Synthesis of α,ω-telechelics by Cu(0)-mediated reversible deactivation radical polymerisation

Alexandre Simula

A thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy in Chemistry

Department of Chemistry

University of Warwick

September 2015

"We are all in the gutter, but some of us are looking at the stars"

Oscar Wilde, *Lady Windermere's fan*

"Vous qui aimez la gloire, soignez votre tombeau; couchez vous y bien; tâchez d'y faire bonne figure car vous y resterez"

François-René, Vicomte de Chateaubriand, *Mémoires d'Outre tombe*.

"C'est au pied du mur, qu'on voit mieux le mur"

Jean-Marie Bigard, *Les expressions*

"… That's because you're stupid!..."

Vasiliki Nikolaou

Table of content

List of figures

List of tables

List of schemes

Abbreviations

AIBN	2,2'-azobis(2-methyproprionitrile)
AGET	Activators generated by electron transfer
AN	Acrylonitrile
ARGET	Activators regenerated by electron transfer
ATRA/C	Atom transfer radical addition/coupling
ATRP	Atom transfer radical polymerisation
n-BA	*n*-Butyl acrylate
BiPy	Bipyridine
BPO	Dibenzoyl peroxide
CCTP	Catalytic chain transfer polymerisation
$CDCl_3$	Deuterated chloroform
CLRP	Controlled/*"living"* radical polymerisation
CoBF	Cobalt(II) dimethylglyoxime-difluoroboryl complex
CTA	Chain transfer agent
C_{tr}	Chain transfer constant
D_2O	Deuterium oxide
DCTB	trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene]malonitrile

DLS	Dynamic light scattering
DEA	*N*,*N*-diethylacrylamide
DMA	*N*,*N*-dimethylacrylamide
DMAEMA	*N*,*N*-dimethyl(aminoethyl) methacrylate
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DOSY	Diffusion-ordered spectroscopy
DP_n	Degree of polymerisation
ESI-MS	Electron-spray ionisation mass spectrometry
EtOH	Ethanol
FRP	Free radical polymerisation
FT-IR	Fourier transformed Infrared spectroscopy
GTP	Group transfer polymerisation
HMTETA	1,1,4,7,10-hexamethyltriethylenetetramine
I	Initiator
ICAR ATRP	Initiators for continuous activator regeneration atom transfer radical polymerisation
Iniferter	Initiator-transfer agent-terminator
IPA	2-isopropanol
ISET	Inner-sphere electron transfer

k_i	Initiation rate constant
k_p	Propagation rate constant
k_t	Termination rate constant
k_{act}	Activation rate constant
k_{add}	Addition rate constant
k_β	β-scission rate constant
k_d	Decomposition rate constant
k_{tr}	Chain transfer rate constant
L	Ligand
LAM	Less activated monomer
LCST	Lower critical solution temperature
LRP	*"Living"* radical polymerisation
M	Monomer
M_n	Number average molecular weight
M_p	Peak molecular weight; molecular weight of the highest peak
M_w	Weight average molecular weight
MALDI	Matrix-assisted LASER desorption ionisation
MAM	More activated monomer
MEMA	2-*N*-morpholinoethyl methacrylate
Me_4-Cyclam	1,4,8,11-tetraaza-1,4,8,11-tetramethylcyclotetradecane

Me_6-TREN	*N,N,N',N',N'',N''*-hexamethyl-[tris(aminoethyl)amine]
MeOD	Deuterated methanol
MeOH	Methanol
MPC	2-methacryloyloxyethyl phosphorylcholine
MS	Mass spectrometry
Mt^m	Transition-metal at oxidation state m; m an integer.
MTS	[1-methoxy-2-methyl-1-propenyl)-oxy] trimethylsilane
MW	Molecular weight; molar mass.
MWCO	Molecular weight cut-off
MWD	Molecular weight distribution
NIPAAm	*N*-isopropylacrylamide
NIR	Near Infrared
NMR	Nuclear magnetic resonnance
NMP	Nitroxide-mediated polymerisation
OSET	Outer sphere electron transfer
P_n	Polymer chain with degree of polymerisation n
PDEA	Poly(*N*,*N*-diethylacrylamide)
PDMA	Poly(*N*,*N*-dimethylacrylamide)
PDMAEMA	Poly(*N*-dimethyl(aminoethyl) methacrylate)
PEG	Poly(ethylene glycol)

$PEGA_{480}$	Poly(ethylene glycol) methyl ether acrylate av. M_n= 480 g.mol^{-1}
$PEGMA_{475}$	Poly(ethylene glycol) methyl ether methacrylate av. M_n= 475 g.mol^{-1}
$PEGMA_{1100}$	Poly(ethylene glycol) methyl ether methacrylate av. M_n= 1100 g.mol^{-1}
PMDETA	*N*,*N*,*N'*,*N''*,*N''*-pentamethyldiethylenetriamine
PNIPAAm	Poly(*N*-isopropylacrylamide)
$PPEGA_{480}$	Poly[poly(ethylene glycol) methyl ether acrylate]
$PPEGMA_{475}$	poly[poly(ethylene glycol) methyl ether methacrylate]
PRE	Persistant radical effect
PS	Poly(styrene)
PVA	Poly(vinyl alcohol)
PVC	Poly(vinyl chloride)
RA	Reducing agent
RAFT	Reversible addition-fragmentation chain transfer polymerisation
RDRP	Reversible deactivation radical polymerisation
ROP	Ring-opening polymerisation
SA	Supplementary activator
SARA ATRP	Supplementary activator and reducing agent atom transfer radical polymerisation

SBMA	[2-(methacryloyloxy)ethyl]dimethyl-(3-sulfopropyl)ammonium hydroxide
SEC	Size exclusion chromatography
SET-LRP	Single electron transfer *"living"* radical polymerisation
T_{cp}	Cloud point temperature
T_g	Glass transition temperature
T_m	Melting temperature
TEA	Triethylamine
TEM	Transmission electron microscopy
TEMPO	2,2,6,6-tetramethylpiperydynyl-1-oxy
TMM-RDRP	Transition-metal mediated reversible deactivation radical polymerisation
ToF	Time-of-flight
TPMA	Tris(2-pyridylmethyl)amine
TREN	Tris(2-aminoethyl) amine
UV-Vis	Ultraviolet-visible
VC	Vinyl chloride

Acknowledgments

I guess it will be hard to acknowledge everyone here, though I'll try to do my best to thank the people who made this PhD, and other moments, what they have been, and perhaps more importantly, made me who I am today.

First, I would start by thanking Pr. David M. Haddleton for giving me the opportunity to come and work in his group in the first place and further pursue a PhD. I can't thank him enough for trusting me enough and offer this PhD position, which made the journey better than I would ever anticipate, and gave me opportunities that I could only dream of. I would like to thank him for his supervision, his "just do it" attitude, his trust hopefully, for being a good person and for everything he has done for me.

I'd like to thank Lubrizol for funding and also the people that I've met there. First I'll thank Dr. Mark Paczkowski, my supervisor in Lubrizol, for his constant help and guidance throughout those years, which made my project more and more interesting and so diverse! I'd also like to thank Dr. Nancy Merchant, Dr. David Moreton, Dr. Tim Smith and Dr. Robert Graf for being so welcoming and for their kind words during meetings and so on. Then, I'd like to thank Dr. Stuart Richards and Dr. Andrew Shooter for being so nice and for asking me tricky questions with such a great smile in conferences.

I will go back in time and thank chronologically the people who made this journey possible. First, I'd like to thank to Pr. Sebastien Lecommandoux, in Bordeaux who welcomed me in his group as a master student. His help, in addition to Dr. C. Schatz changed my path in a way I couldn't imagine. Indeed, Seb, "just" by talking to Dr. Remzi C. Becer, who was Dave's postdoc at the time, introduced me, and Remzi invited me (thank you so much) to come and work in the group in Warwick for 9 months. The experience of being a master student in this group has been extremely enjoyable, thanks to amazing people. I'll thank Dr. Florence Gayet, who helped me so much adapting to the lab/brit life and was, obviously, the

official Google translate for chemicals and glassware. I'd like to thank her for her constant kind words during my PhD, which helped me to keep on going. Then, I will thank Dr. Mathew W. Jones who is, still today, the best chemist I had the chance to work with (no offence). His constant help in any type of chemistry made me actually enjoy chemistry in a way I didn't know before and I couldn't have pursued a PhD if it wasn't for his help and guidance. In addition to the chemistry book that he is, he proved to be extremely useful for my ability to understand someone with a Welsh accent! Following Mat, I'd like to thank Stacy, James, Ant and Kay for being so amazing during this master; who made me want to come back, if it wasn't for the weather, for the people and the group itself.

At the start of my PhD, although plenty of people had left, I could count on someone who proved to be so important for the lab/not lab life, Dr. Jamie "ledge" Godfrey. I'd like to thank him for his views on rugby, pubs, whisky, pubs, awful caps no one should wear in public, pubs, GPC and chemistry from time to time, jokes, pubs, and so on. I'd also like to thank Dr. Qiang Zhang (hopefully soon to be Pr.) who has been a constant source of inspiration for excellence, hard work and modesty. His own investigations and ideas helped, in so many aspects, the way my PhD went and I'd like to thank him for that.

Among the new people who arrived during my PhD time, one of them stands out from the crowd, my dear friend Vasiliki. I am so delighted to see how much she has achieved in her PhD. I am extremely impressed by what she managed to do in hard times and she deserves more than a PhD for what she's done. She has been (and still is) a tremendous friend during those years, from early in the morning to extremely late at night. I can't thank her enough for all the laughs, all the help, all the Domino's, all the whatever during those 3 years. Obviously, I'll thank Chris for being so supportive and for helping her carry on!! Gladly, she also introduced me to some Greek words, which proved to be extremely useful when talking to other greats, namely malaka George, malaka Nikos, jooon Gabit and mori Athina.

Athina, by herself, changed the course of my PhD tremendously. Although at the beginning it wasn't that easy to talk to each other, mainly due to my ability to be stubborn, and/or also the look in the mirror, our exchanges helped me in such a way that I couldn't be more grateful. She spent so much time and dedication trying to teach me how to write properly, design specific experiments and arguing over whatever that the "success" of this PhD wouldn't have been the same without her, definitely not. Then, I'd like to thank Dr. Paul Wilson, for his corrections, help and questions during this PhD, which helped me a lot.

In the rest of the group, I'll thank more particularly Fehaid for making me laugh so much (because I apparently have a good tongue), Chongyu and Muxiu for being so nice. I'd like to thank the rest of the group, postdocs, PhDs, master students, old or new as well, Kristian, Ronan, Olivier, Glen, Jenny, Sam, Danielle, Sam, Patrick, Nutt, Richard, Martijn, Agnes and all others.

The (re)arrival of Pr. S. Perrier in Warwick, especially in Floor 2, changed my PhD experience a lot, thanks to the people he brought with him! I'll start by thanking Dr. Johannes Brendel, who has been a rock for the past year, through his constant kind words, thirst, and by "just" being a good person, a good flatmate and a good friend. I'll thank Dr. Guillaume Gody as well, for his enormous knowledge in chemistry and also, for being a good person. I'd also like to thank Dr. Joachin (Ximo) Sanchis-Martinez, for his advices on life, for being so happy and a source of inspiration for all. After that, come the rest of the greats, namely Liam, Tammie, Alex, Sylvain and all others for all the good times in and outside of chemistry. Last, but not least, I'll thank Sophie for being a good person, a good cook, and for the times we forgot about chemistry and reflected on which wine/cocktails we should drink.

Thanks to Dave, again, I was also able to go in US and work in the University of Florida. Hence, I'd like to thank Pr. Brent Sumerlin for welcoming me in his group with such open arms, and for being in Florida so that I can remember what proper sunshine looks like! My

time in US wouldn't have been so amazing without great people to enjoy it with. Indeed, thanks to Adrian (ze PITSA guy!), we managed to do so much in and outside the lab that I feel like I should have spent more time over there! I'll also thank Nick, Megan, Chris and the rest of the group for all the good times!

Back in Warwick, I'd like to thank Ant, Raj, Kay and Dan for running successively the GPC facilities; Dr. Ivan Prokes, Robert Perry, Philip Aston and Dr. Lijiang Song for the NMR and mass spec facilities, as well as Phil and Steve in stores. I'd also like to thank Pr. Stefan Bon, Pr. Rachel O'Reilly and Pr. Martin Wills for my 1st and 2nd year vivas and for the advices and guidance they provided. I'd like to thank Pr. Sebastien Perrier and Pr. Filip Du Prez for their extremely helpful questions and advices in my PhD viva. I'd like to thank the players in "Thursday touch rugby" who I've been playing with during those last 2 years for making me forget (from time to time) that I was injured and for all the good fun.

After all those people, I would like to thank my dear friends, especially Aurelie and Herve, Claire, Lea, Maelle and Nico, Lucie, Paul, Carole and Manon for being so supportive even when I was in an awful mood.

Finally, I will finish by thanking one of the most precious things I have in my life, my family. Although the rest will have to be translated in French so that they can actually read it, I'll thank my mum, my father, my step father, my cousin/brother Jerome, my uncles and aunts, the rest of my cousins, my brother and my sisters.

Si je devais traduire et étendre ces remerciements, il y en aurait pour des pages, donc je vais me contenter d'aller à l'essentiel. Je commencerais par remercier ma mère, pour tout ce qu'elle a fait pour moi. Ensuite, je voudrais remercier mon père et mon beau père, pour tout. Je ne pourrais jamais assez remercier mon cousin, mon grand frère Jérome, pour toute l'aide qu'il m'a donné depuis bien longtemps et pour être si génial. Lui et Sarah sont juste exceptionnels et il n'y aura jamais assez de mots pour exprimer ma gratitude. Il ne suffirait sûrement pas de quelques lignes pour remercier Angèle et Daniel également, ni Patricia et

François, pour être si bons, si gentils, si formidables et pour tout leur soutien. Je rajouterais une mention particulière pour François et les moments passés sur les toits, qui m'ont appris ce qu'était le vrai travail et aussi l'importance de l'humilité (mais cela va aussi pour Daniel et Jérome). Je voudrais ensuite remercier Tonina et Alex de m'avoir si bien accueilli aux US et pour être si loin et si proche à la fois. Ensuite je voudrais remercier mes cousins et cousines, surtout Céline et Chrystele, car vous êtes formidables. Après je voudrais remercier mon frère et ma soeur, tout particulièrement Claire. Ensuite je voudrais remercier les amis de la famille, en particulier Eric, pour être quelqu'un d'exceptionnel. Pour finir, je voudrais remercier ma plus grande source d'inspiration, mon défunt grand père, pour tout ce qu'il m'a inculqué.

Declaration

Experimental work contained in this thesis is original research carried out by the author, unless stated otherwise, in the Department of Chemistry at the University of Warwick, between October 2012 and September 2015. No material contained herein has been submitted for any other degree, or at any other institution.

Results from other authors are referenced throughout the text in the usual manner.

Date:

Alexandre Simula.

Abstract

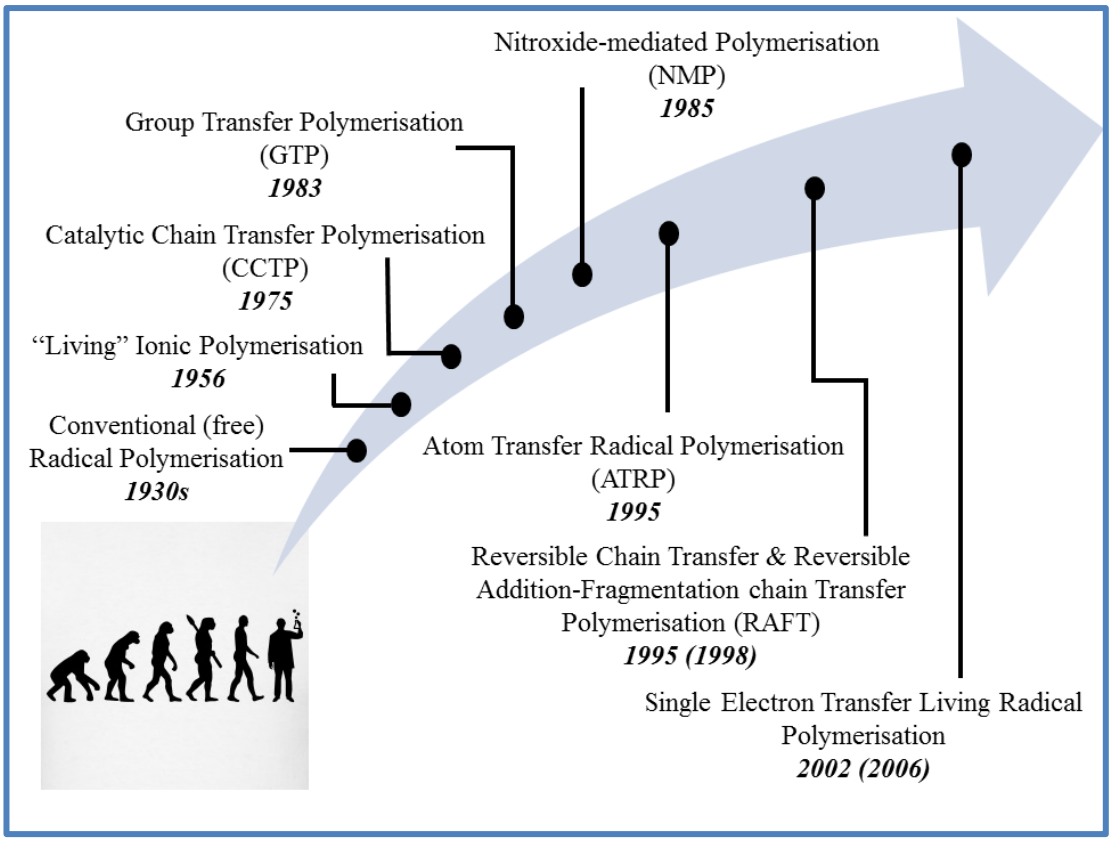
The objective of this thesis is to explore the versatility of Cu(0)-mediated reversible deactivation radical polymerisation (RDRP) in organic and aqueous media, towards the design of functional telechelic polymers.

The interest in telechelic macromolecules, *i.e.* "*prepolymer capable of entering into further polymerisation or other reaction through its reactive end groups*" arises from their use as chain extenders, precursors for block-, graft-copolymers and networks by reaction with appropriate reagents. The design of telechelic polymers has stemmed from the development of sophisticated polymerisation tools, to achieve good control over the polymer architecture, molecular weight distribution and perhaps more importantly, chain end fidelity.

The limitations and potential of Cu(0)-mediated RDRP technique are tested towards different monomer moieties, solvents and chain end functionalities, with the ultimate goal to expand the scope of functional telechelic polymers. Firstly, the reactivity of the halide end groups is exploited to yield functional telechelic poly(acrylates) with α,ω-hydroxyl groups upon post polymerisation modifications. The macro-diols can be further reacted, *via* isocyanate end-capping or ring-opening polymerisation. Then, the versatility of the synthetic tool is further tested towards the design of thermo-responsive polymers in water. Acrylamides and acrylates can be copolymerised with good control over the molecular weight distributions and predominantly, chain end fidelity. The typically unwanted hydrolysis of the halide chain ends is further exploited to yield tailor-made diols. Subsequently, the scope of telechelic materials accessible is expanded by careful selection of monomer, ligand, copper source and solvent, yielding well-defined poly(methacrylates) in organic and aqueous media. In the end, the introduction of external halide salts in aqueous media is exploited to generate functional block copolymers with hydrophilic and/or zwitterionic methacrylates in aqueous media.

Chapter 1

Precise design of telechelic macromolecules: Historical background towards the use of Cu(0)-mediated radical polymerisation



1.1. Introduction

The extensive use of polymeric materials has revolutionised well-known objects, such as bags, windows or clothing and gave birth to inaccessible materials for applications in electronics, biotechnology and nanotechnology. The development of such products would not be possible without extensive efforts to yield tailor-made macromolecules. Indeed, the ability to tune functionality and final properties of one material became accessible through the advances in synthetic polymer science.

In this chapter, the focus is on the presentation of polymer synthesis, from conventional (free) radical polymerisation, to more sophisticated "*living*" polymerisation tools. Although a complete description of polymerisation processes would be appreciated, a presentation of key techniques involved in the design of telechelic polymers will be presented. A brief description of ionic polymerisation techniques will be given, whilst more details will be provided for radical polymerisation processes, as it is the main focus of the following investigations. Subsequently, the discussion will be aimed to the formation of telechelic macromolecules, in which the concept will be defined and the various applications detailed. An historical background will be provided on the development and exploitation of synthetic tolls in order to fully appreciate the objective of this work, utilising Cu(0)-mediated polymerisation processes.

1.2. Polymerisation techniques

1.2.1 Conventional (free) radical polymerisation

Conventional (free) radical polymerisation (FRP) is one of the most widely exploited synthetic tools to yield polymeric materials. Since its early discovery in the 1930s by Flory,[1] this technique has been utilised, thanks to its simplicity and tolerance to various monomers and trace impurities, allowing mass-production with relative ease. Conventional radical polymerisation can be conducted in bulk at elevated temperature (up to 150°C) in organic or aqueous media. Moreover, heterogeneous processes such as suspension and emulsion polymerisation, are tolerant to the use of FRP, providing access to several polymers, such as polystyrene (PS), polyvinylchloride (PVC), polyvinyl alcohol (PVA), poly(meth)acrylics, polyacrylamide and many more. However, the high rates of reactions occurring in FRP often lead to poor molar mass control, moderately high dispersity values and little control over the polymer architecture.[2]

FRP can be viewed as a chain reaction involving three distinctive events, the first of which being the initiation, whereby a decomposable initiator specie generates a radical which subsequently adds to a monomer. The second stage is propagation, whereby a propagating radical will react with a monomer adduct, generating another propagating chain. Subsequently, the growing polymer chain terminates, becoming "dead" *via* two common routes, combination and disproportionation. A growing polymer chain can also terminate *via* side reactions, *i.e.* chain transfer to monomer, polymer, or solvent.

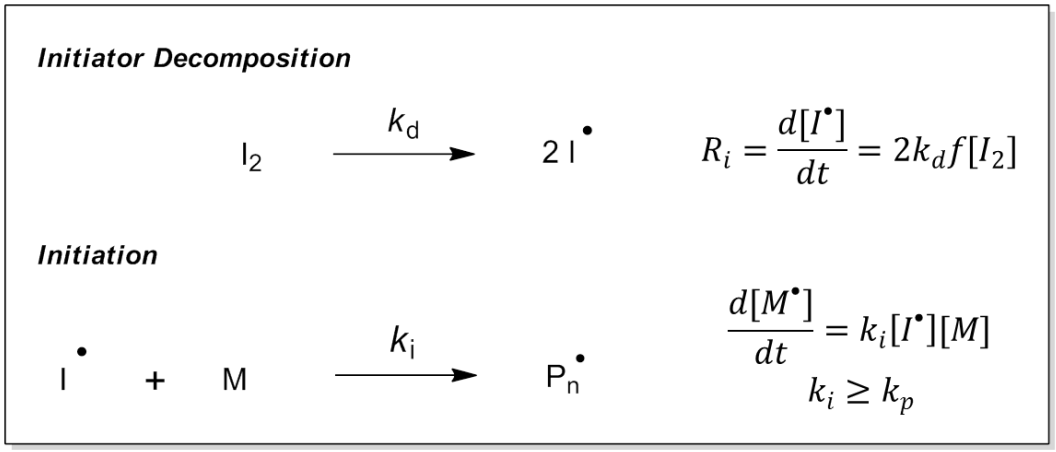


Figure 1.1. Initiation step and rate equations in conventional (free) radical polymerisation, where I_2 is the initiator, M the monomer, k_d and k_i the decomposition and initiation rate constants respectively, f the initiator efficiency. R_i is the rate of initiation and k_p the propagation rate constant.

Initiator decomposition can be triggered by thermolysis, photo-irradiation or redox chemistry depending on the process involved. Common initiators are azo or peroxide reagents, including 2,2'-azobis(2-methylproprionitrile) (AIBN) or dibenzoyl peroxide (BPO), generating carbon centred radicals with release of N_2 and *primary* oxygen centred radicals respectively. Those *primary* radicals ($I^{\bullet}$) can react with the vinyl bond of the monomer (M), yielding an *initiating* radical that can undergo propagation (figure 1.1.). Although the tail addition of a *primary* radical to a monomer is usually favoured, head addition and subsequent rearrangements or loss of the *initiating* radical (*i.e.* β-scission, rearrangement, abstraction, reaction with solvents, termination) can occur, yielding undesired initiating species.[3]

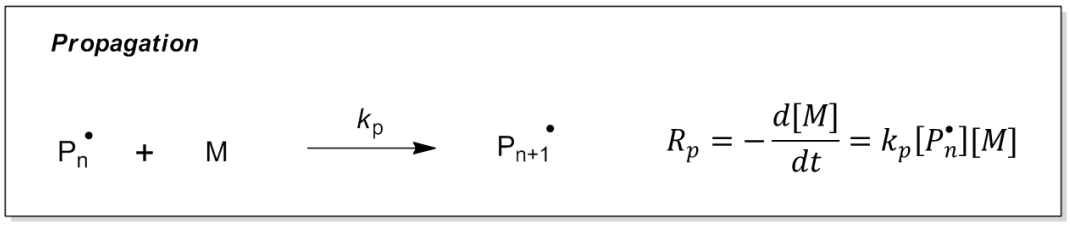


Figure 1.2. Propagation step and rate equations in conventional (free) radical polymerisation, where $P_n^{\bullet}$ is a propagating polymer chain, M the monomer and k_p the propagation rate constant.

Propagation results from the reaction between a growing polymer chain ($P_n^{\bullet}$) with a monomer (M), rapidly yielding a propagating radical (figure 1.2.). The rate constant at which this sequential addition occurs is defined as k_p, typically in the 10^2-10^4 L.mol^{-1}s^{-1} and is influenced by the nature of the monomer and the conditions employed (*e.g.* temperature, monomer concentration).[4, 5] However, the evaluation of the rate of polymerisation (R_p) is difficult, due to the time dependence of [M] and [$P_n^{\bullet}$]. Hence, a steady-state assumption is postulated, in which [$P_n^{\bullet}$] increases dramatically at the early stage of the polymerisation to further reach a plateau value and remain unchanged. Continuous addition of monomer onto a radical will occur until full monomer consumption or side reaction events.

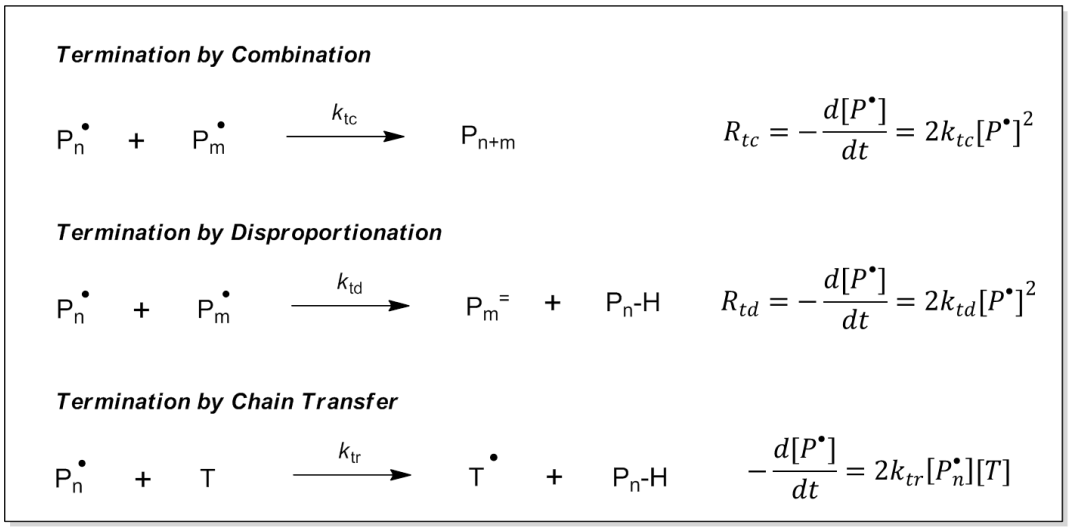


Figure 1.3. Termination reactions and rate equations in conventional (free) radical polymerisation. $P_n^{\bullet}$ and $P_m^{\bullet}$ are growing polymer chains with n and m units respectively, P_n= is a double bond terminated polymer chain, P_n-H is a hydrogen terminated polymer chain, T is a chain transfer agent. k_{tc} is the termination by combination rate constant, k_{td} the termination by disproportionation rate constant and k_{tr} the termination by chain transfer rate constant.

Cessation of the propagation events will occur throughout the polymerisation, yielding "dead" polymer chains, *i.e.* unable to take part in further propagation, *via* two main routes; combination and disproportionation (figure 1.3.). The first results from the reaction between two growing polymer chains ($P_n^{\bullet}$ and $P_m^{\bullet}$), forming a "dead" polymer chain (P_{n+m}) with an increased molar mass. The second route results from a hydrogen transfer from a growing polymer chain ($P_n^{\bullet}$) onto another polymer chain ($P_m^{\bullet}$), yielding two separate "dead" chains, one being ω-vinyl terminated and the other being ω-H terminated. The selectivity between combination and disproportionation is influenced by the nature of the monomer, and could be generalised as vinyl monomers (*e.g.*, styrene, vinyl chloride) predominantly yield to termination by combination[6] whereas α-methylvinyl monomers (*e.g.* methyl methacrylate) favour a certain extent of disproportionation.[7 8]

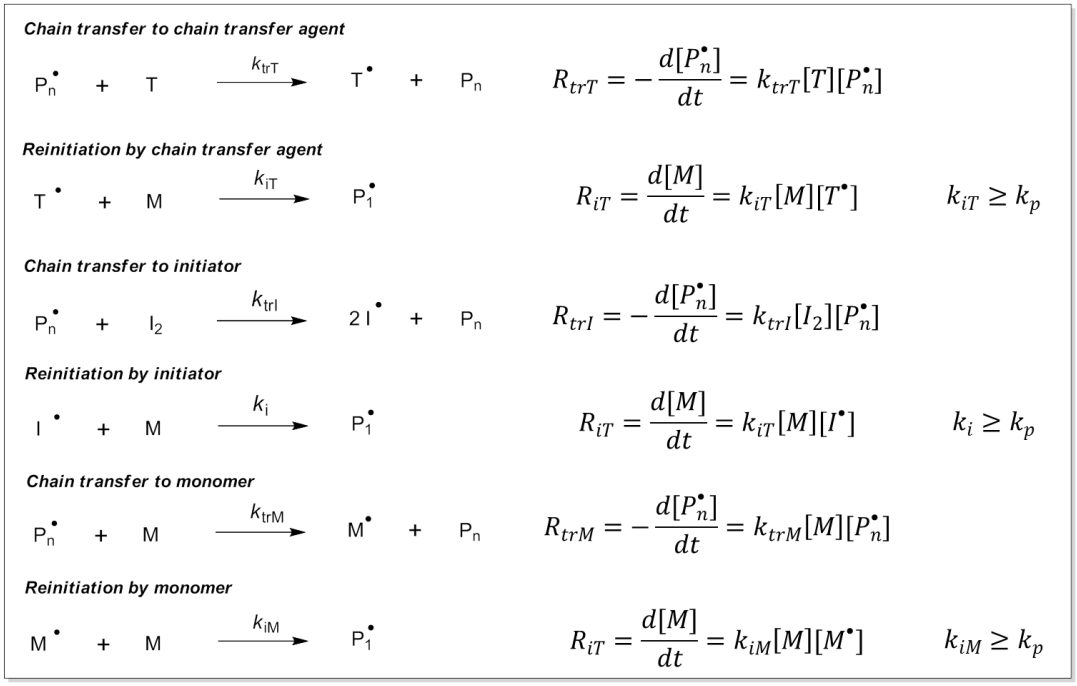


Figure 1.4. Chain transfer and reinitiation events with associated rates. T is a chain transfer agent, M a monomer, I_2 the initiator, $P_n^{\bullet}$ a propagating polymer chain. k_{trT}, k_{trI} and k_{trM} are the chain transfer by chain transfer agent, initiator and monomer rate constants, respectively. k_{iT}, k_i, k_{iM} are the re-initiation by chain transfer agent, initiator and monomer rate constants, respectively.

Side reactions, namely chain transfer, can occur between a propagating radical and a non-radical substrate, *i.e.* monomer (chain transfer to monomer), initiator (chain transfer to initiator), solvent (chain transfer to solvent) or chain transfer agent (CTA).[9] CTAs are intentionally added to the reaction mixture in order to moderate the molecular weight (MW) of the final polymer, ideally *via* a rapid break of a weak bond (typically hydrogen-sulphur). Further details on the importance of chain transfer will be provided in sections 1.2.2, 1.2.6.3 and 1.3.3.4.

1.2.2 Catalytic chain transfer polymerisation (CCTP)

Catalytic chain transfer polymerisation (CCTP) is a conventional FRP with a cobalt based complex chain transfer agent which typically yields low molecular weight polymers bearing a ω-unsaturated carbon-carbon double bond.[10-13] One of the most advantageous features of CCTP is the high chain transfer constant (C_{tr}) of the cobalt based catalysts, which lowers the quantity of CTA employed dramatically.[14] Moreover, CCTP can be conducted in bulk or in emulsion, with similar degree of control over the MW of the final polymer.[15] The reduction of MW compared to a free radical process is mediated by the rapid and reversible combination of the Co^{II} complex (*e.g.* cobalt porphyrins, cobalt cobaloximes) with a propagating radical, or alternatively *via* disproportionation. The resulting alkyl Co^{III} complex can eliminate the Co^{III} hydride to yield a macromonomer bearing an ω-unsaturated carbon-carbon double bond. The Co^{III} hydride can reinitiate polymerisation *via* H-abstraction to monomer, hence generating a propagating radical whilst regenerating the Co^{II} complex (figure 1.5).[16]

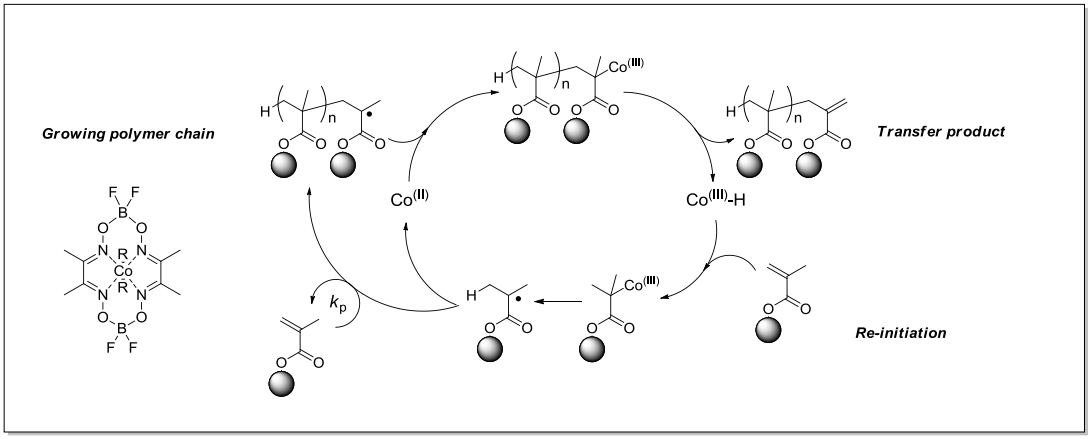


Figure 1.5. Catalytic cycle involved in catalytic chain transfer polymerisation for methacrylic monomer moieties. The cobalt(II) dimethylglyoxime-difluoroboryl complex (CoBF) is an example of cobalt(II) cobaloxime complex.

