react terminal azido functional linear polymer with the multiple pendent acetylene groups in the arms of the CCS polymer via a ‘click’ type reaction. Any number of different azide-containing compounds could have been chosen to demonstrate the increased functionality of this type of polymer, such as an appropriately functionalized protein or fluorescent dye, however for simplicity the use of a linear polymer was favored. This is also in keeping with the concept of modifying the coronal structure of CCS polymers which has been explored throughout this thesis, with the attachment of linear polymers to the densely packed pendent functionalities along the backbone of the arm essential converting the linear arms into ‘brush-like’ structures.

There are several methods for incorporating azido functionality into polymers, the most common of these involving the nucleophilic displacement of alkyl halides by azide ions.[27] Polymers generated by ATRP are an excellent candidate for this type of reaction since they possess a terminal halide group as a result of the polymerization mechanism, providing a very convenient method for obtaining the terminal azido functional polymers required for this work. While this reaction is generally considered to be quite efficient, the rate at which displacement occurs can be significantly affected by various experimental variables including solvent choice, degree of substitution around the halide and even the type of halide itself. For example, it has been shown by Coessens and Matyjaszewski[28] that the displacement of bromine occurs significantly faster than that of chlorine due to the better leaving group potential of bromine. It was also found that ATRP generated PST underwent nucleophilic substitution faster than PMMA due to the greater electron-withdrawing effect of the adjacent phenyl group in PST as opposed to the ester group in PMMA. For these reasons it was decided to generate linear polystyrene via ATRP using an alkyl bromide functional initiator (2-hydroxyethyl 2'-methyl-2'-bromopropionate), such that the subsequent transformation to an azide would be as efficient as possible (Scheme 6.2).
The synthesis of terminal azido functionalized polystyrene (PSt-N₃) was achieved in two steps as illustrated in Scheme 6.2. Firstly, 2-hydroxyethyl 2'-methyl-2'-bromopropionate was used to initiate ATRP of styrene monomer in bulk using a CuBr/bpy catalyst system. The resulting bromine-terminated polystyrene (PSt-Br) was isolated and characterized, with GPC analysis showing a number average molecular weight of 10,400 g/mol and narrow polydispersity (Mₙ/Mₚ = 1.02). The PSt-Br polymer was subsequently reacted with an excess of sodium azide in DMF at 25 °C to generate PSt-N₃. DMF was used as the solvent due to the poor solubility of sodium azide in other organic solvents, ensuring a homogeneous reaction mixture such that substitution could take place more readily. After 42 hours the reaction was stopped and precipitated into methanol, with the filtrate being washed repeatedly with distilled water to remove any unreacted sodium azide. Unfortunately, due to the high molecular weight of the polystyrene, ¹H NMR spectroscopic analysis could not be used to detect the end group functionality of either the initial PSt-Br polymer (-CH(Ph)-Br) or the converted PSt-N₃ polymer (-CH(Ph)-N₃). Therefore to confirm that the reaction had occurred, IR spectroscopy was used to visualize the incorporated azide group. The FTIR spectra before and after functionalization (Figure 6.1) clearly shows the appearance of an additional absorbance at 2094 cm⁻¹ owing to the azide N≡N=N antisymmetric stretch. While this could not be used to quantitatively determine the incorporation of azide groups, it does confirm that the reaction worked. The level of azide functionality is not really an issue in this case as the PSt-N₃ polymer will be added in excess to the acetylene functional polymer, meaning that any residual PSt-Br shouldn’t greatly affect the reaction.
6.2.2 Synthesis of acetylene functional monomer

In order to incorporate pendent acetylene functionality into the arms of a CCS polymer, it was firstly required to synthesize an appropriate acetylene functionalized monomer. Several examples of such monomers appear in the literature, with both vinyl and cyclic based monomers being reported. Of particular interest is the lactone based monomers with allyl substituents α to the carbonyl that have been synthesized by Emrick and coworkers,[12,29] with ROP of such monomers generating linear polyesters with pendent acetylene groups (Scheme 6.3). However, for several potential future applications (Chapter 7) a need was foreseen for the backbone of the pendent acetylene functional polymer segment to be non-degradable, consequently a vinyl based alternative was sought.

Scheme 6.3: Synthesis of pendent acetylene functional polyesters.
One of the most basic acetylene functional vinyl monomers is propargyl methacrylate (PgMA) (Scheme 6.4). The methacrylate based structure of this monomer makes it ideally suited for polymerization by ATRP and as such was consequently chosen for this work. However, it has been found that radical-based polymerization of acetylene containing monomers such as PgMA tend to suffer from a loss of control which can lead to branching and cross-linking at high conversion.[6,9] This poor control is thought to be due to unwanted radical addition reactions occurring at the acetylene group, with the strong coordination of alkyynes to Cu(I) complexes commonly used as ATRP catalysts causing further complications.[30,31] These problems can be overcome by protecting the acetylene functionality of the monomer and subsequently deprotecting after polymerization to regenerate the acetylene group. Consequently, the trimethylsilyl protected version of propargyl methacrylate (TMS-PgMA) was synthesized for this work (Scheme 6.4).

![Scheme 6.4: Synthesis of (trimethylsilyl)propargyl methacrylate (TMS-PgMA)](image)

TMS-PgMA was synthesized according to Scheme 6.4, with the initial step involving the reaction of 2-propyn-1-ol with an excess of methacryloyl chloride. The resulting PgMA monomer was obtained in a reasonable yield (50%), with both NMR and GC-MS analyses confirming synthesis of the desired product and showing that after purification the purity of the PgMA monomer was >99%. The acetylene group of this monomer was subsequently protected with chlorotrimethylsilane using a method published in the literature.[9] The success of this reaction was confirmed by NMR and
GC-MS analyses, with careful distillation of the final reaction product yielding high purity (>99%) TMS-PgMA monomer.

6.2.3 Synthesis of acetylene functional macroinitiator

The protected acetylene functional monomer, TMS-PgMA, can be used to synthesize CCS polymers where the arms possess an outer block segment consisting of multiple pendent acetylene groups. This can be achieved by either initiating polymerization of TMS-PgMA from the periphery of a preformed CCS polymer or by synthesizing a block copolymer macroinitiator which can subsequently be cross-linked to form the desired CCS polymer. As discussed in Chapter 5 (Section 5.2.2.3), ATRP initiated from the periphery of a CCS polymer tends to suffer from low initiation efficiencies, a problem which results in uneven coverage of the CCS surface with the secondary polymer layer. The alternative method of using block copolymer macroinitiator to form CCS polymers (refer Section 5.2.2.1) ensures a uniform layer of the secondary polymer at the surface, with the molecular weight and composition of the arms being well-defined. Since the aim of this work is to increase the functionality of degradable CCS polymers, it is desirable that the distribution of acetylene functionality be as uniform as possible. For this reason the block copolymer macroinitiator method was employed, with synthesis of a suitable macroinitiator being achieved via ATRP chain extension of degradable PCL-Br with TMS-PgMA monomer (Scheme 6.5).

![Scheme 6.5: Synthesis of protected acetylene functional block copolymer macroinitiator (PCL-b-P(TMS-PgMA)-Br).](image)

Formation of the protected acetylene functional block copolymer macroinitiator, PCL-b-P(TMS-PgMA)-Br, was performed according to Scheme 6.5, using previously synthesized PCL-Br macroinitiator to initiate the polymerization of TMS-PgMA under ATRP reaction conditions. The reaction was repeated several times, with the
concentration and molecular weight of the PCL-Br macroinitiator being varied to
generate a range of block copolymer macroinitiators with different degrees of
acetylene functionality (Table 6.1). The molecular weight of the resultant block
copolymers was measured by GPC using an assumption of 100% mass recovery since
the dn/dc values were unknown. This was compared to the molecular weight
determined from integration of the respective polymer segments in the 1H NMR
spectra, as well as the theoretical molecular weight for the calculated monomer
consumption which was measured by GC-MS. As can be seen from Table 6.1, the
molecular weights determined by GPC were slightly higher than those determined by
the other two methods, however the relative difference was still reasonably small and
within the margin for error. From these molecular weights the degree of
polymerization (DP) was calculated, a value which represents the average number of
pendent acetylene groups per macroinitiator. The highest degree of functionalization
was achieved when 4.6 kDa PCL-Br macroinitiator was used to polymerize TMS-
PgMA (Table 6.1, exp 4), resulting in an average of 48.4 pendent acetylene groups
being incorporated into the polymer on the basis of GPC determined molecular
weight.

Table 6.1: Synthesis of protected acetylene functional block copolymer
macroinitiator (PCL-b-P(TMS-PgMA)-Br).

<table>
<thead>
<tr>
<th>exp</th>
<th>PCL-Br Mₙ (g/mol)b</th>
<th>[PCL-Br] (mM)</th>
<th>PCL-b-P(TMS-PgMA)-Br Mₙ (g/mol)</th>
<th>DP TMS-PgMAe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6,100</td>
<td>10</td>
<td>9,000</td>
<td>14.8</td>
</tr>
<tr>
<td>2</td>
<td>6,100</td>
<td>30</td>
<td>11,100</td>
<td>25.5</td>
</tr>
<tr>
<td>3</td>
<td>6,100</td>
<td>50</td>
<td>13,500</td>
<td>37.7</td>
</tr>
<tr>
<td>4</td>
<td>4,600</td>
<td>30</td>
<td>14,100</td>
<td>48.4</td>
</tr>
</tbody>
</table>

a All reactions were performed with [PCL-Br] = [CuBr] = [PMDETA]/2 = [TMS-PgMA]/30 in anisole
at 85°C for 21h, with the exception of exp 4 which had [PCL-Br] = [TMS-PgMA]/50.
b Number average molecular weight (Mₙ) measured by GPC-MALLS.
c Mₙ determined by comparative integration of PCL and P(TMS-PgMA) peaks in 1H NMR spectra.
d Theoretical Mₙ calculated from TMS-PgMA monomer consumption as determined by GC-MS.
e Degree of polymerization (DP) of TMS-PgMA monomer (i.e. number of pendent acetylene groups
per polymer) calculated from molecular weight as determined from respective methods.
6.2.3.1 Deprotection

A sample of the PCL-b-P(TMS-PgMA)-Br macroinitiator was deprotected, removing the trimethylsilyl protecting group to afford a polymer with pendent acetylene functionality (Scheme 6.6). While the protecting group is still required for the subsequent CCS formation step, it was decided to test a small sample of the block copolymer macroinitiator to ensure that it could be deprotected without degrading the PCL segment of the polymer.

![Scheme 6.6: Deprotection of block copolymer macroinitiator to yield pendent acetylene functional polymer (PCL-b-PPgMA-Br).](image)

Tetra-n-butyl ammonium fluoride (TBAF) was used to remove the trimethylsilyl protecting groups from the pendent acetylene functionalities, with acetic acid being used as a buffering agent to stop degradation of the polyester segment of the polymer. The use of acetic acid as a buffering agent is a well-established procedure in organic chemistry when the substrate to deprotect contains functional groups, such as esters or thioesters, which can be cleaved when TBAF alone is employed.\[32,33\] This reaction was carefully monitored by $^1$H NMR spectroscopy (Figure 6.2), which showed that after 18 hours 100% removal of the trimethylsilyl protecting groups had been achieved without any significant degradation of the PCL segment. This was confirmed by the complete disappearance of the resonance due to the trimethylsilyl protecting group (Figure 6.2 a) $\Delta$, $\delta = 0.18$ ppm) combined with the appearance of the resonance corresponding to the deprotected acetylene proton (Figure 6.2 b) $\bullet$, $\delta = 2.47$ ppm). By comparing the relative integral areas of the resonances corresponding to the PPgMA and PCL segments of the polymer, it is possible to calculate the ratio of PCL to PPgMA repeat units as being 2.67:1 before deprotection and 2.58:1 after deprotection. This confirms that little, if any, degradation of the PCL backbone
occurred, with the slight discrepancy in the ratio of PCL to PPgMA before and after deprotection being attributed to the accuracy of the peak integration.