CCTP is mainly conducted for the polymerisation of methacrylic moieties, as acrylic monomers generate a less stable propagating radical, thus allowing the formation of a stable C-Co^{III} bond which subsequently leads to undesired termination and/or branching.[10] The use of methacrylic monomers has been exploited to generated dimers, trimers and macromonomers with predictable molecular weights (see sections 1.2.6.3 and 1.3.3.4).[11,17]

1.2.3 Anionic polymerisation

Conventional (free) radical polymerisation presents undeniable advantages, though the unavoidable presence of termination events affects dramatically the control over the polymerisation, namely relatively high dispersity values. Partly in order to circumvent the issues arising from a radical process, anionic polymerisation was developed, whereby a propagating species is anionic.[18] The propagating anionic centres are not able to be involved in termination events, as transfer to positive species (*e.g.* proton) does not occur in aprotic solvents, whilst combination is disfavoured due to electrostatic repulsion. Consequently, termination by combination and/or disproportionation (commonly seen in FRP) is avoided under carefully selected conditions, maximising the lifetime of propagation events until complete monomer consumption. The propagating chain is referred to as "*living*" (see section 1.2.6. for further details), as propagation will continue unless termination is triggered by addition of an external polar reagent, or by the presence of trace impurities (figure 1.6).[19]

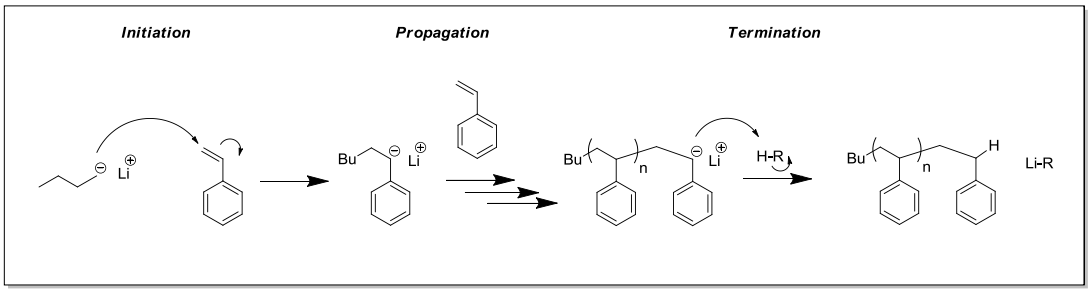


Figure 1.6. "Living" anionic polymerisation of styrene with *n*-butyl lithium as the initiator.

This technique has been widely exploited for the synthesis of well-defined polystyrene with predictable molecular weights and narrow molecular weight distributions (MWD). Nevertheless, the extensive purification of the reagents (*e.g.* initiator, monomer), solvents, in addition to the low temperatures commonly employed (-78°C) make this technique less attractive for a cheap large scale production, albeit it still is a robust tool to yield well-defined (co)polymers.

1.2.4 Cationic polymerisation

Cationic polymerisation presents interesting differences to its anionic counterpart, whereby Lewis acids are utilised as initiating species and a propagating cation is involved (figure 1.7). Nevertheless, the unavoidable termination *via* β-proton transfer, combination with the counterion and/or chain transfer to polymer make the technique less attractive than its sibling.

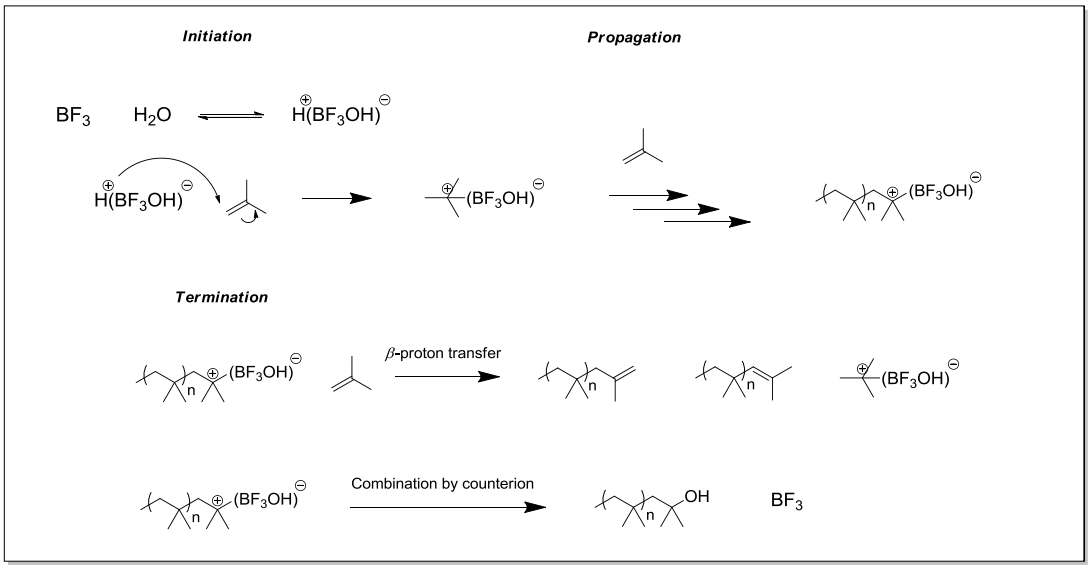


Figure 1.7. Cationic polymerisation of isobutylene initiated by boron trifluoride.

However, the development of "*living*" cationic polymerisation (see section 1.2.6) expanded the use of the technique, through careful selection of initiator, counterion (typically an ion salt) and other components (covalent esters or halides acting as *dormant* species, see section 1.2.6.2).[20] Cationic polymerisation offers a good alternative to FRP to polymerise 1,1-dialkyl olefins (*e.g.* isobutylene) and/or dienes (*e.g.* butadiene, isoprene).

1.2.5 Group Transfer Polymerisation

Anionic polymerisation presents undeniable advantages for the synthesis of well-defined polymers, albeit methacrylates (especially methyl methacrylate) still remained problematic due to undesirable addition of the anion to the carbonyl groups. In order to circumvent this, group transfer polymerisation (GTP) was introduced in 1983 by Webster *et al.* from DuPont central research laboratories,[21] hence expanding the use of "ionic" polymerisation industrially. This robust technique is suitable for the polymerisation of (meth)acrylates in THF without the need for low temperatures (the polymerisation is typically conducted at 50-80°C), whilst retaining good control over the MWD. In GTP, the initiator is a silyl ketene

acetyl (typically [1-methoxy-2-methyl-1-propenyl)-oxy] trimethylsilane, MTS) and requires the presence of either a hard nucleophile or a Lewis Acid catalyst to react with a monomer and undergo propagation.[22]

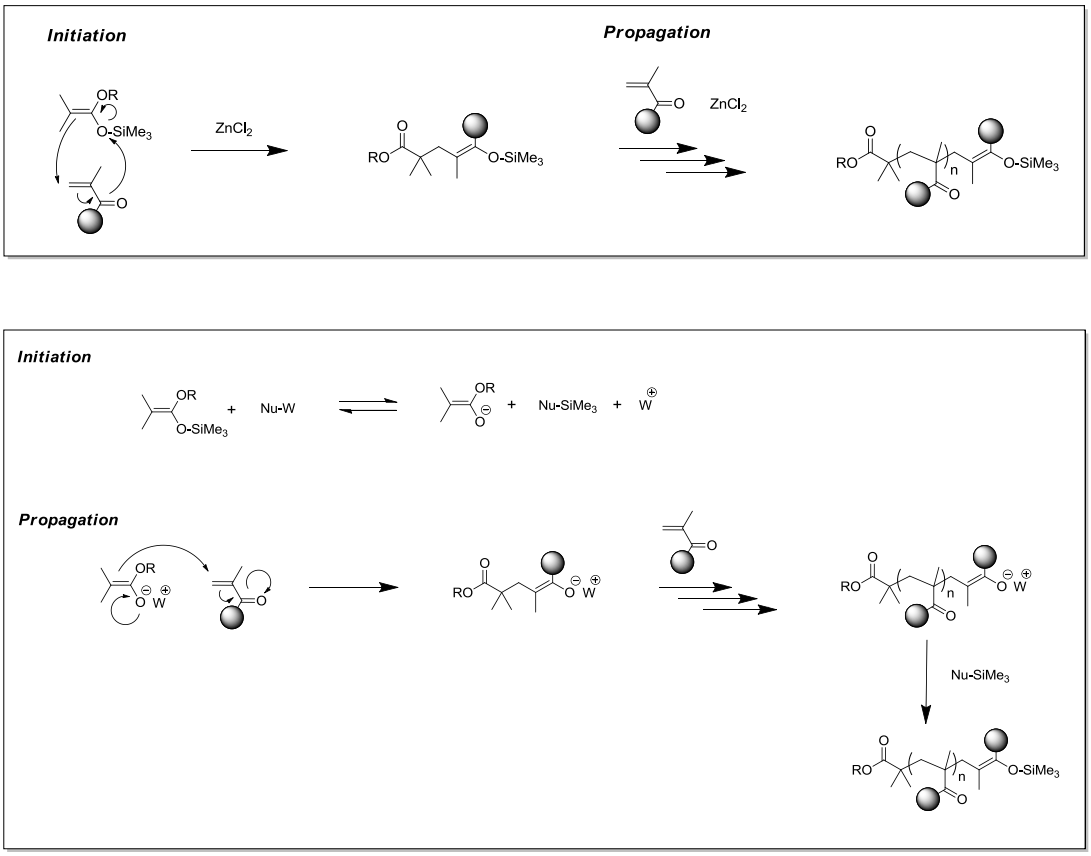


Figure 1.8. Proposed mechanism of Group Transfer Polymerisation *via* an electrophilic (top) or nucleophilic pathway (bottom). R is a functional group on the silyl ketene acetal, Nu a nucleophile and W its counterion.

Originally, GTP was believed to proceed *via* an associative mechanism, whereby the nucleophilic moiety would reversibly associate with the silicon atom. However, this was further contradicted by Quirk *et al.*, by revealing the presence of ester enolates in both initiation and propagation steps.[23, 24] This dissociative mechanism, in which the siloxane would dissociate, yields an anion which would initiate polymerisation. However, this would require lower polymerisation temperatures (which was not the case experimentally), as the presence of such anion would induce termination, as commonly seen in anionic

polymerisation of methacrylates. The heated debate over the "real" mechanism of GTP, however, not fully accepted, is believed to vary depending on the catalyst employed, as presented in figure 1.8.[25]

Nevertheless, GTP requires similar purifications requirements for the reagents and solvent as standard ionic polymerisation, which has made the technique less attractive in recent years (see sections 1.2.6 and 1.3.3.2).

1.2.6 Controlled/"Living" radical polymerisation, Reversible-deactivation radical polymerisation.

Since Szwarc's investigations in anionic polymerisation, the notion of a "*living*" polymer chain became attractive in order to yield macromolecules with predictable molecular weight (MW), relatively narrow distributions, high end-group(s) fidelity and controlled architectures. Innovative and undemanding synthetic tools had to be developed in order to overcome the intolerances associated with ionic processes. Thus, controlled/"*living*" radical polymerisation (CLRP) methods emerged, whereby the control is determined by a reversible activation/deactivation process, which is the case for TMM-LRP and NMP (see sections 1.2.6.1 and 1.2.6.2) but not for RAFT (see section 1.2.6.3). A fast equilibrium exists between an *active* or *transient* macroradical (that can undergo propagation) and a *dormant* species or *persistent* radical (not involved in the propagation step), lowering the concentration of propagating radical, thus limiting the probability of termination events (*via* combination and/or disproportionation). The selectivity in the macroradical capping with external moieties is present in "*living*" processes mediated by a reversible deactivation (*e.g.* NMP and TMM-LRP), and is referred to as the persistent radical effect (PRE).[26] The nature of the *persistent* radical moieties dictates the differences in the polymerisation process, as detailed in the following sections.

Due to the crucial balance between activation and deactivation events, allowing the polymer chains to grow at the same rate, such polymerisation process would preferentially be further referred to as a reversible deactivation radical polymerisation (RDRP) instead of CLRP. RDRP processes exhibit the same characteristics,[27] namely:

1/ Constant concentration of propagating radical, reciprocated by a linear evolution of $Ln([M]/[M]_0)$ as a function of reaction time.

2/ Linear evolution of number average molecular weight (M_n) as a function of monomer conversion. The degree of polymerisation (DP_n) is (pre)determined as the ratio between the monomer concentration and the initial initiator concentration. Noteworthy, the ratio between CTA and monomer is utilised to determine the DP_n in RAFT polymerisation (see section 1.2.6.3).

3/ Minimum presence of termination events reciprocated in narrow molecular weight distributions (M_w/M_n, MWD, $Đ$) and high retention of the reactive chain end(s), thus allowing the formation of block copolymers *via* sequential addition of a second monomer aliquot.

Early reports of "*living*" radical polymerisation include the use of iniferters, *i.e.* species that would allow the *ini*tiation, trans*fer* and *ter*mination of a radical polymerisation, typically organic disulfides.[28] Despite the unsatisfactory control in both the initiation and termination steps, leading to broadly distributed macromolecules, a large variety of monomers could be polymerised, paving the way to the development of more robust RDRP techniques.[29]

1.2.6.1 Nitroxide mediated polymerisation

Among the plethora of RDRP techniques, one major advance in the field has been the development of nitroxide mediated radical polymerisation (NMP), exploiting the early investigations of Rizzardo *et al.* in 1985.[30] The control over the polymerisation is obtained *via* a reversible degeneration of a *dormant* (macro)alkoxyamine, whereby a *persistent* nitroxide can reversibly cap a propagating (*transient*) radical (figure 1.9).[31] Initial investigations exploited the efficient ability of 2,2,6,6-tertamethylpiperidynyl-1-oxy (TEMPO) to trap radical species to mediate the polymerisation of styrene.[32] The alkoxyamine could be reversibly transformed to a propagating radical and a nitroxide at high temperatures (130°C) to successfully control the polymerisation with "*living*" characteristics.[33]

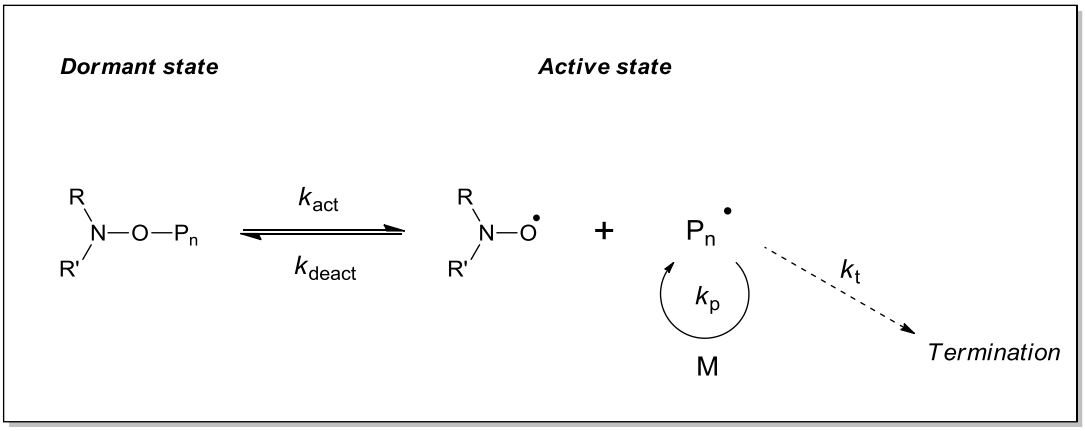


Figure 1.9. Simplified mechanism of nitroxide mediated polymerisation, with $P_n^{\bullet}$ a propagating polymer chain and M a monomer. k_{act}, k_{deact} k_p and k_t are respectively the activation, deactivation, polymerisation and termination rate constants.

Several trapping agents, in addition to functional nitroxides,[34] can be utilised to mediate NMP processes, such as verdazyl,[35] arylazo(oxy),[36] substituted triphenyls,[37] and triazonilyn.[38] NMP has proven to be tolerant to a variety of monomer moieties, namely styrene, acrylamides, (meth)acrylates and 4-vinylpyridine. Nevertheless, the level of control

over the final polymer would differ from one another, depending on the nature (and structure) of the initiator, monomer and *persistent* radical. Generally, styrene, acrylates and acrylamides yield well–defined polymers with narrow MWD,[31] whilst partial control is achieved when utilising methacrylates.[39]

1.2.6.2 Transition metal-mediated radical polymerisation

Transition metal catalysts have been widely investigated in atom transfer radical addition between alkyl halides and vinyl moieties.[40, 41] Interestingly, Sawamoto and Matyjaszewski in their investigations on "*living*" cationic polymerisation, independently exploited this reaction to yield well-defined polymers in 1995, utilising ruthenium[42] and cuprous halide[43] based complexes respectively, opening the door to a new RDRP technique, transition metal-mediated reversible deactivation radical polymerisation (TMM-RDRP).

TMM-RDRP relies on the rapid redox process, whereby a halogen exchange occurs between an alkyl halide and the catalyst, allowing the reversible formation of a propagating radical (see section 1.2.6.2.1). The use of cuprous halides as catalyst has received more attention than ruthenium based catalysts and is commonly referred to as atom transfer radical polymerisation (ATRP).

1.2.6.2.1 Atom Transfer Radical Polymerisation

In classical ATRP, a cuprous halide (Mt^n-X, where X is Br or Cl) is mixed with a nitrogen based ligand (L), which could be σ-donor (*e.g.* *N,N,N',N'',N''*-hexamethyl-[tris(aminoethyl)amine] [Me_6-TREN], *N,N,N',N'',N''*-pentamethyldiethylenetriamine [PMDETA], 1,1,4,7,10-hexamethyltriethylenetetramine [HMTETA]), π-acceptor (bipyridine [Bpy], pyridine-imines) or both (tris(2-pyridylmethyl)amine [TPMA]), yielding the transition-metal complex catalyst ([Mt^m(L)X]).[44] An alkyl halide or *dormant* polymer chain (P_n-X) can react with [Mt^m(L)X] *via* a concerted inner-sphere electron transfer to reversibly yield a propagating radical ($P_n^{\bullet}$) and a deactivating complex ([Mt^{m+1}(L)X]X), at higher oxidation state of the metal (figure 1.10). The equilibrium should favour the *dormant* state for the polymerisation to proceed with an enhanced control over the MWD (see section 4.1.1). The polymer grows whilst in an *active* state by monomer addition to the propagating radical ($P_n^{\bullet}$) with an associated propagation rate constant (k_p). Termination can occur in the form of bimolecular coupling and/or disproportionation, as commonly seen in FRP, with an associated termination rate constant (k_t). However, the probability of termination events to occur is diminished by the efficiency of the deactivation process, *via* the use of *persistent* species, here being [Mt^{m+1}(L)X]X.[45]

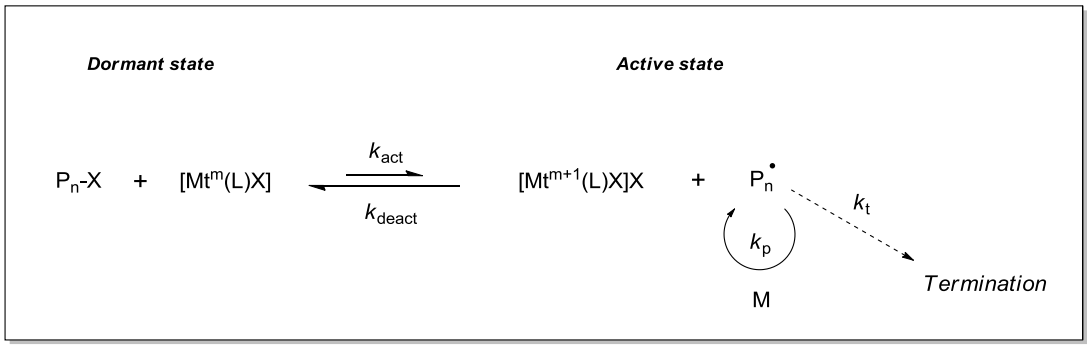


Figure 1.10. Equilibrium in ATRP, where X is a halogen, Mt^m a transition metal at oxidation state m, L a ligand, M a monomer, $P_n^{\bullet}$ a propagating polymer chain. k_p and k_t are respectively the propagation and termination rate constants.

Although copper based catalyst received the most attention in the past decades, a number of other transition metals have been investigated to mediate ATRP, including molybdenum,[46] rhenium,[47] iron,[48] nickel[49] and palladium.[50] The tolerance of the ATRP process extends to a wide variety of monomers, *i.e.* (meth)acrylates,[43, 51, 52] styrene and derivatives,[43, 53] (meth)acrylamides[54, 55] and acrylonitrile.[56] Additionally, ATRP can be conducted utilising different initiator moieties, such as halogenated alkanes,[42, 43] benzylic halides,[57] sulfonyl halides,[58, 59] haloesters,[60] halonitriles[56] and haloketones[24] which offer different initiator efficiency depending on the monomer employed, thus leading to various levels of control.[61, 62] These advantages make ATRP one of the most widely employed polymerisation protocols to yield well-defined polymers.

However, some issues can emerge from the use of ATRP depending on the system employed, *i.e.* solvents (in aqueous medium for instance), copper/ligand catalysts and monomers; but this will be discussed in more detail below (see sections 1.2.6.2.2, 3.1.1, 4.1.1 and 5.1).

1.2.6.2.2 Evolution of ATRP, several derivatives

Under standard conditions, the use of a significant amount of catalyst can interfere with the colour and/or toxicity of the final product if not purified accordingly, which makes the technique less suitable for certain applications.[63] Moreover, some catalysts commonly used in ATRP do not enable the polymerisation of hydrophilic monomers in water or biologically relevant media, due to denaturation (*e.g.* disproportionation, introduction of water molecules).[64] In order to lower the quantity of catalyst and offer a broader range of

applications to the (co)polymers made by ATRP, several derivatives have been introduced over the years.

The activation/deactivation equilibrium existing in ATRP can be tuned utilising external stimuli, in order to favour one of the redox reactions. In the early stages of the development of "novel" ATRP systems, the transition metal complex would be added at the highest oxidation state and would be converted to $[Mt^{m}(L)X]$ upon reaction with a free radical initiator.[65, 66] Nevertheless, the use of the more reactive complex in a reverse ATRP process would not mediate the synthesis of well-defined block copolymers or more advanced macromolecular structures. Consequently, supplementary reducing agents including zero-valent metals were introduced to *generate active* species by *electron transfer*, hence paving the way to activators generated by electron transfer (AGET) ATRP.[67, 68] This process would be the precursor to the development of activator regenerated by electron transfer (ARGET) and initiators for continuous activator regeneration (ICAR) ATRP.

In ARGET ATRP, a small amount of catalyst is continuously regenerated *via* the introduction of low ppm of reducing agent, *i.e.* glucose,[69-71] ascorbic acid,[72] phenol,[73] hydrazine, phenylhydrazine,[70] tin(II) 2-ethylhexanoate ($Sn(Oct)_2$),[68] excess of inexpensive ligands[74] and nitrogen containing monomers.[75] As such, the catalyst-induced side reactions and undesired retardation are diminished, hence allowing the preparation of high molecular weight copolymers with high retention of the halide chain end(s).[76]

The regeneration of low ppm of copper catalyst can also be promoted by a continuous addition of an organic radical. The initiators for continuous activator regeneration (ICAR) ATRP[71] process proved to be less popular than ARGET ATRP, as one of the main drawback of the external initiator is the generation of new, initiator-derived active chains (see section 1.2.6.3).

The addition of zero-valent metals (Cu, Zn, Fe, Mg) to the catalytic system has been noticeably attractive,[67, 77, 78] as the moieties can act as both supplementary activator and reducing agent, paving the way to SARA-ATRP.[79, 80] Indeed, the metal promotes the reduction of the $[Mt^{m+1}(L)X]X$ deactivating complex, hence favouring a dormant state of the polymer chain. The use of SARA-ATRP proved to lower the overall reaction times and reduce the extent of termination, reciprocated in narrow MWD.

In addition to chemical additives, the control over the activation/deactivation equilibrium can be mediated by electrical current (*e*-ATRP), whereby the generation of propagating radicals is temporally and spatially controlled. This interesting feature has been a major advance in ATRP polymerisation, as the synthesis of a polymer chain can be turned "on" and "off" as desired with good degree of control.[81]

The external control can also be achieved by photo-irradiation (Photo-RDRP) with similar success. Light has been a widely investigated stimulus to mediate polymerisation as it offers a non-invasive temporal control over the process.[82] The pioneering work in light-mediated ATRP systems from Yagci[83], Hawker[84] and co-workers, respectively using copper and iridium based complexes as catalysts, offered a strong background in the field.[85] Light was further exploited by Haddleton and co-workers as an external stimuli to mediate the polymerisation of acrylates with unprecedented control over the MWD, α,ω-halide chain ends, whereby the catalyst is generated from an excited $[Cu^{II}(Me_6\text{-TREN})X]X$ complex in the presence of excess ligand.[86-90] Initially, activation was thought to occur through an outer-sphere single electron transfer (OSET), which was questioned in later reports, highlighting the complexity of the photo-RDRP process.[91]

1.2.6.2.3 Single-electron transfer living radical polymerisation

The use of zero-valent metals in addition to the copper catalyst has proved to be extremely effective in improving the synthesis of well defined (co)polymers. However, since Percec reported the "*living*" radical polymerisation of vinyl chloride (VC) in aqueous medium, whilst exploiting the disproportionation of [Cu^{I}(TREN)Cl] in water (TREN is tris(2-aminoethyl)amine),[92] followed in 2006 by the report on the "ultrafast" synthesis of "ultrahigh" molecular weight polymers;[93] the use of Cu(0) (in the form of a wire or mesh)[94-96] as the primary copper source, new doors opened in the development of materials with an excellent degree of control. Single electron transfer living radical polymerisation (SET-LRP), enables the polymerisation at ambient temperatures and below of functional monomers, *i.e.* (meth)acrylates,[93, 97-104] (meth)acrylamides,[105-108] styrene,[109, 110] acrylonitrile[111] and vinyl chloride[67, 93] in polar solvents (*e.g.* DMSO, alcohols[95, 99, 112] and water[105, 113]) in the presence of *N*-containing ligands. This Cu(0)-mediated polymerisation technique offers great advantages as it exhibits near quantitative initiator efficiency,[114] good control over the MWDs and unprecedented halide end-group fidelity at high monomer conversion.[115-118] Similarly as in ATRP, an equilibrium exists between dormant and active species. Nevertheless, the proposed activator is Cu(0) which acts as an electron donor and abstracts an halogen from an alkyl halide *via* a heterolytic outer-sphere electron transfer (OSET) process (figure 1.11).[119, 120]

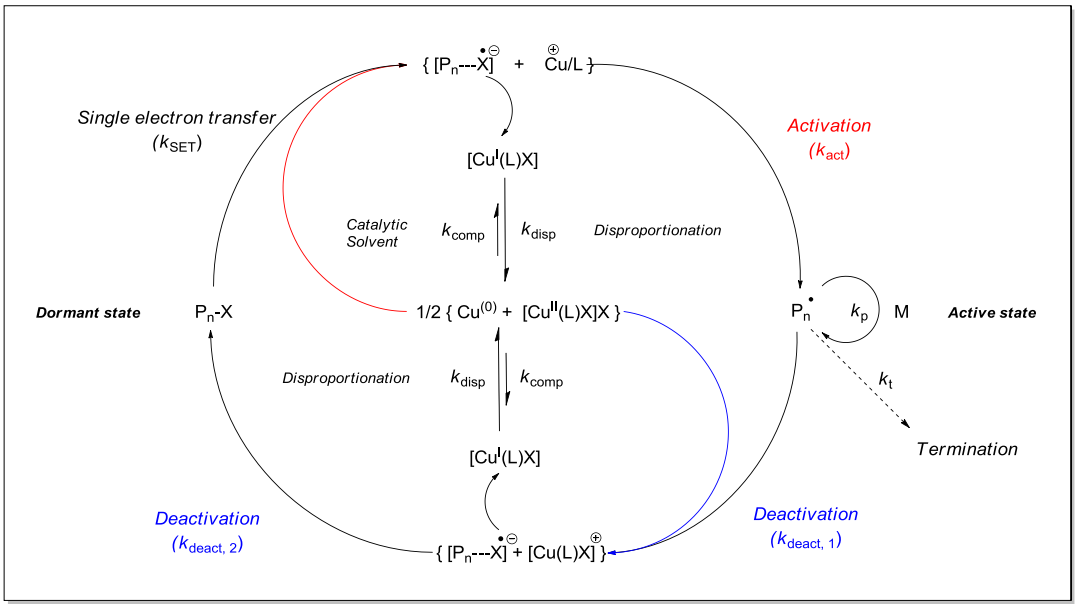


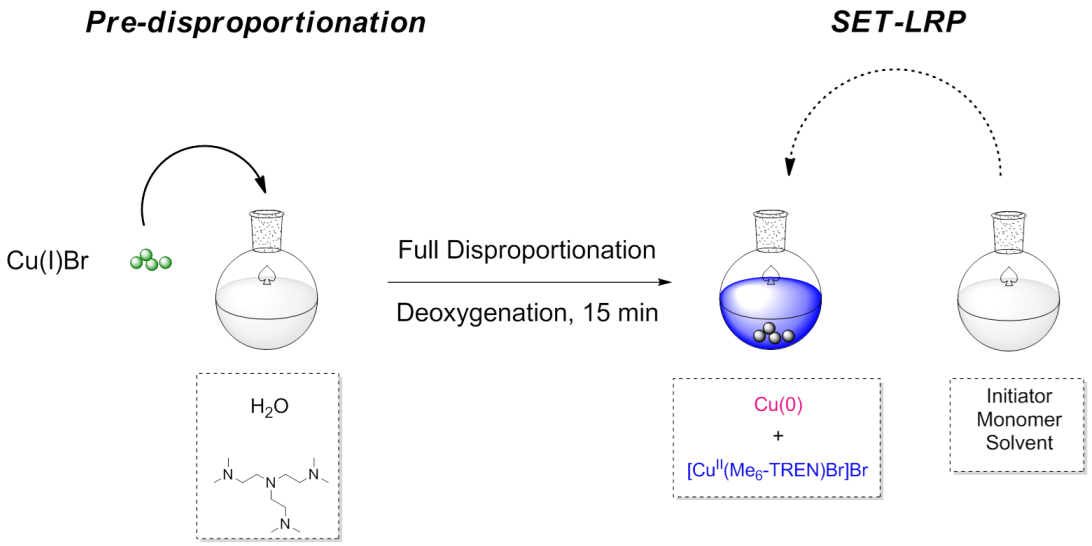
Figure 1.11. Proposed mechanism of single electron transfer living radical polymerisation, adapted from references 93 and 119.

The key equilibrium in the SET-LRP mechanism is the self-regulated disproportionation of $[Cu^{I}(L)X]$ generated upon activation/deactivation processes. The disproportionation in polar media generates "nascent" Cu(0) particles (acting as activating species) and accumulates $[Cu^{II}(L)X]X$ (acting as deactivating species). The choice of the aliphatic ligand (*e.g.* Me_6-TREN, PMDETA) as well as the polarity of the solvent plays a crucial role in the efficient disproportionation of $[Cu^{I}(L)X]$.[121, 122]

The traditional use of Cu(0)-wire as the primary copper source offers advantageous features over Cu(0) powder or mesh, including the facile tuning of reaction rates and easy experimental setup, *i.e.* catalyst removal, preparation and recyclability.[94] Moreover, Cu(0)-wire offers greater control over the MWD compared to Cu(0)-mesh or powder.[123] The robustness of the catalyst was tested in different solvents, though partial control was observed in aqueous medium (see sections 3.1.1 and 4.1).[113]

Interestingly, a different approach to the use of traditional Cu(0)-wire allowed better control over the polymerisation in aqueous media (water,[107, 124, 125] phosphate buffer,[107] blood

serum[126] and complex alcoholic mixtures[127]), by exploiting the rapid and quantitative disproportionation of [Cu^{I}(L)X] into Cu(0) particles and [Cu^{II}(L)X]X prior to initiator and monomer addition.



Scheme 1.1. Schematic representation on how to conduct aqueous single electron transfer living radical polymerisation exploiting the pre-disproportionation of [Cu^{I}(L)X] whereby X is an halogen and L a ligand (Me_6-TREN, PMDETA).

This provides a robust tool for the synthesis of functional hydrophilic monomers (acrylamides, acrylates) with controlled chain length and narrow distributions and circumvents some issues arising from ATRP processes in aqueous media (see sections 3.1 and 5.1). The reactive halide chain end(s) can be retained within the time scale of polymerisation, even at full monomer conversion, in order to yield sophisticated multiblock copolymers.[128] Further details on the use of a pre-disproportionation strategy will be provided in the following chapters.

1.2.6.2.4 SARA-ATRP vs. SET-LRP

Cu(0)-mediated RDRP is a versatile technique to yield well-defined (co)polymers, with narrow MWD and excellent retention of the halide chain ends, even at high monomer conversion. However, the similarities in the nature of the reagents present in both SARA-ATRP and SET-LRP has given rise to a heated debate over the "true" mechanism of Cu(0)-mediated RDRP in DMSO and water (figure 1.12).[77, 121, 122, 129-138] Several claims have been made by different research groups to "prove" the nature of the catalyst involved in the activation process (Cu(0) *vs.* [Cu^{I}(L)X]), the mechanistic route in which the activation takes place (OSET *vs.* ISET), and the extent of disproportionation.

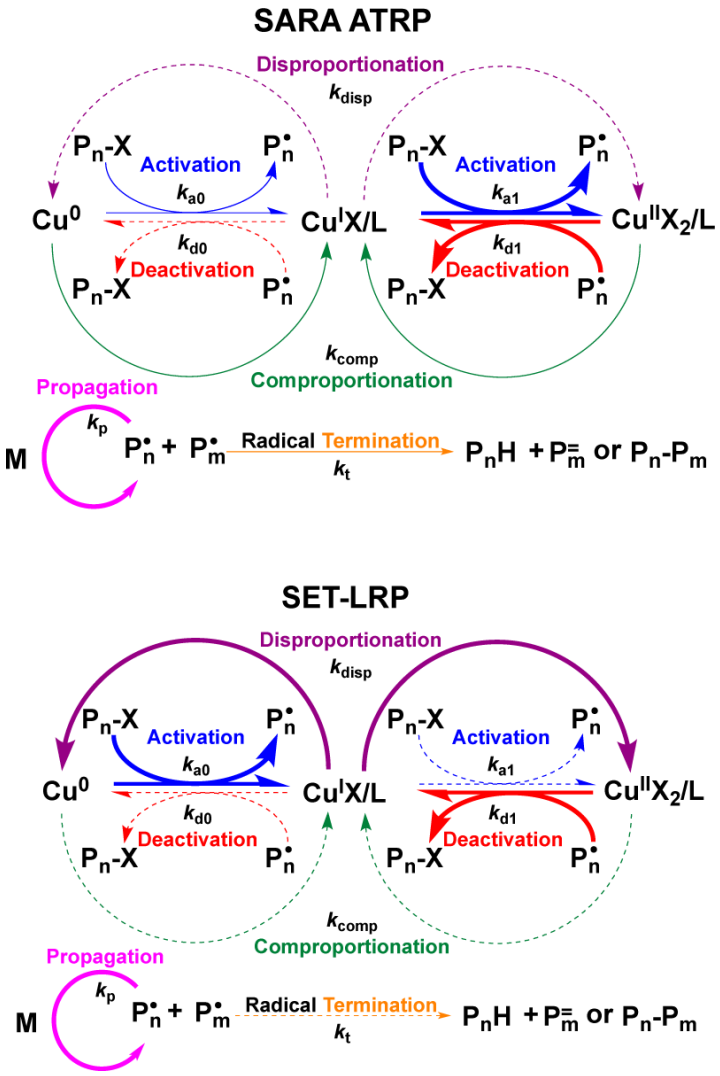


Figure 1.12. Proposed mechanisms of SARA-ATRP and SET-LRP, according to Matyjaszewski *et al.*[133] Bold arrows indicate dominating reactions, thin solid arrows indicate contributing reactions and dashed arrows indicate reactions that have minimal contribution and can be neglected.[133] k_{an} and k_{dn} are the rate constant of activation and deactivation respectively, involving a metal in the transitional state n (with n a integer). k_{disp} and k_{comp} are the rate constants of disproportionation and comproportionation respectively.