Figure 6.2: $^1$H NMR spectra of PCL-\(b\)-P(TMS-PgMA)-Br (Table 6.1, entry 3) a) before and b) after acetylene deprotection.

GPC analysis of the deprotection reaction was also performed (Figure 6.3), with a slight reduction in molecular weight being observed upon removal of the trimethylsilyl groups. The initial polymer (Table 6.1, entry 3) had a molecular weight of 13,500 g/mol with approximately 37.7 pendent trimethylsilyl protected acetylene groups. After TBAF mediated deprotection the molecular weight dropped to 10,300 g/mol, correlating to the theoretical molecular weight of 10,780 g/mol predicted for complete removal of the trimethylsilyl group without any degradation of the PCL segment. The combined GPC and NMR results show that this is a viable method for regenerating the acetylene functionality of this macroinitiator and hence should be appropriate for the subsequent CCS formation reaction.
6.2.3.2 ‘Click chemistry’ attachment of PSt-N₃

The pendent acetylene functional macroinitiator generated in the previous section was subsequently used to determine appropriate reaction conditions for the grafting of linear PSt-N₃ onto the macroinitiator via cycloaddition of the terminal azide and pendent acetylene moieties (Scheme 6.7). The end product of this reaction is essentially a molecular brush, i.e. a linear polymer with a high density of side chains grafted onto the backbone, which is in its own right a very interesting class of macromolecule. However, for the purposes of this investigation the brush polymer is only a stepping stone towards the generation of CCS polymers with increased functionality.

Scheme 6.7: ‘Click coupling’ reaction to generate polystyrene grafted brush polymer.
The ‘click coupling’ reaction between the acetylene functional macroinitiator and azido functional polystyrene was performed using standard conditions reported in the literature.[14] A solution of CuBr/PMDETA catalyst in DMF was added to a degassed mixture of PCL-\textit{b}-PPgMA-Br and PST-N\textsubscript{3} in DMF and allowed to react overnight. An excess of PST-N\textsubscript{3} was used in respect to the pendent acetylene groups of the macroinitiator (1.5:1 molar ratio) to ensure complete conversion of the acetylene functionality. The reaction was monitored via GPC, with the traces before and after ‘click coupling’ being shown in Figure 6.4.

![Figure 6.4: GPC traces of ‘click coupling’ reaction between PST-N\textsubscript{3} and PCL-\textit{b}-PPgMA-Br macroinitiator a) before and b) after reaction.](image)

The trace of the initial reaction solution (before addition of Cu(I) catalyst) (Figure 6.4 a)) shows only a monomodal peak due to the PST-N\textsubscript{3} polymer ($M_n = 10,400$ g/mol, $M_w/M_n = 1.02$), with the acetylene functional polymer ($M_n = 10,300$ g/mol, $M_w/M_n = 1.15$) being masked due to the higher concentration (almost 60 times) of the azide functional polymer. While this is a large excess of PST-N\textsubscript{3} on a mass basis, it only equates to a 0.5 molar excess of azide with respect to the acetylene groups due to each PCL-\textit{b}-PPgMA-Br macroinitiator containing an average of 37.7 pendent acetylene groups. After 22 hours of reaction (Figure 6.4 b)) a higher molecular weight product was observed which was subsequently fractionated to remove any unreacted PST-N\textsubscript{3} and determined to have a number-average molecular weight of 334,200 g/mol ($M_w/M_n = 1.08$). This indicates that the ‘click coupling’ reaction proceeded to high conversion, with the theoretical molecular weight of the polystyrene grafted brush polymer being calculated as 402,380 g/mol. From this information we can determine
that approximately 83% of the pendent acetylene groups underwent cycloaddition reactions with the terminal azido functional polystyrene. The fact that not all of the acetylene groups reacted could be due to the sterically crowded nature of these brush polymers, with the terminal azide group of the 10 kDa polystyrene not being able to access the unreacted acetylene groups along the backbone of the brush polymer at high conversion. Analysis of the brush polymers via NMR spectroscopy was also conducted; however no useful information could be obtained due to the large signal intensities from the polystyrene chains which made accurate determination of the extent of grafting via peak integration impractical. In addition to this, the resonances due to the formed triazole rings and any potentially unreacted acetylene groups could not be detected due to their relatively low signal strengths in comparison to that of PST. Despite this, the GPC analysis shows that ‘click coupling’ has occurred and hence this acetylene functional macroinitiator provides a viable means of incorporating a higher degree of functionality into the periphery of degradable CCS polymers, an area which is investigated in the following sections of this chapter.

6.2.4 CCS polymers with ‘brush-like’ arms

With the successful synthesis of a block copolymer macroinitiator with multiple protected acetylene groups (PCL-\(b\)-P(TMS-PgMA)-Br), it is now possible to generate a CCS polymer with increased functionality in the periphery of the arms. This was achieved according to Scheme 6.8, where the terminal hydroxy group of the TMS-protected macroinitiator is used to initiate ROP of the bislactone monomer BOD, thereby cross-linking the arms together to form CCS polymer. Subsequent removal of the TMS protecting groups via TBAF mediated cleavage should regenerate the pendent acetylene functionality without degrading the polyester-based structure of the star polymer. The increased functionality of the resulting acetylene functional CCS polymer, (1) in Scheme 6.8, can be demonstrated by grafting terminal azido functional polystyrene, PST-N₃, onto the star via ‘click chemistry’ coupling with the pendent acetylene groups. This will result in a CCS polymer with ‘brush-like’ arm structures, (2) in Scheme 6.8, the BOD core and PCL arm segment of which can subsequently be hydrolyzed to liberate polystyrene grafted poly(propargyl methacrylate) molecular brushes, (3) in Scheme 6.8.
Scheme 6.8: Synthesis of acetylene functional CCS polymer (1) followed by ‘click chemistry’ coupling to generate CCS polymer with ‘brush-like’ arms (2) and subsequent hydrolysis to liberate molecular brushes (3).

6.2.4.1 Synthesis of acetylene functional CCS polymer

Synthesis of acetylene functional CCS polymer was achieved by using the terminal hydroxy group of the PCL-b-P(TMS-PgMA)-Br macroinitiator (M_n = 14,100 g/mol, M_w/M_n = 1.19) (Table 6.1, entry 4) to initiate ring-opening polymerization of the bislactone 4,4′-bioxepanyl-7,7′-dione (BOD). Similar reaction conditions to those found to be optimal for the synthesis of fully degradable CCS polymer (Section 4.2.2) were employed, with both GC-MS and GPC being used to monitor the extent of reaction. After 45 hours the conversion of BOD cross-linker was so high that the unreacted monomer could not be detected (>99% conversion). The reaction was stopped at this point and analyzed by GPC (Figure 6.5) which revealed that ~50% of the macroinitiator had been converted into CCS polymer, with subsequent fractionation yielding pure CCS polymer (M_n = 774,800 g/mol, M_w/M_n = 1.10). Using this information the average number of arms incorporated into each CCS polymer was calculated to be 38.5, each of which contains 48.4 pendent TMS-protected acetylene groups, resulting in each star having a potential functionality of 1863 acetylene groups.
The trimethylsilyl protecting groups were removed by TBAF mediated cleavage using similar conditions to those reported for the deprotection of PCL-\(b\)-P(TMS-PgMA)-Br macronitiator (Section 6.2.3.1). Success of this reaction was confirmed by \(^{1}\)H NMR spectroscopy (Figure 6.6), the proton resonances corresponding to the TMS protecting group (\(\delta = 0.18 \text{ ppm}\)) were not evident and a strong signal from the acetylene proton (\(\delta = 2.47 \text{ ppm}\)) was apparent. A comparison of the relative integral peak areas corresponding to the PPgMA and PCL segments of the polymer (Figure 6.6; resonances \(i\) and \(a\) respectively) revealed that the average number of pendent acetylene groups per arm was 28.4. This is significantly less than the predicted value of 48.4, with the integral area of the PCL segment possibly being higher than it otherwise should be due to reinforcement from a resonance overlap with the BOD cross-linked core. However, any increase in signal strength due to reinforcement from the core is expected to be fairly small due to the reduced segmental mobility of the core domain. Another possible explanation is that partial cleavage of the PCL arms occurred during the deprotection step, essentially cleaving the PPgMA segment from some of the arms. This can better be confirmed via GPC analysis of the fractionated CCS polymer before and after deprotection, with Figure 6.5 showing a reduction in molecular weight from 774,800 g/mol down to 617,200 g/mol. This can be compared

**Figure 6.5:** GPC traces showing the synthesis of acetylene functional CCS polymer.
to the theoretical molecular weight of the deprotected CCS polymer (assuming 38.5 arms per star and 48.4 acetylene groups per arm) which was calculated to be 640,300 g/mol. While the correlation between the theoretical molecular weight and that measured via GPC is reasonably close, it still shows that a greater mass was lost than predicted by theory. This backs up the results observed in the NMR analysis that a small amount of arm degradation possibly occurred during the deprotection step, resulting in less pendent acetylene groups being present in the CCS polymer than originally estimated. Nevertheless, the results from both GPC and NMR analysis confirm that high molecular weight CCS polymer has been successfully synthesized with the desired high degree of acetylene functionality being present in the corona.

**Figure 6.6:** $^1$H NMR spectrum of deprotected acetylene functional CCS polymer.

### 6.2.4.2 ‘Click chemistry’ attachment of PST-N$_3$

To demonstrate the increased functionality of this acetylene functional CCS polymer, it was proposed to attach terminal azido functionalized linear polystyrene to the outer segment of the arms via a Cu(I) catalyzed cycloaddition reaction between the azide and acetylene groups, i.e. ‘click coupling’, to generate a CCS polymer with ‘brush-like’ arm structures ([2] in Scheme 6.8). This was attempted by using similar reaction
conditions to those reported for the ‘click’ attachment of PST-N\textsubscript{3} to the deprotected linear macroinitiator (Section 6.2.3.2). In this reaction a solution of CuBr/PMDETA catalyst in DMF was added to a degassed mixture of PST-N\textsubscript{3} and acetylene functional CCS polymer in DMF and allowed to react overnight. However, the reaction didn’t appear to work in this case, with GPC analysis showing that the peak due to the CCS polymer disappeared upon reaction but there was no corresponding high molecular weight peak representative of the grafted polymer. Instead, a very small amount of low molecular weight polymer (30-50 kDa) was observed in conjunction with residual unreacted PST-N\textsubscript{3} polymer. This additional peak is believed to be due to the small amount of unconverted linear macroinitiator which wasn’t fully removed during the fractionation step, with its increased molecular weight suggesting that several PST-N\textsubscript{3} chains had been grafted onto it. The fact that the molecular weight of this peak was significantly less than expected for full grafting of the macroinitiator (\(M_n \sim 400\) kDa) indicates that this polymer underwent radical termination during the chain extension reaction with TMS-PgMA monomer, resulting in the incorporation of only a few pendant acetylene bonds.

This ‘click coupling’ reaction was repeated several times with similar effect, with a subsequent investigation into the reaction conditions revealing some interesting results. It was found that when the reaction was performed in the absence of an azide, i.e. stirring a mixture of CuBr/PMDETA catalyst and acetylene functional CCS polymer in DMF overnight, similar results were still observed, with the peak due to the CCS polymer disappearing in the GPC trace to be left with a low molecular weight peak which in this case matched that of the unconverted macroinitiator. This suggests that the problem lies with the acetylene functional CCS polymer and is believed to be a result of star-star coupling. The mechanism of formation for this type of CCS polymer means that the periphery of each arm is functionalized with an ATRP initiating site. The addition of a high concentration of CuBr/PMDETA (an ATRP catalyst) and a highly polar solvent (DMF) could potentially result in some of these ATRP initiating sites becoming active even at low temperatures and generating radicals. The high density of these radical sites and the extended reaction time could potentially result in some of these sites undergoing radical-radical termination and linking the stars together to form an insoluble gel. While gel was not observed visually, possibly due to the small scale of the reactions, this would explain why high molecular weight grafting product was not generated, with any insoluble material
being removed by a syringe filter before analysis. This could also mean that a similar problem occurred during the grafting of deprotected linear macroinitiator (Section 6.2.3.2), where in this case two macroinitiators could couple together to form a polymer twice the predicted molecular weight. If this did occur then it would mean that the grafting efficiency would be half that previously calculated, with approximately only 41% of the pendant acetylene groups undergoing cycloaddition with the terminal azido functional polystyrene. This value is more typical of what is expected for the grafting of high molecular weight polymers in sterically crowded environments, with the large size and bulky nature of the polystyrene acting to limit the extent of grafting.\textsuperscript{[14]} This suggests that coupling of the macroinitiators did occur under these reaction conditions, however it is hard to confirm. Hydrolysis of the grafted macroinitiator could have been used to investigate this, with the molecular weight decrease due to degradation of the PCL segment being used to determine whether or not coupling had occurred. Unfortunately, the low molecular weight of the PCL segment compared to the grafted polymer (4.6 kDa compared to 334.2 kDa) doesn’t allow for sufficient change to resolve the difference between coupled and uncoupled polymer, with the theoretical molecular weight of the hydrolysis products being 329.6 kDa and 325.0 kDa respectively.