Interestingly, the literature reports contradicting interpretations of the "real" mechanism (mainly due to tailored reaction conditions, hence favouring one side of the coin); albeit a portion of them (mimicking polymerisation conditions) are reliable and key pieces of data include,

1/ Disproportionation of [Cu^{I}(L)X] in DMSO (L is Me_6-TREN or PMDETA) is limited, and the remaining quantities of the complex present act in conjunction with activation by Cu(0)-wire.[139] Consequently, the claim of quantitative and instantaneous disproportionation of [Cu^{I}(L)X] is compromised.

2/ Activation of an alkyl halide by Cu(0) *via* an OSET mechanism is disfavoured compared to an ISET mechanism in solvents that disfavour disproportionation.[140]

3/ Disproportionation of [Cu^{I}(L)X] in water (L is Me_6-TREN or PMDETA) is quantitative,[107, 141-143] or near quantitative in the presence of monomers, whilst the order of addition of the reagents has a dramatic impact on the control over the polymerisation.

Although ambiguities between SARA-ATRP and SET-LRP remain, it is undeniable that Cu(0)-mediated polymerisation offers great opportunity to yield sophisticated macromolecular structures. As Cu(0) remains the main copper source in the following chapters, the technique will be referred to as Cu(0)-mediated RDRP.

1.2.6.3 Reversible-Addition Fragmentation chain Transfer polymerisation (RAFT)

The pioneering work of Otsu on iniferters highlighted the importance of an efficient chain transfer agent (CTA) to mediate polymerisation with good "*living*" characteristics. More importantly, chains could be re-initiated from the degenerated chain transfer agent, though with no further control. Moad and Rizzardo exploited the reversible chain transfer step for chain equilibration in radical polymerisation, whereby the CTA is a methacrylic macromonomer (bearing a terminal vinyl functionality).[144] This technique exploited the reversible chain transfer of a propagating chain (active species) with the (macro)-CTA

(*dormant* species), regulated by a homolytic substitution or addition-fragmentation (RAFT) to yield a "*living*" polymerisation.

However, RAFT polymerisation with an appropriate (or more effective) CTA, such as dithio-compounds (figure 1.13), became more attractive in 1998,[145] as excellent control over the MWD was obtained. This was subsequently expanded to a wider range of monomers than NMP and/or ATRP.[146]

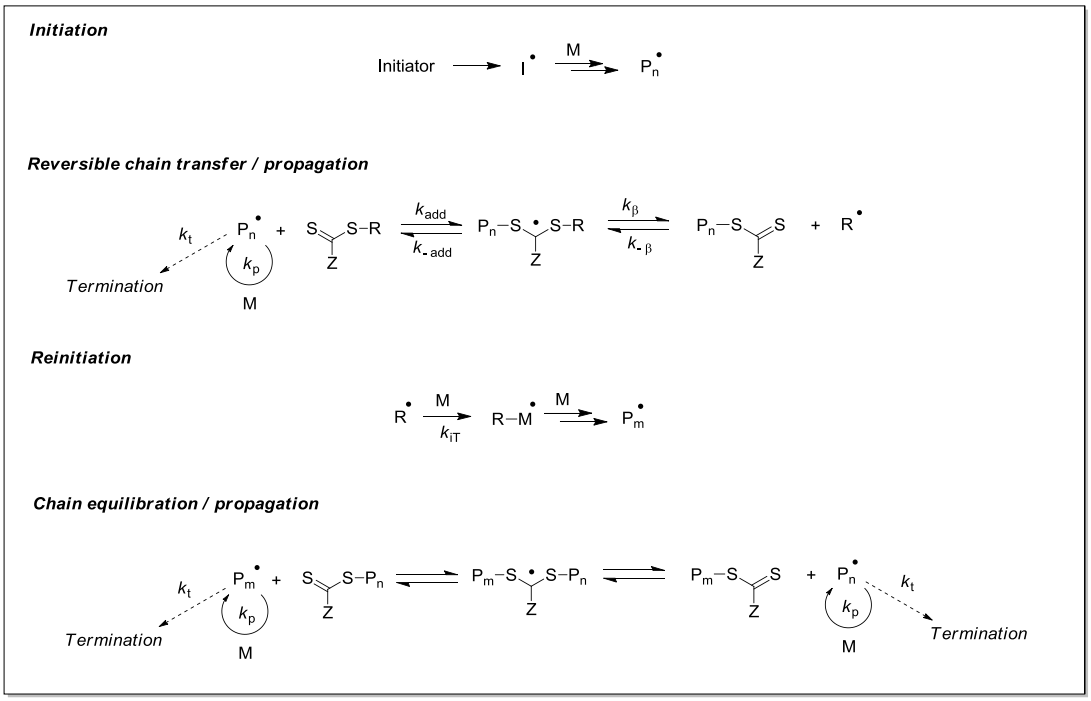


Figure 1.13. Mechanism of reversible addition fragmentation polymerisation. k_{add} is the addition rate constant, k_{β} is the β-scission rate constant and k_p the propagation rate constant.

RAFT agents are selected depending on the monomer employed, with dithioesters or trithiocarbonates utilised to mediate the polymerisation of more activated monomers (MAMs) such as (meth)acrylates, styrene and derivatives. Dithiocarbamates and xanthates are unsuitable for the controlled polymerisation of MAMs, though they are predominantly utilised for less activated monomers (LAMs), *i.e.* vinyl acetate, *N*-vinyl pyrrolidone and *N*-

vinyl carbazole.[147] Some RAFT agents can be tuned in order to control the polymerisation of MAMs and LAMs, allowing the synthesis of sophisticated block copolymers.[148]

RAFT polymerisation has gained considerable interest for the synthesis of sophisticated macromolecular structures (multiblock copolymers,[149-151] stars,[152] bio-conjugates[153]) as a result of its simplicity and robustness. The main commercial product made by an RDRP technique is still made by RAFT polymerisation.

1.2.6.4 Ring opening polymerisation (ROP)

Ring-opening polymerisation (ROP) is a robust tool mediated by successive additions of cyclic monomers such as epoxides, lactams, lactides or siloxanes (figure 1.14). Early findings on ROP in the 1950s, whereby the addition is mediated by an ionic source (cationic or anionic),[154, 155] have been exploited to yield materials of upmost importance, such as poly(ethylene oxide) (PEO, PEG),[156] poly(propylene oxide) (PPO)[157] and Nylon 6.[158] These investigations were succeeded by numerous investigations to achieve "*living*" characteristics.[159, 160 161]

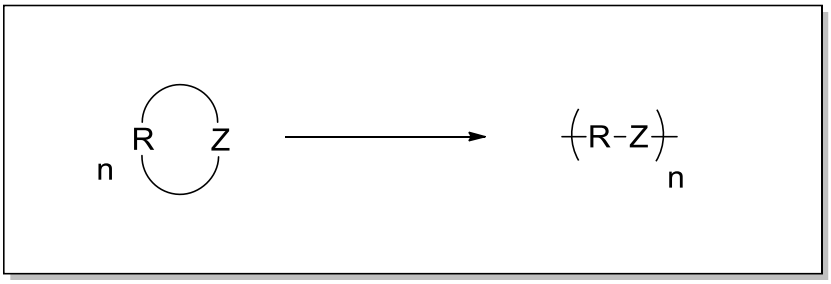


Figure 1.14. General reaction scheme of a ring-opening polymerisation, where Z is a linking group (*e.g.* ether, ester, amide).

Coordination-insertion ROP is one of the most common forms of ROP, whereby the polymerisation follows a pseudo-anionic pathway which could be divided into four steps: (a) coordination of the monomer to the catalyst, (b) insertion of the monomer onto the metal-oxygen bond of the catalyst by electronic rearrangement, (c) ring-opening of the cyclic monomer and (d) continuous insertion of the cyclic monomer (figure 1.15). This method is usually employed to yield well-defined polycaprolactones or polylactides.[162, 163]

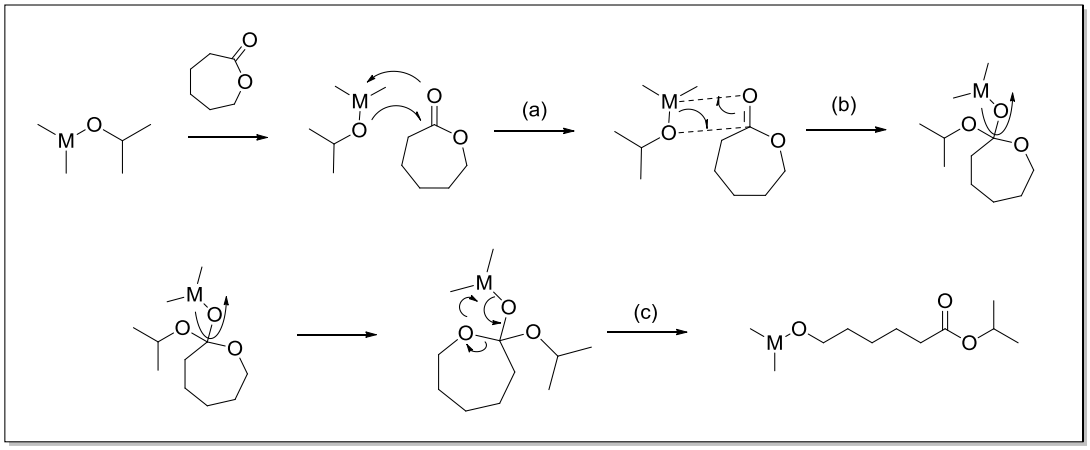


Figure 1.15. Mechanism of the initiation step of coordination-insertion ROP, according to Khanna *et al* [163]and Labet & Tielmanns,[160] where M is a metal catalyst.

ROP is tolerant to a wide variety of catalyst/initiators, namely metals and rare earth derivatives, such as tin alkoxides, aluminium alkoxides, zinc alkoxides, zincoxanes and aluminoxanes. Interestingly, these catalyst/initiators are capable of producing stereoregular polymers with targeted MW and narrow MWD.[162]

1.3. Telechelic polymers

1.3.1 Nomenclature of telechelic polymers

The development of RDRP techniques enabled the design of well-defined polymeric structures, with controlled architectures and MW, along with excellent retention of end-group fidelity. The reactivity of the functional chain end(s) has been exploited to yield block copolymers, star polymers, dendrimers, and/or polymer-peptide conjugates, through the reactivity of the α- and/or ω-ends.[164] However, when more than one functionality is present, allowing further reactions, the polymer is often described as telechelic.

The term telechelic was first introduced in polymer chemistry by Uranek,[165, 166] whilst describing oligomers that would display two reactive chain ends; and is derived from the greek *tele* ($\tau\eta\lambda\varepsilon$), meaning at distance or far from each other and *chelos* ($\chi\eta\lambda\iota\kappa o$) meaning claw. The term telechelic polymer was subsequently defined by the IUPAC as a "*prepolymer capable of entering into further polymerisation or other reaction through its reactive end groups*" whereby the "*reactive end groups in telechelic polymers come from initiator or chain transfer agent in chain polymerisation, but not from monomer as in polycondensation and polyadditions*".[167]

Nevertheless, extensive confusion arises from the definition of a telechelic polymer, mainly due to the number of functional group involved in further reactions.[168] As such, a telechelic macromolecule can be classified as mono- or semi-telechelic when bearing one functionality. The presence of two functional groups will be related to telechelic, homo-telechelic, α,ω-telechelic or di-telechelic compounds (*e.g.* diols, diamines and diacides). However, if the functional groups on the α- and ω-ends of the polymer are different, the

macromolecule will be ascribed as hetero-telechelic (table 1.2.). Telechelic polymers can also contain more than two functional ends, hence described as multifunctional telechelics.

Table 1.1. Schematic representation and classification of telechelic macromolecules.

Entry	Structural family	Chain end(s) functionality
1	Homo-telechelic Telechelic	
2	Hetero-telechelic	
3	Mono- or semi-telechelic	

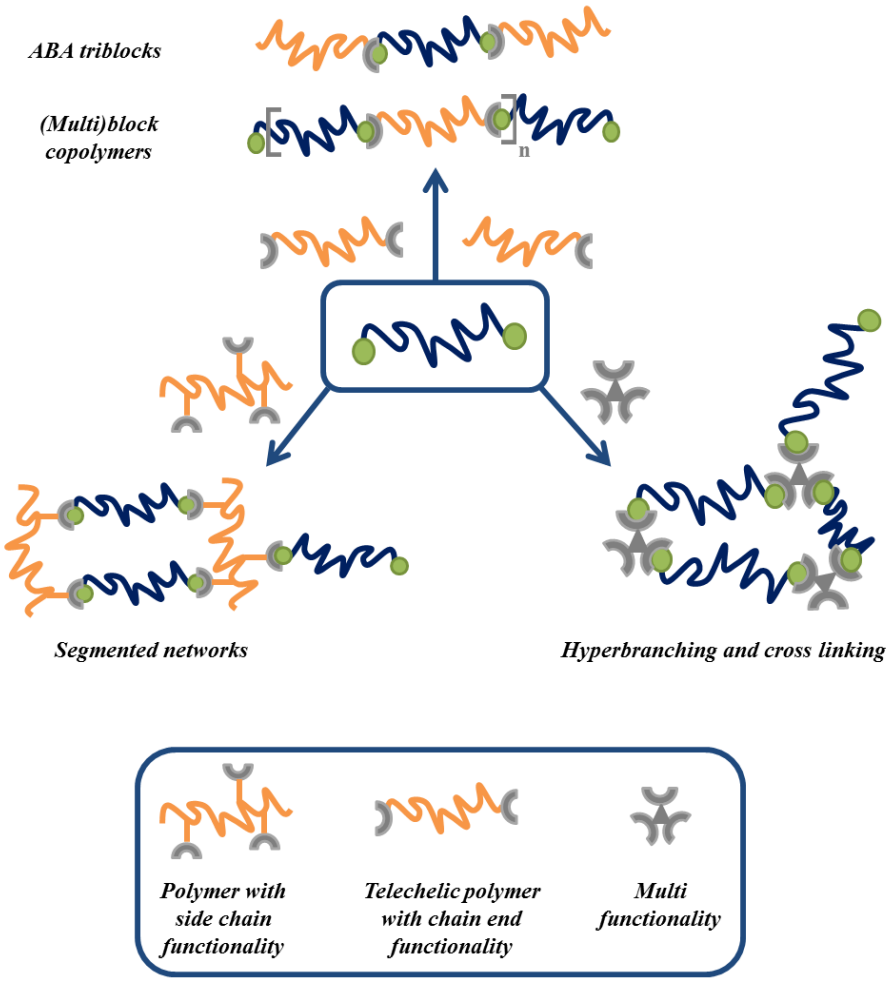
The concept of telechelic macromolecules expanded from classical linear and bi-functional architectures to more sophisticated designs. Thus, the denomination of the final prepolymer will vary depending on the topology (*e.g.* star-, dendridic-, multicyclic-) and the nature of the functional ends, *i.e.* hydroxyl-, amino- and/or carboxyl-telechelics.[169]

In the following sections, we will focus our interest on the development and uses of homo-telechelics, also referred to as telechelics.

1.3.2 Reactions and applications of telechelic macromolecules

The interest in telechelics has stemmed from their use as prepolymers, *via* the use of suitable reagents, in order to perform end group modifications and further polymerisation, *i.e.* polyaddition or polyconsensation. The prepolymers can be regarded as chain extenders, cross-linkers and precursors for block-,[170, 171] graft-copolymers[172, 173] and networks[174] by reaction with the appropriate reagents. The functionality present on the telechelic chain ends

as well as the nature of the reagents will dictate the process involved and the final macromolecule.[175] This can be exemplified by the reaction of a macro-diol with a diisocyanate to yield a polyurethane; similarly, the synthesis of polyesters *via* polycondensation, whereby a hydroxyl-telechelic is reacted with a carboxyl-telechelic polymer.



Scheme 1.2. Various architectures achievable by the reaction of telechelics. Adapted from Yagci *et al.*[169]

Historically, the development of telechelic macromolecules was stimulated by the design of thermoplastic elastomers, involving ABA triblock copolymers and/or multiblock copolymers.[176] The physical properties of the chain extenders, *i.e* the telechelics, would subsequently have a dramatic impact on the final product properties. Indeed, modification of

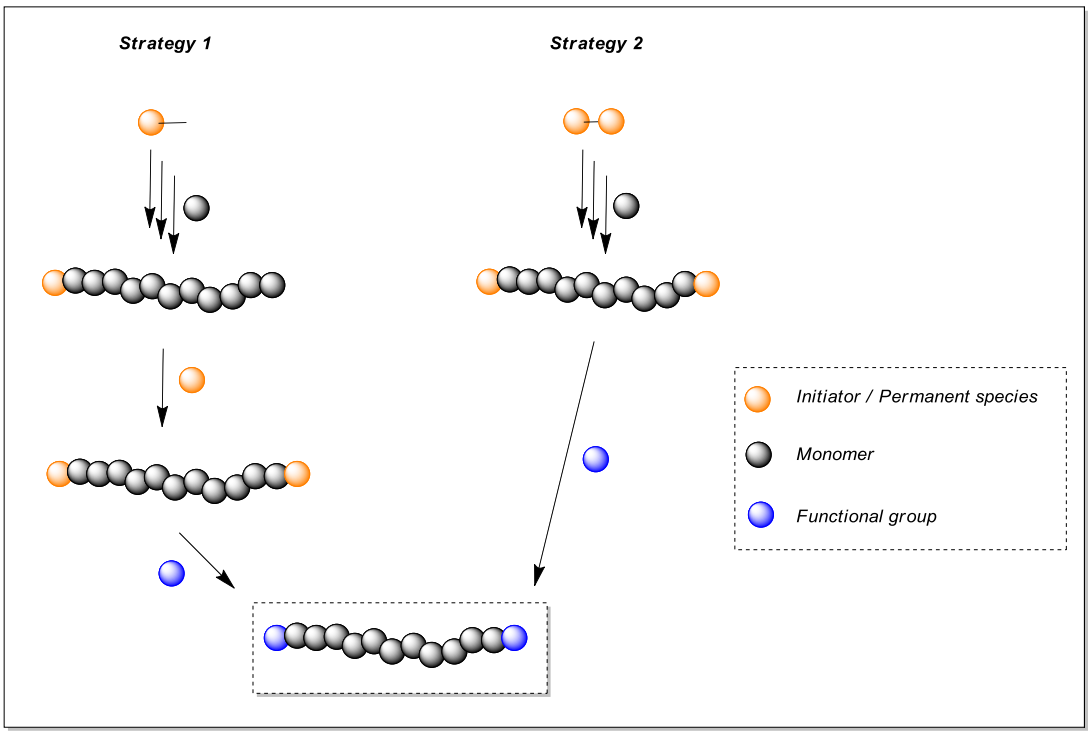
solubility, glass transition temperature (T_g), melting temperature (T_m) is in great depth mediated by careful tuning of the telechelic polymers.[177] Towards this end, the design of tailor-made telechelics gave tremendous advantages for the processing of such functional polymers *via* injection molding.[178]

Among the diverse applications of telechelics, the extensive employment of diols in polyurethane industry is of upmost importance. Since the first polyurethane by Bayer in 1947,[179] a spectacular growth is evident in the use of this versatile group of plastics.[180] The wide variety of forms accessible for polyurethanes (*e.g.* films, foams, soft rubbers, hard plastics, etc.) makes this functional polymer matrix, extremely attractive for various industries. By adapting the properties of the telechelic diols and diisocyanates, the resulting matrix can provide a diverse range of commercially important products, *i.e.* flexible foams (mattresses), packaging films and foams, fabric coatings, car bumpers and other vehicle furniture/protections, paints and thermoplastic elastomers.[181]

1.3.3 Synthesis of telechelics by reversible deactivation radical polymerisation and end-group modifications

Telechelics are extremely versatile prepolymers to achieve functional materials, through the reactivity of their chain ends. The plethora of synthetic tools presented in section 1.2. gives various routes to precisely design telechelic polymers, with broad variety over the monomer moieties. However, the necessity to carefully retain good chain end fidelity (to undergo further polymerisation or reaction) encourages the use of ionic polymerisation or RDRP instead of FRP, due to the extensive presence of undesired termination events; albeit investigations were carried out utilising FRP in the presence of functional initiators and/or chain transfer agents.[182]

The strategy to yield telechelics remains unchanged regardless of the selected polymerisation route.[171] The first strategy, utilises an initiating specie bearing a desired functionality on the α-end. Upon complete polymerisation, the ω-end functional group is introduced *via* a *persistent* specie (*cf.* section 1.2.6, *e.g.* CTA) or subsequently modified post polymerisation. A second strategy is to exploit bi-functional intitiating species and/or a bi-functional *persistent* species. Hence, α,ω-telechelics can be obtained and the functionality can be easily altered on the chain ends *via* orthogonal chemistry.



Scheme 1.3. Various strategies to yield functional telechelics.

Unfortunately, the two strategies are not always available depending on the pre-selected polymerisation route, as detailed in the next sections.

1.3.3.1 Telechelics by ionic polymerisations

The development and understanding of "*living*" ionic polymerisation was subsequently exploited to design telechelic macromolecules, with narrow MWD and good retention of the *α,ω*-end groups.[183,184] In anionic polymerisation, the main strategy to yield telechelics utilises a protected initiating species (*e.g.*, siloxane, acetal) and an electrophile to terminate the polymerisation.[185, 186] For example, reaction with carbon dioxide[187] and ethylene oxide[188, 189] would terminate the macromolecular chain with carboxyl and hydroxyl groups respectively. The need for a protected group on the functional initiator lies in the harsh conditions employed in anionic polymerisation (see section 1.2.3) which would be detrimental for hydroxyl, amino and/or carboxyl groups. For instance the protection/deprotection strategy was successfully employed to yield *α,ω*-hydroxy poly(1,3-butadiene)-*b*-poly(styrene)-*b*-poly(1,3-butadiene) *via* an anionic process, which upon further modification, generated well-defined vesicles.[190] In other reports, *α,ω*-carboxy poly(isopropylene)-*b*-poly(styrene)-*b*-poly(isopropylene) could be obtained post polymerisation by addition of carbon dioxide in the reaction medium.[191]

Cationic polymerisation utilises similar strategy to its sibling, by employing a nucleophile to terminate the polymerisation, such as sodiomalonate to yield a carboxy-telechelic polymer.[192] Interestingly, the association of bi-functional 1,4-bis(2-chloroisopropyl) chloride initiator with BCl_3 catalyst would yield a *α,ω*-Cl terminated (most commonly but not limited to) polyisobutylene.[193, 194] Subsequently the halide chain ends can be altered to obtain diols or diamines. Hence, cationic polymerisation offers a good alternative to design functional telechelics through an ionic process.[195, 196]

1.3.3.2 Telechelics by group transfer polymerisation

Quenching agents utilised in cationic polymerisation, such as silyl ketene acetals, to yield hetero-telechelics are of upmost importance for the design of telechelics by GTP.[197] Indeed, a protected silyl functionality can be introduced on the silyl ketene acetal, which upon hydrolysis of the chain ends, would yield hydroxyl or carboxyl groups.[197] This has been applied for the GTP of methyl methacrylate (MMA) with [(2-methyl-1-[2-(trimethylsiloxy)ethoxy]1-propenyloxy]-trimethyl silane, under the presence of HF_2^-. Upon polymerisation, the polymer chain can be coupled with 1,4-bis(bromomethyl)-benzene and the chain ends hydrolysed to yield *α,ω*-hydroxy-PMMA. Similarly, 1,1'-bis(trimethylsiloxy)-2-methyl-1-propene can be utilised as the initiator, which will yield a *α,ω*-carboxy PMMA. The use of protected silanes and mild reaction conditions made GTP extremely attractive to yield telechelics, though the limited selectivity over the monomer moieties (*e.g.* methacrylates) and the need of extensive purification of the reagents, arguably allowed for the use of different RDRP processes, as presented below.

1.3.3.3 Telechelics by nitroxide-mediated polymerisation

The tolerance over the nitroxide functionality allows the preparation of telechelic macromolecules by NMP with relative ease.[31] Functionalities can be introduced either *via* a bi-functional alkoxyamine (uni-molecular process), or with the dual combination of a mono-functional alkoxyamine with a functional initiator (bi-molecular process). Although hydroxyl[198] and carboxyl[199] groups can be easily introduced on the *α,ω*-ends of the polymer, the presence of amines and alkynes requires protective chemistry.[200] The high level of functionalisation attainable with NMP (> 95%) provides good alternative to an ionic process.[201]

Post polymerisation modifications are also common in NMP, by alteration or denaturation of the nitroxide post polymerisation, yielding the desired functionalities.[202] This includes the introduction of terpyridine on the ω-end of an hetero-telechelic polystyrene *via* maleimide substitution, thus yielding a functional α,ω-telechelic.[203]

1.3.3.4 Telechelics by addition-fragmentation and reversible addition-fragmentation chain transfer polymerisation

The synthesis of macromonomers by CCTP enabled the use of functional macro-CTAs as transfer agent in addition-fragmentation polymerisation. Interestingly, DuPont[204] and subsequently Haddleton *et al.*[205] exploited the use of dimers as CTAs (figure 1.16), yielding a major distribution of α,ω-telechelic for the resulting polymer (whilst a minor distribution will be hetero-telechelic due to unavoidable terminations events).[206] Functional dimers would include benzyl methacrylate dimer (BzMA-dimer)[207] or 2-hydroxyethyl methacrylate dimer (HEMA-dimer).[205]

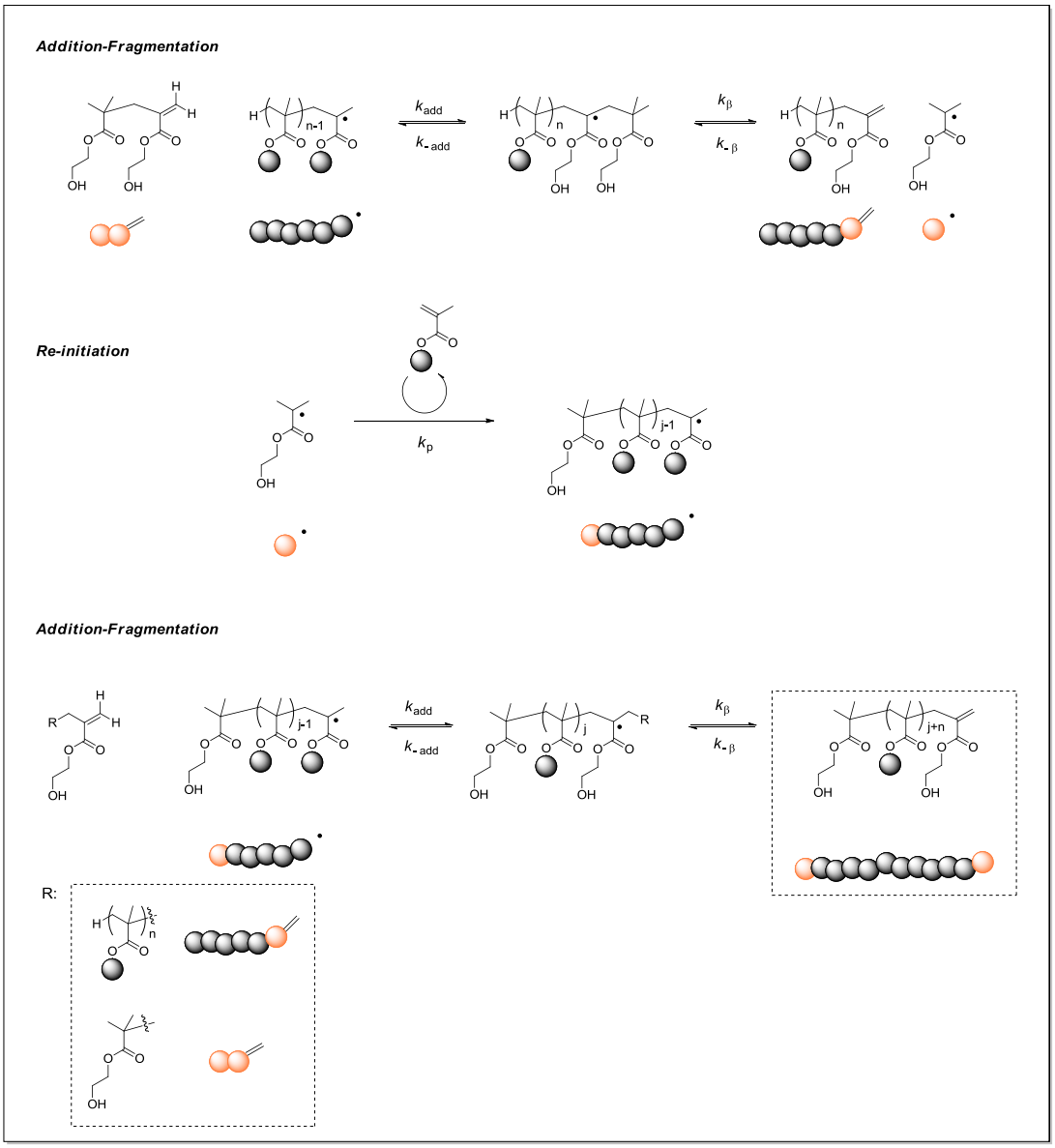


Figure 1.16. Proposed mechanism for the addition-fragmentation polymerisation of methacrylate moieties under the presence of HEMA-dimer.

Despite the relative ease inherent with addition fragmentation polymerisation, the low chain transfer constant of the dimers was detrimental to maximise the yield of telechelics. This could be circumvented by the use of mixed trimers (hence increasing the C_{tr} constant),[17] albeit their production and purification can be arduous. Another alternative was to utilise highly efficient CTAs, *i.e.* dithio-containing compounds which can be further modified to the desired functionality.

The tolerance of RAFT polymerisation to a wider range of monomer moieties than ATRP or NMP with various side chain and CTAs functionalities allows the design of sophisticated telechelic architectures with good control over the MWD.[208] The use of symmetrical CTAs with allyl,[209] hydroxyl[210] or carboxyl[211, 212] groups could successfully mediate the polymerisation of acrylamides, (meth)acrylate and styrene. Symmetrical CTAs bearing no functionalities can also be utilised and altered post-polymerisation.[213, 214] Alternatively, R-functional CTAs (introducing α-end functionality) could be employed to obtain hetero-telechelics, whilst the ω-end functionality would be introduced *via* post-polymerisation modifications, *i.e.* hydrolysis,[215] aminolysis,[216] metal-assisted and radical-induced reactions.[217]

1.3.3.5 Telechelics by ring opening polymerisation

ROP has been extensively utilised to yield polymers (*e.g.* PEO) which find interest in various industrial applications.[218, 219] The ROP of cyclic esters (*e.g.* lactones, lactams) has been widely developed *via* a coordination-insertion mechanism whereby the catalyst is a coordination complex, typically an alkoxide (see section 1.2.5.4). Although this synthetic tool would provide a versatile route to yield well-defined hetero-telechelics, this was unsatisfactory to yield diols.[220] Consequently, numerous efforts have been undertaken to design a catalyst which would yield a α,ω-hydroxy telechelic, *i.e.* borohydride complexes.[221]

Another strategy arising from the development of functional polyesters/polycarbonates was to utilise an existing diol as initiating species for the ROP of cyclic ester. This would provide an easy access to tailor-made macro diols which can be further reacted. Indeed, polycaprolactone, polylactide diols have been utilised as prepolymers to yield macro-ATRP initiators,[222] biodegradable polyesters and polyurethanes.[223]

Interestingly, the design of telechelics by ROP has not been limited to cyclic esters and has been widely investigated. The use of oxazolines for example, highlights the versatility of the technique,[224] and introduces new functionalities (*e.g.* alkyl, phenyl) on the polymer side chains.[225] The ROP of oxazolines would be ascribed as cationic ROP, considering the propagating species. Functional groups are introduced *via* the initiator and a nucleophile which terminates the polymerisation (figure 1.17).

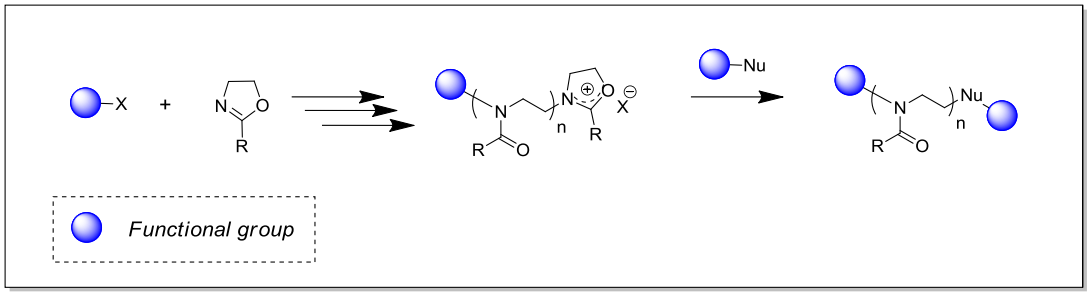


Figure 1.17. Synthesis of telechelic polyoxazolines by cationic ring-opening polymerisation. X is an halogen (Cl, Br), R a functional group and Nu a nucleophile.

1.3.3.6 Telechelics by ATRP

ATRP and to a greater extent TMM-RDRP, is a versatile technique to yield polymers with good chain end fidelity for a wide range of monomer functionality. Moreover, the presence of halides on the chain ends facilitates the modification, *via* nucleophilic substitution, electrophillic addition and subsequent "*click*" reactions (see section 2.1).[226] Hence, the synthesis of telechelics has received great attention in the literature and several strategies have emerged. The use of functional initiators (with protected or unprotected functionalities) can be employed, with the necessity of post polymerisation modifications.[227, 228] Additionally, bi-functional initiating species can be utilised, thus yielding *α,ω*-halide telechelics.[229-231] Interestingly, a novel strategy, atom transfer radical addition or coupling (ATRA/C) was also exploited to yield telechelic macromolecules.[232] Functionalisation could

be performed utilising a co-monomer which would not homopolymerise (*e.g.* allyl alcohol, maleic anhydride),[233-235] a chain transfer agent, or a combination of oligomeric and polymeric materials (figure 1.18). Unfortunately, an ATRA/C route would not be possible for monomers which would terminate *via* disproportionation (*e.g.* MMA). Consequently, the strategy was in great depth applied to polystyrene and polyacrylates.