In order to avoid this type of problem it may be necessary to protect or convert the ATRP initiating functionality before performing any ‘click coupling’ reactions. Alternatively, the block copolymer macroinitiator could be synthesized using another form of controlled polymerization, such as RAFT, which doesn’t require the use of functional groups which may cause potential problems during the subsequent ‘click coupling’. However, for this work it was decided to repeat the reaction using the unmodified CCS polymer and simply changing the method of addition, this time slowly adding the acetylene polymer into an excess of the azide with close monitoring. It was hoped that in this case the grafting reaction would occur in preference to any star-star coupling, with the brush polymer arms effectively shielding the ATRP initiation sites once the grafting density was sufficiently high.

The GPC traces for this reaction are shown in Figure 6.7, with the evolution of a high molecular weight product being clearly evident after only 150 minutes, at which point the reaction was stopped to avoid any possible gelation and loss of product. The early termination of this grafting reaction resulted in a large amount of residual PSt-N\textsubscript{3} and unconverted CCS polymer being present in the final reaction solution (Figure 6.7,
‘click coupling’ trace), with subsequent fractionation being required to isolate the coupling product (Figure 6.7, fractionation trace) which was determined to have a $M_n$ of 6,138,000 g/mol ($M_w/M_n = 1.20$). $^1$H NMR spectroscopy of this isolated polymer showed that its structure was comprised of both PCL and PSt which confirms that grafting did occur and that this high molecular weight polymer wasn’t simply a product of star-star coupling. Integration of the relative PCL and PSt peak areas to determine the extent of grafting was considered to be impractical, with the comparatively weak signal strength of the PCL segment making accurate integration impossible. The fact that the outer PSt structure could potentially be shielding the inner PCL domain and thereby reducing its apparent peak area would also affect the accuracy of these calculations. However, if it is assumed that star-star coupling did not occur then the extent of grafting can be estimated on the basis of molecular weight, resulting in approximately 28% of the pendent acetylene groups within the CCS polymer undergoing cycloaddition reactions with the terminal azido functional polystyrene. This is significantly lower than what was observed for the grafting of linear macroinitiator (Section 6.2.3.2), a result which is to be expected due to the more sterically hindered structure of the CCS polymer and the shorter reaction times involved.

![Figure 6.7: GPC traces of the ‘click coupling’ reaction between acetylene functional CCS polymer and PSt-N$_3$, with subsequent fractionation of the grafted CCS polymer.](image)

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The change in hydrodynamic size of these polymers was monitored via dynamic light scattering, with the traces before and after ‘click coupling’ being shown in Figure 6.8. As expected from the large increase in molecular weight experienced as a result of the grafting reaction, the corresponding size of the CCS polymer also increases fairly significantly, with the hydrodynamic diameter increasing from an average value of 20.1 nm up to 52.6 nm.

![DLS traces of acetylene functional CCS polymer before and after grafting with linear PST-N3 via ‘click chemistry’.](image)

**Figure 6.8:** DLS traces of acetylene functional CCS polymer before and after grafting with linear PST-N3 via ‘click chemistry’.

### 6.2.4.3 Hydrolysis

As illustrated in Scheme 6.8, it is possible to hydrolyze the BOD cross-linked core and the PCL arm segments of this ‘click coupled’ CCS polymer and therefore liberate the molecular brushes which were attached to the periphery of the arms. To demonstrate this, the isolated CCS polymer with ‘brush-like’ arms synthesized in the previous section was hydrolyzed under acidic conditions. This reaction was monitored via GPC (Figure 6.9) which revealed that the molecular weight decreased from 6,138,000 g/mol down to 163,400 g/mol. This can be compared to the theoretical molecular weight of the liberated molecular brushes which was calculated to be 149,400 g/mol, showing good correlation with that of the hydrolyzed polymer. This result suggests that little, if any, star-star coupling had occurred and that the high
molecular weight product isolated in the previous section was purely a product of the grafting of linear polystyrene to the acetylene functional CCS polymer. It should also be noted that the polydispersity of the hydrolyzed molecular brushes is quite high ($M_w/M_n = 1.65$), indicating that the degree of grafting per arm was quite varied, an issue which can be attributed to the sterically hindered structure of the CCS polymer arms during the grafting reaction.

**Figure 6.9:** GPC traces showing the fractionated CCS polymer with ‘brush-like’ arms before and after hydrolysis.
6.3 Conclusions
In summary, this Chapter has shown that the potential functionality of CCS polymers can be significantly increased by incorporating pendent functionalities along the polymeric backbone of the arms. In this work the incorporation of pendent acetylene groups was investigated due to their potential for subsequent ‘click chemistry’ type reactions to couple appropriately functionalized (i.e. azide) molecules. This was achieved by synthesizing a methacrylate based monomer with TMS-protected acetylene functionality and using it to generate a block copolymer macronitiator. This macronitiator was subsequently cross-linked with degradable bislactone monomer to generate a CCS polymer with protected acetylene functionality in the outer segment of the arms. Appropriate conditions were found to cleave the TMS protecting group without destroying the polyester based structure of the star, thereby generating CCS polymer with many pendent acetylene groups along the arms. The increased functionality of this CCS polymer was demonstrated by attaching azide functionalized linear polystyrene via a copper (I) catalyzed cycloaddition reaction between the azide and acetylene groups. This resulted in a CCS polymer with ‘brush-like’ arm structures, the grafted segment of which could be liberated via hydrolysis of the polyester star structure to generate molecular brushes.

6.4 References

Chapter 7 - Conclusions and Future Work

7.1 Conclusions

7.2 Future Work

7.2.1 Amphiphilic CCS polymers

7.2.2 Attachment of targeting/imaging functionality

7.2.3 Tuning degradation rates

7.2.4 Shell cross-linking (nanocapsules)

7.3 References
7.1 Conclusions

From the work presented in this thesis it has been shown that a range of selectively degradable CCS polymers can be synthesized, where either the arms or the core can be selectively targeted for degradation. This was achieved by using a combination of controlled polymerization techniques, specifically ATRP and ROP, to incorporate acid-labile ester linkages into the structure of these CCS polymers. Subsequent hydrolysis of these bonds proved an efficient and precise means for cleaving the targeted moieties without damaging the ‘non-degradable’ component of the star’s structure.

A method for synthesizing CCS polymers with degradable PCL arms and non-degradable ATRP cross-linked cores was developed. Various reaction parameters, especially the concentration, the ratio of cross-linker to macroinitiator and the molecular weight of the arms, were found to significantly affect the extent of CCS formation. The use of both EGDMA and DVB cross-linkers was investigated, with EGDMA being found to be much more reactive and capable of yielding higher conversion of arms into CCS polymer compared to DVB. Hydrolysis experiments showed that the PCL arms could be selectively degraded, liberating the highly cross-linked EGDMA and DVB cores which were further analyzed by GPC and DLS. The arms of the CCS polymers were shown to provide a significant solubilizing effect, with their removal resulting in the core becoming only sparingly soluble.

Incorporation of degradable functionality into the core domain was also shown to be possible, with a novel method for generating CCS polymers via ROP based cross-linking of bislactone monomers being developed. This approach was subsequently applied to the synthesis of fully degradable CCS polymers, resulting in a polymerization which could be achieved in a one-pot process and thus eliminate the need for isolation and purification of the intermediate macroinitiator. The CCS polymers generated via this ROP cross-linking approach were shown to be comparable to those generated by CRP cross-linking, having high molecular weights and narrow polydispersities. The effectiveness of two bislactone cross-linkers (BOD and BCP) was examined, with a higher conversion of arms into CCS polymer being achieved when BOD was used compared to BCP. Thus it was proposed that this result arose as a consequence of the added steric bulk of the BCP monomer making formation of the dense core region unfavorable. Both BOD and BCP cross-linked cores were shown to be fully hydrolysable, liberating the arms in the case of core-
degradable CCS polymer or small acid units in the case of fully degradable CCS polymer.

The phenomenon of star-star coupling was also investigated, with hydroxyl impurities such as water being found to be the main cause of star-star coupling during ROP based cross-linking. Issues of continued star-star coupling after precipitation of the CCS polymers was also found to be a problem, with Sn(Oct)$_2$ trapped within the core domain thought to be promoting coupling reactions between the cores and resulting in a decreased solubility. This problem of reduced shelf life was overcome by either storing the fully degradable CCS polymers at low temperature (<2°C) or in the presence of a solvent such as THF, with both methods effectively stopping any further coupling reactions.

The versatility of these selectively degradable CCS polymers was subsequently investigated, with several different techniques for post-synthesis modification of the coronal structure being developed. A range of CCS polymers with miktoarm, block copolymer arm and mikto/block copolymer arm structures were generated and shown to be a viable means of manipulating properties such as the size, density and chemical composition of the CCS corona. Further functionalization to incorporate multiple pendant acetylene groups into the arms of the CCS polymer was also carried out. The increased functionality of this CCS polymer was demonstrated by attaching azide functionalized linear polystyrene via a copper (I) catalyzed cycloaddition reaction between the azide and acetylene groups. This resulted in a CCS polymer with ‘brush-like’ arm structures, the grafted segment of which could be liberated via hydrolysis of the polyester star structure to generate molecular brushes.

7.2 Future Work

The successful incorporation of selectively degradable functionality into the structure of CCS polymers opens up an array of potential future applications, ranging from templating materials for nanoporous thin films to viscosity modifiers. Of even greater interest is their use as potential drug delivery devices, an area we believe to be of significant importance and in need of further investigation.

As highlighted in Chapter 1 (Section 1.5), CCS polymers are excellent candidates for use as drug delivery devices, with the incorporation of degradable functionality being a significant step towards realizing this, even more so with the use of biodegradable and biocompatible polymers such as PCL. However, there are still many other aspects
to this work which require further investigation before CCS polymers can be successfully employed in the biomedical field as drug delivery devices. While outside the scope of the work presented in this thesis, what follows in this chapter is an outline of several key areas which have been tagged for future investigation.

7.2.1 Amphiphilic CCS polymers

One of the drawbacks to using CCS polymers as potential drug delivery devices is the hydrophobic nature of the polymer. While this is a desired characteristic of the core, i.e. to facilitate loading of hydrophobic drug molecules, it causes a problem in terms of solubility within the body. This can be overcome by functionalizing the corona to make it more hydrophilic, essentially generating amphiphilic CCS polymer with hydrophobic core and hydrophilic coronal domains. One potential way to achieve this is through the attachment of hydrophilic polymers, such as poly(ethylene glycol) (PEG), to the periphery of the star, with the ‘click’ functionalized CCS polymer synthesized in Chapter 6 providing an ideal intermediary for this work.

An added benefit of functionalizing the surface of a molecule with PEG is that it has been shown to prolong circulation times \textit{in vivo} \cite{1,2,3}, a property which can actually lead to significant passive targeting of tumours through the ‘enhanced permeability and retention’ (EPR) effect\cite{4}. As such, an investigation into synthesizing amphiphilic CCS polymers via surface functionalization with PEG is considered to be very important.

7.2.2 Attachment of targeting/imaging functionality

Apart from degradability there are several other factors which are just as important in the design of CCS polymers for drug delivery applications. One of these is the ability to introduce various functional groups which allow for the incorporation of targeting, imaging, or other biocompatible functionalities. The attachment of targeting ligands to create drug delivery devices capable of recognizing disease affected sites (cancerous cells, tumours) has significant potential. Not only does this allow for more effective drug delivery but in combination with imaging functionalities could be used as a diagnostic tool to identify diseased tissue.
7.2.3 Tuning degradation rates

The work presented in this thesis investigated the viability of incorporating degradable functionality into CCS polymers, specifically focusing on the use of polycaprolactone based polymers to achieve this. For applications like drug delivery, it is desirable to have a polymer where properties such as the rate of degradation can be tuned in order to achieve greater control over the kinetics of drug release. For this reason, the incorporation of a range of degradable polymers with differing rates of degradation needs to be investigated. The use of miktoarm or block copolymer arm structures (Chapter 5) to introduce more than one type of degradable polymer into the CCS structure would allow for very specific control over the degradation rate. For example, the incorporation of poly(lactic acid) into poly(caprolactone) based polymers has been shown to significantly effect the rate of degradation, with greater mass loss being observed for block copolymers of PCL and PLA compared to that of either of the two homopolymers.[5,6]

7.2.4 Shell cross-linking (nanocapsules)

Another very interesting area of investigation which has arisen from the work presented in Chapter 6 is the potential synthesis of polymeric nanocapsules. Rather than attaching terminal azido functionalized linear polymers to the acetylene functional CCS polymer as demonstrated in Chapter 6, a diazide could be applied to cross-link the high density of pendent acetylene bonds within the corona, essentially performing shell cross-linking as illustrated in Scheme 7.1. The degradable core and inner arm segment of such a polymer could subsequently be hydrolyzed to generate hollow polymeric nanocapsules (Scheme 7.1) which could potentially be loaded with drug molecules.

Scheme 7.1: Shell cross-linking of acetylene functional CCS polymer to generate polymeric nanocapsules.
7.3 References


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8.1 Characterization Techniques

8.1.1 Gel Permeation Chromatography (GPC)

An example of the GPC experimental setup used for the work presented in this thesis is shown in Scheme 8.1. All GPC analysis was performed on a Shimadzu system with a Wyatt DAWN EOS multiangle laser light scattering detector (690 nm, 30 mW) and a Wyatt OPTILAB DSP interferometric refractometer (690 nm). HPLC grade THF was used as the eluent with three Phenomenex phenogel columns (500, $10^4$ and $10^6$ Å porosity; 5 μm bead size) operated at 1 mL/min with column temperature set at 30°C. Astra software (Wyatt Technology Corp.) was used to process the data using known $dn/dc$ values to determine the molecular weight or an assumption of 100% mass recovery of the polymer where the $dn/dc$ value was unknown.

![Figure 8.1: Schematic representation of GPC experimental setup.](image)
Gel Permeation Chromatography (GPC) was used extensively for the work presented in this thesis and as such the basic principles will be described here. GPC, also known as Size Exclusion Chromatography (SEC), is essentially a chromatography technique which separates polymers on the basis of their size. The injected sample and eluent (mobile phase) passes through a series of columns packed with finely divided, porous particles (stationary phase). Polymer molecules that are smaller than the pore sizes can enter the pores and therefore have a longer transit time than larger molecules that cannot enter the pores. Thus, the larger molecules elute earlier in the chromatogram while the smaller molecules elute later, which, in conjunction with appropriate detectors, can be used to determine molecular weight as a function of elution volume.

In the past, GPC systems were typically operated using only a refractive index (RI) detector, i.e. a concentration detector. This required that the GPC columns be calibrated with standard samples of known molecular weight in order to determine the molecular weight of unknown samples. Unfortunately, appropriate standards having the same composition and conformation as the unknown specimen are often not available, leading to errors in the calculated molecular weight for many polymer systems. However, when a light scattering (LS) detector is used in series with a concentration detector, it is possible to obtain absolute molecular weights without the need for column calibration. This is particularly useful for determining the molecular weight of polymers with complex architectures such as CCS polymers, where standards for column calibration are non-existent.

The determination of molecular weight via light scattering operates on the principle that the light scattering intensity of a polymer is proportional to:

a) the molecular weight of the polymer,

b) the concentration of the polymer, and

c) the square of $dn/dc$

Therefore to determine the molecular weight of a polymer one must know the light scattering intensity (measured by LS detector), the concentration of the polymer (measured by RI detector), and the specific refractive index increment ($dn/dc$) of the polymer. This $dn/dc$ value describes the change of the refractive index of a polymer solution relative to the change of the polymer concentration. For accurate molecular weight determination via LS, it is very important that the $dn/dc$ of the actual polymer, in the actual solvent, at the actual measured wavelength be accurately known. Values for $dn/dc$ can either be taken from the literature for well known polymers, measured
on-line with an assumption of 100% injected mass recovery from the columns (generally considered ok for SEC in organic solvents), or measured off-line. For block copolymers the $dn/dc$ can be calculated as the weighted average of the $dn/dc$ values for both homopolymers. However, the $dn/dc$ of a random copolymer is not as straightforward to calculate, and should probably be measured directly.

8.1.2 Nuclear Magnetic Spectroscopy (NMR)
Proton ($^1$H) and carbon ($^{13}$C) NMR spectra were obtained using a Varian Unity Plus 400 Spectrometer operating at 400 MHz and 100 MHz respectively. All samples were collected in deuterated chloroform (unless otherwise stated) with chemical shifts ($\delta$) being referenced to that of either tetramethylsilane (TMS) or the appropriate deuterated solvent. Analysis of all spectra was performed using MestRe-C 2.0.2 software.

8.1.3 Gas Chromatography – Mass Spectroscopy (GC-MS)
Monomer conversion was determined by gas chromatography using a Shimadzu GC 17-A gas chromatograph equipped with an Agilent J+W DB-5ms capillary column (30m $\times$ 0.25mm $\times$ 0.25$\mu$m, 5% phenyl siloxane) and coupled to a GCMS-QP5000 mass spectrometer. Ultra high purity helium (BOC) was used as the carrier gas. Monomer conversions were calculated from standard response versus concentration curves, generated using pure monomers, or by comparing peak areas before and after reaction with reference to an internal standard, typically toluene. GC conditions were as follows: Initial Temp: 40$^\circ$C; Initial Time: 2.00 min; Rate: 10$^\circ$C/min; Final Temp: 320$^\circ$C; Final Time: 2 min; Injector Temp: 250$^\circ$C; Detector Temp: 230$^\circ$C; M/z detection range: 40 - 350. Typical sampling procedure involved taking a 0.1 mL sample of the polymer reaction mixture and diluting it with methanol (1.0 mL) to precipitate any polymer. This solution was then passed through a 0.4 $\mu$m syringe filter before being injected into the GC.
8.1.4 Dynamic Light Scattering (DLS)
Dynamic light scattering measurements were performed using a Malvern HPPS particle sizer with a 3.0 mW He-Ne laser operated at 633 nm. Analysis was performed at an angle of 173° and a constant temperature of 20°C with all samples being passed through a 0.4 μm syringe filter prior to analysis. Each sample was measured at least 3 times with the average size distribution being reported as a function of number. THF (RI = 1.407, μ = 0.55 cPoise @ 20°C) was used as solvent for all samples unless otherwise stated.

8.1.5 Fourier Transform Infrared Spectroscopy (FTIR)
Fourier transform infrared spectra (FTIR) were obtained in a nitrogen atmosphere using a Bio-Rad Digilab FTS-165 spectrophotometer. Solid samples were prepared in KBr discs with 16 scans being collected at a resolution of 4 cm⁻¹. The samples are reported as absorption maxima (ν_max) with units of reciprocal centimeters (cm⁻¹).
8.2 Experiments for Chapter 2

8.2.1 Materials

2-Bromoisobutyrylbromide (98%), anisole (anhydrous, 99.7%), copper (I) bromide (CuBr, 98%), 2,2'-bipyridine (bpy, 99%), ethylene glycol (>99%) and stannous 2-ethylhexanoate (Sn(Oct)₂, 95%) were purchased from Aldrich and used as received. ε-Caprolactone (CL, 99+%%) (Aldrich) was dried over CaH₂ for 24 hours and distilled under high vacuum prior to use. Methyl methacrylate (MMA, 99%), ethylene glycol dimethacrylate (EGDMA, 98%), divinylbenzene (DVB, 80% mixture of isomers) and N, N, N', N', N"-pentamethyldiethylenetriamine (PMDETA, 99%) were all purchased from Aldrich and washed three times with 5% w/w aq. NaOH, once with water, then distilled from calcium hydride and stored at -5°C. p-Toluenesulfonyl chloride (TsCl, 99+%%) (Aldrich) was dissolved in minimum chloroform, diluted with petroleum ether (bp 40-60°C), clarified with charcoal, filtered, concentrated and collected by filtration.

8.2.2 Synthesis of 2-hydroxyethyl 2'-methyl-2'-bromopropionate

2-Hydroxyethyl 2'-methyl-2'-bromopropionate was synthesized according to literature.\(^1\) 2-Bromoisobutyril bromide (5.45 g, 23.7 mmol) was added into a molar excess (25 times) of ethylene glycol (33.0 mL, 0.593 mol) and stirred for 16h at 0°C. The mixture was then dissolved in water and extracted with dichloromethane. The organic phase was washed with a saturated aqueous sodium bicarbonate solution followed by water and extracted with dichloromethane. The solvent was distilled off under reduced pressure to yield a colorless liquid (3.90 g, 78%)

\(^1\)H NMR (400 MHz, CDCl₃), δ (ppm): 1.95 (s, 6H, −C(CH₃)₂), 2.17 (s, 1H, −OH), 3.87 (t, 2H, −CH₂OH), 4.31 (t, 2H, −COOC(CH₃)₂).  
\(^{13}\)C NMR (100 MHz, CDCl₃), δ (ppm): 171.8 (C=O), 67.3 (−COOCH₂−), 60.6 (−CH₂OH), 55.7 (−CCOO−), 30.6 (−CH₃).  
MS (EI) m/z (rel. int.): 211 (M⁺, 0.1%), 169 (10.6), 167 (11.0), 151 (5.7), 149 (5.9), 123 (18.5), 121 (19.8), 113 (12.0), 103 (3.4), 87 (18.0), 83 (8.8), 69 (63.8), 59 (26.4).
FTIR (KBr): O–H $\nu_{\text{max}} = 3300$ cm$^{-1}$, C=O $\nu_{\text{max}} = 1735$ cm$^{-1}$.

8.2.3 Typical synthesis of PCL-Br macroinitiator
In a typical reaction a round bottom flask was charged with a mixture of CL (10.0 g, 87.6 mmol), Sn(Oct)$_2$ (2.366 g, 5.840 mmol), and 2-hydroxyethyl 2'-methyl-2'-bromopropionate (2.465 g, 11.68 mmol). A condenser and CaCl$_2$ drying tube were attached to the flask which was heated at 130ºC. After 24h the reaction solution was diluted with THF and precipitated into cold methanol with the precipitate being collected by filtration and dried for 16h in a desiccator to yield PCL-Br macroinitiator (yield: 8.73 g; $M_n = 2,700$ g/mol, $M_w/M_n = 1.12$).

8.2.4 Synthesis of PCL-$_b$-PMMA to test livingness of PCL-Br macroinitiator
HO-PCL-Br macroinitiator (1.54 g, 0.571 mmol; $M_n = 2,700$ g/mol) was added to a round bottom flask and dissolved in 38 mL of anisole. A mixture of CuBr (0.106 g, 0.743 mmol), PMDETA (0.156 mL, 0.743 mmol) and MMA (2.45 mL, 22.8 mmol) was added to the reaction solution and purged with argon for 2h. The flask was then sealed and heated at 100ºC for 48h. The reaction was stopped by quenching in liquid nitrogen and diluted with THF before being passed through a column of basic alumina to remove the copper complex. The product was isolated by precipitation into cold methanol and dried in a desiccator for 16h (yield: 2.66 g; $M_n = 6,900$ g/mol, $M_w/M_n = 1.09$).