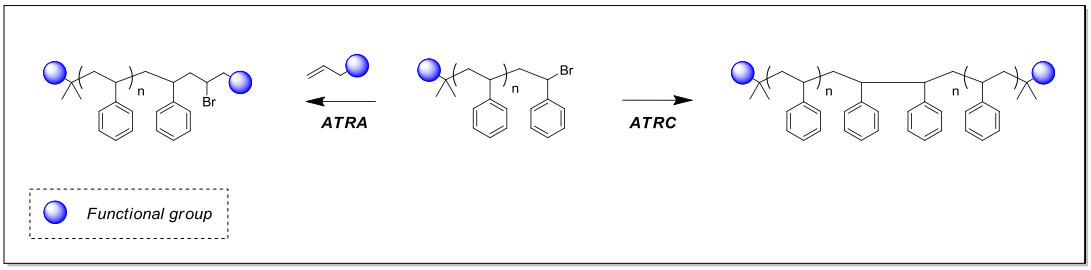


Figure 1.18. Atom transfer radical addition/coupling of polystyrene.

The combination of ATRP with other RDRP techniques has also been investigated to design functional telechelics. Transformation of the bromide chain ends could be performed utilising a $Co^{(II)}$ cobaloxime complex (genuinely employed in CCTP, see section 1.2.2), thus yielding to an unsaturated macromonomer. This has been applied to polyacrylates, which cannot be obtained by conventional CCTP.[236, 237]

1.3.3.7 Telechelics by Cu(0)-mediated reversible deactivation radical polymerisation

One of the main drawbacks of an ATRP process to yield telechelics is the loss of chain end fidelity at high conversion, hence adding purification processes post polymerisation. This can be circumvented by utilising Cu(0) (in the form of a wire, mesh or particles) as the primary copper source.[238, 239] This technique, referred to as SET-LRP (see section 1.2.6.2.3.)

displays excellent end group fidelity at quantitative monomer conversion, which allows alteration of the halide chain ends without purification steps.[117, 240] This has been applied to a variety of initiating moieties, mainly bi-functional, which would support the synthesis of cleavable or phase-transitional polymers.[106, 241, 242]

Unfortunately, the poorer tolerance of Cu(0)-mediated RDRP to the polymerisable moieties has limited the design of telechelics to acrylates, while block copolymers are yet to be investigated. Moreover, the polymerisation of acrylamides and/or methacrylates has not been assessed to yield functional telechelics.

1.4. Motivation: Towards tailor-made telechelic polymers via Cu(0)-mediated radical polymerisation

The plethora of polymerisation techniques available today allows the design of tailor-made macromolecular structures, whilst retaining chain end fidelity and narrow MWD. The extensive work conducted while focusing on telechelics clearly showed the potential and impact of such materials in polymer science. However, it is not yet evident which technique would be the most attractive to yield telechelics depending on the targeted materials. Indeed, in an attempt to highlight the advantages/drawbacks of RDRP techniques towards the synthesis of telechelics, it can be argued that none of the technique, on their own, can fulfil all criteria (*e.g.* high chain end fidelity, good tolerance over multiple functionalities and arguably undemanding processes). However, the wide range of possibilities arising from the combination of synthetic tools would yield to sophisticated materials. Moreover, deeper understanding of emerging techniques, in addition to the re-discovery of "old" synthetic tools could offer great opportunities to design tailor-made telechelics, further expanding the scope of available polymeric materials.

In this work, the focus is on the development of "novel" strategies towards the design of telechelic polymers *via* Cu(0)-mediated RDRP. The good chain end fidelity attainable at high monomer conversion in organic media makes this process attractive for the synthesis of telechelics. However, exploring the limits of this tool in terms of tolerance and reactivity of the chain ends functionalities (*e.g.* hydroxyl groups) has not been investigated in depth and would be highly desirable to access tailor-made (co)polymers. Moreover, the development of methacrylic based copolymers *via* a Cu(0)-mediated process would broaden the range of materials accessible as well as the versatility of the technique. In the end, the robustness of this synthetic tool in aqueous media could pave the way to sophisticated "smart" materials, whilst polymerising stimuli-responsive monomers with (meth)acrylic or acrylamide backbones.

1.5. References

1. P. J. Flory, *J. Am. Chem. Soc.*, 1937, **59**, 241-253.
2. G. G. Odian, *Principles of Polymerization*, 4th edn., Wiley-Interscience, Hoboken, N.J., 2004.
3. G. Moad and D. H. Solomon, in *The Chemistry of Radical Polymerization (Second Edition)*, ed. G. M. H. Solomon, Elsevier Science Ltd, Amsterdam, 2005, pp. 49-166.
4. S. Beuermann and M. Buback, *Prog. Polym. Sci.*, 2002, **27**, 191-254.
5. G. Moad and D. H. Solomon, in *The Chemistry of Radical Polymerization (Second Edition)*, ed. G. M. H. Solomon, Elsevier Science Ltd, Amsterdam, 2005, pp. 167-232.
6. V. Schreck, A. Serelis and D. Solomon, *Aust. J. Chem.*, 1989, **42**, 375-393.
7. S. Bizilj, D. Kelly, A. Serelis, D. Solomon and K. White, *Aust. J. Chem.*, 1985, **38**, 1657-1673.
8. H. Çatalgil-Giz, A. Giz and A. Öncül-Koç, *Polym. Bull.*, 1999, **43**, 215-222.
9. J. Chiefari and E. Rizzardo, in *Handbook of Radical Polymerization*, John Wiley & Sons, Inc., 2003, pp. 629-690.
10. A. A. Gridnev and S. D. Ittel, *Chem. Rev.*, 2001, **101**, 3611-3660.
11. C.T. Berge, M. J. Darmon and J. A. Antonelli, USPatent, 5362826 A, **1994**.
12. A. H. Janowicz, USPatent, 4694054 A, **1987**.
13. G. M. Carlson and K. J. Abbey, USPatent, 4526945 A, **1985**.
14. D. M. Haddleton, M. C. Crossman, K. H. Hunt, C. Topping, C. Waterson and K. G. Suddaby, *Macromolecules*, 1997, **30**, 3992-3998.

15. K. G. Suddaby, D. M. Haddleton, J. J. Hastings, S. N. Richards and J. P. O'Donnell, *Macromolecules*, 1996, **29**, 8083-8091.
16. D. A. Morrison, T. P. Davis, J. P. A. Heuts, B. Messerle and A. A. Gridnev, *J. Polym. Sci., Part A: Polym. Chem.*, 2006, **44**, 6171-6189.
17. C. L. Moad, G. Moad, E. Rizzardo and S. H. Thang, *Macromolecules*, 1996, **29**, 7717-7726.
18. M. Szwarc, M. Levy and R. Milkovich, *J. Am. Chem. Soc.*, 1956, **78**, 2656-2657.
19. M. Szwarc, *Nature*, 1956, **178**, 1168-1169.
20. K. Matyjaszewski and M. Sawamoto, in *Cationic Polymerizations; Mecheniasms, Synthesis, and Appplications*, eds. K. Matyjaszewski and M. Dekker, CRC Press, New York, 1996.
21. O. W. Webster, W. R. Hertler, D. Y. Sogah, W. B. Farnham and T. V. RajanBabu, *J. Am. Chem. Soc.*, 1983, **105**, 5706-5708.
22. W. R. Hertler, *Macromol. Symp.*, 1994, **88**, 55-69.
23. R. Quirk and G. Bidinger, *Polym. Bull.*, 1989, **22**, 63-70.
24. R. P. Quirk and J. Ren, *Macromolecules*, 1992, **25**, 6612-6620.
25. O. W. Webster, *J. Polym. Sci., Part A: Polym. Chem.*, 2000, **38**, 2855-2860.
26. H. Fischer, *J. Polym. Sci., Part A: Polym. Chem.*, 1999, **37**, 1885-1901.
27. R. P. Quirk and B. Lee, *Polym. Int.*, 1992, **27**, 359-367.
28. T. Otsu and M. Yoshida, *Die Makromol. Chem., Rap. Commun.*, 1982, **3**, 127-132.
29. T. Otsu, *J. Polym. Sci., Part A: Polym. Chem.*, 2000, **38**, 2121-2136.
30. D. H. Solomon, E. Rizzardo, P. Cacioli, USPatent, 4581429 A, **1986**.
31. C. J. Hawker, A. W. Bosman and E. Harth, *Chem. Rev.*, 2001, **101**, 3661-3688.
32. G. Moad, E. Rizzardo and D. H. Solomon, *Macromolecules*, 1982, **15**, 909-914.
33. M. K. Georges, R. P. N. Veregin, P. M. Kazmaier and G. K. Hamer, *Macromolecules*, 1993, **26**, 2987-2988.
34. R. D. Puts and D. Y. Sogah, *Macromolecules*, 1996, **29**, 3323-3325.
35. B. Yamada, Y. Nobukane and Y. Miura, *Polym. Bull.*, 1998, **41**, 539-544.
36. J. D. Druliner, *Macromolecules*, 1991, **24**, 6079-6082.
37. E. De León-Sáenz, G. Morales, R. Guerrero-Santos and Y. Gnanou, *Macromol. Chem. Phys.*, 2000, **201**, 74-83.
38. M. Steenbock, M. Klapper and K. Müllen, *Macromol. Chem. Phys.*, 1998, **199**, 763-769.
39. Y. Guillaneuf, D. Gigmes, S. R. A. Marque, P. Astolfi, L. Greci, P. Tordo and D. Bertin, *Macromolecules*, 2007, **40**, 3108-3114.
40. F. Minisci, *Acc. Chem. Res.*, 1975, **8**, 165-171.
41. J. Iqbal, B. Bhatia and N. K. Nayyar, *Chem. Rev.*, 1994, **94**, 519-564.
42. M. Kato, M. Kamigaito, M. Sawamoto and T. Higashimura, *Macromolecules*, 1995, **28**, 1721-1723.
43. J.-S. Wang and K. Matyjaszewski, *J. Am. Chem. Soc.*, 1995, **117**, 5614-5615.
44. T. Pintauer and K. Matyjaszewski, *Coord. Chem. Rev.*, 2005, **249**, 1155-1184.
45. K. Matyjaszewski and J. Xia, *Chem. Rev.*, 2001, **101**, 2921-2990.
46. J. A. M. Brandts, P. van de Geijn, E. E. van Faassen, J. Boersma and G. van Koten, *J. Organomet. Chem.*, 1999, **584**, 246-253.
47. Y. Kotani, M. Kamigaito and M. Sawamoto, *Macromolecules*, 1999, **32**, 2420-2424.
48. T. Ando, M. Kamigaito and M. Sawamoto, *Macromolecules*, 1997, **30**, 4507-4510.
49. C. Granel, P. Dubois, R. Jérôme and P. Teyssié, *Macromolecules*, 1996, **29**, 8576-8582.
50. P. Lecomte, I. Drapier, P. Dubois, P. Teyssié and R. Jérôme, *Macromolecules*, 1997, **30**, 7631-7633.
51. T. Grimaud and K. Matyjaszewski, *Macromolecules*, 1997, **30**, 2216-2218.
52. D. M. Haddleton, C. B. Jasieczek, M. J. Hannon and A. J. Shooter, *Macromolecules*, 1997, **30**, 2190-2193.

53. J. Qiu and K. Matyjaszewski, *Macromolecules*, 1997, **30**, 5643-5648.
54. M. Teodorescu and K. Matyjaszewski, *Macromolecules*, 1999, **32**, 4826-4831.
55. J. T. Rademacher, M. Baum, M. E. Pallack, W. J. Brittain and W. J. Simonsick, *Macromolecules*, 1999, **33**, 284-288.
56. K. Matyjaszewski, S. Mu Jo, H.-j. Paik and S. G. Gaynor, *Macromolecules*, 1997, **30**, 6398-6400.
57. K. Matyjaszewski, J.-L. Wang, T. Grimaud and D. A. Shipp, *Macromolecules*, 1998, **31**, 1527-1534.
58. V. Percec and B. Barboiu, *Macromolecules*, 1995, **28**, 7970-7972.
59. V. Percec, B. Barboiu and H. J. Kim, *J. Am. Chem. Soc.*, 1998, **120**, 305-316.
60. T. Ando, M. Kamigaito and M. Sawamoto, *Tetrahedron*, 1997, **53**, 15445-15457.
61. W. Tang and K. Matyjaszewski, *Macromolecules*, 2007, **40**, 1858-1863.
62. W. Tang, Y. Kwak, W. Braunecker, N. V. Tsarevsky, M. L. Coote and K. Matyjaszewski, *J. Am. Chem. Soc.*, 2008, **130**, 10702-10713.
63. N. V. Tsarevsky and K. Matyjaszewski, *Chem. Rev.*, 2007, **107**, 2270-2299.
64. N. V. Tsarevsky, W. A. Braunecker, A. Vacca, P. Gans and K. Matyjaszewski, *Macromol. Symp.*, 2007, **248**, 60-70.
65. J.-S. Wang and K. Matyjaszewski, *Macromolecules*, 1995, **28**, 7572-7573.
66. J. Gromada and K. Matyjaszewski, *Macromolecules*, 2001, **34**, 7664-7671.
67. K. Matyjaszewski, S. Coca, S. G. Gaynor, M. Wei and B. E. Woodworth, *Macromolecules*, 1997, **30**, 7348-7350.
68. W. Jakubowski, K. Min and K. Matyjaszewski, *Macromolecules*, 2005, **39**, 39-45.
69. A. de Vries, B. Klumperman, D. de Wet-Roos and R. D. Sanderson, *Macromol. Chem. Phys.*, 2001, **202**, 1645-1648.
70. K. Matyjaszewski, W. Jakubowski, K. Min, W. Tang, J. Huang, W. A. Braunecker and N. V. Tsarevsky, *P. Natl. Acad. Sci. USA.*, 2006, **103**, 15309-15314.
71. W. Jakubowski and K. Matyjaszewski, *Angew. Chem. Int. Ed.*, 2006, **45**, 4482-4486.
72. K. Min, H. Gao and K. Matyjaszewski, *Macromolecules*, 2007, **40**, 1789-1791.
73. Y. Gnanou and G. Hizal, *J. Polym. Sci., Part A: Polym. Chem.*, 2004, **42**, 351-359.
74. Y. Kwak, A. J. D. Magenau and K. Matyjaszewski, *Macromolecules*, 2011, **44**, 811-819.
75. H. Dong and K. Matyjaszewski, *Macromolecules*, 2008, **41**, 6868-6870.
76. J. Pietrasik, H. Dong and K. Matyjaszewski, *Macromolecules*, 2006, **39**, 6384-6390.
77. K. Matyjaszewski, N. V. Tsarevsky, W. A. Braunecker, H. Dong, J. Huang, W. Jakubowski, Y. Kwak, R. Nicolay, W. Tang and J. A. Yoon, *Macromolecules*, 2007, **40**, 7795-7806.
78. V. Percec, B. Barboiu and M. van der Sluis, *Macromolecules*, 1998, **31**, 4053-4056.
79. Y. Zhang, Y. Wang and K. Matyjaszewski, *Macromolecules*, 2011, **44**, 683-685.
80. Y. Zhang, Y. Wang, C.-h. Peng, M. Zhong, W. Zhu, D. Konkolewicz and K. Matyjaszewski, *Macromolecules*, 2011, **45**, 78-86.
81. A. J. D. Magenau, N. C. Strandwitz, A. Gennaro and K. Matyjaszewski, *Science*, 2011, **332**, 81-84.
82. F. A. Leibfarth, K. M. Mattson, B. P. Fors, H. A. Collins and C. J. Hawker, *Angew. Chem. Int. Ed.*, 2013, **52**, 199-210.
83. M. A. Tasdelen, M. Uygun and Y. Yagci, *Macromol. Rapid Commun.*, 2011, **32**, 58-62.
84. B. P. Fors and C. J. Hawker, *Angew. Chem. Int. Ed.*, 2012, **51**, 8850-8853.
85. S. Dadashi-Silab, M. Atilla Tasdelen and Y. Yagci, *J. Polym. Sci., Part A: Polym. Chem.*, 2014, **52**, 2878-2888.
86. A. Anastasaki, V. Nikolaou, Q. Zhang, J. Burns, S. R. Samanta, C. Waldron, A. J. Haddleton, R. McHale, D. Fox, V. Percec, P. Wilson and D. M. Haddleton, *J. Am. Chem. Soc.*, 2013, **136**, 1141-1149.

87. A. Anastasaki, V. Nikolaou, G. S. Pappas, Q. Zhang, C. Wan, P. Wilson, T. P. Davis, M. R. Whittaker and D. M. Haddleton, *Chem. Sci.*, 2014, **5**, 3536-3542.
88. A. Anastasaki, V. Nikolaou, A. Simula, J. Godfrey, M. Li, G. Nurumbetov, P. Wilson and D. M. Haddleton, *Macromolecules*, 2014, **47**, 3852-3859.
89. A. Anastasaki, V. Nikolaou, F. Brandford-Adams, G. Nurumbetov, Q. Zhang, G. J. Clarkson, D. J. Fox, P. Wilson, K. Kempe and D. M. Haddleton, *Chem. Commun.*, 2015, **51**, 5626-5629.
90. A. Anastasaki, V. Nikolaou, N. W. McCaul, A. Simula, J. Godfrey, C. Waldron, P. Wilson, K. Kempe and D. M. Haddleton, *Macromolecules*, 2015, **48**, 1404-1411.
91. E. Frick, A. Anastasaki, D. M. Haddleton and C. Barner-Kowollik, *J. Am. Chem. Soc.*, 2015, **137**, 6889-6896.
92. V. Percec, A. V. Popov, E. Ramirez-Castillo, M. Monteiro, B. Barboiu, O. Weichold, A. D. Asandei and C. M. Mitchell, *J. Am. Chem. Soc.*, 2002, **124**, 4940-4941.
93. V. Percec, T. Guliashvili, J. S. Ladislaw, A. Wistrand, A. Stjerndahl, M. J. Sienkowska, M. J. Monteiro and S. Sahoo, *J. Am. Chem. Soc.*, 2006, **128**, 14156-14165.
94. N. H. Nguyen, B. M. Rosen, G. Lligadas and V. Percec, *Macromolecules*, 2009, **42**, 2379-2386.
95. G. Lligadas and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2008, **46**, 2745-2754.
96. X. Jiang, B. M. Rosen and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 2716-2721.
97. S. R. Samanta, M. E. Levere and V. Percec, *Polym. Chem.*, 2013, **4**, 3212-3224.
98. A. Anastasaki, C. Waldron, V. Nikolaou, P. Wilson, R. McHale, T. Smith and D. M. Haddleton, *Polym. Chem.*, 2013, **4**, 4113-4119.
99. W. Wang, Z. Zhang, J. Zhu, N. Zhou and X. Zhu, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 6316-6327.
100. S. Fleischmann and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 4884-4888.
101. S. Fleischmann and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 2236-2242.
102. S. Fleischmann and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 2243-2250.
103. B. D. Hornby, A. G. West, J. C. Tom, C. Waterson, S. Harrisson and S. Perrier, *Macromol. Rapid Commun.*, 2010, **31**, 1276-1280.
104. N. H. Nguyen, X. Leng and V. Percec, *Polym. Chem.*, 2013, **4**, 2760-2766.
105. N. H. Nguyen, C. Rodriguez-Emmenegger, E. Brynda, Z. Sedlakova and V. Percec, *Polym. Chem.*, 2013, **4**, 2424-2427.
106. J. A. Syrett, M. W. Jones and D. M. Haddleton, *Chem. Commun.*, 2010, **46**, 7181-7183.
107. Q. Zhang, P. Wilson, Z. Li, R. McHale, J. Godfrey, A. Anastasaki, C. Waldron and D. M. Haddleton, *J. Am. Chem. Soc.*, 2013, **135**, 7355-7363.
108. N. H. Nguyen, B. M. Rosen and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 1752-1763.
109. J. Tom, B. Hornby, A. West, S. Harrisson and S. Perrier, *Polym. Chem.*, 2010, **1**, 420-422.
110. J. Gao, Z. Zhang, N. Zhou, Z. Cheng, J. Zhu and X. Zhu, *Macromolecules*, 2011, **44**, 3227-3232.
111. X.-H. Liu, G.-B. Zhang, B.-X. Li, Y.-G. Bai and Y.-S. Li, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 5439-5445.
112. N. H. Nguyen, B. M. Rosen, X. Jiang, S. Fleischmann and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 5577-5590.

113. N. H. Nguyen, J. Kulis, H.-J. Sun, Z. Jia, B. van Beusekom, M. E. Levere, D. A. Wilson, M. J. Monteiro and V. Percec, *Polym. Chem.*, 2013, **4**, 144-155.
114. N. H. Nguyen, B. M. Rosen and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2011, **49**, 1235-1247.
115. F. Nyström, A. H. Soeriyadi, C. Boyer, P. B. Zetterlund and M. R. Whittaker, *J. Polym. Sci., Part A: Polym. Chem.*, 2011, **49**, 5313-5321.
116. N. Zhang, S. R. Samanta, B. M. Rosen and V. Percec, *Chem. Rev.*, 2014, **114**, 5848-5958.
117. A. H. Soeriyadi, C. Boyer, F. Nyström, P. B. Zetterlund and M. R. Whittaker, *J. Am. Chem. Soc.*, 2011, **133**, 11128-11131.
118. N. H. Nguyen, M. E. Levere and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2012, **50**, 860-873.
119. B. M. Rosen and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2008, **46**, 5663-5697.
120. B. M. Rosen and V. Percec, *Chem. Rev.*, 2009, **109**, 5069-5119.
121. M. E. Levere, N. H. Nguyen, X. Leng and V. Percec, *Polym. Chem.*, 2013, **4**, 1635-1647.
122. N. H. Nguyen, H.-J. Sun, M. E. Levere, S. Fleischmann and V. Percec, *Polym. Chem.*, 2013, **4**, 1328-1332.
123. X. Jiang, B. M. Rosen and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 403-409.
124. A. Anastasaki, A. J. Haddleton, Q. Zhang, A. Simula, M. Droesbeke, P. Wilson and D. M. Haddleton, *Macromol. Rapid Commun.*, 2014, **35**, 965-970.
125. S. R. Samanta, V. Nikolaou, S. Keller, M. J. Monteiro, D. A. Wilson, D. M. Haddleton and V. Percec, *Polym. Chem.*, 2015, **6**, 2084-2097.
126. Q. Zhang, Z. Li, P. Wilson and D. M. Haddleton, *Chem. Commun.*, 2013, **49**, 6608-6610.
127. C. Waldron, Q. Zhang, Z. Li, V. Nikolaou, G. Nurumbetov, J. Godfrey, R. McHale, G. Yilmaz, R. K. Randev, M. Girault, K. McEwan, D. M. Haddleton, M. Droesbeke, A. J. Haddleton, P. Wilson, A. Simula, J. Collins, D. J. Lloyd, J. A. Burns, C. Summers, C. Houben, A. Anastasaki, M. Li, C. R. Becer, J. K. Kiviaho and N. Risangud, *Polym. Chem.*, 2014, **5**, 57-61.
128. F. Alsubaie, A. Anastasaki, P. Wilson and D. M. Haddleton, *Polym. Chem.*, 2015, **6**, 406-417.
129. A. P. Haehnel, S. Fleischmann, P. Hesse, K.-D. Hungenberg and C. Barner-Kowollik, *Macromolecular Reaction Engineering*, 2013, **7**, 8-23.
130. C.-H. Peng, M. Zhong, Y. Wang, Y. Kwak, Y. Zhang, W. Zhu, M. Tonge, J. Buback, S. Park, P. Krys, D. Konkolewicz, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 3803-3815.
131. Y. Wang, M. Zhong, W. Zhu, C.-H. Peng, Y. Zhang, D. Konkolewicz, N. Bortolamei, A. A. Isse, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 3793-3802.
132. M. Zhong, Y. Wang, P. Krys, D. Konkolewicz and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 3816-3827.
133. D. Konkolewicz, P. Krys, J. R. Góis, P. V. Mendonça, M. Zhong, Y. Wang, A. Gennaro, A. A. Isse, M. Fantin and K. Matyjaszewski, *Macromolecules*, 2014, **47**, 560-570.
134. D. Konkolewicz, Y. Wang, P. Krys, M. Zhong, A. A. Isse, A. Gennaro and K. Matyjaszewski, *Polym. Chem.*, 2014, **5**, 4396-4417.
135. S. Smolne and M. Buback, *Macromol. Chem. Phys.*, 2015, **216**, 894-902.
136. S. Harrisson, P. Couvreur and J. Nicolas, *Macromolecules*, 2012, **45**, 7388-7396.
137. M. E. Levere, N. H. Nguyen and V. Percec, *Macromolecules*, 2012, **45**, 8267-8274.

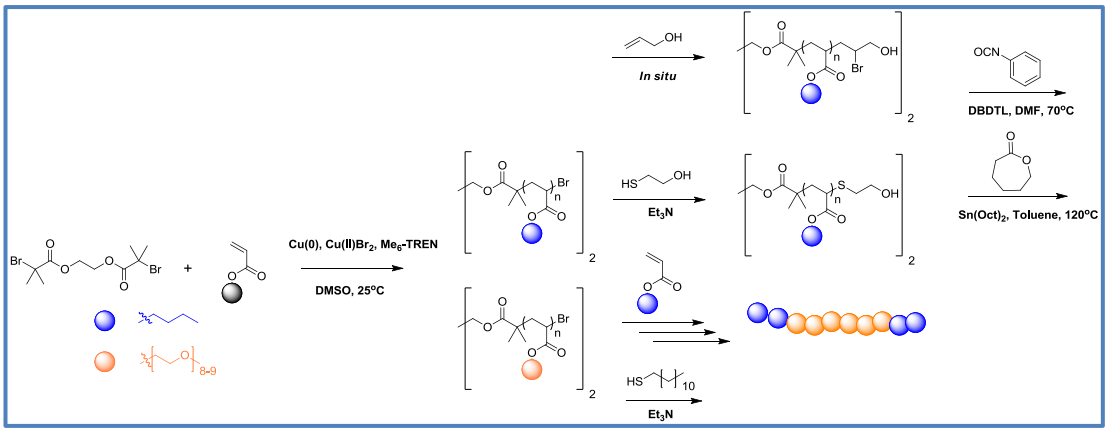
138. M. E. Levere, N. H. Nguyen, H.-J. Sun and V. Percec, *Polym. Chem.*, 2013, **4**, 686-694.
139. F. Alsubaie, A. Anastasaki, V. Nikolaou, A. Simula, G. Nurumbetov, P. Wilson, K. Kempe and D. M. Haddleton, *Macromolecules*, 2015, **48**, 5517-5525.
140. A. A. Isse, A. Gennaro, C. Y. Lin, J. L. Hodgson, M. L. Coote and T. Guliashvili, *J. Am. Chem. Soc.*, 2011, **133**, 6254-6264.
141. E. Kimura, T. Koike, M. Kodama and D. Meyerstein, *Inorg. Chem.*, 1989, **28**, 2998-3001.
142. N. Navon, G. Golub, H. Cohen, P. Paoletti, B. Valtancoli, A. Bencini and D. Meyerstein, *Inorg. Chem.*, 1999, **38**, 3484-3488.
143. G. Golub, A. Lashaz, H. Cohen, P. Paoletti, B. Andrea, B. Valtancoli and D. Meyerstein, *Inorg. Chim. Acta*, 1997, **255**, 111-115.
144. J. Krstina, G. Moad, E. Rizzardo, C. L. Winzor, C. T. Berge and M. Fryd, *Macromolecules*, 1995, **28**, 5381-5385.
145. J. Chiefari, Y. K. Chong, F. Ercole, J. Krstina, J. Jeffery, T. P. T. Le, R. T. A. Mayadunne, G. F. Meijs, C. L. Moad, G. Moad, E. Rizzardo and S. H. Thang, *Macromolecules*, 1998, **31**, 5559-5562.
146. G. Moad, E. Rizzardo and S. H. Thang, *Aust. J. Chem.*, 2012, **65**, 985-1076.
147. D. J. Keddie, G. Moad, E. Rizzardo and S. H. Thang, *Macromolecules*, 2012, **45**, 5321-5342.
148. M. Benaglia, J. Chiefari, Y. K. Chong, G. Moad, E. Rizzardo and S. H. Thang, *J. Am. Chem. Soc.*, 2009, **131**, 6914-6915.
149. G. Gody, T. Maschmeyer, P. B. Zetterlund and S. Perrier, *Nat. Commun.*, 2013, **4**.
150. G. Gody, T. Maschmeyer, P. B. Zetterlund and S. Perrier, *Macromolecules*, 2014, **47**, 3451-3460.
151. L. Martin, G. Gody and S. Perrier, *Polym. Chem.*, 2015, **6**, 4875-4886.
152. C. Barner-Kowollik, T. P. Davis, J. P. A. Heuts, M. H. Stenzel, P. Vana and M. Whittaker, *J. Polym. Sci., Part A: Polym. Chem.*, 2003, **41**, 365-375.
153. C. Boyer, V. Bulmus, T. P. Davis, V. Ladmiral, J. Liu and S. Perrier, *Chem. Rev.*, 2009, **109**, 5402-5436.
154. A. Hofman, S. Slomkowski and S. Penczek, *Die Makromol. Chem.*, 1987, **188**, 2027-2040.
155. Z. Jedliński, W. Wałach, P. Kurcok and G. y. Adamus, *Die Makromol. Chem.*, 1991, **192**, 2051-2057.
156. Q. Roderic P and S. Norman S, in *Ring-Opening Polymerization*, American Chemical Society, 1985, vol. 286, pp. 37-45.
157. C. C. Price and M. Osgan, *J. Am. Chem. Soc.*, 1956, **78**, 4787-4792.
158. J. A. N. Šebenda, *J. Macromol. Sci. Chem.*, 1972, **6**, 1145-1199.
159. L. Sipos, M. Zsuga and T. Kelen, *Polym. Bull.*, 1992, **27**, 495-502.
160. M. Labet and W. Thielemans, *Chem. Soc. Rev.*, 2009, **38**, 3484-3504.
161. A. P. Dove, *Chem. Commun.*, 2008, 6446-6470.
162. K. Stridsberg, M. Ryner and A.-C. Albertsson, in *Degradable Aliphatic Polyesters*, Springer Berlin Heidelberg, 2002, vol. 157, pp. 41-65.
163. A. Khanna, Y. Sudha, S. Pillai and S. Rath, *J. Mol. Model.*, 2008, **14**, 367-374.
164. C. J. Hawker and K. L. Wooley, *Science*, 2005, **309**, 1200-1205.
165. C. A. Uraneck, H. L. Hsieh and O. G. Buck, *Journal of Polymer Science*, 1960, **46**, 535-539.
166. C. A. Uraneck, H. L. Hsieh and R. J. Sonnenfeld, *J. Appl. Polym. Sci.*, 1969, **13**, 149-168.
167. K. Horie, M. Barón, R. B. Fox, J. He, M. Hess, J. Kahovec, T. Kitayama, P. Kubisa, E. Maréchal, W. Mormann, R. F. T. Stepto, D. Tabak, J. Vohlídal, E. S. Wilks and W. J. Work, in *Pure Appl. Chem.*, 2004, vol. 76, p. 889.

168. B. Boutevin, G. David and C. Boyer, in *Oligomers - Polymer Composites - Molecular Imprinting*, Springer Berlin Heidelberg, 2007, vol. 206, pp. 31-135.
169. M. A. Tasdelen, M. U. Kahveci and Y. Yagci, *Prog. Polym. Sci.*, 2011, **36**, 455-567.
170. H. A. Nguyen and E. Maréchal, *Journal of Macromolecular Science, Part C*, 1988, **28**, 187-291.
171. K. V. Bernaerts and F. E. Du Prez, *Prog. Polym. Sci.*, 2006, **31**, 671-722.
172. C. S. Sheppard, H. N. Schack and O. L. Mageli, *Journal of Cellular Plastics*, 1966, **2**, 97-111.
173. N. Hadjichristidis, S. Pispas, M. Pitsikalis, H. Iatrou and D. J. Lohse, in *Encyclopedia of Polymer Science and Technology*, John Wiley & Sons, Inc., 2002.
174. K. Dušek, *Rubber Chem. Technol.*, 1982, **55**, 1-22.
175. R. Jerome, M. Henrioulle-Granville, B. Boutevin and J. J. Robin, *Prog. Polym. Sci.*, 1991, **16**, 837-906.
176. R. D. Athey Jr, *Journal of Coatings Technology*, 1982, **54**, 47-50.
177. R. D. Athey Jr, *Prog. Org. Coat.*, 1979, **7**, 289-329.
178. E. Goethals, J. , in *Telechelic polymers: synthesis and applications*, ed. E. J. Goethals, CRC press, Editon edn., 1989, p. 416.
179. O. Bayer, *Angew. Chem.*, 1947, **59**, 257-272.
180. H. Ulrich, in *Kirk-Othmer Encyclopedia of Chemical Technology*, John Wiley & Sons, Inc., 2000.
181. G. Woods, *The ICI Polyurethanes Book*, Wiley, Philadelphia, 1987.
182. B. Boutevin, in *New Polymer Materials*, Springer Berlin Heidelberg, 1990, vol. 94, pp. 69-105.
183. J. Jagur-Grodzinski, *J. Polym. Sci., Part A: Polym. Chem.*, 2002, **40**, 2116-2133.
184. N. Hadjichristidis, M. Pitsikalis, S. Pispas and H. Iatrou, *Chem. Rev.*, 2001, **101**, 3747-3792.
185. A. Hirao and M. Hayashi, *Acta Polym.*, 1999, **50**, 219-231.
186. D. N. Schulz, A. F. Halasa and A. E. Oberster, *Journal of Polymer Science: Polymer Chemistry Edition*, 1974, **12**, 153-166.
187. J. Kim, S. S. Kim, K. H. Kim, Y. H. Jin, S. M. Hong, S. S. Hwang, B.-G. Cho, D. Y. Shin and S. S. Im, *Polymer*, 2004, **45**, 9071.
188. D. H. Richards and M. Szwarc, *Transactions of the Faraday Society*, 1959, **55**, 1644-1650.
189. R. P. Quirk and J.-J. Ma, *J. Polym. Sci., Part A: Polym. Chem.*, 1988, **26**, 2031-2037.
190. A. K. Brannan and F. S. Bates, *Macromolecules*, 2004, **37**, 8816-8819.
191. S. Choi and C. D. Han, *Macromolecules*, 2003, **36**, 6220-6228.
192. M. Sawamoto, T. Enoki and T. Higashimura, *Macromolecules*, 1987, **20**, 1-6.
193. J. P. Kennedy and R. A. Smith, *Journal of Polymer Science: Polymer Chemistry Edition*, 1980, **18**, 1523-1537.
194. J. P. Kennedy and R. A. Smith, *Journal of Polymer Science: Polymer Chemistry Edition*, 1980, **18**, 1539-1546.
195. J. P. Kennedy, *J. Polym. Sci., Part A: Polym. Chem.*, 1999, **37**, 2285-2293.
196. M. Sawamoto, *Prog. Polym. Sci.*, 1991, **16**, 111-172.
197. D. Y. Sogah and O. W. Webster, *Journal of Polymer Science: Polymer Letters Edition*, 1983, **21**, 927-931.
198. C. J. Hawker, G. G. Barclay and J. Dao, *J. Am. Chem. Soc.*, 1996, **118**, 11467-11471.
199. R. Nicolaÿ, L. Marx, P. Hémery and K. Matyjaszewski, *Macromolecules*, 2007, **40**, 6067-6075.
200. N. L. Hill and R. Braslau, *J. Polym. Sci., Part A: Polym. Chem.*, 2007, **45**, 2341-2349.