8.2.5 Hydrolysis of PCL-$_b$-PMMA to test selective degradability
In order to confirm that the PCL could be selectively degraded without effecting the PMMA segment, 0.2 g of PCL-$_b$-PMMA was dissolved in 20 mL THF to which was added 1.5 mL H$_2$O and 0.5 mL 12 M HCl. Hydrolysis was carried out at 60ºC for 24h after which time the reaction solution was precipitated into cold methanol with the residual polymer being collected via vacuum filtration and analyzed via GPC and $^1$H NMR spectroscopy.

8.2.6 Typical synthesis of arm-degradable CCS polymer
In a typical reaction PCL-Br macroinitiator (0.304 g, 0.132 mmol; $M_n = 2,300$ g/mol) was reacted with a mixture of CuBr (24.7 mg, 0.172 mmol), PMDETA (36.0 μL, 0.172 mmol), EGDMA (0.622 mL, 3.30 mmol) and anisole (26 mL) in a Schlenk
flask and degassed by three freeze-pump-thaw cycles. The flask was then backfilled with argon and immersed in an oil bath at 100°C. After 65h (93% EGDMA conversion) the reaction was stopped via exposure to air and diluted with THF before being passed through a column of basic alumina to remove the copper complex. The solution was then concentrated and precipitated into methanol with the precipitate being collected by filtration and dried under vacuum. (Mn, CCS = 367,100 g/mol, Mw/Mn = 1.19, 85% arm conversion)

8.2.7 Typical procedure for kinetic sampling during CCS formation reaction

Reaction conditions were the same as described for standard CCS formation reaction (Section 8.2.6). Samples (0.1 mL) were taken using an oven-dried syringe under a positive flow of argon. Samples to be analyzed by GPC were diluted with THF (1 mL) and passed through a microcap syringe to remove the copper catalyst before analysis. Samples to be analyzed by GC-MS were precipitated by direct addition of methanol (2 mL) to the sample in a 5 mL vial which was shaken vigorously. The solution was then filtered using a 0.4 μm syringe filter to remove the precipitated polymer before being analyzed by GC-MS using anisole as an internal reference to determine relative monomer conversion.

8.2.8 Synthesis of PMMA macroinitiator

A mixture of MMA (10.0 mL, 93.5 mmol), CuBr (0.135 g, 0.941 mmol), bpy (0.44 g, 2.8 mmol), TsCl (0.179 g, 0.939 mmol) and anisole (13.2 mL) was added to a Schlenk flask and degassed by three freeze-pump-thaw cycles. The flask was then backfilled with argon and immersed in an oil bath at 80°C. After 17h the reaction was stopped via exposure to air and diluted with THF before being passed through a column of basic alumina to remove the copper complex. The solution was then concentrated and precipitated into cold methanol with the precipitate being collected by filtration and dried for 16h in a desiccator to yield PMMA macroinitiator as a white solid (yield: 7.55 g; Mn = 11,800 g/mol, Mw/Mn = 1.08).

8.2.9 Typical synthesis of non-degradable CCS polymer

A mixture of PMMA macroinitiator (0.73 g, 0.062 mmol; Mn = 11,800 g/mol), EGDMA (0.18 mL, 0.93 mmol), CuBr (8.9 mg, 0.062 mmol) and bpy (29 mg, 0.19 mmol) in anisole (12.2 mL) was added to a Schlenk flask equipped with a magnetic
stirrer. The mixture was degassed by three freeze-pump-thaw cycles, backfilled with argon and then heated at 100°C. After 90h the reaction was stopped via exposure to air and diluted with THF before being passed through a column of basic alumina to remove the copper complex. The solution was then concentrated and precipitated into methanol with the precipitate being collected by filtration and dried under vacuum. 

\( \text{M}_{n,\text{CCS}} = 504,300 \text{ g/mol}, \text{M}_{w}/\text{M}_{n} = 1.08, 94\% \text{ arm conversion} \)

8.2.10 Typical hydrolysis of CCS polymer

In a typical hydrolysis reaction 40 mg of CCS polymer was dissolved in 4 mL THF to which was added 0.3 mL H\(_2\)O and 0.1 mL 12 M HCl. Hydrolysis was carried out at 60°C for 24h after which time the sample was precipitated into cold methanol and isolated before characterization. For the case of arm-degradable CCS polymer, the hydrolysis solution was diluted with THF and analyzed directly by GPC due to the low solubility of the hydrolysis product (i.e. the cross-linked core particles) once they had been remove from solution.
8.3 Experiments for Chapter 3

8.3.1 Materials
Copper (I) bromide (CuBr, 98%), 2,2'-bipyridine (bpy, 99%), stannous 2-ethylhexanoate (Sn(Oct)$_2$, 95%), $m$-chloroperoxybenzoic acid (77% max) and urea hydrogen peroxide adduct (98%) were purchased from Aldrich and used as received. Formic acid (99%, Ajax Finechem) and 4,4'-bicyclohexanone (Lomb Scientific) were also used as received. Tetrahydrofuran (THF) and toluene were distilled from sodium benzophenone ketyl and sodium metal under argon and stored over 4Å molecular sieves. Methyl methacrylate (MMA, 99%), styrene (St, 99%) and N, N, N', N', N''-pentamethyldiethylenetriamine (PMDETA, 99%) were all purchased from Aldrich and washed three times with 5% w/w aq. NaOH, once with water, then distilled from calcium hydride and stored at -5°C.

8.3.2 Synthesis of 4,4'-bioxepanyl-7,7'-dione (BOD)

![Diagram of 4,4'-bioxepanyl-7,7'-dione (BOD)]

$^1$H NMR (400 MHz, CDCl$_3$), $\delta$ (ppm): 4.34 (R, R) 4.17 (S, R) (t, 2H, $-\text{CH}_2\text{OOC}$−), 2.73 (R, R) 2.60 (S, R) (t, 2H, $-\text{CH}_2\text{COO}$−), 1.93-1.83 (m, 2H, $-\text{CH}_2\text{CH}_2\text{OOC}$−), 1.70-1.60 (m, 2H, $-\text{CH}_2\text{CH}_2\text{COO}$−), 1.49 (q, 1H, $-\text{CHCH}_2$−).

$^{13}$C NMR (100 MHz, CDCl$_3$), $\delta$ (ppm): 175.4 (C=O), 68.0 ($-\text{CH}_2\text{OOC}$−), 45.7 ($-\text{CH}_2\text{CH}_2\text{COO}$−), 33.2 ($-\text{CH}_2\text{COO}$−), 32.1 (R, R) 31.9 (S, R) ($-\text{CH}_2\text{CH}_2\text{OOC}$−), 25.8 (R, R) 25.6 (S, R) ($-\text{CHCH}_2$−).

MS (EI) m/z (rel. int.): 226 (M$^+$, 0.4%), 208 (0.9), 198 (1.5), 181 (4.4), 168 (6.5), 153 (6.4), 137 (8.2), 123 (10.1), 113 (18.2), 96 (14.7), 83 (64.0), 67 (30.1), 55 (100.0).

FTIR (KBr): C=O $\nu_{\text{max}}$ = 1724 cm$^{-1}$.

8.3.2.1 $m$-Chloroperoxybenzoic acid method
A Baeyer-Villiger oxidation was carried out according to literature,$^{[2]}$ slowly adding $m$-chloroperoxybenzoic acid (13.32 g, 77.19 mmol) in batches to a stirred solution of 4,4'-bicyclohexanone (5.00 g, 25.7 mmol) in 50 mL of dichloromethane. After 5 hours
of vigorous stirring the reaction was stopped by adding 200 mL of water followed by extraction with chloroform. The organic fractions were collected, washed with a saturated aqueous sodium bicarbonate solution and dried with Na₂SO₄. The organic fraction was concentrated and the solvent removed under reduced pressure to yield a white powder (5.61 g, 96%).

8.3.2.2 Hydrogen peroxide/formic acid method
Following a procedure previously reported in the literature,[³] a solution of urea hydrogen peroxide (CO(NH₂)₂·H₂O₂) (10.0 g, 106 mmol) in 50 mL of formic acid (99%) was stirred at 23ºC for 90 minutes. 4,4'-Bicyclohexanone (5.0 g, 25.7 mmol) was then slowly added over 5-10 minutes and stirred for a further 4h. The reaction was stopped by adding 200 mL of water to the mixture followed by extraction with chloroform. The organic fractions were collected, washed with a saturated aqueous sodium bicarbonate solution and dried with Na₂SO₄. The organic fraction was then concentrated and the solvent removed under reduced pressure to yield a white powder (3.50 g, 60%).

8.3.3 Synthesis of 2-hydroxyethyl 2'-methyl-2'-bromopropionate
Refer Section 8.2.2 for details.

8.3.4 Synthesis of PMMA-OH macroinitiator
A mixture of MMA (3.04 mL, 28.4 mmol), CuBr (68.0 mg, 0.474 mmol), PMDETA (0.104 mL, 0.474 mmol) and 2-hydroxyethyl 2'-methyl-2'-bromopropionate (0.100 g, 0.474 mmol) was added to a Schlenk flask and degassed by three freeze-pump-thaw cycles. The flask was then backfilled with argon and immersed in an oil bath at 100ºC for 44h. The reaction was stopped via exposure to air and diluted with THF before being passed through a column of basic alumina to remove the copper complex. The solution was then concentrated and precipitated into cold methanol with the precipitate being collected by filtration and dried for 16h in a desiccator to afford PMMA-OH macroinitiator (yield: 2.17 g; Mₙ = 23,100 g/mol, Mₘ/Mₙ = 1.51).

8.3.5 Synthesis of PSt-OH macroinitiator 10k
A mixture of St (3.26 mL, 28.4 mmol), CuBr (68.0 mg, 0.474 mmol), bpy (0.222 g, 1.42 mmol) and 2-hydroxyethyl 2'-methyl-2'-bromopropionate (0.100 g, 0.474 mmol)
was added to a Schlenk flask and degassed by three freeze-pump-thaw cycles. The flask was then backfilled with argon and immersed in an oil bath at 80ºC for 16h. The reaction was stopped via exposure to air and diluted with THF before being passed through a column of basic alumina to remove the copper complex. The solution was then concentrated and precipitated into cold methanol with the precipitate being collected by filtration and dried for 16h in a desiccator to afford PST-OH macroinitiator (yield: 2.12 g; $M_n = 10,700$ g/mol, $M_w/M_n = 1.09$).

8.3.6 Synthesis of PST-OH macroinitiator 7k
A mixture of St (3.26 mL, 28.4 mmol), CuBr (68.0 mg, 0.474 mmol), PMDETA (99.3 μL, 0.474 mmol) and 2-hydroxyethyl 2'-methyl-2'-bromopropionate (0.100 g, 0.474 mmol) was added to a Schlenk flask and degassed by three freeze-pump-thaw cycles. The flask was then backfilled with argon and immersed in an oil bath at 80ºC for 16h. The reaction was stopped via exposure to air and diluted with THF before being passed through a column of basic alumina to remove the copper complex. The solution was then concentrated and precipitated into cold methanol with the precipitate being collected by filtration and dried for 16h in a desiccator to afford PST-OH macroinitiator (yield: 1.90 g; $M_n = 7,700$ g/mol, $M_w/M_n = 1.03$).

8.3.7 Synthesis of core-degradable CCS polymer
PST-OH macroinitiator (1.52 g, 0.142 mmol; $M_n = 10,700$ g/mol) was reacted with a mixture of Sn(Oct)$_2$ (0.023 mL, 0.071 mmol), BOD (0.321 g, 1.42 mmol) and toluene (7.1 mL) in a dry round bottom flask at 110ºC with a condenser and CaCl$_2$ drying tube attached. After 48h (87% BOD conversion) the reaction solution was filtered and precipitated into methanol with the precipitate being collected by filtration and dried under vacuum. ($M_n,_{CCS} = 214,800$ g/mol, $M_w/M_n = 1.18$, 55% arm conversion)

8.3.8 Hydrolysis of core-degradable CCS polymer
Fractionated CCS polymer (40.0 mg, $1.86 \times 10^{-7}$ mol) of was dissolved in 4 mL THF to which was added 0.3 mL H$_2$O and 0.1 mL 12 M HCl. Hydrolysis was carried out at 60ºC for 24h and then stopped by precipitating into cold methanol.
8.4 Experiments for Chapter 4

8.4.1 Materials
Stannous 2-ethylhexanoate (Sn(Oct)₂, 95%) and urea hydrogen peroxide adduct (98%) were purchased from Aldrich and used as received. Formic acid (99%, Ajax Finechem) and 2,2-bis(4-oxocyclohexyl)propane (Lomb Scientific) were also used as received. Tetrahydrofuran (THF) and toluene were distilled from sodium benzophenone ketyl and sodium metal under argon and stored over 4Å molecular sieves. Butanol (Merck) and ε-caprolactone (CL, 99+%) (Aldrich) were dried over CaH₂ for 24 hours and distilled under high vacuum prior to use. Deuterated solvents CDCl₃ (D, 99.8%) and D₂O (D, 99.9%) were purchased from Cambridge Isotope Laboratories while d₈-THF (D, 99.5%) was purchased from Aldrich and used as received.

8.4.2 Investigation of temperature dependence on kinetics of solution based ROP
A series of round bottom flasks were charged with a mixture of CL (1.30 g, 11.4 mmol), Sn(Oct)₂ (44.3 mg, 0.109 mmol), butanol (20.0 μL, 0.218 mmol), and toluene (11.4 mL). A condenser and CaCl₂ drying tube was attached to each of the flasks which were subsequently placed in oil baths set at designated temperatures (130ºC, 80ºC and 65ºC). 0.2 mL samples were taken at regular intervals and quenched immediately with 2 mL hexane to precipitate the polymer. These quenched solutions were subsequently filtered with a 0.4 μm syringe filter to remove the precipitated polymer and then stored in the fridge until they were ready to be analyzed. The extent of monomer conversion for these samples was determined via GC-MS using toluene as an internal reference, with a plot of ln([CL]₀/[CL]) vs time being used to determine the rate of polymerization.

8.4.3 Synthesis of 4,4'-bioxepanyl-7,7'-dione (BOD)
Refer Section 8.3.2.2 for details.
8.4.4 Synthesis of 2,2-bis(ε-caprolactone-4-yl)propane (BCP)

A solution of urea hydrogen peroxide (CO(NH₂)₂·H₂O₂) (8.16 g, 86.7 mmol) in 50 mL of formic acid (99%) was stirred at 23°C for 90 minutes. 2,2-Bis(4-oxocyclohexyl)propane (5.00 g, 21.2 mmol) was then slowly added over 5-10 minutes and stirred for a further 5h. The reaction was stopped by adding 200 mL of water to the mixture followed by extraction with chloroform. The organic fractions were collected, washed with a saturated aqueous sodium bicarbonate solution and dried with Na₂SO₄. The organic fraction was then concentrated and the solvent removed under reduced pressure to yield a white powder (4.72 g, 83%).

¹H NMR (400 MHz, CDCl₃), δ (ppm): 4.35 (R, R) 4.15 (S, R) (t, 2H, −CH₂OOC−), 2.73 (R, R) 2.57 (S, R) (t, 2H, −CH₂COO−), 2.01-1.90 (m, 2H, −CH₂CH₂OOC−), 1.66-1.52 (m, 2H, −CH₂CH₂COO−), 1.40 (q, 1H, −CHCH₂−), 0.80 (t, 3H, −CH₃).

¹³C NMR (100 MHz, CDCl₃), δ (ppm): 175.8 (C=O), 68.2 (−CH₂OOC−), 45.9 (−CH₂CH₂COO−), 37.9 (−C−), 33.2 (−CH₂COO−), 29.66 (R, R) 29.62 (S, R) (−CH₂CH₂OOC−), 23.01 (R, R) 22.98 (S, R) (−CHCH₂−), 20.4 (−CH₃).

MS (EI) m/z (rel. int.): 287 (0.7%), 207 (2.8), 191 (0.4), 155 (56.9), 137 (15.2), 125 (1.4), 119 (3.2), 114 (18.7), 109 (18.5), 95 (30.7), 86 (35.6), 67 (18.9), 55 (100.0).

FTIR (KBr): C=O νₘₐₓ = 1741 cm⁻¹.

8.4.5 Typical synthesis of fully degradable PCL/BOD CCS polymer

CL (2.00 g, 17.5 mmol) was added to a mixture of toluene (17.5 mL), butanol (30.8 μL, 0.337 mmol) and Sn(Oct)₂ (54.5 μL, 0.169 mmol). A condenser and CaCl₂ drying tube were attached to the flask which was then heated at 110°C with stirring. After 24h (CL conversion >99%; Mₙ = 5,300 g/mol) a solution of BOD (0.762 g, 3.37 mmol) in 3 mL chloroform was injected into the reaction mixture ([BOD]/[PCL] = 10) and left to react for a further 16h (86% BOD conversion). The reaction mixture was then cooled and the solvent removed under reduced pressure with the crude polymer being dissolved in THF and precipitated into methanol. The precipitate was collected by filtration and dried under vacuum. (Mₙ, CCS = 362,000 g/mol, Mₙ/Mₚ = 1.13, 85% arm conversion)
8.4.6 Synthesis of fully degradable PCL/BCP CCS polymer

CL (1.30 g, 11.4 mmol) was added to a mixture of toluene (11.4 mL), butanol (20.0 μL, 0.218 mmol) and Sn(Oct)2 (35.4 μL, 0.109 mmol) in a round bottom flask. A condenser and CaCl2 drying tube were attached to the flask which was then heated at 110°C with stirring. After 24h (CL conversion >99%; $M_n = 5100$ g/mol) a solution of BCP (0.602 g, 2.25 mmol) in 3 mL chloroform was injected into the reaction mixture ([BCP]/[PCL] = 10) and left to react for a further 48h (83% BCP conversion). The reaction mixture was then cooled and the solvent removed under reduced pressure, with the crude polymer being dissolved in THF and precipitated into methanol. The precipitate was collected by filtration and dried under vacuum. ($M_n, ccs = 335800$ g/mol, $M_w/M_n = 1.27$, 41% arm conversion)

8.4.7 Hydrolysis of fully degradable CCS polymers monitored via $^1$H NMR

Hydrolysis of the fully degradable CCS polymers was achieved by dissolving 40 mg of degradable polymer in 4 mL d8-THF to which was added 0.3 mL D2O and 0.1 mL 12 M HCl. Hydrolysis was carried out at 60°C for 24h with $^1$H NMR analysis of the reaction solution being used to monitor the extent of ester hydrolysis.

8.4.8 Two-stage high purity synthesis to form fully degradable CCS polymer with minimal star-star coupling

All reagents were purified by distillation just prior to use and transferred to a flame-dried round bottom flask under high purity argon. A mixture of CL (6.48 g, 56.8 mmol), butanol (0.100 mL, 1.09 mmol) and Sn(Oct)2 (0.177 mL, 0.546 mmol) in toluene (56.8 mL) was heated at 110°C under a continuous flow of argon with a CaCl2 drying tube attached to a condenser to eliminate atmospheric moisture. After 24h the reaction was stopped by precipitating into cold methanol, with the isolated polymer being dried under high vacuum for 5h and analyzed via GPC ($M_n = 6070$ g/mol, $M_w/M_n = 1.14$; yield = 5.97 g). The purified PCL (1.327 g, 0.2186 mmol) was subsequently resolubilized in dry toluene (11.36 mL) with a catalytic amount of Sn(Oct)2 (35.4 μL, 0.109 mmol) and heated to 110°C under a continuous flow of argon with a condenser and CaCl2 drying tube attached. A solution of BOD (0.494 g, 2.18 mmol) in 3 mL chloroform was then injected into the reaction mixture ([BOD]/[PCL] = 10) and left to react for a further 30h (90.8% BOD conversion). The
reaction mixture was then cooled and precipitated into methanol with the polymer being collected by filtration and dried under vacuum. \((M_n, CCS = 159,400 \text{ g/mol, } M_w/M_n = 1.24, 85\% \text{ arm conversion})\)

8.4.9 **Storage conditions for shelf life experiments**
Fully degradable CCS polymer was synthesized according Section 8.4.5 with a 1 mL sample of the final reaction solution being stored in an airtight sample vial and stored out of direct sunlight. The remaining reaction solution was diluted with THF and filtered through an alumina plug to remove any insolubles. Another sample was taken at this point and dried under high vacuum to remove all solvent, with this sample being stored in a similar manner to the reaction solution sample. The remaining polymer solution was precipitated into two different non-solvents (methanol and hexane) with the isolated polymer being divided and stored under different conditions (room temperature (25°C), low temperature (<2°C), under vacuum in a desiccator, and in THF (20 mg/mL)). After 38 days the samples were reanalyzed by GPC and then again after 4 months of storage.
8.5 Experiments for Chapter 5

8.5.1 Materials
2-Bromoisoobutyrylbromide (98%), anisole (anhydrous, 99.7%), copper (I) bromide (CuBr, 98%), 2,2'-bipyridine (bpy, 99%) and stannous 2-ethylhexanoate (Sn(Oct)₂, 95%) were purchased from Aldrich and used as received. Tetrahydrofuran (THF) and toluene were distilled from sodium benzophenone ketyl and sodium metal under argon and stored over 4Å molecular sieves. ε-Caprolactone (CL, Aldrich, 99+%), dichloromethane (99.8%, Merck) and triethylamine (99%, Ajax) were dried over CaH₂ for 24 hours and distilled prior to use. Methyl methacrylate (MMA, 99%), styrene (St, 99%), ethylene glycol dimethacrylate (EGDMA, 98%) and N, N, N', N', N''-pentamethyldiethylenetriamine (PMDETA, 99%) were all purchased from Aldrich and washed three times with 5% w/w aq. NaOH, once with water, then distilled from calcium hydride and stored at -5°C. p-Toluenesulfonyl chloride (TsCl, 99+%)(Aldrich) was dissolved in minimum chloroform, diluted with petroleum ether (bp 40-60°C), clarified with charcoal, filtered, concentrated and collected by filtration.

8.5.2 Synthesis of 2-hydroxyethyl 2'-methyl-2'-bromopropionate
Refer Section 8.2.2 for details.

8.5.3 Synthesis of 4,4'-bioxepanyl-7,7'-dione (BOD)
Refer Section 8.3.2.2 for details.

8.5.4 Typical synthesis of PCL-Br macroinitiator
A round bottom flask was charged with a mixture of CL (9.00 g, 78.9 mmol), Sn(Oct)₂ (0.743 g, 1.83 mmol), 2-hydroxyethyl 2'-methyl-2'-bromopropionate (0.774 g, 3.67 mmol) and toluene (80 mL). A condenser and CaCl₂ drying tube were attached to the flask which was heated to 110°C with vigorous stirring. After 24h the reaction was stopped and precipitated into cold methanol with the precipitate being collected by filtration and dried for 16h in a desiccator to yield PCL-Br macroinitiator (yield: 7.78 g; Mₙ = 4,600 g/mol, Mₘ/Mₙ = 1.11).
8.5.5 Synthesis of PMMA-Cl macroinitiator
A mixture of MMA (1.95 mL, 18.2 mmol), CuBr (93.2 mg, 0.650 mmol), bpy (0.305 g, 1.95 mmol), TsCl (0.124 g, 0.650 mmol) and anisole (2.60 mL) was added to a Schlenk flask and degassed by three freeze-pump-thaw cycles. The flask was then backfilled with argon and immersed in an oil bath at 100°C. After 48h (87% MMA conversion) the reaction was stopped via exposure to air and diluted with THF before being passed through a column of basic alumina to remove the copper complex. The solution was then concentrated and precipitated into cold methanol with the precipitate being collected by filtration and dried for 16h in a desiccator to yield PMMA-Cl macroinitiator (yield: 1.51 g; $M_n = 7,500$ g/mol, $M_w/M_n = 1.08$).