201. M. Rodlert, E. Harth, I. Rees and C. J. Hawker, *J. Polym. Sci., Part A: Polym. Chem.*, 2000, **38**, 4749-4763.
202. E. Harth, C. J. Hawker, W. Fan and R. M. Waymouth, *Macromolecules*, 2001, **34**, 3856-3862.
203. B. G. G. Lohmeijer and U. S. Schubert, *J. Polym. Sci., Part A: Polym. Chem.*, 2004, **42**, 4016-4027.
204. M. J Darmon, C. T Berge, J. A. Antonelli, C. E Murphy, Patent, WO1993022355 A1, **1994**.
205. D. M. Haddleton, C. Topping, J. J. Hastings and K. G. Suddaby, *Macromol. Chem. Phys.*, 1996, **197**, 3027-3042.
206. D. M. Haddleton, D. R. Maloney, K. G. Suddaby Adam Clarke and S. N. Richards, *Polymer*, 1997, **38**, 6207-6217.
207. D. M. Haddleton, C. Topping, D. Kukulj and D. Irvine, *Polymer*, 1998, **39**, 3119-3128.
208. L. John, E. Dave, H. Raymond, L. Carole, L. Alex, P. Anthony and S. Ronald, in *Controlled/Living Radical Polymerization*, American Chemical Society, 2006, vol. 944, pp. 547-563.
209. L. Zhang and Y. Chen, *Polymer*, 2006, **47**, 5259-5266.
210. J. Liu, C.-Y. Hong and C.-Y. Pan, *Polymer*, 2004, **45**, 4413-4421.
211. S. Venkataraman and K. L. Wooley, *J. Polym. Sci., Part A: Polym. Chem.*, 2007, **45**, 5420-5430.
212. J. T. Lai, D. Filla and R. Shea, *Macromolecules*, 2002, **35**, 6754-6756.
213. F. Segui, X.-P. Qiu and F. M. Winnik, *J. Polym. Sci., Part A: Polym. Chem.*, 2008, **46**, 314-326.
214. X.-P. Qiu and F. M. Winnik, *Macromolecules*, 2007, **40**, 872-878.
215. D. B. Thomas, A. J. Convertine, R. D. Hester, A. B. Lowe and C. L. McCormick, *Macromolecules*, 2004, **37**, 1735-1741.
216. J. Xu, J. He, D. Fan, X. Wang and Y. Yang, *Macromolecules*, 2006, **39**, 8616-8624.
217. G. Moad, Y. K. Chong, A. Postma, E. Rizzardo and S. H. Thang, *Polymer*, 2005, **46**, 8458-8468.
218. F. E. Bailey Jr and J. V. Koleske, in *Poly (ethylene Oxide)*, eds. F. E. Bailey and J. V. Koleske, Academic Press, 1976, pp. 163-169.
219. J. M. Harris and Z. Samuel, *Poly(ethylene glycol)*, American Chemical Society, 1997.
220. S. M. Guillaume, *Eur. Polym. J.*, 2013, **49**, 768-779.
221. S. M. Guillaume, M. Schappacher and A. Soum, *Macromolecules*, 2003, **36**, 54-60.
222. M. Schappacher, N. Fur and S. M. Guillaume, *Macromolecules*, 2007, **40**, 8887-8896.
223. Y. Nakayama, S. Okuda, H. Yasuda and T. Shiono, *React. Funct. Polym.*, 2007, **67**, 798-806.
224. K. Aoi and M. Okada, *Prog. Polym. Sci.*, 1996, **21**, 151-208.
225. S. Kobayashi and H. Uyama, *J. Polym. Sci., Part A: Polym. Chem.*, 2002, **40**, 192-209.
226. R. K. Iha, K. L. Wooley, A. M. Nyström, D. J. Burke, M. J. Kade and C. J. Hawker, *Chem. Rev.*, 2009, **109**, 5620-5686.
227. D. M. Haddleton, C. Waterson, P. J. Derrick, C. B. Jasieczek and A. J. Shooter, *Chem. Commun.*, 1997, 683-684.
228. M. Ouchi, T. Terashima and M. Sawamoto, *Chem. Rev.*, 2009, **109**, 4963-5050.
229. N. V. Tsarevsky and K. Matyjaszewski, *Macromolecules*, 2005, **38**, 3087-3092.
230. H. Keul, A. Neumann, B. Reining and H. Höcker, *Macromol. Symp.*, 2000, **161**, 63-72.
231. V. Percec, H. J. Kim and B. Barboiu, *Macromolecules*, 1997, **30**, 6702-6705.
232. S. Yurteri, I. Cianga and Y. Yagci, *Macromol. Chem. Phys.*, 2003, **204**, 1771-1783.

233. S. A. F. Bon, A. G. Steward and D. M. Haddleton, *J. Polym. Sci., Part A: Polym. Chem.*, 2000, **38**, 2678-2686.
234. T. Sarbu, K.-Y. Lin, J. Spanswick, R. R. Gil, D. J. Siegwart and K. Matyjaszewski, *Macromolecules*, 2004, **37**, 9694-9700.
235. V. Coessens and K. Matyjaszewski, *Macromol. Rapid Commun.*, 1999, **20**, 127-134.
236. S. A. F. Bon, S. R. Morsley, C. Waterson and D. M. Haddleton, *Macromolecules*, 2000, **33**, 5819-5824.
237. C. W. Bielawski, J. M. Jethmalani and R. H. Grubbs, *Polymer*, 2003, **44**, 3721-3726.
238. G. Lligadas and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2007, **45**, 4684-4695.
239. C. Boyer, A. Atme, C. Waldron, A. Anastasaki, P. Wilson, P. B. Zetterlund, D. Haddleton and M. R. Whittaker, *Polym. Chem.*, 2013, **4**, 106-112.
240. C. Boyer, A. H. Soeriyadi, P. B. Zetterlund and M. R. Whittaker, *Macromolecules*, 2011, **44**, 8028-8033.
241. K. Ghosh and J. S. Moore, *J. Am. Chem. Soc.*, 2011, **133**, 19650-19652.
242. X. Tang, X. Liang, Q. Yang, X. Fan, Z. Shen and Q. Zhou, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 4420-4427.

Synthesis and reactivity of *α,ω*-homotelechelic polyacrylates by Cu(0)-mediated reversible deactivation radical polymerisation



Telechelic poly(n-butyl acrylate) and poly[poly(ethylene glycol) methyl ether acrylate] are obtained with high monomer conversions and narrow molecular weight distributions (Đ < 1.2) by Cu(0)-mediated reversible deactivation radical polymerisation (SET-LRP). The high end group fidelity of the polymer is confirmed by a combination of ^{1}H NMR and MALDI-ToF-MS analysis. The reactivity of the telechelics is exploited to yield amphiphilic BAB triblocks, by sequential addition of a second monomer, which self-assemble in water. Furthermore, nucleophilic thiol-bromine substitution using 2-mercaptoethanol post-polymerisation enables the incorporation of primary alcohols on both the α- and ω- polymer chain ends. The presence and reactivity of hydroxyl end-groups is confirmed upon reaction with isocyanates and further exploited to induce the ring opening polymerisation (ROP) of ε-caprolactone.

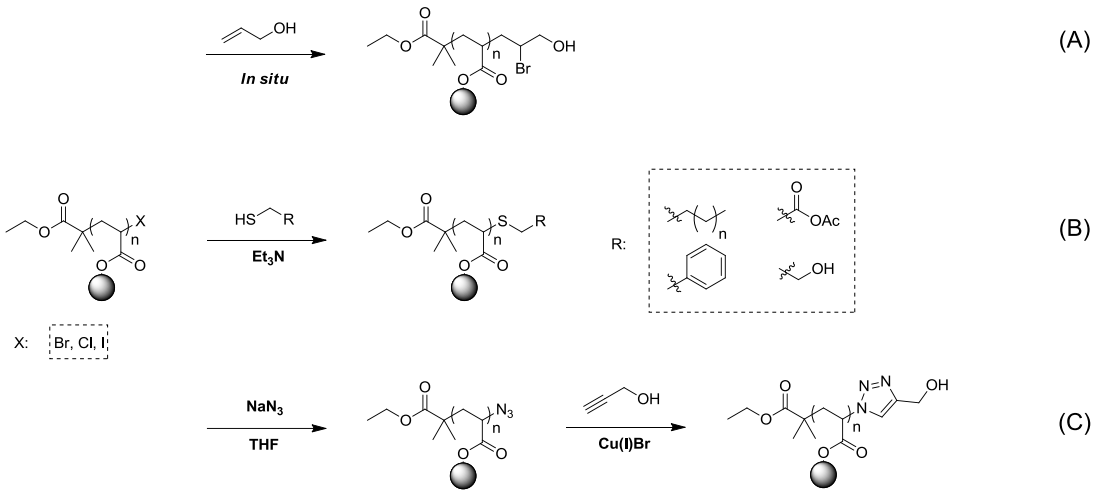
2.1 Introduction

Homo and hetero-telechelic polymers[1] provide access to a large variety of architectures *via* chain extension including simple BAB triblock copolymers, cross-linked co-networks[2] and higher ordered self-assembled structures.[3, 4] The reactivity of end groups of telechelic polymers[5] has been exploited in the preparation of functional polyesters[2, 6] and polyurethanes[2] *via* polycondensation chain extension protocols. However, the ability to tune macromolecular composition and architecture, thus tailoring mechanical, physical and chemical properties has a major influence on the final application of such polymeric materials ranging from therapeutic drug delivery[7, 8] to personal care applications.[9] Indeed, none of these supramolecular structures can be achieved without a control over the morphology and chain end composition.[10]

Recent advances in RDRP provide the necessary control required to design increasingly complex architectures with good tolerance to side chain chemical functionality and with the maximum retention of chain-end functionality.[11, 12] Predictable molecular weights (MW), narrow distributions ($Đ = M_w/M_n$) and high end group fidelity can be achieved by many techniques including RAFT,[13-15] NMP[16, 17] and ROP[18-20] processes. TMM-RDRP remains a widely used technique to yield precision polymeric structures and materials.[21-24] Functionalities can be introduced *via* the initiator,[25, 26] the monomer through functional pendant groups, or by post-polymerisation modifications[27-31] to yield functional scaffolds. Such techniques have been applied to introduce reactive hydroxyl, carboxylic acid and amine functional groups to the polymer chain ends and along (meth)acrylic side chains.[2]

The focus of this chapter is on the introduction of hydroxyl chain ends, because of their reactivity and versatility towards further uses. Existing halide-end group modification

include thio-halogen S_N2 nucleophilic substitution,[32, 33] addition of allyl moieties[27, 34] and the widely exploited copper(I)-catalysed azide-alkyne cycloaddition (CuAAC).[35-37]



Scheme 2.1. Modification of *ω*-halide *via* (A) allyl moieties *in situ*; (B) nucleophilic substitution utilising thiols; (C) copper(I)-catalysed alkyne-azide 1,3-dipolar cycloaddition.

However, the use of azides and large quantities of copper catalyst makes the technique less attractive for industrial applications;[38, 39] hence it will not be investigated in this work.

Additionally, RDRP processes have unavoidable termination reactions, imposing a deleterious effect upon end group fidelity.[40, 41] Pleasingly, Cu(0)-mediated RDRP (SET-LRP)[42] enables the polymerisation of acrylates[43, 44] in polar organic media, leads to relatively fast polymerisation, exhibits very high initiator efficiency, with minimal termination which is reciprocated by unprecedented control over end group fidelity for a radical process (up to >99%).[45, 46] Moreover, the use of Cu(0) as a primary copper source reduces the amount of copper in the reaction medium, giving a "greener" alternative compared to classical copper-mediated polymerisation protocols.[47, 48] This has been exploited to yield bi-functional hydrophobic polymers with a wide range of molecular weights.[32] Furthermore, using increasingly hydrophobic monomers has resulted in the development of self-generating biphasic systems with the retention of catalytic activity, polymerisation control and in some

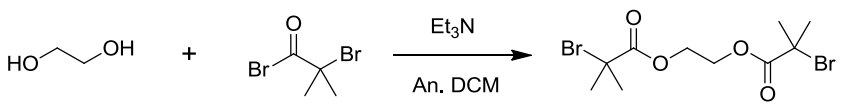
cases, *enhanced* end-group fidelity.[49-51] Typically, phase separation furnishes a catalyst-free polymer-rich layer ready to use for further modifications without the need for additional purification steps.

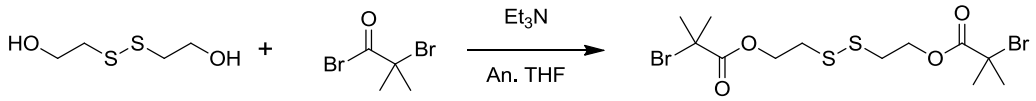
In this chapter, the high *α,ω*-chain end fidelity of hydrophilic and hydrophobic polymer chains is exploited to give functional polymeric diols. Poly(*n*-butyl acrylate) (PBA) and poly[poly(ethylene glycol) methyl ether acrylate] (M_n= 480 g.mol^{-1}, $PPEGA_{480}$) are polymerised by Cu(0)-mediated RDRP using the bi-functional initiator ethylene bis(2-bromoisobutyryl bromide) in DMSO. Primary hydroxyl groups are then introduced post-polymerisation or *via* sequential addition of allyl alcohol or *via* nucleophilic thio-bromo substitution, using 2-mercaptoethanol. The combination of ^{1}H NMR spectroscopy, Size Exclusion Chromatography (SEC) and Matrix-Assisted Laser Desorption Ionization Time-of-Flight mass spectroscopy (MALDI-ToF MS), together with chain extension and chain-end modification demonstrate the high end group fidelity and successful functionalisation of these polyacrylates. The reactivity of the hydroxyl groups is exploited by reaction with isocyanates and the ring opening polymerisation of *ε*-caprolactone.

2.2 Results and discussions

2.2.1 Synthesis of bi-functional initiators

The selected approach towards the design of functional telechelics requires use of bi-functional initiating moieties, in order to retain similar *α*- and *ω*- chain ends throughout polymerisation. Consequently, two different initiators, ethylene bis(2-bromoisobutyrate) (EbBiB) and bis[2-(2-bromoisobutyryloxy)ethyl] disulphide were synthesised.





Scheme 2.2. Synthesis of ethylene bis(2-bromoisobutyrate) (EbBiB) and bis[2-(2-bromoisobutyryloxy)ethyl] disulphide.

NMR analysis revealed a successful esterification of the hydroxyl groups, highlighted by the appearance of the $-(C\boldsymbol{H}_3)_2$ peaks at 1.8-1.9 ppm.

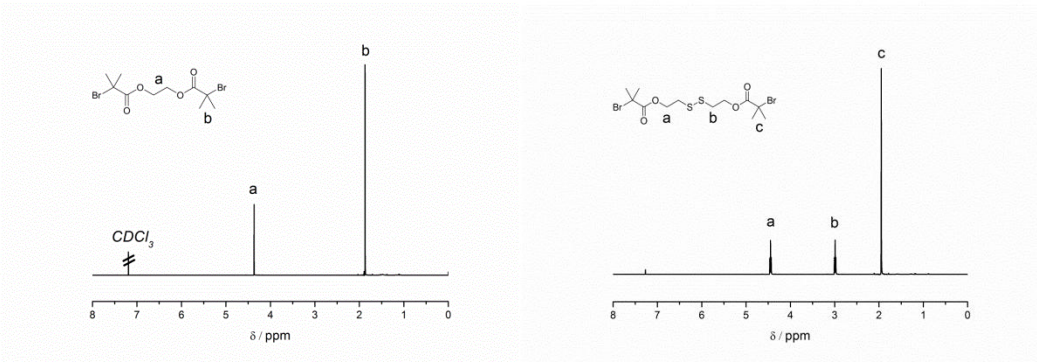
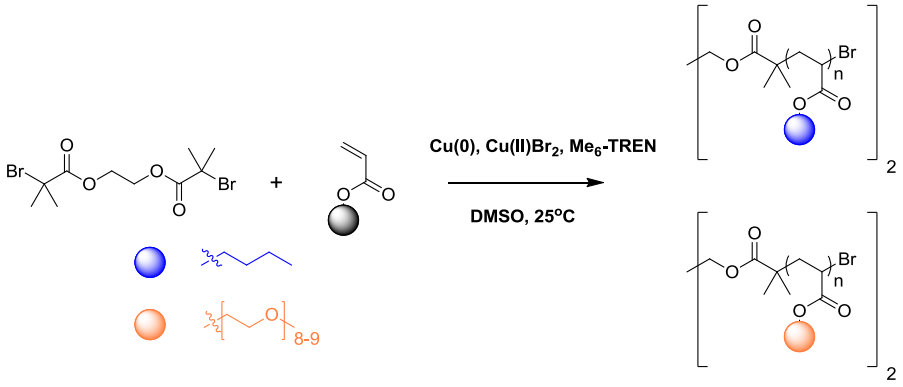


Figure 2.1. ^{1}H NMR spectra ($CDCl_3$, 400MHz) of ethylene bis(2-bromoisobutyrate) (EbBiB) and bis[2-(2-bromoisobutyryloxy)ethyl] disulphide initiators.

2.2.2 Polymerisation of hydrophilic and hydrophobic acrylates with high end-group fidelity

Telechelic homopolymerisation of hydrophobic butyl acrylate (*n*-BA) and hydrophilic poly(ethylene glycol) methyl ether acrylate ($PEGA_{480}$) were carried out according to the general procedure using EbBiB, activated Cu(0)-wire, sub-stoichiometric amounts of $Cu^{II}Br_2$ and *σ*-donor ligand Me_6-TREN, in DMSO at 25°C (Scheme 2.3).



Scheme 2.3. Cu(0)-mediated polymerisation of acrylates, [I]:[M]:[Cu(0) wire]:[$Cu^{II}Br_2$]:[Me_6-TREN] = 1:DP_n:5 cm:0.05:0.18 in DMSO at 25°C.

The Cu(0)-mediated, telechelic polymerisation of *n*-BA exhibited "*living*" characteristics, exemplified by a linear evolution of M_n with respect to monomer conversion, in keeping with previously reported results (Figure 2.3A).[50] However, a small induction period is observed in figure 2.3C, which could be due to the heterogeneous nature of the system, with the presence of undesired oxides on the copper wire surface. Monitoring of the polymerisation of *n*-BA was conducted utilising ^{1}H NMR, by comparing the monomer vinyl peaks (6.5-5.5 ppm, $CDCl_3$, 250 MHz) to the PBA –C***H***$_3$ (0.9 ppm, $CDCl_3$, 250 MHz). Quantitative conversion (>99%) was reached in less than 3 hours and the resulting polymer retained a narrow MWD ($Đ$ < 1.12). The linear and telechelic polymerisation of *n*-BA has previously been reported to proceed through a self-generating biphasic system.[50] Pleasingly, the expected phase separation was observed during this investigation when the growing polymer chain reached a molecular weight of ~2500 g.mol^{-1} generating an unstable emulsion with stirring during the reaction giving a polymer rich top layer and a catalyst rich bottom layer immediately following cessation of agitation (Figure 2.2).

Figure 2.2. Schlenk tube of *n*-butyl acrylate polymerisation using Cu(0)-wire in DMSO at 25°C, [I]:[M]:[Cu(0) wire]:[$Cu^{II}Br_2$]:[Me_6-TREN] = 1:40:5 cm:0.05:0.18 after cessation of agitation.

The final polymer can be used without further purification for mass spectrometry analysis or for end group modifications. The MALDI-ToF MS analysis of the unpurified polymer reveals a single mass distribution, corresponding to a *n*-BA unit (128 Da, Figure 2.3D). Moreover, each peak follows an isotopic distribution consistent of *α,ω*-bromo chain ends, suggesting a high end group fidelity of telechelic PBA which is further supported by symmetrical and monomodal SEC traces throughout the molecular weight evolution (Figure 2.3B).

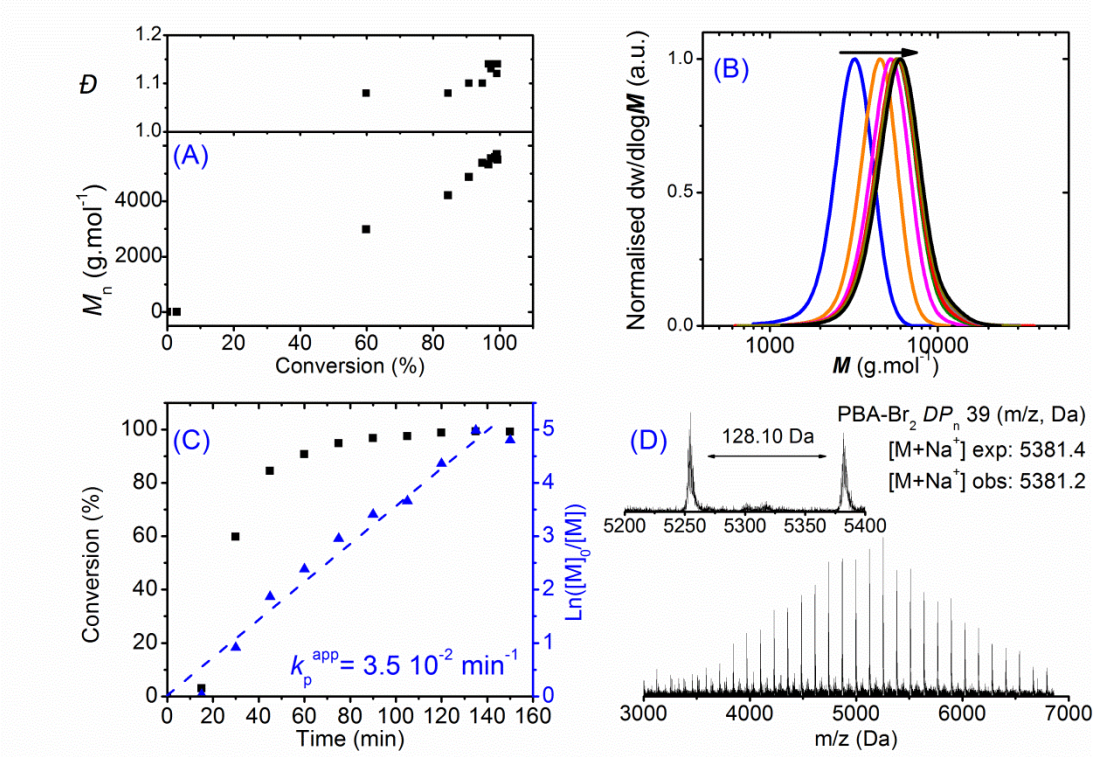


Figure 2.3. Cu(0)-mediated polymerisation of *n*-butyl acrylate ([I]:[M]:[Me_6-TREN]:[Cu(0) wire]:[$Cu^{II}Br_2$] = 1:40:5 cm:0.18:0.05) in DMSO at 25°C. (A) Experimental molecular weights and dispersities at different monomer conversions. (B) Normalised dw/dlog***M*** vs. ***M*** at different monomer conversions. (C) Ln([M]$_0$/[M]) vs. time (mins) and linear fit (dash line). (D) MALDI-ToF-MS spectrum obtained at 98 % monomer conversion.

The telechelic nature, and "*livingness*" of both *α,ω*-chain ends of the polymer was also assessed using a "cleavable" initiator, bis[2-(2-bromoisobutyryloxy)ethyl] disulphide. For comparison, *n*-BA was polymerised under the same conditions as described above. Upon completion of the polymerisation, an excess of tributylphosphine was added in order to reduce the disulphide bond. It should be noted that the use of phosphines may result in an undesired loss of halide chain ends.[52] Nevertheless, within an hour, full reduction was observed by SEC as illustrated by complete shift in the MWD to approximately 50% of the original value, with retention of monomodality and narrow dispersity (Figure 2.2). This is indicative of the propagation proceeding from both chain ends with minimal termination at either end. However, a broadening of the MWD is noticeable, which could be due the

residual presence of non-reduced polymer chains and/or undesired phosphonium salts end groups. Additional evidence for disulfide bond cleavage was observed in ^{1}H NMR (Figure 2.4), whereby the -S-C***H***$_2$ peaks were found to shift from 2.8 ppm to 3.8 ppm upon addition of the reducing agent. ^{13}C NMR spectra of the corresponding polymers can be found in appendix A.

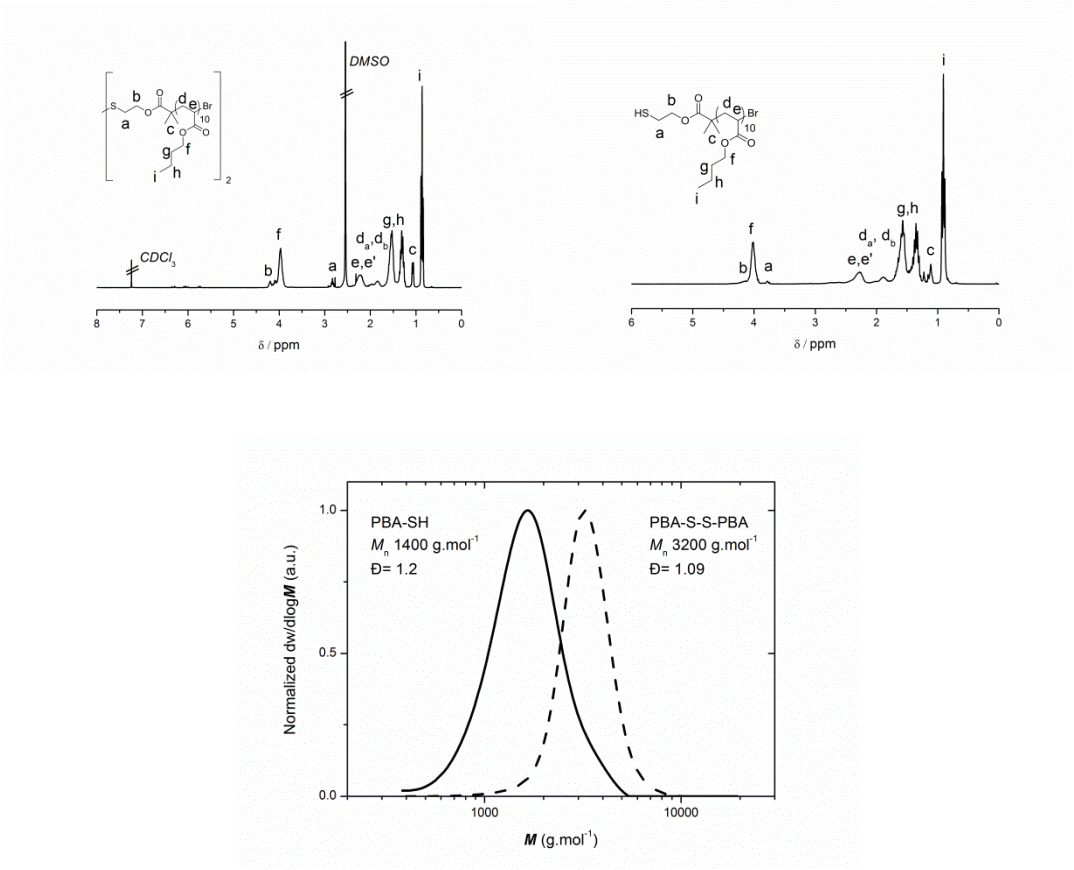


Figure 2.4. Reduction of poly(*n*-butyl acrylate) initiated by bis[2-(2-bromoisobutyryloxy)ethyl] disulphide upon addition of tributylphosphine. (Top) ^{1}H NMR ($CDCl_3$, 300MHz). (Bottom) SEC traces ($CHCl_3$ eluent).

The polymerisation of water soluble $PEGA_{480}$ was conducted in DMSO using the bi-functional initiator EbBiB. Monitoring of the monomer consumption was assessed by ^{1}H NMR by comparing the consumption of the monomer vinyl peaks (6.6-5.5 ppm, $CDCl_3$, 250 MHz) to the polymer pendant –C***H***$_3$ (3.3 ppm, $CDCl_3$, 250 MHz). The "*living*" nature of the polymerisation was again confirmed by the first order kinetics (Figure 2.5B) observed

following a short induction period (~ 90 mins) and linear evolution of molar mass with conversion (Figure 2.5A). A shoulder at high molecular weight is observed on the molecular weight distribution which is common when performing RDRP of PEGA based monomers and could be explained *via* two hypotheses. Firstly, the high molecular weight possibly results from the presence of diacrylate species present in the starting material.[53] Indeed, the SEC analysis revealed for the last sample (300 minutes, 92% conversion) an increase in the polymer M_n and M_p; the main peak distribution displays M_n =14700 g.mol^{-1} and M_p =15200 g.mol^{-1} whilst the shoulder reveals M_n = 29400 g.mol^{-1} and M_p =26200 g.mol^{-1}, corresponding to an increase by 2 fold in the molecular weights compared to the main peak distribution. Hence, the presence of diacrylates is hypothesised, as both calculated molecular weight values are affected. However, the presence of a shoulder at high molecular weight could also be due to undesired termination of the polyacrylate, *via* β-scission and/or branching, which would result in similar increase of the MWD. Such hypotheses will be questioned further in sections 3.2 and 4.2.

Despite the induction period and the presence of undesired diacrylates, very high monomer conversions are obtained, observed molecular weights correlate well with theoretical values and the molecular weight distribution remains narrow ($Đ$ < 1.16, Figure 2.5A and 2.5C).

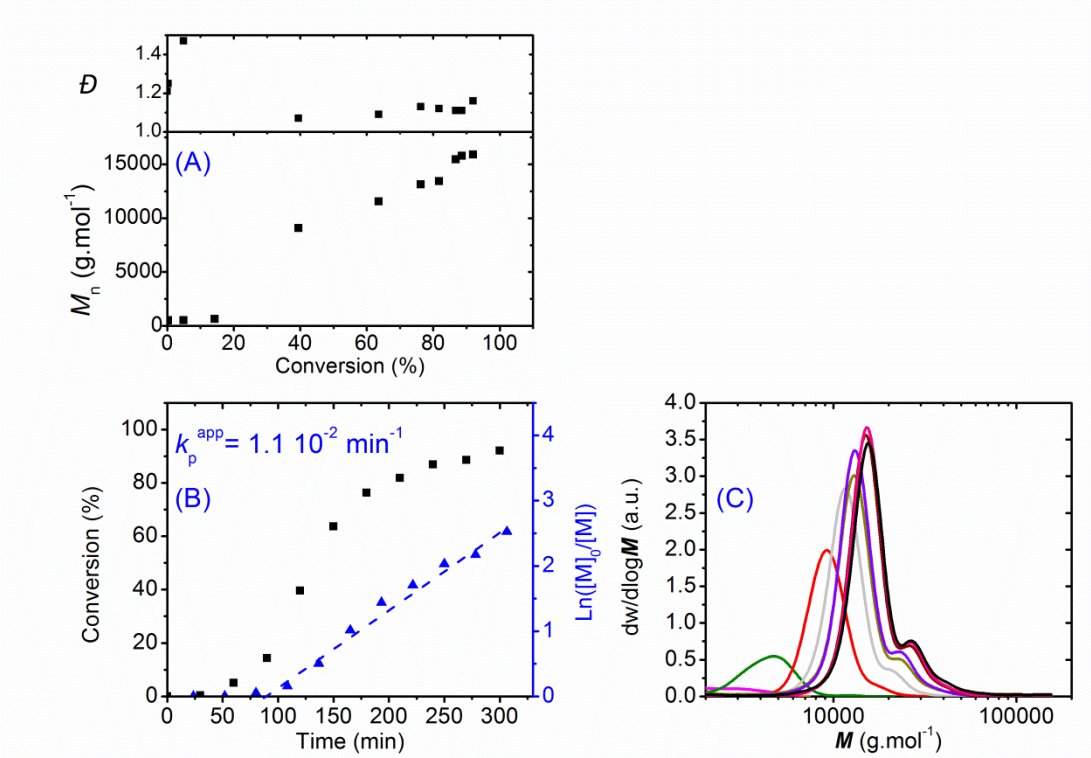


Figure 2.5. Cu(0)-mediated polymerisation of poly(ethylene glycol) methyl ether acrylate (av. M_n= 480 g.mol^{-1}, [I]:[M]:[Me_6-TREN]:[Cu(0) wire]:[$Cu^{II}Br_2$] = 1:40: 0.18: 5 cm: 0.05) in DMSO at 25°C. (A) Experimental molecular weights and distributions *vs.* monomer conversion. (B) Ln([M]$_0$/[M]) *vs.* time and linear fit (dash line). (C) dw/dlog***M*** *vs.* ***M*** at different monomer conversions.

The high end group fidelity of the $PPEGA_{480}$ was experimentally verified by chain extension with varying ratios of *n*-BA to furnish amphiphilic BAB tri-block copolymers (Table 2.1). Chain extension was realised upon addition of a deoxygenated aliquot of comonomer (*n*-BA) when the homopolymerisation had reached high conversion (>91 %, by ^{1}H NMR, Figure 2.6). The resulting BAB triblocks were obtained in high conversion, with respect to the comonomer (> 80 %), and with narrow molecular weight distributions (*Đ* < 1.18, Figure 2.6). The complete shift to higher molecular weight is indicative of minimal loss of the *α,ω*-Br end groups, even at high conversion, during homopolymerisation. The high molecular weight shoulder can again be attributed to impurities in the $PEGA_{480}$ monomer.

Table 2.1. PBA-PPEGA-PBA BAB triblocks and statistical copolymers prepared by SET-LRP.

Entry	DP_n $PEGA_{480}$: *n*-BA	Time (h)	Conv. ($PEGA_{480}$/*n*BA)[a] (%)	$M_{n,SEC}$[b] ($g.mol^{-1}$)	$Đ$ (M_w/M_n)
1	10	5	95 / n.a.	7200	1.09
2	10:20	17	> 99 / 83	9900	1.12
3	10:40	17	> 99 / > 99	11300	1.11
4	10:80	17	> 99 / > 99	17300	1.12
5	40:10	17	> 99 / > 99	18300	1.14
6	80:10	17	98 / 86	29000	1.18
7	80:10*	17	> 99 / 94	29300	1.17

**Random copolymers.[a] Determined by ^1H NMR ($CDCl_3$).[b] Determined by $CHCl_3$ SEC, over PMMA standards.*

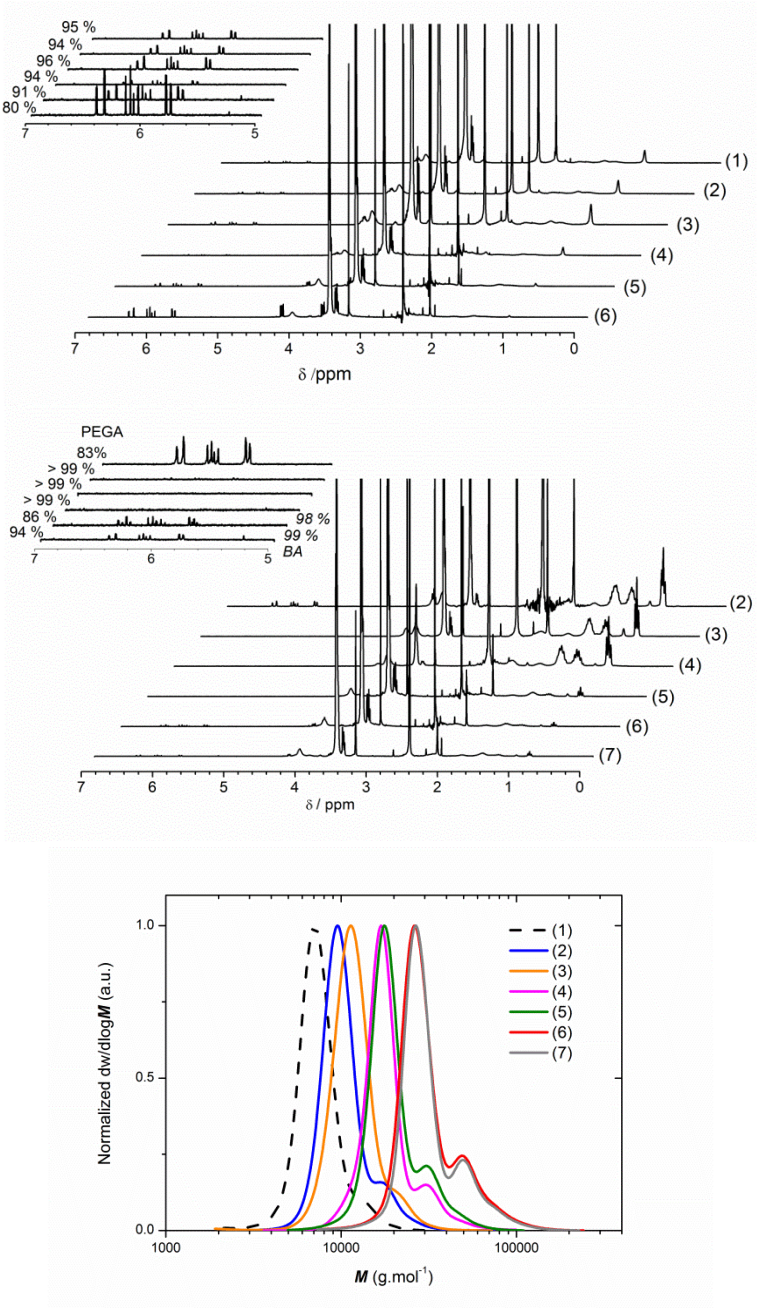


Figure 2.6. Chain extension of telechelic poly[poly(ethylene glycol) methyl ether acrylate] (av. M_n= 480 g.mol^{-1}) with different amounts of *n*-butyl acrylate in DMSO at 25°C. Numbers correspond to the entry numbers in Table 2.1.

Further evidence for the high chain-end fidelity was provided by thio-bromine nucleophilic substitution at the *α,ω*-chain ends of a low molecular weight (DP_n= 10, M_n > 5000 g.mol^{-1}) $PPEGA_{480}$. $PPEGA_{480}$ was synthesised in 5 hours exhibiting quantitative monomer conversion (> 99 % by ^{1}H NMR) and narrow molecular weights distributions (M_n= 7100

g.mol^{-1}, $Đ$= 1.10). Thio-bromine substitution was achieved upon addition of an excess of the nucleophilic dodecanethiol in the presence of triethylamine. The solution was then dialyzed against water (MWCO 3.5 kDa) to remove the reaction solvent and by-products. During dialysis, the product solution became cloudy implying aggregation into higher order structures. Examination of a sample of the cloudy solution by optical microscopy revealed the presence of microparticles with a diameter between 2-4 μm. This indicates that substitution of the α,ω-chain ends of the hydrophilic PPEGA$_{480}$ polymer with a hydrophobic molecule such as dodecanethiol confers surfactant like properties on the resulting polymers leading to the observed self-assembly in aqueous media.

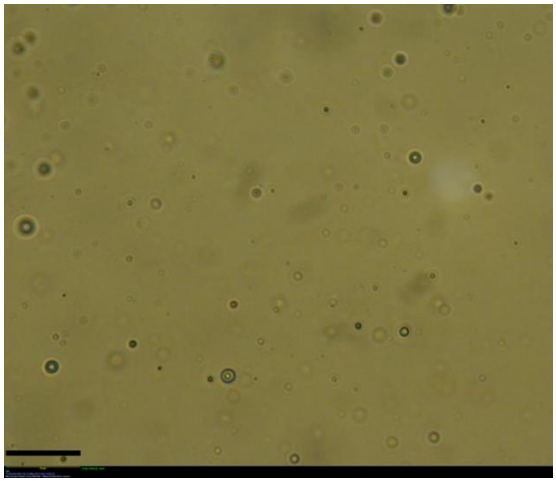


Figure 2.7. Optical microscopy image of self-assembled dodecanethiol modified poly[poly(ethylene glycol) methyl ether acrylate] [M]:[I] = 1:10. Zoom x40, scale bar 25 μm.

The dialyzed product was collected by lyophilisation and the resulting viscous solution was analysed by ^{1}H NMR and SEC (Figure 2.8) to reveal the successful modification of the halogen chain ends. The SEC chromatogram shifts to lower molecular weights (M_n = 5900 g.mol^{-1}, $Đ$= 1.11), as a result of an enhanced hydrophobicity and solvability in the eluent, without affecting the molecular weight distribution. In ^{1}H NMR, the appearance of new peaks between 1.5-2.5 ppm suggests the successful nucleophilic substitution of the halogen chain ends with dodecanethiol.

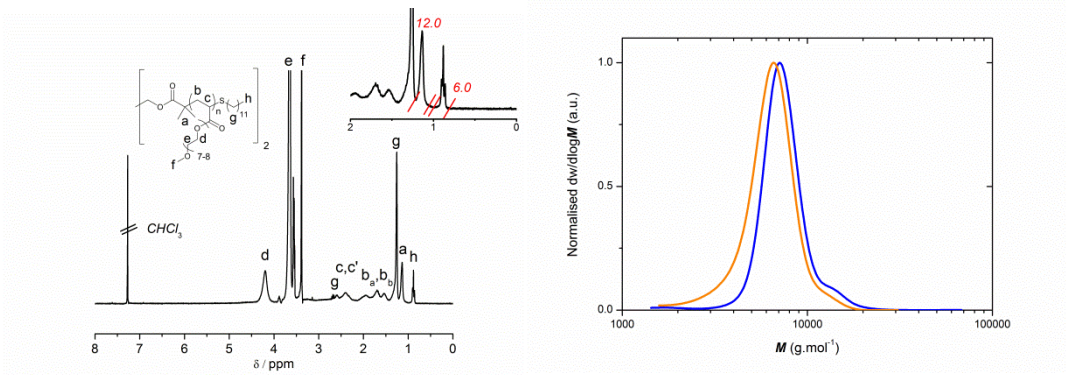


Figure 2.8. (Left) ^{1}H NMR ($CDCl_3$, 300 MHz) of dodecanethiol modified poly[poly(ethylene glycol) methyl ether acrylate] [M]:[I] 1:10 with integrations. (Right) Shift in molecular weight of poly[poly(ethylene glycol) methyl ether acrylate], [M]:[I] = 10:1 (blue, M_n= 7100 g.mol^{-1}, $Đ$= 1.10) upon addition of dodecanethiol (orange, M_n= 5900 g.mol^{-1}, $Đ$= 1.11).

Integration of the peaks corresponding to the *α,ω*-end –C***H***$_3$ (t, 0.88 ppm) of the triblock copolymer has an integration of 6, using the –(C***H***$_3$)$_2$ initiator peaks as a reference (1.14 ppm, s, 12H, Figure 2.8). This confirms the high end group fidelity of the telechelic PPEGA$_{480}$ polymer as two thiol moieties are incorporated onto the polymer *α,ω*-chain ends.

Assessment of the *α,ω*-Br end group fidelity of hydrophilic PPEGA through chain extension and nucleophilic substitution of hydrophobic moieties (*e.g.* PBA, dodecanthiol) revealed interesting dispersing behaviour in water. Indeed, the amphiphilic nature of the obtained copolymers yielded nanostructures with potential use as dispersants, expanding the use of functional telechelics.

2.2.3 Incorporation of hydroxyl chain ends

2.2.3.1 Thio-bromo nucleophilic substitution

The reactivity of the halogen chain ends of hydrophobic PBA was also investigated *via* nucleophilic substitution reactions. The telechelic *n*-BA homopolymer was synthesised by Cu(0)-mediated polymerisation in DMSO reaching high monomer conversion (> 99 % by ^{1}H NMR) within 3 hours whilst retaining narrow dispersity (M_n= 3500 g.mol^{-1}, $Đ$= 1.11). In this case, 2-mercaptoethanol was selected as the nucleophile to introduce *α,ω*-hydroxyl functionality to the polymer chains. Successful substitution was achieved following addition of an excess of 2-mercaptoethanol in the presence of triethylamine to yield the *α,ω*-hydroxyl terminated PBA as characterized by NMR and MALDI-ToF MS analysis. The shift in ^{1}H NMR of the –C***H***$_2$ peaks of 2-mercaptoethanol from 3.7 ppm to 3.9 ppm and 2.7 ppm to 2.9 ppm respectively, suggest a significant incorporation of the nucleophile into the polymer end groups (Figure 2.9).

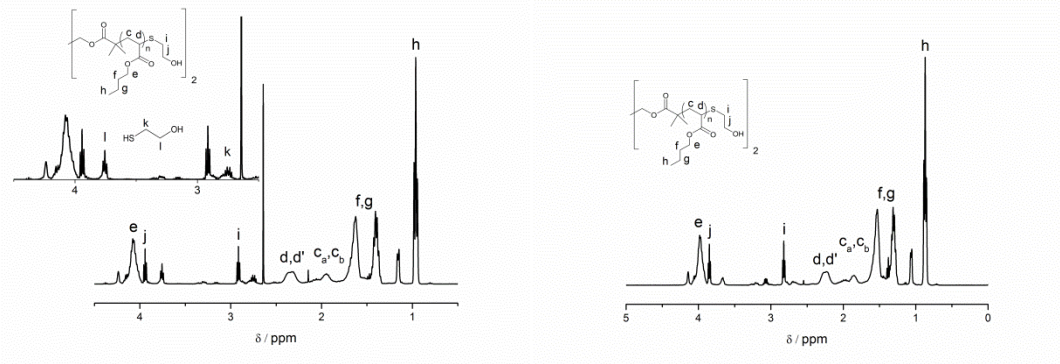


Figure 2.9. ^{1}H NMR ($CDCl_3$, 400 MHz) of *α,ω*-hydroxyl terminated poly(*n*-butyl acrylate) (M_n=3600 g.mol^{-1}, $Đ$=1.09) before (left) and after purification (right).

^{1}H NMR spectra of both unpurified and purified (Figure 2.9) polymer were recorded in order to confirm the presence of hydroxyl groups on the chain ends and to ascertain the purity of the final material. The remaining thiols were removed by dialysis against IPA (MWCO 1

kDa) overnight and the resulting product was isolated by removal of volatiles under reduced pressure. The nucleophilic substitution was also monitored by MALDI-ToF MS analysis which confirmed successful incorporation of primary alcohols on both ends of the polymer chain (Figure 2.10).

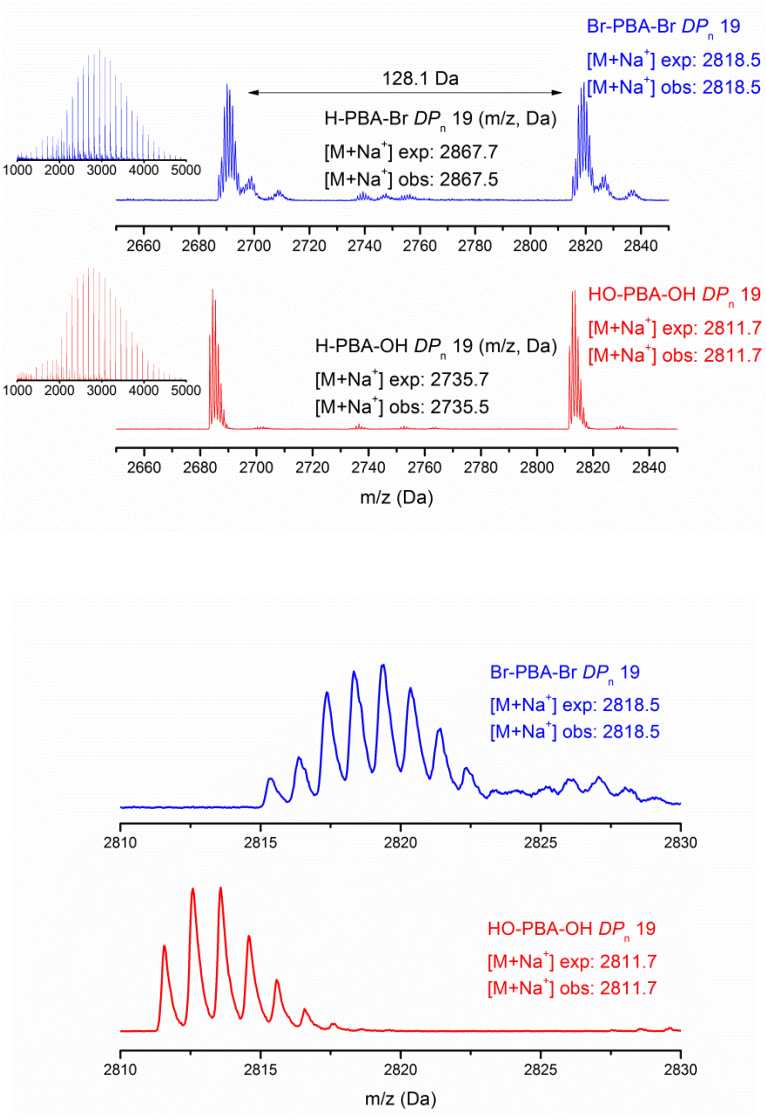


Figure 2.10. MALDI-ToF spectra of poly(*n*-butyl acrylate) before (blue) and after (red) addition of 2-mercaptoethanol. Expansion of the isotope pattern of the major distributions.

The major distribution corresponding to the end-functional telechelic polymer (blue) was observed to shift upon thio-bromo substitution to furnish a macromolecular diol (red). A

minor distribution, attributed to hydrogen termination on one of the chain ends, taking place during the initial homopolymerisation cannot be ignored.

2.2.3.2 Allyl alcohol "end-capping"

Transformation of the *α,ω*-halide chain ends into hydroxyl groups has also been investigated *via* a "thiol-free" route, which could be appreciated in an industrial process, utilising allyl alcohol. Reported procedures give clear insight into this reaction with respect to monofunctional, linear PMA polymers with good *ω*-end group fidelity .[27, 34] Thus, it becomes of interest to investigate the viability of this approach towards the synthesis of functional macrodiols. Whilst exploiting this process, one focus will be to understand the effect of self-generated phase separation of the polymeric system on the yield of *α,ω*-Br modification. Consequently, polymerisation of *n*-BA was performed in both DMSO, which promotes phase separation, and IPA which does not. Subsequently, when high monomer conversion were reached (> 95% conversion, M_n= 2800 g.mol^{-1}, $Đ$=1.11), a large excess of allyl alcohol was injected *in situ*.

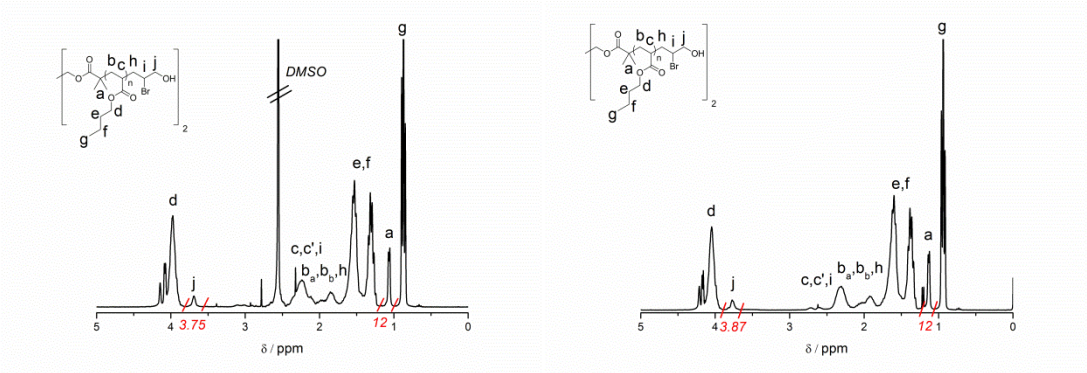


Figure 2.11. Monitoring the functionalisation of telechelic PBA with allyl alcohol in DMSO (left) and IPA (right) by ^{1}H NMR ($CDCl_3$, 300MHz).

The degree of incorporation was monitored by NMR and MALDI-ToF MS analysis, revealing 94% yield of addition in DMSO and 97% in IPA respectively, by comparing the initiator peak $-(CH_3)_2$ (1.1 ppm) to the HO-CH_2 of the functionalised PBA (3.7-3.8 ppm).

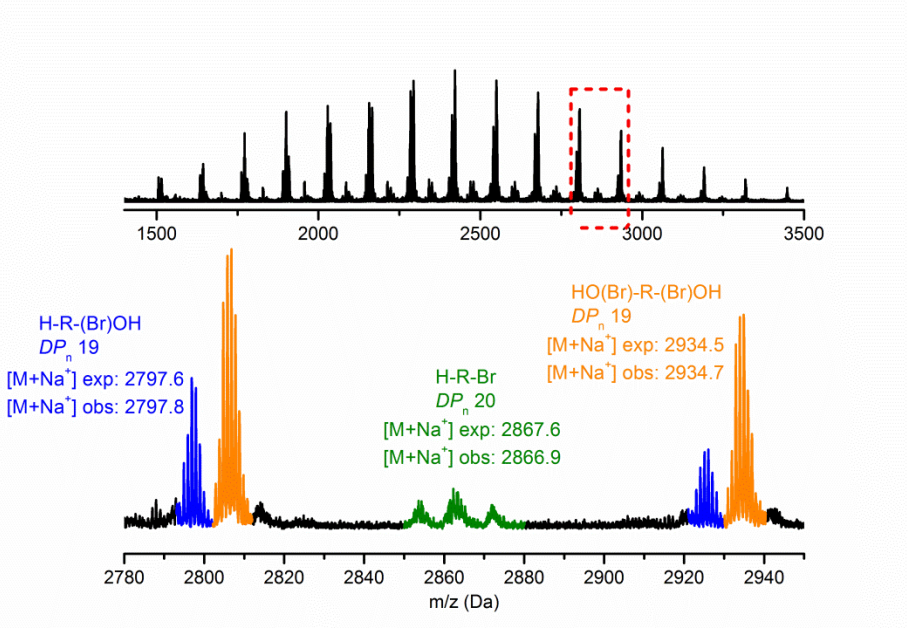


Figure 2.12. MALDI-ToF mass spectrum of hydroxyl terminated PBA utilising 100 equivalents of allyl alcohol in DMSO.

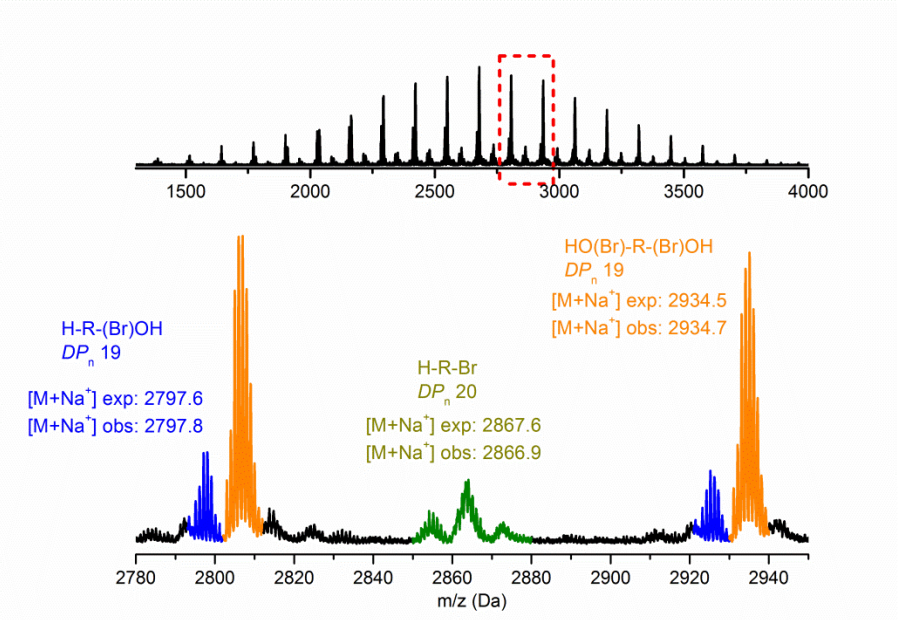


Figure 2.13. MALDI-ToF mass spectrum of hydroxyl terminated PBA utilising 100 equivalents of allyl alcohol in IPA.

A minor distribution in the mass spectra can be observed (figures 2.12 and 2.13), attributed to hydrogen termination on one of the halide chain ends. It is noticeable that the self-generated phase separation has a slightly negative effect on the degree of substitution of both halide end groups, thus, IPA became a solvent of choice for the "end-capping" of telechelic PBA utilising allyl alcohol.

The large excess of "end-capping" moieties employed might be problematic for an industrial process if the unreacted reagents cannot be recovered. Consequently, the influence of the excess of allyl alcohol was investigated by MALDI-ToF MS analysis in order to get the best yield of macrodiols (figure 2.14).

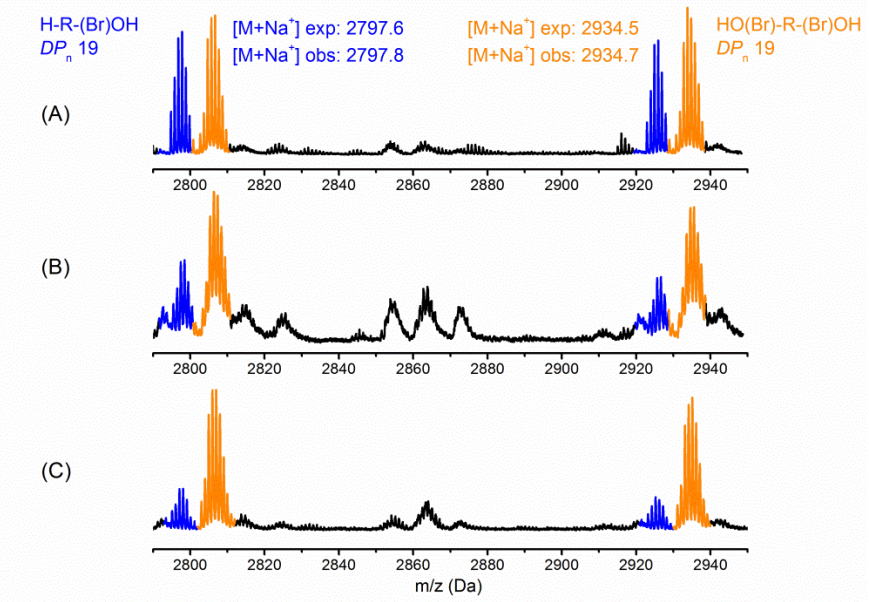


Figure 2.14. Influence of the amount of allyl alcohol on the yield of substitution of telechelic PBA (M_n =2800 g.mol^{-1}, $Đ$=1.12) by MALDI-ToF analysis. (A) 10 equivalents compared to initiator; (B) 40 equivalents; (C) 100 equivalents. R: PBA.

It is evident that a large excess of allyl alcohol (100 eq. compared to initiator) is needed to achieve good degree of substitution on both α- and ω-Br end groups. Indeed, an increase in intensity is observed for the minor distribution (corresponding to hydrogen termination on one halogen end group) as the amount of "end-capping" reagent is diminished. Nevertheless, the good yield of reaction makes allyl alcohol a promising candidate for the introduction of hydroxyl chain ends, as long as careful monitoring of the end group fidelity is performed.

2.2.4 Reactivity of the hydroxyl chain ends

The reactivity of the terminal alcohols was examined using isocyanates to further modify the terminal functionalities of the polymer chains. The reactivity between isocyanate and hydroxyl groups is well-studied.[54-57] Thus, hydroxyl-terminated PBA (obtained by nucleophilic substitution with 2-mercaptoethanol) was reacted with an excess (40 eq.) of

phenyl isocyanate, in the presence of a tin(II) catalyst under anhydrous conditions, and monitored by ^{1}H NMR, FT-IR and SEC analysis. The shift of the thioether –C***H***$_2$ peaks and the appearance of the aromatic signals at 7.3 ppm corresponding to the phenyl ring confirms the incorporation of the urethane group (Figure 2.15). Moreover, the comparison of the integrations of C***H***$_2$ peaks (3.8 ppm, 4H) to the phenyl peaks (6.8-7.6 ppm, 10H) suggests near quantitative urethane formation.

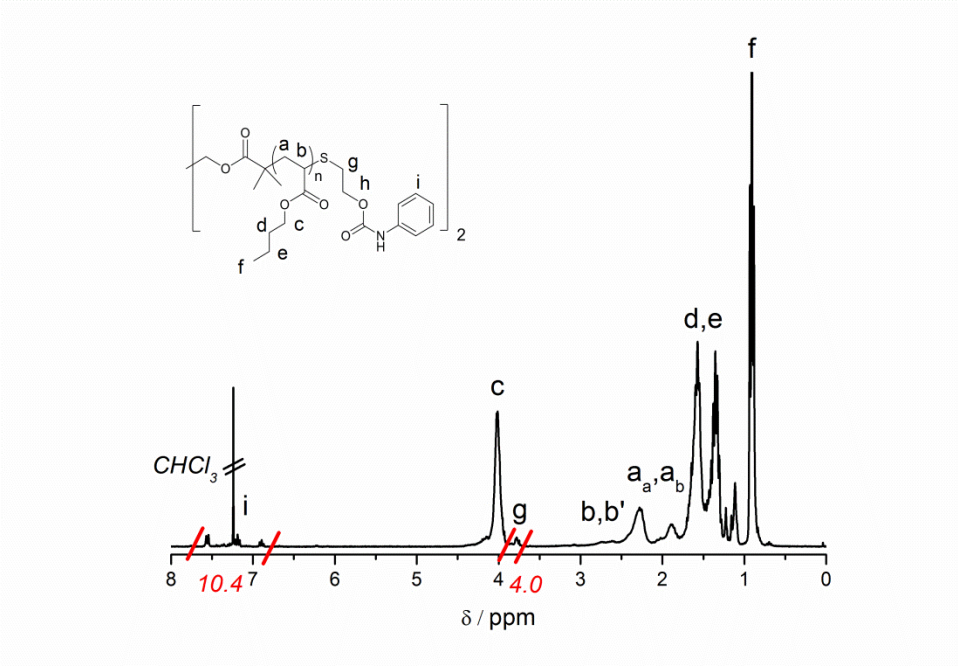


Figure 2.15. ^{1}H NMR ($CDCl_3$, 400 MHz) of 'end-capped' *α,ω*-hydroxyl terminated poly(*n*-butyl acrylate) (M_n= 3600 g.mol^{-1}, *Đ*= 1.09) with phenyl isocyanate.

Additional evidence for the chain end modification was elicited from FT-IR analysis. The isocyanate band (2275-2250 cm^{-1}) was found to gradually decrease throughout the reaction, coinciding with the evolution of a urethane stretch (1650 cm^{-1}) and appearance of the aromatic signals (1540 cm^{-1}). The absence of remaining isocyanates or hydroxyl signals confirms successful modification of the *α,ω*-terminal hydroxyl groups (Figure 2.16).

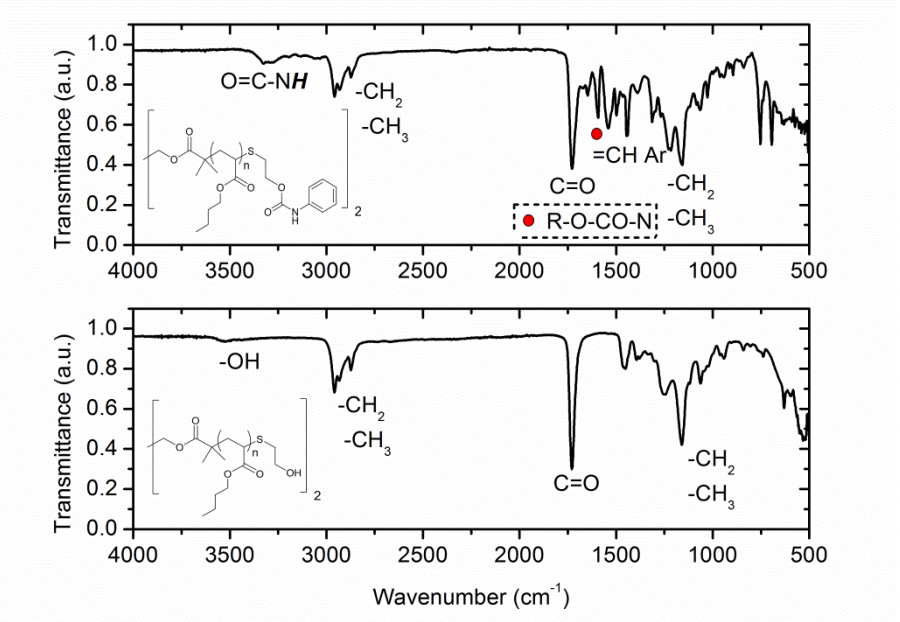


Figure 2.16. FT-IR of *α,ω*-hydroxyl terminated poly(*n*-butyl acrylate) before (bottom) and after 'end-capping' with phenyl isocyanate (top).

The incorporation of the isocyanate onto the polymer chain ends was also verified by SEC equipped with sequential RI and UV detectors (λ=280 nm). The coincidence of the peaks obtained from both detectors confirms the addition of the phenyl ring throughout the molecular weight distribution (Figure 2.17).

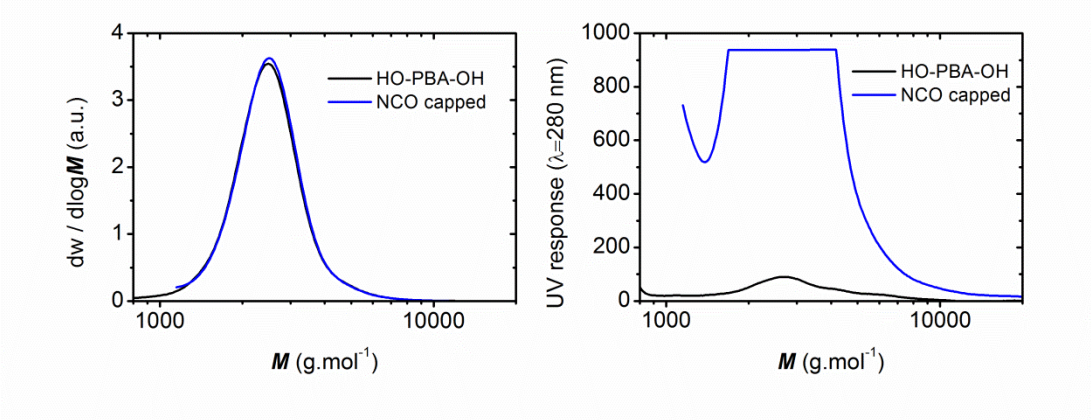


Figure 2.17. SEC traces (DMF eluent) of *α,ω*-hydroxyl terminated poly(*n*-butyl acrylate) (M_n= 2300 g.mol^{-1}, $Đ$= 1.10) before (black) and after 'end-capping' with phenyl isocyanate (blue). Normalised dw/dlog***M*** response (left) and UV response at λ= 280 nm (mV, right).

The reactivity of the hydroxyl group was also used to initiate a ring-opening polymerisation of the cyclic lactone *ε*-caprolactone (*ε*-CL) as an alternative route to synthesising BAB triblock copolymers. ROP is considerably more sensitive than Cu(0)-mediated polymerisation; therefore, all reagents and solvents were stringently dried prior to reaction to minimize the chance of side reactions. The polymerisation was monitored by ^{1}H NMR, using the appearance of the peaks at 3.9 and 2.2 ppm corresponding to the *α,ω*–C***H***$_2$ of the ring-opened *ε*-caprolactone (Figure 2.18). The complementary SEC analysis revealed a shift to higher molecular weight values and the final obtained molecular weight was close to the calculated value by ^{1}H NMR. Nevertheless, the dispersity of the PCL-*b*-PBA-*b*-PCL triblock copolymer was found to increase (*Đ*> 1.2) reflecting a loss of control during the ring opening process. This could be attributed to the presence of moisture, as water can competitively initiate polymerisation, or inaccuracies in the calculated stoichiometries (that would arise from termination in the homopolymerisation beforehand) both of which result in a loss of integrity of the targeted triblocks and highlight the importance of maximum retention of the *α,ω*-hydroxyl end groups.

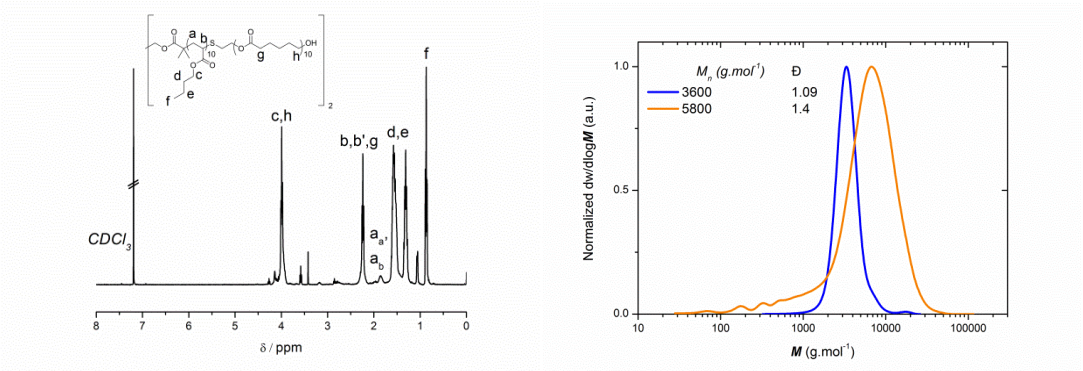


Figure 2.18. (Left) ^{1}H NMR ($CDCl_3$, 400 MHz) of poly(ε-caprolactone)-*b*-poly(*n*-butyl acrylate)-*b*-poly(ε-caprolactone) (M_n= 5800 g.mol^{-1}, *Đ*= 1.4). (Right) SEC traces ($CHCl_3$ eluent) of *α,ω*-hydroxyl terminated poly(*n*-butyl acrylate) (M_n= 3600 g.mol^{-1}, *Đ*= 1.09) before [blue] and after ring-opening of ε-caprolactone (M_n= 5800 g.mol^{-1}, *Đ*= 1.4) [orange].

However, the current analyses do not confirm that a triblock copolymer is obtained with absolute certainty. Consequently, Diffusion-Ordered Spectroscopy (DOSY) NMR,[58] which separates moieties depending on their diffusion coefficients, was performed. Pleasingly, a single distribution is observed in diffusion, corresponding to a unique (supra)molecular domain, thus confirming the presence of a block copolymer instead of a mixture of homopolymers (figure 2.19).