8.5.6 Synthesis of HO-PSt-Br macroinitiator
A mixture of St (3.26 mL, 28.4 mmol), CuBr (68.0 mg, 0.474 mmol), PMDETA (99.3 μL, 0.474 mmol) and 2-hydroxyethyl 2'-methyl-2'-bromopropionate (0.100 g, 0.474 mmol) was added to a Schlenk flask and degassed by three freeze-pump-thaw cycles. The flask was then backfilled with argon and immersed in an oil bath at 80°C for 16h. The reaction was stopped via exposure to air and diluted with THF before being passed through a column of basic alumina to remove the copper complex. The solution was then concentrated and precipitated into cold methanol with the precipitate being collected by filtration and dried for 16h in a desiccator to afford HO-PSt-Br macroinitiator (yield: 1.90 g; $M_n = 7,700$ g/mol, $M_w/M_n = 1.03$).

8.5.7 Synthesis of PCL-$b$-PMMA-Br macroinitiator
PCL-Br macroinitiator (1.00 g, 0.217 mmol; $M_n = 4,600$ g/mol) was added to a round bottom flask and dissolved in 10 mL of anisole. A mixture of CuBr (35.9 mg, 0.250 mmol), PMDETA (52.4 μL, 0.250 mmol) and MMA (1.23 mL, 11.5 mmol) was added to the reaction solution and purged with argon for 2h. The flask was then sealed and heated at 100°C for 1h. The reaction was stopped (MMA conversion = 53%) by quenching in liquid nitrogen and diluted with THF before being passed through a column of basic alumina to remove the copper complex. The product was isolated by precipitation into cold methanol and dried in a desiccator for 16h (yield: 0.711 g; $M_n = 8,300$ g/mol, $M_w/M_n = 1.07$).
8.5.8 Synthesis of PCL/EGDMA CCS

PCL-Br macroinitiator (3.20 g, 0.696 mmol; \(M_n = 4,600 \text{ g/mol}\)) was reacted with a mixture of CuBr (0.115 g, 0.800 mmol), PMDETA (0.168 mL, 0.800 mmol), EGDMA (1.74 mL, 9.23 mmol) and anisole (80 mL) in a Schlenk flask and degassed by three freeze-pump-thaw cycles. The flask was then backfilled with argon and immersed in an oil bath at 100\(^\circ\)C. After 21h (80% EGDMA conversion) the reaction was stopped and fractionally precipitated into methanol with the polymer being collected and dried under vacuum (\(M_n,\text{CCS} = 152,300 \text{ g/mol}, \frac{M_w}{M_n} = 1.18\), 60% arm conversion). The polymer was then fractionally precipitated by re-dissolving it in a minimal amount of THF and slowly adding methanol, with the separate fractions being analyzed by GPC to obtain pure CCS polymer.

8.5.9 Synthesis of miktoarm CCS polymer

8.5.9.1 ‘In-out’ approach

The fractionated PCL/EGDMA CCS polymer synthesized in Section 8.5.8 (0.20 g, 0.024 mmol arms; \(M_n = 152,300 \text{ g/mol}\)) was used to initiate ATRP chain extension from the core via reaction with a mixture of MMA (4.71 mL, 44.0 mmol), CuBr (31.6 mg, 0.220 mmol) and PMDETA (46.1 \(\mu\)L, 0.220 mmol). Argon was bubbled through the reaction solution for 2h and then the vessel was sealed and immersed in an oil bath at 100\(^\circ\)C. The reaction was stopped after 210 minutes by exposure to air and precipitated into methanol with the precipitate being collected by filtration and dried under vacuum (\(M_n = 277,900 \text{ g/mol}, \frac{M_w}{M_n} = 1.33\)).

8.5.9.2 ‘Simultaneous cross-linking’ approach

A mixture of PCL-Br macroinitiator (0.250 g, 0.110 mmol; \(M_n = 2,300 \text{ g/mol}\) and PMMA-Cl macroinitiator (0.825 g, 0.110 mmol; \(M_n = 7,500 \text{ g/mol}\) was reacted with CuBr (24.7 mg, 0.172 mmol), PMDETA (36.0 \(\mu\)L, 0.172 mmol), EGDMA (0.374 mL, 1.98 mmol) and anisole (17 mL) in a Schlenk flask. The flask was degassed by three freeze-pump-thaw cycles and backfilled with argon before being immersed in an oil bath at 100\(^\circ\)C. After 68h (80% EGDMA conversion) the reaction was stopped via exposure to air and diluted with THF before being passed through a column of basic alumina to remove the copper complex. The solution was then concentrated and precipitated into methanol with the precipitate being collected by filtration and dried.
under vacuum. \(M_n, \text{CCS} = 559,600 \text{ g/mol, } M_w/M_n = 1.24\), 28% combined arm conversion)

8.5.10 Synthesis of block copolymer arm CCS polymer

8.5.10.1 Block copolymer method

A round bottom flask was charged with a mixture of PCL-\(b\)-PMMA-Br macroinitiator (0.300 g, 0.0361 mmol; \(M_n = 8,300 \text{ g/mol}\)), CuBr (6.7 mg, 0.047 mmol), PMDETA (9.8 \(\mu\text{L}, 0.047 \text{ mmol}\)), EGDMA (0.102 mL, 0.542 mmol) and anisole (4.7 mL) and purged with argon for 2h. The reaction vessel was then sealed and immersed in an oil bath at 100ºC. After 48h (70% EGDMA conversion) the reaction was stopped via exposure to air and fractionally precipitated into methanol to remove any unreacted macroinitiator. The precipitate was collected by filtration and dried under vacuum \(M_n, \text{CCS} = 226,200 \text{ g/mol, } M_w/M_n = 1.18\), 10% arm conversion).

8.5.10.2 ROP chain extension method

HO-PSt-Br macroinitiator (0.500 g, 0.0649 mmol; \(M_n = 7,700 \text{ g/mol}\)) was reacted with a mixture of CuBr (12.1 mg, 0.084 mmol), PMDETA (35.2 \(\mu\text{L}, 0.168 \text{ mmol}\)), EGDMA (0.183 mL, 0.970 mmol) and anisole (8.4 mL) in a Schlenk flask and degassed by three freeze-pump-thaw cycles. The flask was then backfilled with argon and immersed in an oil bath at 100ºC. After 46h (82% EGDMA conversion) the reaction was stopped and fractionally precipitated into methanol with the polymer being collected and dried under vacuum \(M_n, \text{CCS} = 265,700 \text{ g/mol, } M_w/M_n = 1.16\), 45% arm conversion). The hydroxyl surface functional CCS polymer (0.151 g, 0.012 mmol arms) was then used to initiate ROP chain extension via reaction with a mixture of CL (0.127 mL, 1.15 mmol), Sn(Oct)\(_2\) (0.002 mL, 0.006 mmol) and toluene (1.15 mL) in a dry round bottom flask at 110ºC with a condenser and CaCl\(_2\) drying tube attached. After 24h (>99% CL conversion) the reaction solution was precipitated into methanol with the precipitate being collected by filtration and dried under vacuum \(M_n = 544,400 \text{ g/mol, } M_w/M_n = 1.25\).
8.5.10.3 ATRP chain extension method

PCL-Br macroinitiator (2.57 g, 0.559 mmol; $M_n = 4,600$ g/mol) was added to a mixture of Sn(Oct)$_2$ (70.8 $\mu$L, 0.219 mmol), BOD (0.988 g, 4.37 mmol) and toluene (22.7 mL). A condenser and CaCl$_2$ drying tube were attached to the flask which was then heated at 110ºC with stirring. After 31h (81% BOD conversion) the reaction was stopped by quenching in liquid nitrogen and the solvent removed under reduced pressure. The crude polymer was dissolved in THF and fractionally precipitated into methanol with the precipitate being collected and dried under vacuum ($M_n$, CCS = 179,400 g/mol, $M_w/M_n = 1.15$, 68% arm conversion). The alkyl bromide surface functional CCS polymer (0.05 g, 0.007 mol arms) was then used to initiate ATRP chain extension via reaction with a mixture of MMA (1.60 mL, 14.9 mmol), CuBr (10.7 mg, 0.0746 mmol) and PMDETA (15.6 $\mu$L, 0.0746 mmol). Argon was bubbled through the reaction solution for 2h and then the vessel was sealed and immersed in an oil bath at 100ºC. The reaction was stopped after 45 minutes by exposure to air and precipitated into methanol with the precipitate being collected by filtration and dried under vacuum ($M_n = 618,500$ g/mol, $M_w/M_n = 1.24$).

8.5.11 Synthesis of miktoarm/block copolymer arm CCS polymer

The fractionated PCL/EGDMA CCS polymer synthesized in Section 8.5.8 (0.50 g, 0.061 mmol arms; $M_n = 152,300$ g/mol) was dissolved in a mixture of dichloromethane (40 mL) and triethylamine (0.754 mL, 5.44 mmol) to which 2-bromoisobutyrylbromide (0.673 mL, 5.44 mmol) was slowly added under argon. The reaction was stirred at 25ºC for 18h and then precipitated twice into methanol to purify. The alkyl bromide core/surface functionalized CCS polymer (0.20 g, $M_n = 155,000$ g/mol, 0.024 mmol arms) was then used to initiate ATRP chain extension via reaction with a mixture of MMA (4.71 mL, 44.0 mmol), CuBr (31.6 mg, 0.220 mmol) and PMDETA (46.1 $\mu$L, 0.220 mmol). Argon was bubbled through the reaction solution for 2h and then the vessel was sealed and immersed in an oil bath at 100ºC. The reaction was stopped after 30 minutes by exposure to air and precipitated into methanol with the precipitate being collected by filtration and dried under vacuum ($M_n = 514,600$ g/mol, $M_w/M_n = 1.26$).
8.5.12 Typical hydrolysis conditions

In a typical hydrolysis reaction 40 mg of degradable polymer was dissolved in 4 mL THF to which was added 0.3 mL H₂O and 0.1 mL 12 M HCl. Hydrolysis was carried out at 60°C for 24h, with the unhydrolyzed polymer being isolated via precipitation into methanol.
8.6 Experiments for Chapter 6

8.6.1 Materials
Anisole (anhydrous, 99.7%), copper (I) bromide (CuBr, 98%), 2,2'-bipyridine (bpy, 99%), methacryloyl chloride (97%), chlorotrimethylsilane (98%), 2-propyn-1-ol (99%), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 98%), tetra-n-butyl ammonium fluoride (TBAF, 1M solution in THF) and stannous 2-ethylhexanoate (Sn(Oct)2, 95%) were all purchased from Aldrich and used as received. Acetic acid (99.8%, Merck), N,N-dimethylformamide (DMF, 99.8%, Merck), sodium azide (NaN3, 99%, Chem-Supply) and silver chloride (AgCl, 99.5%, Fluka) were also used as received. Tetrahydrofuran (THF) and toluene were distilled from sodium benzophenone ketyl and sodium metal under argon and stored over 4Å molecular sieves. ε-Caprolactone (CL, Aldrich, 99+%), dichloromethane (99.8%, Merck), diethyl ether (99%, Merck) and triethylamine (99%, Ajax) were dried over CaH2 for 24 hours and distilled prior to use. Styrene (St, 99%) and N,N,N',N',N"-pentamethyldiethylenetriamine (PMDETA, 99%) were purchased from Aldrich and washed three times with 5% w/w aq. NaOH, once with water, then distilled from calcium hydride and stored at -5°C.