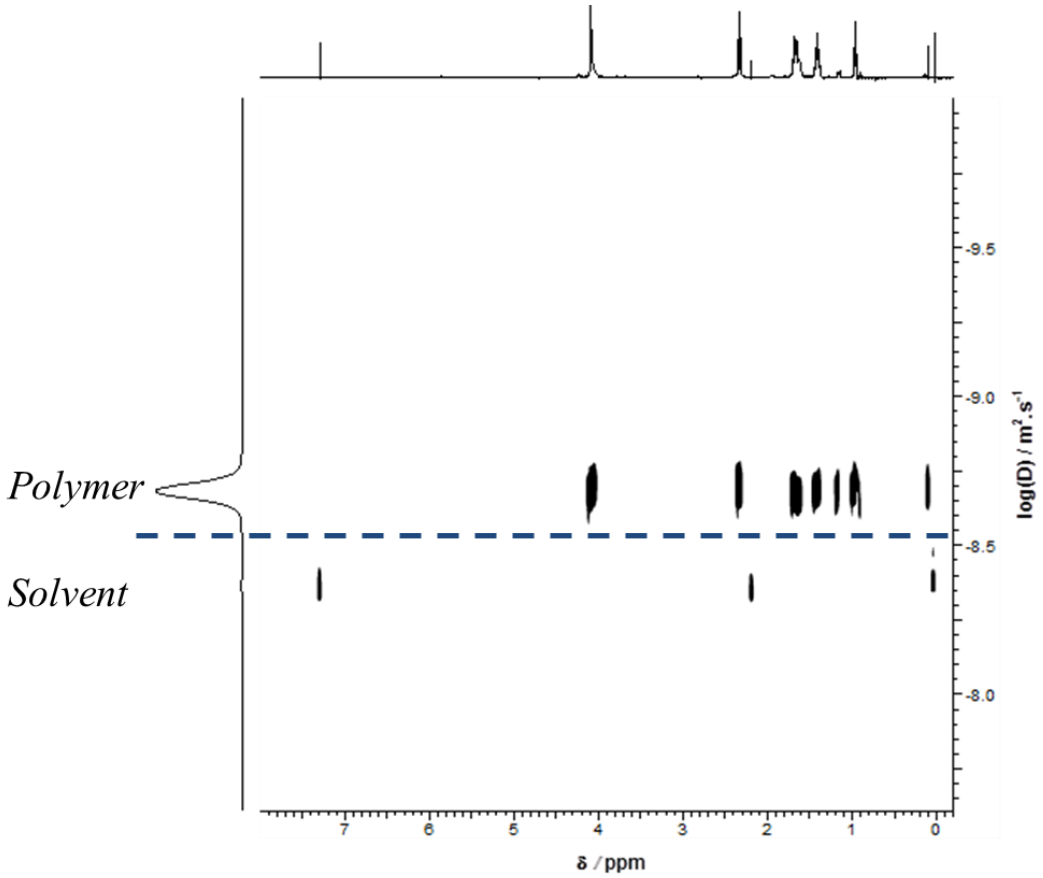


Figure 2.19. DOSY ($CDCl_3$, 500 MHz) of poly(ε-caprolactone)-*b*-poly(*n*-butyl acrylate)-*b*-poly(ε-caprolactone) (M_n= 5800 g.mol^{-1}, $Đ$=1.4).

2.3 Conclusions

Cu(0)-mediated reversible-deactivation radical polymerisation has been exploited to prepare hydrophobic, hydrophilic and amphiphilic telechelic polymers with excellent *α,ω*-end groups functionality. The high end group fidelity has been confirmed both through characterisation (NMR, SEC, MALDI-ToF MS) and experimentally by sequential monomer addition and thio-bromine substitutions at the *α,ω*-bromide chain ends. Subsequent incorporation of hydroxyl end groups furnishes prepolymers capable of initiating ring-opening polymerisation of *ε*-caprolactone and also possess the expected reactivity towards isocyanates. The combination of all of the results enhances the use of telechelics as prepolymers to generate functional materials.

2.4 Experimental

2.4.1 Materials

n-Butyl acrylate (*n*-BA, 99 %, Sigma-Aldrich), poly(ethylene glycol) methyl ether acrylate ($PEGA_{480}$, av. M_n= 480 $g.mol^{-1}$, Sigma-Aldrich), dimethylsulfoxide (DMSO, reagent grade, Fisher scientific), dimethylformamide (DMF, reagent grade, Fisher scientific), tetrahydrofuran (THF, reagent grade, Fisher scientific), 2-mercaptoethanol (99 %, Sigma-Aldrich), 1-dodecanethiol (98 %, Sigma-Aldrich) and copper(II) bromide (98 %, Sigma-Aldrich) were used as received without further purification. Copper(0) wire (Ø 0.25 mm) was pre-treated by washing in hydrochloric acid (35 %) for 10 minutes, then rinsed with acetone, dried under nitrogen and used immediately. *N,N,N',N'',N''*-Hexamethyl-[tris(aminoethyl)amine] (Me_6-TREN) was synthesised according to a reported procedure,[59] deoxygenated and stored at 4°C under nitrogen prior to use. ε-Caprolactone (97 %, Sigma-Aldrich) was distilled under reduced pressure and stored under nitrogen at 4°C prior to use.

All other reagents and solvents were obtained at the highest purity available from Sigma-Aldrich, Fisher Chemicals, or VWR and used without further purification unless specified otherwise.

2.4.2 Characterisation

^{1}H, ^{13}C NMR spectra were recorded on Bruker ACF-250, DPX-300 and DPX-400 spectrometers using deuterated solvents obtained from Sigma-Aldrich. DOSY NMR was performed on AV-500 spectrometer with the kind help of Robert Perry. IR spectra were collected on a Bruker VECTOR-22 FT-IR spectrometer using a Golden Gate diamond attenuated reflection cell. ESI-MS data were collected in positive mode, using a Bruker HCT Ultra ESI spectrometer. MALDI-ToF MS spectra were recorded in reflection mode on a Bruker Daltonics Ultraflex II MALDI-ToF mass spectrometer, equipped with a nitrogen laser delivering 2 ns laser pulses at 337 nm with positive ion ToF detection performed using an accelerating voltage of 25 kV. The matrix solution was prepared by dissolving trans-2-[3-(4-tertbutylphenyl)-2-methyl-2-propenylidene] malononitrile (DCTB) in THF (200 mg/mL). Sodium iodide was dissolved in THF (2 mg/ mL). Polymer samples were dissolved in THF (1 to 5 mg/mL). Samples were prepared by mixing 5 µL of polymer solution, 5 µL of salt solution and 20 µL of matrix solution. Calibration was performed with a poly(ethylene glycol) methyl ether acrylate M_n= 1100 g.mol^{-1} standard. SEC using a $CHCl_3$ eluent (+ 2 % *v/v*) was carried out at 30°C on a Varian 390-LC system, equipped with 2 × PLgel 5 mm mixed D columns (300 × 7.5 mm), 1 × PLgel 5 mm guard column (50 × 7.5 mm), autosampler and a refractive index detector. DMF SEC traces were obtained on a Varian 390-LC system using a DMF (+5 mM NH_4BH_4) eluent at 50°C, equipped with refractive index, UV and viscometry detectors, 2 × PLgel 5 mm mixed D columns (300 × 7.5 mm), 1 × PLgel 5 mm guard column (50 × 7.5 mm) and autosampler. Narrow linear poly (methyl

methacrylate) standards in range of 200 to 1.0 × 10^6 g·mol^{-1} were used to calibrate the system. All samples were passed through 0.45 µm PTFE filter before analysis.

Optical microscopy analysis was performed with Dr. Gabit Nurumbetov, using a LEICA DM2500 microscope equipped with a Nikon D5100 DSLR camera. Mean diameter of the polymer micelles, coefficient of variation and normal distribution values were calculated by analysing images in ImageJ® software.

2.4.3 Initiator synthesis

NMR (^{1}H and ^{13}C) and FT-IR spectra can be visualized in appendix A.

2.4.3.1 Synthesis of ethylene bis(2-bromoisobutyrate)

The synthesis was adapted from a reported procedure.[50] To a 2 L 3 neck RB flask equipped with a magnetic stirring bar and a dropping funnel ethylene glycol (8 mL, 0.14 mol) was added under nitrogen. Anhydrous dichloromethane (700 mL) was cannulated into the flask and triethylamine (60 mL, 3 eq.) was added to the reaction mixture *via* a deoxygenated syringe and allowed to cool to 0 °C. 2-Bromoisobutyryl bromide (37.6 mL, 2.5 eq.) was added dropwise under nitrogen (over the course of one hour). Subsequently, the reaction mixture was allowed to stir at 0 °C for one hour and at ambient temperature overnight. The mixture was filtered and the volatiles removed by rotary evaporation. The resulting brown solution was dissolved in chloroform (300 mL) and treated with 1M HCl solution (250 mL), saturated $NaHCO_3$ solution (250 mL) and deionised water (3 x 250 mL). The organic layer were dried over anhydrous $MgSO_4$ and passed twice through a basic activated alumina oxide column. The volatiles were removed *in vacuo* to give a light brown solid (40.66 g, 78 % yield).

^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 4.37 (s, 4H, RO-(C***H***$_2$)$_2$-OR) and 1.87 (s, 12H, -(C***H***$_3$)$_2$).^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 63.2 and 30.7. IR (ν, cm^{-1}): 3000 (C-H stretch) 1750 (O-CO-R), 1380 (-$(CH_3)_2$), 1300 (CH stretch), 1200 (CH stretch). HRMS (ESI; m/z, Da): [M + Na$^+$] 382.9 (*382.94 th*).

2.4.3.2 Synthesis of bis[2-(2-bromoisobutyryloxy)ethyl] disulfide [DSDBr]

The synthesis of DSDBr was conducted according to a reported procedure.[60]

^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 4.45 (t, 4H, J=6.5 Hz, RO-C***H***$_2$-), 2.99 (t, 4H, J=6.5 Hz, -C***H***$_2$-SR) and 1.95 (s, 12H, -(C***H***$_3$)$_2$).^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 63.5, 36.7 and 30.7. FT-IR (ν, cm^{-1}): 3000 (C-H stretch) 1750 (O-CO-R), 1380 (-$(CH_3)_2$), 1300 (CH stretch), 1200 (CH stretch), 510 (RS-SR). HRMS (ESI, m/z, Da): [M + Na$^+$] 474.8 (*474.9 Th*).

2.4.4 General procedures

^{13}C NMR can be visualized in appendix A.

2.4.4.1 Cu(0)-mediated polymerisation of acrylates in organic solvents

This procedure is generic for both the polymerisation of *n*-BA and $PEGA_{480}$ in various solvents. The polymerisation of *n*-BA with ethylene bis(2-bromoisobutyrate) initiator in DMSO is described. In an oven dried Schlenk tube ethylene bis(2-bromoisobutyrate) (0.5 g, 1.39 mmol), copper(II) bromide (15.5 mg, 0.05 eq.), *n*-BA (7.96 mL, 40 eq.) and DMSO (8 mL) were added. The stirring bar with the pre-activated copper wire was subsequently added and the Schlenk tube sealed with a rubber septum. The reaction was kept stirring with nitrogen sparging for 10 min prior to addition of Me_6-TREN ligand (75 µL, 0.18 eq.) *via* a

deoxygenated microsyringe and the reaction was left to polymerise at ambient temperature (25°C). Samples of the reaction mixture were taken periodically for ^{1}H NMR, SEC and MALDI-ToF MS analysis. Samples were passed through a basic alumina oxide column to remove metal salts prior any analysis. Samples for ^{1}H NMR were diluted in deuterated chloroform while the samples for SEC were diluted in the corresponding eluent. Chain extension was performed by injecting a pre-deoxygenated aliquot of monomer in DMSO (50% *v/v*) to the reaction mixture *via* a deoxygenated syringe.

2.4.4.2 Nucleophilic substitution of polymer end groups with 2-mercaptoethanol

Following the polymerisation, poly(*n*-BA) was used without further modification, which was possible due to the phase separation of the polymer from the catalyst. Poly(*n*-BA) (0.5 g, 0.14 mmol, M_n= 3500 g.mol^{-1}) was charged to a vial fitted with a magnetic stirring bar and a rubber septum with THF (5 mL), triethylamine (1 mL, 50 eq.) and 2-mercaptoethanol (500 µL, 50 eq.). The reaction mixture was left to stir overnight at ambient temperature. After filtration, the volatiles were removed by rotary evaporation and the remaining product analysed by ^{1}H NMR and SEC analysis. The remaining thiols were removed by dialysis against 2-isopropanol (IPA, MWCO 1 kDa) and the product isolated under vacuum prior to analysis by ^{1}H , ^{13}C NMR and MALDI-ToF MS.

2.4.4.3 End-capping with allyl alcohol

Following the polymerisation of *n*-BA in IPA (see section 2.4.4.1), allyl alcohol (100 eq. compared to initiator) was injected to the reaction medium *via* a deoxygenated syringe and the mixture was left to stir at ambient temperature overnight. Subsequently, the volatiles were removed by reduced pressure to yield the *α,ω*-OH terminated polymer.

2.4.4.4 Nucleophilic substitution of the polymer end groups with dodecanethiol.

Following polymerisation poly($PEGA_{480}$) (10 g, 1.40 mmol, M_n= 7100 $g.mol^{-1}$) was diluted in THF (20 mL) and passed through a basic activated alumina column to remove metal salts. The solution was placed in a 50 mL RB flask fitted with a magnetic stirring bar and a rubber septum. Triethylamine (9.8 mL, 50 eq.) and dodecanethiol (4.9 mL, 50 eq.) were added to the solution and left to stir overnight at ambient temperature. After filtration, the solution was dialysed over water (MWCO 1 kDa) overnight. One part of the solution was analysed by optical microscopy, while the remainder was freeze dried prior to analysis by ^{1}H, ^{13}C NMR and SEC.

2.4.4.5 Phenyl isocyanate modification.

α,ω-Hydroxyl terminated PBA (M_n= 3600 $g.mol^{-1}$, 0.5 g, 0.28 mmol) was added to a 50 mL RB flask equipped with a magnetic stirring bar and a rubber septum. The polymer was isolated by removal of volatiles under vacuum at 70°C overnight before anhydrous DMF (10 mL) was added under nitrogen flow. The mixture was deoxygenated using 3 freeze-pump thaw cycles. Phenyl isocyanate (604 µL, 40 eq.) and dibutyltin dilaurate (3 drops) were added *via* a deoxygenated syringe. The reaction mixture was placed in an oil bath at 60°C and left to stir for 9h. Following the reaction, the polymer was isolated by removal of volatiles under vacuum at 70°C overnight. The success of the functionalisation of the hydroxyl end groups was assessed by FT-IR, SEC, ^{1}H , ^{13}C NMR and MALDI-ToF MS.

2.4.4.6 Ring-Opening polymerisation of ε-caprolactone initiated by *α,ω*-hydroxyl terminated poly(*n*-BA)

This procedure is adapted from Zhang *et al.*[61] In an oven dried Schlenk tube, OH-terminated PBA (M_n= 3600 g.mol^{-1}, 0.5 g, 0.28 mmol) was dried at 70°C under vacuum for one day. *ε*-Caprolactone (308 µL, 20 eq.) was added to the polyol followed by three evacuation/N_2 refilling cycles. Stannous octanoate (36 mg, 0.65 eq.) was dissolved in anhydrous toluene (2 mL) in a vial and the mixture injected into the Schlenk tube *via* a deoxygenated syringe and the evacuation/N_2 refilling cycles repeated three times. The reaction mixture was left to stir at 120°C under nitrogen for 12 hours. Subsequently, the polymer mixture was dialysed (MWCO 3.5 kDa) against MeOH/H_2O 9/1 *v/v* and isolated by rotary evaporation. The copolymer was analysed by ^{1}H, ^{13}C NMR, DOSY and SEC.

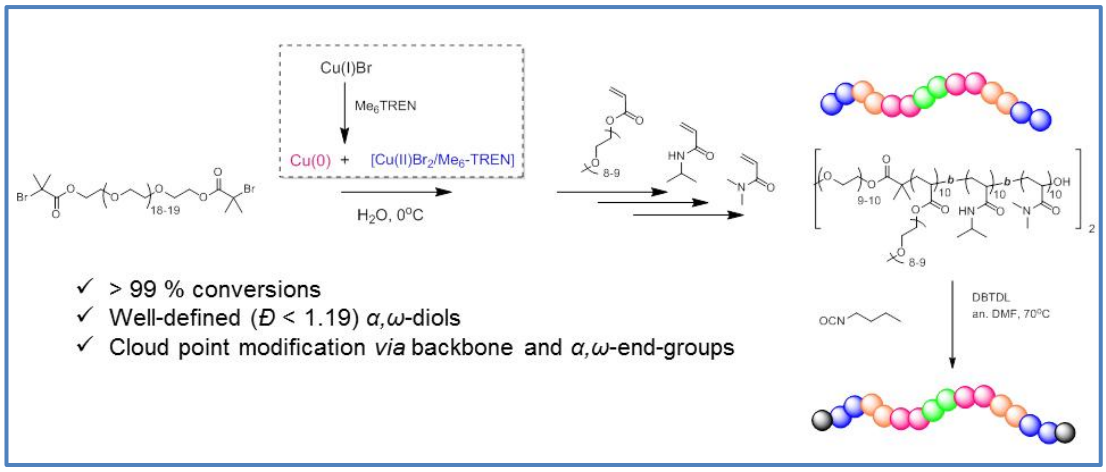
2.5 References

1. B. Boutevin, in *New Polymer Materials*, Springer Berlin Heidelberg, 1990, vol. 94, pp. 69-105.
2. M. A. Tasdelen, M. U. Kahveci and Y. Yagci, *Prog. Polym. Sci.*, 2011, **36**, 455-567.
3. J. Grumelard, A. Taubert and W. Meier, *Chem. Commun.*, 2004, 1462-1463.
4. A. Blanazs, S. P. Armes and A. J. Ryan, *Macromol. Rapid Commun.*, 2009, **30**, 267-277.
5. K. Horie, M. Báron, R. B. Fox, J. He, M. Hess, J. Kahovec, T. Kitayama, P. Kubisa, E. Maréchal, W. Mormann, R. F. T. Stepto, D. Tabak, J. Vohlídal, E. S. Wilks and W. J. Work, *Pure Appl. Chem.*, 2004, **76**, 889-906.
6. S. M. Guillaume, *Eur. Polym. J.*, 2013, **49**, 768-779.
7. H. A. Klok and S. Lecommandoux, *Adv. Mater.*, 2001, **13**, 1217-1229.
8. J.-M. Lehn, in *Supramol. Chem.*, Wiley-VCH Verlag GmbH & Co. KGaA, 2006, pp. 89-138.
9. E. D. Goddard and J. V. Gruber, *Principles of Polymer Science and Technology in Cosmetics and Personal Care*, Marcel Dekker, 1999.
10. K. Matyjaszewski, Y. Gnanou and L. Leibler, in *Macromolecular Engineering*, Wiley-VCH Verlag GmbH & Co. KGaA, 2007, pp. 1-6.
11. R. P. Quirk and B. Lee, *Polym. Int.*, 1992, **27**, 359-367.
12. T. Otsu, *J. Polym. Sci., Part A: Polym. Chem.*, 2000, **38**, 2121-2136.

13. J. Chiefari, Y. K. Chong, F. Ercole, J. Krstina, J. Jeffery, T. P. T. Le, R. T. A. Mayadunne, G. F. Meijs, C. L. Moad, G. Moad, E. Rizzardo and S. H. Thang, *Macromolecules*, 1998, **31**, 5559-5562.
14. M. Benaglia, J. Chiefari, Y. K. Chong, G. Moad, E. Rizzardo and S. H. Thang, *J. Am. Chem. Soc.*, 2009, **131**, 6914-6915.
15. C. Barner-Kowollik, T. P. Davis, J. P. A. Heuts, M. H. Stenzel, P. Vana and M. Whittaker, *J. Polym. Sci., Part A: Polym. Chem.*, 2003, **41**, 365-375.
16. M. K. Georges, R. P. N. Veregin, P. M. Kazmaier and G. K. Hamer, *Macromolecules*, 1993, **26**, 2987-2988.
17. C. J. Hawker, A. W. Bosman and E. Harth, *Chem. Rev.*, 2001, **101**, 3661-3688.
18. M. Labet and W. Thielemans, *Chem. Soc. Rev.*, 2009, **38**, 3484-3504.
19. K. Stridsberg, M. Ryner and A.-C. Albertsson, in *Degradable Aliphatic Polyesters*, Springer Berlin Heidelberg, 2002, vol. 157, pp. 41-65.
20. A. Khanna, Y. Sudha, S. Pillai and S. Rath, *J. Mol. Model.*, 2008, **14**, 367-374.
21. M. Kamigaito, T. Ando and M. Sawamoto, *Chem. Rev.*, 2001, **101**, 3689-3746.
22. K. Matyjaszewski, *Macromolecules*, 2012, **45**, 4015-4039.
23. J.-S. Wang and K. Matyjaszewski, *J. Am. Chem. Soc.*, 1995, **117**, 5614-5615.
24. K. Matyjaszewski and J. Xia, *Chem. Rev.*, 2001, **101**, 2921-2990.
25. D. M. Haddleton, C. Waterson, P. J. Derrick, C. B. Jasieczek and A. J. Shooter, *Chem. Commun.*, 1997, 683-684.
26. X. Zhang and K. Matyjaszewski, *Macromolecules*, 1999, **32**, 7349-7353.
27. V. Coessens and K. Matyjaszewski, *Macromol. Rapid Commun.*, 1999, **20**, 127-134.
28. T. Ando, M. Kamigaito and M. Sawamoto, *Macromolecules*, 1998, **31**, 6708-6711.
29. V. Coessens and K. Matyjaszewski, *Macromol. Sci., Part A*, 1999, **36**, 667-679.
30. J. A. Opsteen and J. C. M. van Hest, *Chem. Commun.*, 2005, **0**, 57-59.
31. J.-F. Lutz, *Angew. Chem. Int. Ed.*, 2007, **46**, 1018-1025.
32. G. Lligadas and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2007, **45**, 4684-4695.
33. C. E. Hoyle, A. B. Lowe and C. N. Bowman, *Chem. Soc. Rev.*, 2010, **39**, 1355-1387.
34. B. Radhakrishnan, P. Chambon, E. Cloutet and H. Cramail, *Colloid. Polym. Sci.*, 2003, **281**, 516-530.
35. R. Huisgen, *Angew. Chem. Int. Ed.*, 1963, **2**, 565-598.
36. J.-F. Lutz, H. G. Börner and K. Weichenhan, *Macromol. Rapid Commun.*, 2005, **26**, 514-518.
37. R. K. Iha, K. L. Wooley, A. M. Nyström, D. J. Burke, M. J. Kade and C. J. Hawker, *Chem. Rev.*, 2009, **109**, 5620-5686.
38. C. R. Becer, R. Hoogenboom and U. S. Schubert, *Angew. Chem. Int. Ed.*, 2009, **48**, 4900-4908.
39. K. Kempe, A. Krieg, C. R. Becer and U. S. Schubert, *Chem. Soc. Rev.*, 2012, **41**, 176-191.
40. H. Fischer, *Chem. Rev.*, 2001, **101**, 3581-3610.
41. H. Fischer, *J. Polym. Sci., Part A: Polym. Chem.*, 1999, **37**, 1885-1901.
42. V. Percec, T. Guliashvili, J. S. Ladislaw, A. Wistrand, A. Stjerndahl, M. J. Sienkowska, M. J. Monteiro and S. Sahoo, *J. Am. Chem. Soc.*, 2006, **128**, 14156-14165.
43. B. M. Rosen and V. Percec, *Chem. Rev.*, 2009, **109**, 5069-5119.
44. S. R. Samanta, A. Anastasaki, C. Waldron, D. M. Haddleton and V. Percec, *Polym. Chem.*, 2013, **4**, 5555.
45. A. H. Soeriyadi, C. Boyer, F. Nyström, P. B. Zetterlund and M. R. Whittaker, *J. Am. Chem. Soc.*, 2011, **133**, 11128-11131.
46. F. Nyström, A. H. Soeriyadi, C. Boyer, P. B. Zetterlund and M. R. Whittaker, *J. Polym. Sci., Part A: Polym. Chem.*, 2011, **49**, 5313-5321.

47. K. Matyjaszewski, S. Coca, S. G. Gaynor, M. Wei and B. E. Woodworth, *Macromolecules*, 1997, **30**, 7348-7350.
48. N. V. Tsarevsky and K. Matyjaszewski, *Chem. Rev.*, 2007, **107**, 2270-2299.
49. A. Anastasaki, C. Waldron, P. Wilson, R. McHale and D. M. Haddleton, *Polym. Chem.*, 2013, **4**, 2672.
50. C. Boyer, A. Atme, C. Waldron, A. Anastasaki, P. Wilson, P. B. Zetterlund, D. Haddleton and M. R. Whittaker, *Polym. Chem.*, 2013, **4**, 106-112.
51. C. Waldron, A. Anastasaki, R. McHale, P. Wilson, Z. Li, T. Smith and D. M. Haddleton, *Polym. Chem.*, 2014, **5**, 892-898.
52. V. Coessens and K. Matyjaszewski, *Macromol. Sci., Part A*, 1999, **36**, 653-666.
53. A. J. Grice, *Investigationsof Single Electron Transfer Living Radical Polymerisation (SET-LRP)*, University of Warwick, 2010.
54. J. D. Flores, N. J. Treat, A. W. York and C. L. McCormick, *Polym. Chem.*, 2011, **2**, 1976-1985.
55. G. Gody, C. Rossner, J. Moraes, P. Vana, T. Maschmeyer and S. Perrier, *J. Am. Chem. Soc.*, 2012, **134**, 12596-12603.
56. F. Biedermann, E. A. Appel, J. s. del Barrio, T. Gruendling, C. Barner-Kowollik and O. A. Scherman, *Macromolecules*, 2011, **44**, 4828-4835.
57. A. A. P. Mansur, O. L. d. Nascimento, R. L. Oréfice and H. S. Mansur, *Surf. Interface Anal.*, 2011, **43**, 738-743.
58. G. A. Morris, in *eMagRes*, John Wiley & Sons, Ltd, 2007.
59. M. Ciampolini and N. Nardi, *Inorg. Chem.*, 1966, **5**, 41-44.
60. J. A. Syrett, M. W. Jones and D. M. Haddleton, *Chem. Commun.*, 2010, **46**, 7181-7183.
61. Q. Zhang, G.-Z. Li, C. R. Becer and D. M. Haddleton, *Chem. Commun.*, 2012, **48**, 8063-8065.

Synthesis of well-defined *α,ω*-telechelic multiblock copolymers in aqueous medium: *In situ* generation of *α,ω*-diols



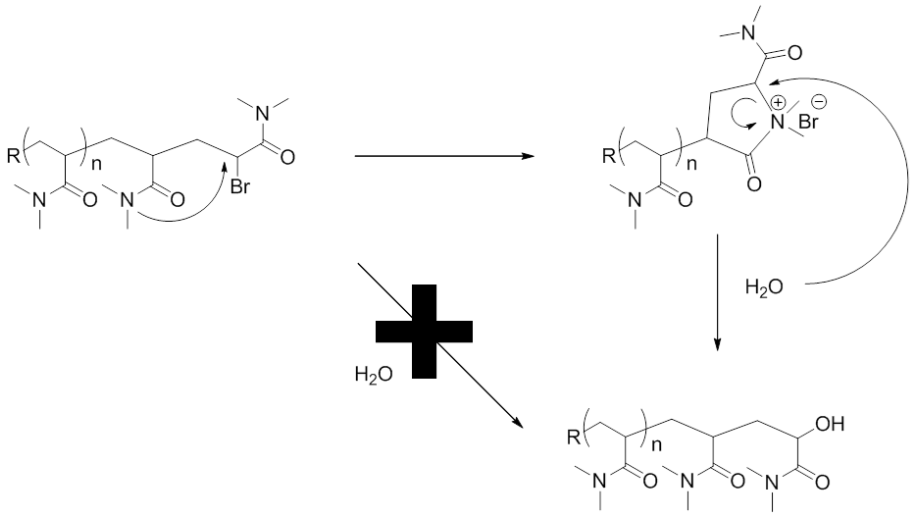
The synthesis of well-defined α,ω-dihydroxyl telechelic multiblock copolymers by sequential in situ chain extensions via aqueous Cu(0)-mediated RDRP (SET-LRP) is reported. The rapid disproportionation of Cu(I)Br in the presence of Me_6-TREN in water has been exploited to generate Cu(0) and [Cu^{II}(Me_6-TREN)Br]Br in situ, resulting in rapid reaction rates and narrow molecular weight distributions. Under optimised conditions, a telechelic heptablock copolymer was obtained within 2 hours with a final dispersity of ~ 1.1 while the monomer conversion was > 99% for each block. A range of acrylamides and acrylates have been successfully incorporated within the same polymer backbone, including N-isopropylacrylamide (NIPAAm), N,N-diethylacrylamide (DEA), N,N-dimethylacrylamide (DMA) and poly(ethylene glycol) methyl ether acrylate ($PEGA_{480}$). The thermo-responsive nature of these materials was subsequently demonstrated via cloud point measurements as both a function of molecular weight and backbone functionality. In addition, the typically unwanted hydrolysis of the α- and ω- end groups in aqueous media was further exploited via isocyanate post-polymerisation modifications to alter the end-group functionality.

3.1 Introduction

In the previous chapter, the synthesis of hydrophilic and hydrophobic polyacrylates was thoroughly investigated utilising Cu(0)-mediated polymerisation in organic media. It subsequently came to light that utilising Cu(0) as the primary copper source could be advantageous for the design of functional telechelics. Indeed, the high retention of both halide end-group(s) fidelity and narrow molecular weight distributions allows the formation of amphiphiles and/or macrodiols which can be further reacted, yielding various materials. Thus, utilising this robust technique for the synthesis of more sophisticated architectures including stimuli-responsive hydrogels,[1] double-hydrophilic (co)polymers[2] and organized nanostructures[3] (such as micelles,[4] flower-like micelles,[5-7] vesicles, polymersomes) would be highly desirable. Such architectures can be obtained using functional initiators and post-polymerisation modifications.[8] Towards this, the use of bi-functional entities could maximize the time limit arising from chain-end hydrolysis[9, 10] in aqueous medium as more functionality can be introduced upon each monomer addition.[11] Nevertheless, the use of such initiators is rather challenging in water, considering the high rate of termination due to the increase in number of generated radicals. The controlled incorporation of different hydrophilic and/or thermo-responsive monomers such as poly(ethylene glycol) methyl ether acrylate ($PEGA_{480}$), *N*-isopropylacrylamide (NIPAAm), *N*,*N*-dimethylacrylamide (DMA) and *N*,*N*-diethylacrylamide (DEA) into the same polymer backbone is highly desirable and has not yet been realised *via* a copper-mediated polymerisation process.

3.1.1 Current limitations of copper-mediated polymerisation in aqueous medium

The synthesis of acrylamide, acrylate or methacrylate based polymers has been widely reported using NMP,[12] RAFT[13] and TMM-RDRP[14, 15] in organic solvents. However, the introduction of water in the solvent composition has proved to be challenging, as the control over the molecular weight distributions is often difficult to retain, especially in copper mediated-RDRP polymerisations, due to a reported increase in termination events.[16, 17] Undesired side reactions, such as reversible dissociation and substitution of the halide ligand from the Cu(II) complex can occur, resulting in inefficient deactivation of a growing polymer chain and loss of control.[18] Moreover, additional side reactions are commonly reported in water, such as loss of end group fidelity *via* hydrolysis (Scheme 3.1).[9, 19]



Scheme 3.1. Hydrolysis of halide end-group *via* cyclisation of the penultimate unit.[9, 19]

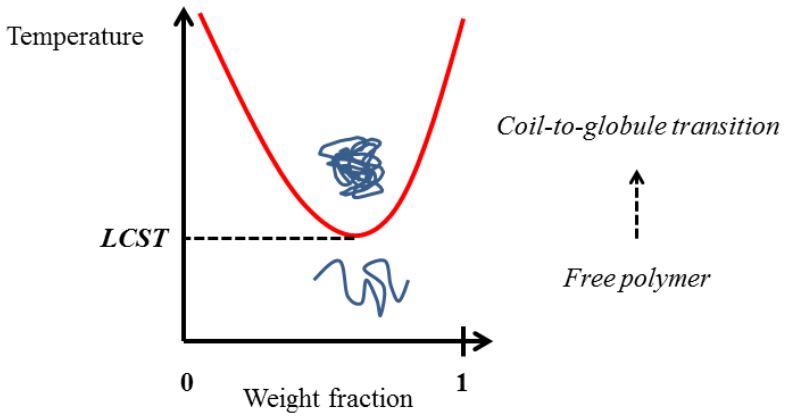
Numerous optimisations in both aqueous solutions and organic solvents have been conducted to diminish side reactions and retain narrow MWD and high end group(s) fidelity, mainly by *in situ* regeneration of the transition metal catalyst by various stimuli.[20] Several transition-metal mediated techniques (ICAR-ATRP, e-ATRP, ARGET-ATRP, SARA-ATRP

and SET-LRP)[21-40] have proved to be powerful tools, yielding functional macromolecular structures in various solvents. Nevertheless, the synthesis of bio-compatible monomers such as NIPAAm and/or other acrylamides has remained a challenge in water.[9, 19, 41, 42] Indeed, the use of highly polar organic solvents (alcohols and DMF preferentially) or binary mixtures with water are necessary to achieve good control over the molecular weight distributions under standard ATRP conditions.

It was demonstrated in the previous chapters (see section 1.2.5.2.3) and in recent publications[37, 43] that exploiting the rapid and quantitative disproportionation of Cu(I)Br in the presence of the *N*-donor aliphatic ligand Me_6-TREN, in water[37, 44] and complex aqueous mixtures[45, 46] prior to polymerisation yields poly(acrylates) and pleasingly, poly(acrylamides) with an excellent degree of control. However, this tool has not been exploited for the design of telechelics with tailored stimuli-responsive behaviour.

3.1.2 Thermo-responsive materials

Functional monomers such as NIPAAm have been extensively incorporated in (co)polymer compositions for their interesting phase transition at elevated temperatures. Indeed, following early reports in 1963,[47] as well as Scarpa *et al* report in 1967[48] and the more detailed investigation from Heskins and Guillet in 1968 on the aqueous solution properties of poly(NIPAAm) (PNIPAAm),[49] this hydrophilic polymer has received enormous attention.[50] The concept of a polymer that is soluble in a medium until reaching a critical solution temperature is commonly referred to as lower critical solution temperature (LCST, scheme 3.2). The change in solubility of the polymer, here PNIPAAm, is due to an entropically favourable coil-to-globule transition. This effect is driven by the expulsion of water molecules associated with the polymer and the formation of hydrogen bonds.[49]



Scheme 3.2. Representative scheme of lower critical solution temperature (LCST) transition.

For instance, the LCST of PNIPAAm has been observed for temperature in the range 32-35°C, which becomes of interest considering its proximity to body temperature. Nevertheless, the LCST transition can be influenced by several polymer properties, such as molecular weight (MW),[51] stereochemistry,[52] co-solvency,[53] ionic strength[54, 55] and monomer composition.

The facile tuning of the reversible thermally-induced transition, providing access to the rapid synthesis of "smart-materials" has attracted significant interest, especially in biomedical applications,[56] from tissue engineering to biosensing. Thus, studies have been conducted in to the design of macromolecular architectures[57, 58] through side chain functionalities and end-group modifications, in order to manipulate the LCST, as small changes can have a significant effect on the performance of the material.[59]

It is evident that the full understanding and presentation of the concept of LCST transition and uses of thermo-responsive polymers requires more than short paragraphs. However, this is not the main focus of this work, hence it will not be detailed further. Moreover, the coil-to-globule transition temperature will be monitored through the recording of the cloud point

temperature (T_{cp}),[60] as the influence of the weight fraction will not be fully investigated in this work.

3.1.3 Motivation: towards multiblock copolymers

The ability to tune the physical properties (*e.g*. LCST) of a polymer through the variation of monomer composition can be challenging and requires an adapted tool to yield well-defined multiblock copolymers. Perrier and co-workers have recently reported the synthesis of multiblock copolymers in both aqueous and organic media utilising an optimised RAFT approach.[61, 62] Although different degrees of polymerisation have been achieved (DP_n=3-100 per block), the high reaction temperature (70°C) is not suitable for the polymerisation of thermo-responsive monomers in water (*e.g.* NIPAAm, DEA) that possess an LCST below 70°C in aqueous solution. In addition, RAFT is limited to acrylamides as polymerisation of other monomers (*e.g*. acrylates) at these temperatures results in unwanted side reactions and unavoidable termination.[63, 64] More recently, the same research group managed to lower the polymerisation temperature to 25°C, through the use of different radical initiator and additional reducing agents, which together act as a redox couple enabling radical (re)generation, to yield multiblock copolymers in aqueous medium.[65] Hence, the incorporation of NIPAAm, $PEGA_{480}$ and DEA in the copolymer composition became possible, with good control over the final molecular weight distributions (*Đ*~1.35).