8.6.2 Synthesis of 2-hydroxyethyl 2'-methyl-2'-bromopropionate
Refer Section 8.2.2 for details.

8.6.3 Synthesis of 4,4'-bioxepanyl-7,7'-dione (BOD)
Refer Section 8.3.2.2 for details.

8.6.4 Synthesis of PSt-N3
A mixture of St (3.26 mL, 28.4 mmol), CuBr (68.0 mg, 0.474 mmol), bpy (0.222 g, 1.42 mmol) and 2-hydroxyethyl 2'-methyl-2'-bromopropionate (0.100 g, 0.474 mmol) was added to a Schlenk flask and degassed by three freeze-pump-thaw cycles. The flask was then backfilled with argon and immersed in an oil bath at 80°C for 16h. The reaction was stopped via exposure to air and diluted with THF before being passed through a column of basic alumina to remove the copper complex. The solution was then concentrated and precipitated into cold methanol with the precipitate being collected by filtration and dried for 16h in a desiccator to afford linear PSt-Br (yield:
2.09 g; \( M_n = 10,400 \text{ g/mol}, M_w/M_n = 1.02 \). The PSt-Br polymer (1.50 g, 0.144 mmol) was subsequently reacted with an excess of sodium azide (0.110 g, 1.69 mmol) in DMF (5 mL) at 25 °C. After 42 hours the reaction was stopped and precipitated into methanol, with the filtrate being washed repeatedly with distilled water to remove any unreacted sodium azide. The precipitate was subsequently dried under vacuum. (yield: 1.44 g; FTIR: \( \nu_{\max} = 2094 \text{ cm}^{-1} \))

8.6.5 Synthesis of propargyl methacrylate (PgMA)

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \equiv & \quad \text{H} \\
\end{align*}
\]

Methacryloyl chloride (6.19 g, 59.2 mmol) in ether (10 mL) was added dropwise to a mixture of 2-propyn-1-ol (3.00 g, 53.5 mmol) and triethyl amine (14 mL, 0.10 mol) in ether (30 mL) at 0°C over a period of 30 minutes under nitrogen. The mixture was stirred at room temperature overnight and filtered to remove triethylamine hydrochloride. The filtrate was washed with 2M HCl, saturated aqueous NaHCO₃, and water and then dried over anhydrous MgSO₄. After concentration of the ether solution, vacuum distillation from CaH₂ gave a colorless liquid of propargyl methacrylate (yield: 3.62 g).

\(^1\)H NMR (400 MHz, CDCl₃), \( \delta \) (ppm): 6.16 (m, 1H, C=CH₂ \text{ trans}), 5.61 (m, 1H, C=CH₂ \text{ cis}), 4.73 (d, 2H, −COOCH₂−), 2.47 (t, 1H, −C=CH), 1.95 (m, 3H, −CH₃).

\(^{13}\)C NMR (100 MHz, CDCl₃), \( \delta \) (ppm): 166.1 (C=O), 135.2 (C=CH₂), 126.2 (C=CH₂), 77.4 (−C=CH), 74.4 (−C=CH), 51.8 (−COOCH₂−), 17.9 (−CH₃).

MS (EI) m/z (rel. int.): 124 (M⁺, 0.9%), 95 (9.7), 77 (10.1), 69 (100.0), 55 (8.0).

FTIR (KBr): C=C \( \nu_{\max} = 2186 \text{ cm}^{-1} \), C=O \( \nu_{\max} = 1719 \text{ cm}^{-1} \).

8.6.6 Synthesis of (trimethylsilyl)propargyl methacrylate (TMS-PgMA)

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \equiv & \quad \text{Si} \\
\end{align*}
\]

A method for TMS protection of acetylene functionality was taken from the literature.\(^{[4]}\) Silver chloride (0.387 g, 2.70 mmol) was suspended in 40 mL of dry
dichloromethane and to this suspension was added propargyl methacrylate (3.62 g, 29.2 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (5.67 g, 37.3 mmol). The reaction mixture was then heated to 40°C and chlorotrimethylsilane (4.49 g, 41.4 mmol) added dropwise. After stirring for 24 hours at 40 °C the mixture was cooled to room temperature and diluted with 200 mL of n-hexane. The organic phase was washed successively with saturated aqueous NaHCO₃, 2M HCl and water. The extracts were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude product was then distilled under high vacuum (<3 mm Hg) to give (trimethylsilyl)propargyl methacrylate as a colorless liquid (yield: 3.76 g).

¹H NMR (400 MHz, CDCl₃), δ (ppm): 6.17 (m, 1H, C=CH₂ trans), 5.61 (m, 1H, C=CH₂ cis), 4.75 (d, 2H, −COOCH₂−), 1.96 (m, 3H, −CH₃), 0.18 (s, 9H, −Si(CH₃)₃).

¹³C NMR (100 MHz, CDCl₃), δ (ppm): 166.5 (C=O), 135.7 (C=CH₂), 126.4 (C=CH₂), 99.1 (−CH₂C≡C–), 94.7 (−CH₂C≡C–), 52.9 (−COOCH₂−), 18.3 (−CH₃), -0.3 (−Si(CH₃)₃).

MS (EI) m/z (rel. int.): 196 (M⁺, 13.2%), 181 (15.2), 166 (6.6), 163 (10.1), 153 (33.7), 143 (12.9), 137 (15.3), 127 (98.7), 109 (44.4), 105 (23.9), 97 (42.9), 83 (78.2), 73 (100.0), 69 (95.3), 59 (75.8), 55 (34.7).

FTIR (KBr): C≡C νmax = 2241 cm⁻¹, C=O νmax = 1725 cm⁻¹.

8.6.7 Typical synthesis of PCL-Br macroinitiator
A round bottom flask was charged with a mixture of CL (9.00 g, 78.9 mmol), Sn(Oct)₂ (0.743 g, 1.83 mmol), 2-hydroxyethyl 2'-methyl-2'-bromopropionate (0.774 g, 3.67 mmol) and toluene (80 mL). A condenser and CaCl₂ drying tube were attached to the flask which was heated to 110°C with vigorous stirring. After 24h the reaction was stopped and precipitated into cold methanol with the precipitate being collected by filtration and dried for 16h in a desiccator to yield PCL-Br macroinitiator (yield: 7.78 g; Mₙ = 4,600 g/mol, Mₓ/Mₙ = 1.11).

8.6.8 Typical synthesis of PCL-b-P(TMS-PgMA)-Br macroinitiator
PCL-Br macroinitiator (2.00 g, 0.434 mmol; Mₙ = 4,600 g/mol) was added to a Schlenk flask and dissolved in 14.5 mL of anisole. A mixture of CuBr (62.3 mg, 0.434 mmol), PMDETA (0.182 mL, 0.869 mmol) and TMS-PgMA (4.263 g, 21.71 mmol) was added with the reaction mixture which was subsequently degassed by three freeze-pump-thaw cycles. The flask was then backfilled with argon and heated
at 85°C for 21h. The reaction was stopped (TMS-PgMA conversion = 77%) by exposing to air and diluting with THF before being passed through a column of basic alumina to remove the copper complex. The reaction solution was subsequently concentrated under vacuum and precipitated into cold methanol, with the isolated polymer being collected by vacuum filtration and dried in a desiccator for 16h (yield: 3.269 g; $M_n = 14,100$ g/mol, $M_w/M_n = 1.19$).

8.6.9 Deprotection of PCL-$b$-P(TMS-PgMA)-Br macroinitiator
Deprotection of the acetylene functionality was achieved according to a literature method.[5] PCL-$b$-P(TMS-PgMA) macroinitiator (67.3 mg, 0.188 mmol based on alkyne-trimethylsilyl groups; $M_n = 13,500$ g/mol) and acetic acid (16.1 μL, 0.282 mmol) were dissolved in THF (5 mL). Argon was bubbled through the solution for 10 minutes which was cooled to 0°C. A 0.2 M solution of TBAF in THF (1.41 mL 0.282 mmol) was added slowly via syringe with vigorous stirring, with the resulting solution being kept at 0°C for 30 minutes before being allowed to warm to ambient temperature. The reaction solution was stirred for a further 18h before being concentrated under reduced pressure and precipitated into methanol twice to purify. The isolated polymer was dried under vacuum with $^1$H NMR analysis confirming 100% removal of the trimethylsilyl protecting groups and no degradation of the PCL backbone (yield: 35.8 mg; $M_n = 10,300$ g/mol, $M_w/M_n = 1.15$).

8.6.10 Grafting of PST-N$_3$ onto PCL-$b$-PPgMA-Br via Cu(I) catalyzed cycloaddition reaction
The ‘click coupling’ reaction between the acetylene and azido functionalities was performed using standard conditions reported in the literature.[6] A mixture of PST-N$_3$ (0.685 g, $6.59 \times 10^{-5}$ mol; $M_n = 10,400$ g/mol) and PCL-$b$-PPgMA-Br (12.0 mg, $4.39 \times 10^{-5}$ mol of acetylene groups; $M_n = 10,300$ g/mol) was dissolved in DMF (1.0 mL) which was subsequently degassed by bubbling argon through it for 10 minutes. A previously degassed solution of CuBr (4.7 mg, $3.3 \times 10^{-5}$ mol) and PMDETA (6.8 μL, $3.3 \times 10^{-5}$ mol) in DMF (0.5 mL) was added to the reaction solution under a constant flow of argon and stirred vigorously. 0.1 mL samples were periodically taken for GPC analysis with the reaction being stopped after 22h by exposing to air and fractionally precipitating into methanol ($M_n = 334,200$ g/mol, $M_w/M_n = 1.08$).
8.6.11 Synthesis of acetylene functional CCS polymer

PCL-\text{-}b-\text{-}P(\text{TMS-}\text{PgMA})-\text{Br} macroinitiator (3.00 g, 0.213 mmol; $M_n = 14,100$ g/mol) was added to a mixture of Sn(Oct)$_2$ (46.2 $\mu$L, 0.143 mmol), BOD (0.643 g, 2.85 mmol) and toluene (14.8 mL). A condenser and CaCl$_2$ drying tube were attached to the flask which was then heated at 110ºC with stirring. After 45h (>99% BOD conversion) the reaction was stopped by taking it off the heat and removing the solvent under reduced pressure. The crude polymer was dissolved in THF and fractionally precipitated into methanol with the precipitate being collected and dried under vacuum ($M_{n,\text{ CCS}} = 774,800$ g/mol, $M_w/M_n = 1.10$, 50% arm conversion). The fractionated CCS polymer (1.25 g, 3.01 mmol based on alkyne-trimethylsilyl groups) and acetic acid (0.136 mL, 2.38 mmol) were dissolved in THF (60 mL) and argon bubbled through the solution for 15 minutes which was cooled to 0ºC. A 0.2 M solution of TBAF in THF (11.9 mL 2.38 mmol) was added slowly via syringe with vigorous stirring, with the resulting solution being kept at 0ºC for 30 minutes before being allowed to warm to ambient temperature. The reaction solution was stirred for a further 15h before being concentrated under reduced pressure and precipitated into methanol twice to purify. The isolated polymer was dried under vacuum with $^1$H NMR analysis confirming 100% removal of the trimethylsilyl protecting groups and no degradation of the PCL backbone (yield: 0.919 g; $M_n = 617,200$ g/mol, $M_w/M_n = 1.06$).

8.6.12 Grafting of PSt-N$_3$ onto acetylene functional CCS polymer via Cu(I) catalyzed cycloaddition reaction

A mixture of PSt-N$_3$ (70.0 mg, $6.73 \times 10^{-6}$ mol; $M_n = 10,400$ g/mol), CuBr (6.2 mg, $4.3 \times 10^{-5}$ mol) and PMDETA (9.0 $\mu$L, $4.3 \times 10^{-5}$ mol) was dissolved in DMF (1.0 mL) which was subsequently degassed by bubbling argon through it for 10 minutes. A previously degassed solution of fractionated acetylene functional CCS polymer (64.6 mg, 0.195 mmol of acetylene groups (based on theory); $M_n = 617,200$ g/mol) in DMF (1.5 mL) was slowly added to the reaction solution over a period of 15 minutes under a constant flow of argon and vigorous stirring. 0.1 mL samples were periodically taken for GPC analysis with the reaction being stopped after 150 minutes by exposing to air and fractionally precipitating into methanol ($M_n = 6,138,000$ g/mol, $M_w/M_n = 1.20$).
8.6.13 Hydrolysis of PSt grafted (brush arm) CCS polymer

36.4 mg of fractionated brush arm CCS polymer ($M_n = 6,138,000$ g/mol) was dissolved in 2 mL THF to which was added 0.15 mL H$_2$O and 0.05 mL 12 M HCl. Hydrolysis was carried out at 60$^\circ$C for 24h, with the unhydrolyzed polymer being isolated via precipitation into methanol ($M_n = 163,400$ g/mol, $M_W/M_n = 1.65$).

8.7 References