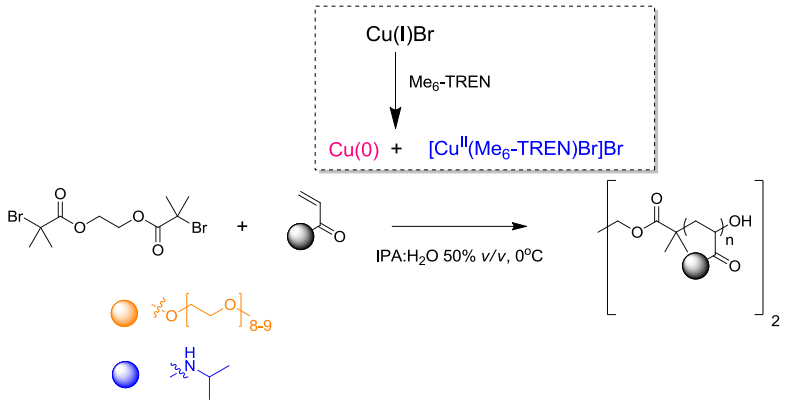
Copper-mediated RDRP approaches have attempted to address the issues arising from high temperatures, although only organic solvent systems were successfully employed.[66-68] There is only one example in literature reporting the synthesis of multiblocks at ambient temperature or below in water and in this study only acrylamides were reported avoiding issues arising from different reactivity ratios (*e.g.* acrylamides and acrylates).[10]

In this present work, the versatility of aqueous SET-LRP is exploited for the polymerisation of hydrophilic and/or thermo-responsive monomers including $PEGA_{480}$, NIPAAm, DEA and DMA in both aqueous and organic/aqueous mixtures (Scheme 3.3 and 3.5). Two different types of bi-functional initiators are employed to yield well-defined multiblock copolymers with narrow dispersity values ($Đ$ < 1.19) and quantitative conversions (> 99 % by ^{1}H NMR) by sequential monomer addition. Remarkably, both acrylates and acrylamides can be combined within the same polymer backbone, yielding a heptablock copolymer with narrow dispersity (> 99 % conversions, $Đ$< 1.11) in two hours. The LCST response of the copolymers[49, 69-71] are further investigated as a function of molecular weight, monomer composition and chain-end functionalities. Moreover, the unavoidable hydrolysis of the halogen end groups has been exploited to incorporate additional functionalities *via* isocyanate coupling post-polymerisation.

3.2 Results and discussion

3.2.1. Polymerisations using a water insoluble initiator, ethylene bis(2-bromoisobutyrate)

The polymerisation of $PEGA_{480}$ in water was attempted using the bi-functional initiator, ethylene bis(2-bromoisobutyrate) (see section 2.2.1). However, the solubility of the initiator in water proved to be limited and was rectified by the addition of a co-solvent, (up to a 50 % *v/v* ratio). 2-Isopropanol (IPA) became the co-solvent of choice due to low toxicity and high polarity, which was thought would minimize disruption of the disproportionation equilibrium of [$Cu^I(Me_6$-TREN)Br].



Scheme 3.3. Cu(0)-mediated polymerisation of $PEGA_{480}$ and NIPAAm with bi-functional initiator ethylene bis(2-bromoisobutyrate) in IPA/H_2O 50 % *v/v*.

In order to test this, UV-Vis NIR experiments were conducted, revealing quantitative disproportionation of [Cu^{I}(Me_6-TREN)Br] when a binary mixture of IPA and water (50 % *v/v*) was employed (Figure 3.1). The complex was allowed to disproportionate in water (15 min) prior to polymerisation to ensure the rapid and quantitative formation of Cu(0) and [Cu^{II}(Me_6-TREN)Br]Br.

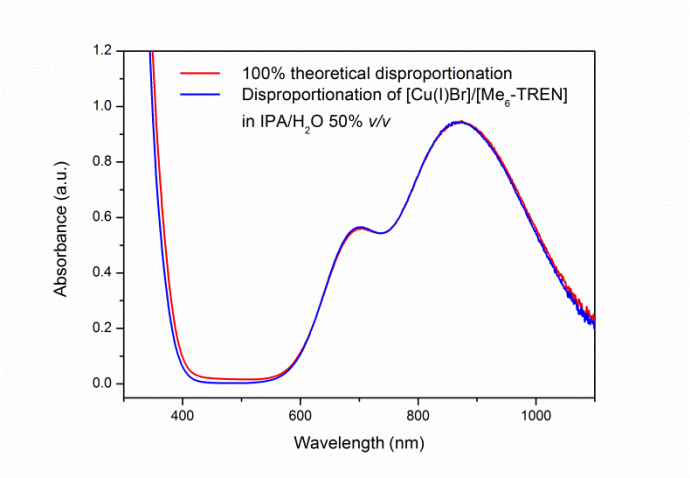


Figure 3.1. Monitoring the disproportionation of Cu(I)Br in the presence of Me_6-TREN in 50% *v/v* IPA/H_2O.

Upon addition of monomer ($PEGA_{480}$, DP_n= 20), initiator and solvent (IPA/water), near quantitative monomer conversion (> 99%) and narrow molecular weight distributions (M_n=

5500 g.mol^{-1}, *Đ*= 1.11) were observed within 2 hours, as evidenced by both ^{1}H NMR and SEC (Figure 3.2). It is important to note that in comparison to mono-functional initiators, higher amounts of Cu(I)Br (which subsequently disproportionates yielding more deactivator [Cu^{II}(Me$_6$-TREN)Br]Br) are required in order to achieve good control over the molecular weight distribution due to the increase (2 fold) in the number of initiation sites. The [I]:[M]:[Me$_6$-TREN]:[Cu(I)Br] was adjusted from 1:20:0.4:0.4 (typically employed for monofunctional initiators)[37] to 1:20:0.4:0.8. The amount of ligand was maintained as an excess of ligand has been previously reported to compromise the end group fidelity due to termination events and side reactions.[17, 18, 72]

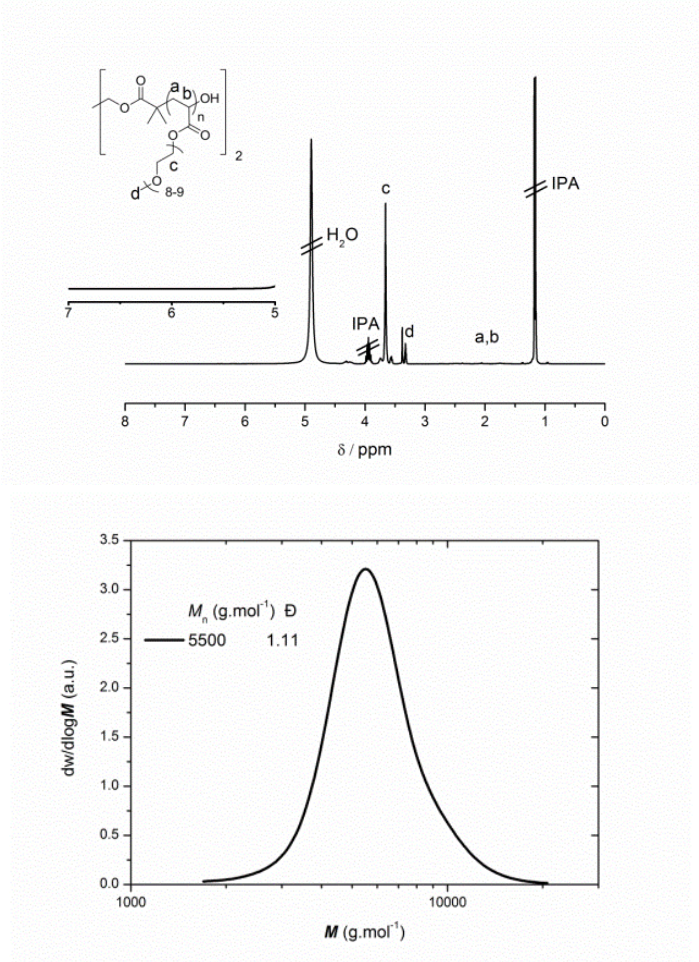


Figure 3.2. Monitoring of the polymerisation of poly(ethylene glycol) methyl ether acrylate (av. M_n= 480 g.mol^{-1}) in 50 % *v/v* IPA/H$_2$O at 0°C after 2 hours, [I]:[M]:[Me$_6$-TREN]:[Cu(I)Br]= 1:8:0.4:0.8 initiated by ethylene bis(2-bromoisobutyrate); by ^{1}H NMR (MeOD, 300 MHz, top) and SEC (DMF eluent, bottom).

The polymerisation of $PEGA_{480}$ was significantly slower than previously reported in pure water,[37] suggesting that IPA was responsible for a retardation in the rate of polymerisation. Interestingly, the residual high molecular weight shoulder observed in chapter 2 when polymerising $PEGA_{480}$ in DMSO (Cu(0)-wire at 25°C, see section 2.2.2) is not present under pre-disproportionation conditions at 0°C. Further discussions on the nature of this high molecular weight shoulder will be provided in section 4.2. Similar results with respect to rate of polymerisation (2 hours) were obtained when low molecular weight PNIPAAm were targeted, though high monomer conversions (92 % by ^{1}H NMR) and narrow dispersities (*Đ*= 1.11) were achieved (figure 3.3).

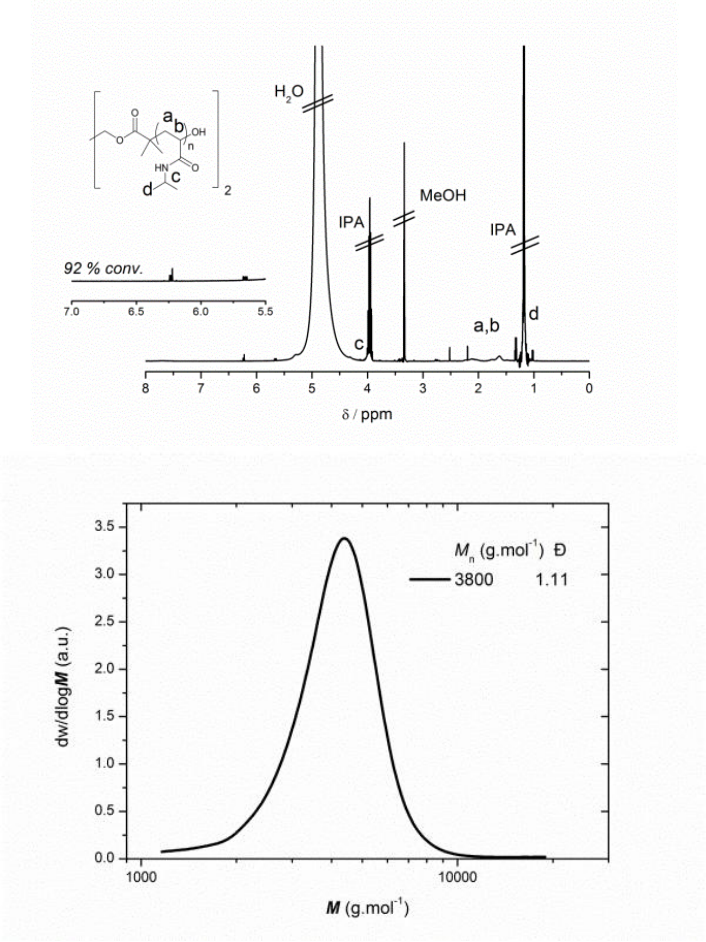


Figure 3.3. Monitoring the polymerisation of *N*-isopropylacrylamide in 50% *v/v* IPA/H_2O at 0°C, [I]:[M]:[Me_6-TREN]:[Cu(I)Br]= 1:20:0.4:0.8 initiated by ethylene bis(2-bromoisobutyrate); after 2 hours by ^{1}H NMR (MeOD, 400 MHz, top) and SEC (DMF eluent, bottom)

The simplicity of the reaction setup as well as the good control over the MWD was tested on a larger scale (~50 g scale), with similar degree of control retained. Noteworthy, the *in situ* monitoring of the reaction temperature revealed a significant exotherm (10°C) upon initiator and monomer addition (see appendix B).

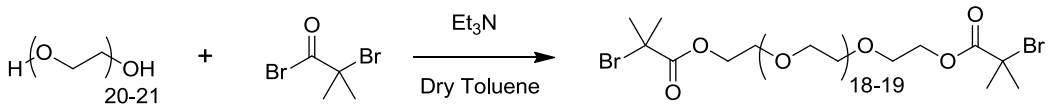
Figure 3.4. (Left) Disproportionation of Cu(I)Br in the presence of Me_6-TREN in water. (Middle) Polymerisation of *N*-isopropylacrylamide [I]:[M]:[Me_6-TREN]:[Cu(I)Br]= 1:20:0.4:0.8 initiated by ethylene bis(2-bromoisobutyrate) in IPA/H_2O 50% *v/v*. (Right) Lyophilized polymer after copper removal with Cuprisorb™ resin.

Interestingly, when higher molecular weights of PNIPAAm (M_n > 4000 g.mol^{-1}) were targeted, the use of co-solvents had a detrimental effect, resulting in cessation of polymerisation. The insolubility of PNIPAAm in the selected alcoholic mixtures[46, 73, 74] results in phase separation of the polymer from the catalytic system. Consequently, investigations were carried out to lower the amount of alcoholic co-solvent. Unfortunately, the initiator was not fully soluble in mixtures of IPA and water lower than 50 % *v/v* which compromised the monomer conversion (< 90 %) for degrees of polymerisation greater than 30 (M_n > 4000 g.mol^{-1}). Moreover, at the end of the polymerisation, the reaction mixture was green suggesting the formation of Cu(II) species, while no visible Cu(0) was observed. This implies a large extend of termination events[33] and compromises the control over the polymerisation in that particular solvent composition.

3.2.2. Polymerisation using a water soluble initiator, poly(ethylene glycol) bis(2-bromoisobutyrate)

3.2.2.1 Synthesis of poly(ethylene glycol) bis(2-bromoisobutyrate)

A second bi-functional, water soluble initiator derived from linear poly(ethylene glycol) (PEG, av. M_n= 1000 g.mol^{-1}) was synthesised to overcome both solubility and precipitation issues. The telechelic initiator was obtained *via* esterification of the PEG hydroxyl ends. In order to unsure a minimal water contamination, the PEG was dissolved in toluene prior to an azeotropic distillation of the solvent.



Scheme 3.4. Synthesis of poly(ethylene glycol) bis(2-bromoisobutyrate).

Successful esterification was monitored by ^{1}H NMR, revealing the appearance of –(C***H***$_3$)$_2$ peaks at 1.9 ppm (300 MHz, $CDCl_3$, figure 3.5). Moreover, MALDI-ToF MS confirmed the *α,ω*-Br telechelic nature of the initiator without any impurities.

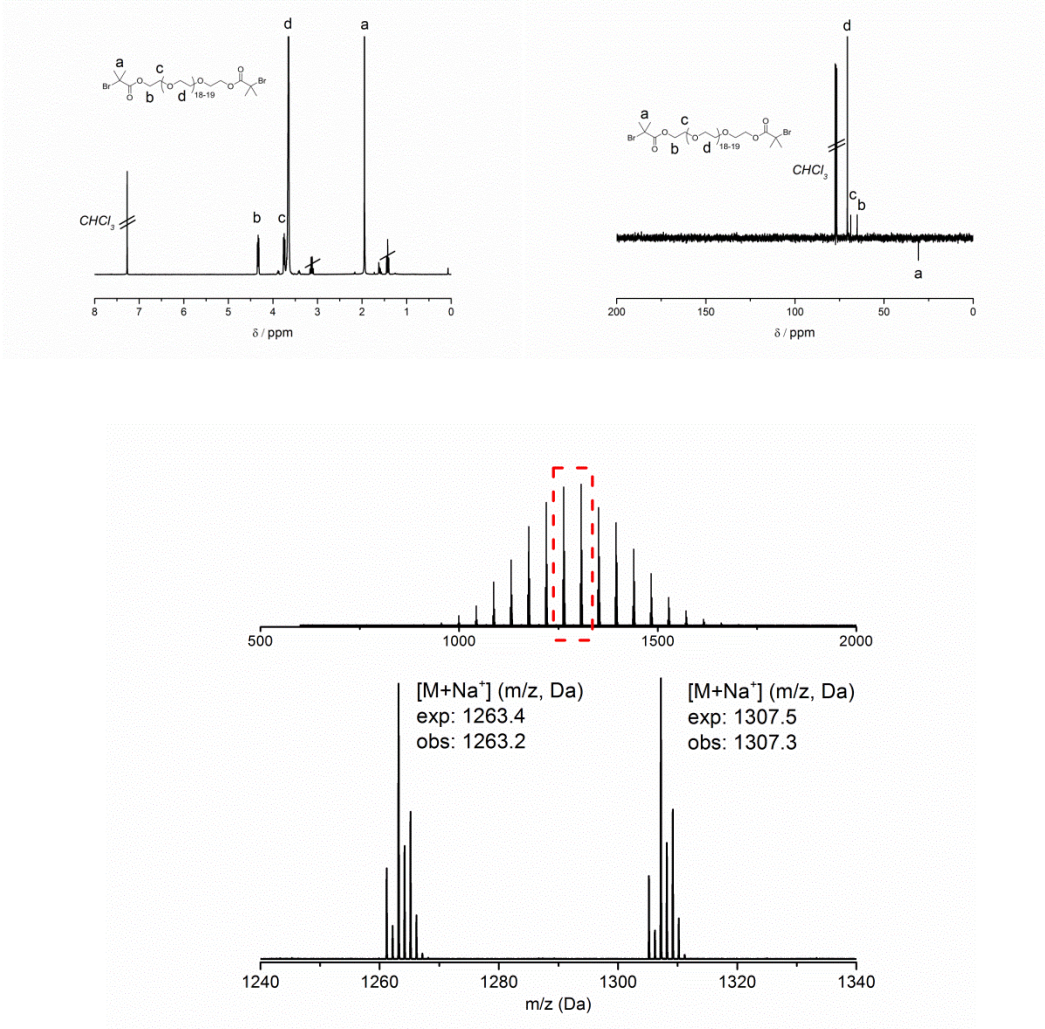
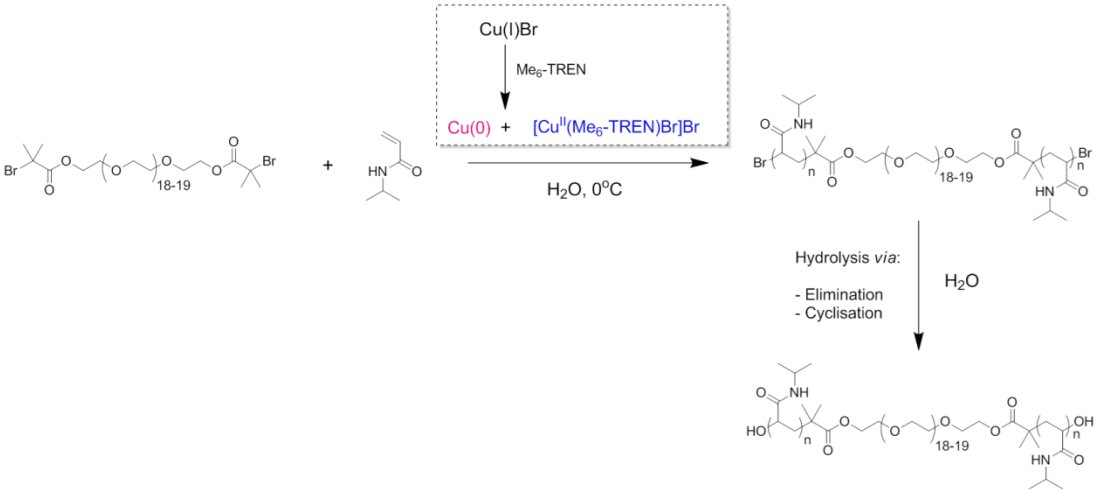


Figure 3.5. ^{1}H NMR (300 MHz, $CDCl_3$, top left), ^{13}C NMR (75 MHz, $CDCl_3$, top right) and MALDI-ToF MS (bottom) spectrum of poly(ethylene glycol) bis(2-bromoisobutyrate).

Similar mono-functional PEG ATRP/SET-LRP initiators have been widely studied for the synthesis of responsive block copolymers that self-assemble in micelles, vesicles and rods.[4] However, the synthesis of such functional macromolecules has been challenging by Cu-mediated processes in aqueous systems[75] due to enhanced termination events as discussed previously.[17]

3.2.2.2 Polymerisation of NIPAAm, in aqueous media

The synthesised telechelic PEG macroinitiator was employed to investigate the aqueous polymerisation of NIPAAm.



Scheme 3.5. Cu(0)-mediated polymerisation of NIPAAm, with bi-functional initiator poly(ethylene glycol) bis(2-bromoisobutyrate) (av. M_n= 1000 g.mol^{-1}) in H_2O. Possible hydrolysis routes according to references 9, 19 and 85.

Unexpectedly, when a ratio [I]:[Me_6-TREN]:[Cu(I)Br]= 1:0.4:0.8 was employed, relatively limited conversions were observed after 30 minutes (80 % by ^{1}H NMR, Figure 3.6, Table 3.1 entry 1), by comparing the integration of the vinyl peaks (δ = 6.5-5.5 ppm) to the PNIPAAm –(C***H***$_3$)$_2$ (δ = 1.1 ppm, 6H) in the ^{1}H NMR spectrum.

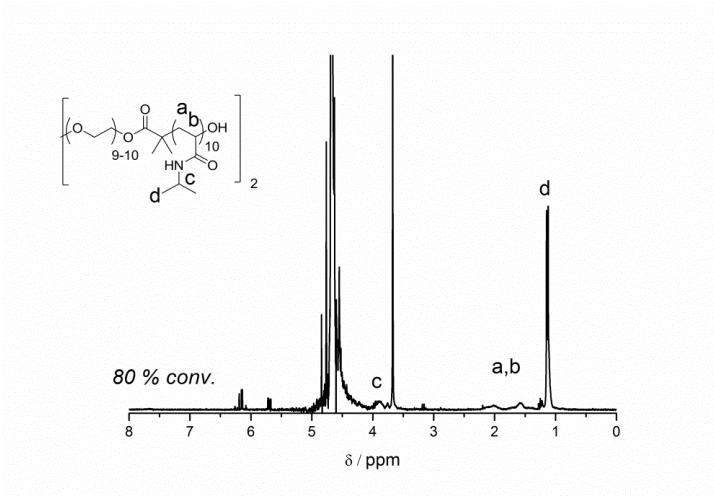


Figure 3.6. NMR spectrum (D_2O, 250 MHz) of poly(*N*-isopropylacrylamide)$_{10}$-*b*-poly(ethylene glycol)-*b*-poly(*N*-isopropylacrylamide)$_{10}$ (80 % conv. by ^{1}H NMR) using a lack of Me_6-TREN ligand [I]:[M]:[Cu(I)Br]:[Me_6-TREN]= 1:20:0.8:0.4.

This result was unsatisfactory in our attempts to yield (multi)block copolymers without the use of any purification steps, as the monomer conversion was too limited. Thus, in order to enhance the polymerisation rate, the [Cu(I)Br]/[ligand] ratio was adjusted by slightly increasing the ligand concentration. The optimised ratio of [I]:[Me_6-TREN]:[Cu(I)Br] = 1:0.6:0.8 resulted in a pronounced increase of the polymerisation rate (> 99 % by ^{1}H NMR in 30 minutes) while narrow dispersities were retained ($Đ$< 1.15) (Figure 3.7).

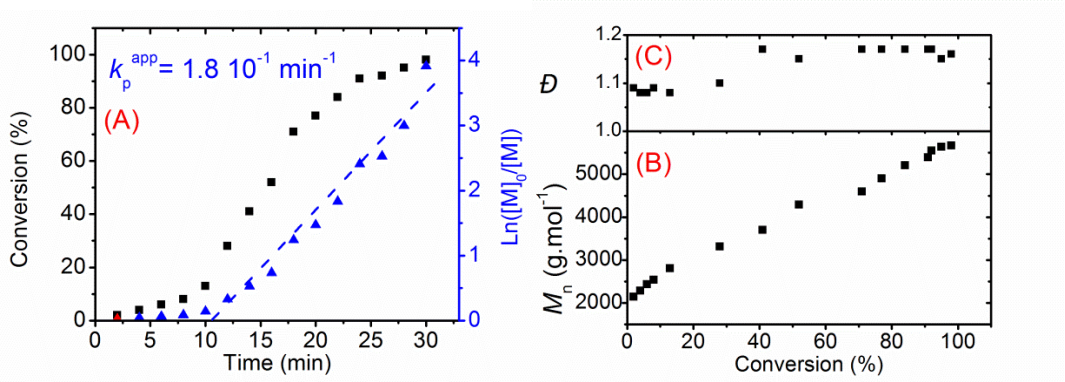


Figure 3.7. Disproportionation of Cu(I)Br in the presence of Me_6-TREN to catalyse the polymerisation of *N*-isopropylacrylamide [I]:[M]:[Me_6-TREN]:[Cu(I)Br]= 1:20:0.6:0.8 with poly(ethylene glycol) bis(2-bromoisobutyrate) in H_2O at 0°C. (A) Evolution of Ln([M]$_0$/[M]) as a function of time. (B) Evolution of molecular weight (M_n obtained by DMF SEC) and dispersity ($Đ=M_w/M_n$) as a function of monomer conversion (by ^{1}H NMR).

When higher degrees of polymerisation were targeted (DP_n= 160-320), higher concentrations of both ligand and copper were needed to retain control, in agreement with previously reported experiments.[37, 43] When higher concentrations of just ligand were employed, poorer control over the molecular weight distributions was observed (Table 3.1, entry 3).

Table 3.1. Polymerisations of *N*-Isopropylacrylamide using poly(ethylene glycol) bis(2-bromoisobutyrate) in water at 0°C.

Entry	*NIPAAm* DP_n	[I]:[CuBr]:[Me_6-TREN]	Conv. (%)[a]	M_n ($g.mol^{-1}$)[b]	M_w/M_n
1	20	[1]:[0.8]:[0.4]	80	n/a	n/a
2	20	[1]:[0.8]:[0.6]	>99	5600	1.08
3	20	[1]:[0.8]:[0.8]	>99	6900	1.16
4	40	[1]:[0.8]:[0.6]	>99	7600	1.11
5	80	[1]:[0.8]:[0.6]	>99	12500	1.14
6	160	[1]:[1.2]:[0.8]	>99	20400	1.16
7	320	[1]:[1.2]:[0.8]	>99	34200	1.19

[a] Determined by ^1H NMR (250 MHz, $CDCl_3$). [b] Determined by SEC (DMF + 5 mM NH_4BH_4) using PMMA standards.

It is therefore evident that careful optimisation of ligand to copper concentration is required to achieve good control while maintaining a rapid polymerisation rate, as small changes can have unsatisfactory effects on the polymerisation. Pleasingly, near quantitative monomer conversions (> 99 % by ^1H NMR) were attained within 30 minutes for various degrees of polymerisation of NIPAAm (DP_n= 20-320) with SEC showing symmetrical narrow molecular weight distributions in all cases ($Đ$ < 1.19, Figure 3.8).

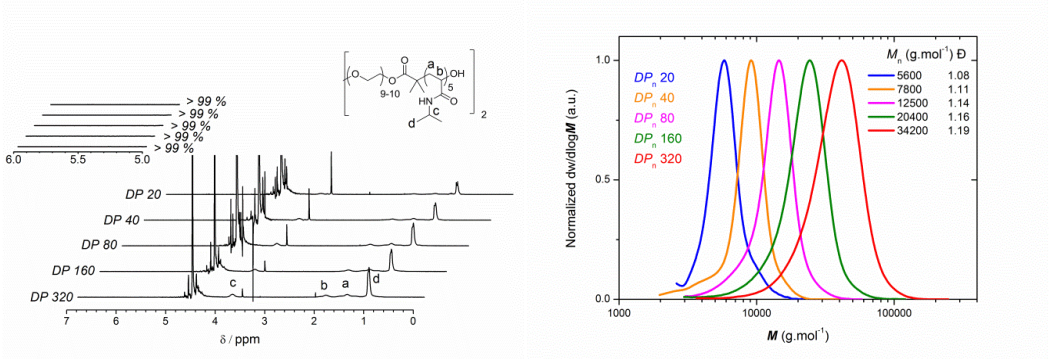


Figure 3.8. Monitoring the polymerisation of *N*-isopropylacrylamide in H_2O at 0°C after 30 minutes by ^1H NMR (D_2O, 250 MHz, left) and SEC traces (DMF eluent, right) using poly(ethylene glycol) bis(2-bromoisobutyrate).

In order to probe the end group fidelity of the obtained telechelic poly(NIPAAm), a second aliquot of NIPAAm was added *in situ* at high conversion (first NIPAAm block, DP_n = 80, > 99 % conversion by ^1H NMR after 30 minutes, M_n= 13800 g.mol^{-1}, $Đ$= 1.17) without the need for purification steps prior to addition. Excellent control was observed (> 99 % conversion by ^1H NMR, M_n = 24700 g.mol^{-1}, $Đ$ = 1.17) with the MWD shifting to higher molecular weight, albeit slight tailing is visible at low molecular weights (Figure 3.9), suggesting high retention of the *α,ω*-bromine end-groups throughout the polymerisation.

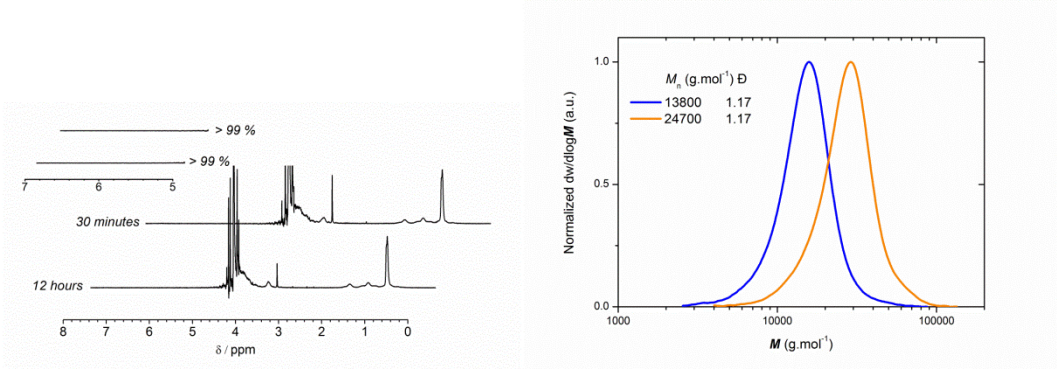


Figure 3.9. Monitoring the chain extension of poly(*N*-isopropylacrylamide) in H_2O at 0°C (initiated by poly(ethylene glycol) bis(2-bromoisobutyrate)) with *N*-isopropylacrylamide (DP_n = 80); by ^1H NMR (D_2O, 250 MHz, left) and SEC (DMF eluent, right).

3.2.2.3 Synthesis of multiblock copolymers

Since end group fidelity appeared to be high throughout polymerisation, and assuming that chain extension should occur in a reasonable timescale prior to hydrolysis,[10] we were intrigued to test the potential towards multiple side chain functionalities *via* sequential addition processes. Secondary (NIPAAm), and tertiary (DMA, DEA) acrylamides as well as acrylates ($PEGA_{480}$) show stimuli-responsive behaviour and are popular due to their commercial availability, ease of handling and breadth of understanding in functional macromolecular design. Thus, the effect of combining the properties of these monomers, *via* rapid and quantitative polymerisation in aqueous media, merited investigation. Firstly, the synthesis of acrylamide-based block copolymers was tested using the bi-functional PEG initiator. The high *α,ω*-bromide end group fidelity of the telechelic PNIPAAm structure enables the synthesis of well-defined $PDEA_{4\text{-}5}$-*b*-$PNIPAAm_5$-*b*-PEG-*b*-$PNIPAAm_5$-*b*-$PDEA_{4\text{-}5}$ with near quantitative monomer conversion (> 98 %) and low dispersities (*Đ*< 1.13, Figure 3.10), albeit residual shoulders at high molecular weight are observed.

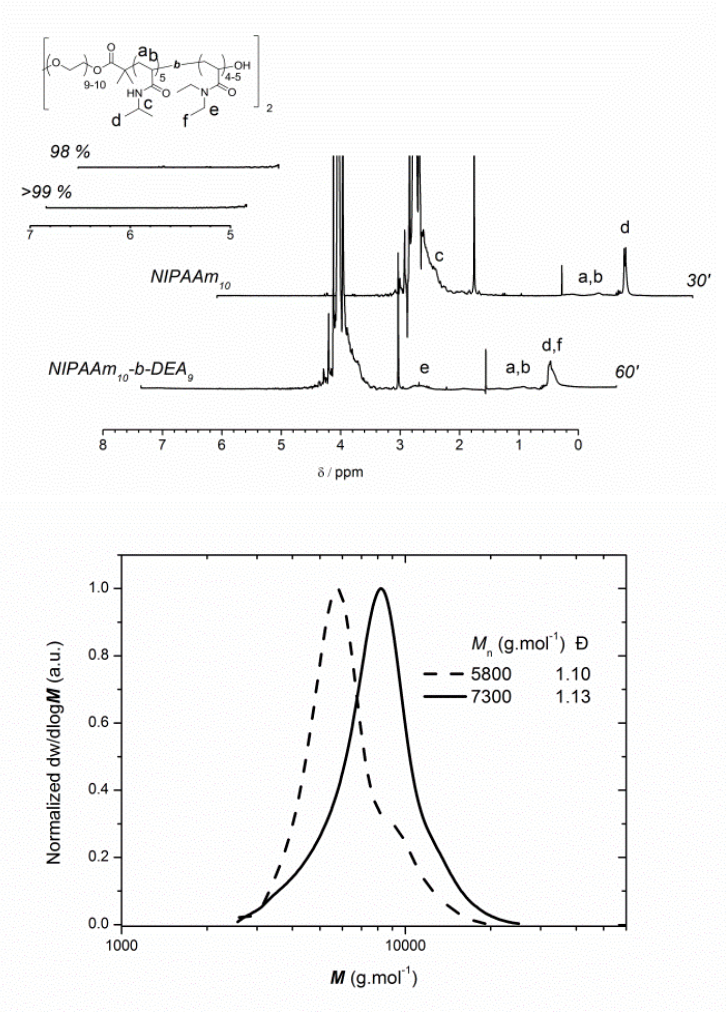


Figure 3.10. Monitoring the chain extension of poly(*N*-isopropylacrylamide) in H_2O at 0°C with *N*,*N*-diethylacrylamide (DP_n=9) by ^1H NMR (D_2O, 250 MHz, top). SEC traces (DMF eluent, bottom).

Encouraged by these initial results, we were intrigued to test the versatility of the technique by combining acrylate and acrylamides (secondary and tertiary). Although, the incorporation of monomers that exhibit different reactivities (*e.g.* acrylates and acrylamides) is rather challenging, a well-defined telechelic heptablock copolymer DMA_{10}-*b*-$NIPAAm_{10}$-*b*-$PEGA_{480,10}$-*b*-PEG-*b*-$PEGA_{480,10}$-*b*-$NIPAAm_{10}$-*b*-DMA_{10} was obtained within two hours of reaction time. To the best of our knowledge, this is the first time that such a complex composition has been achieved within such a short time frame.

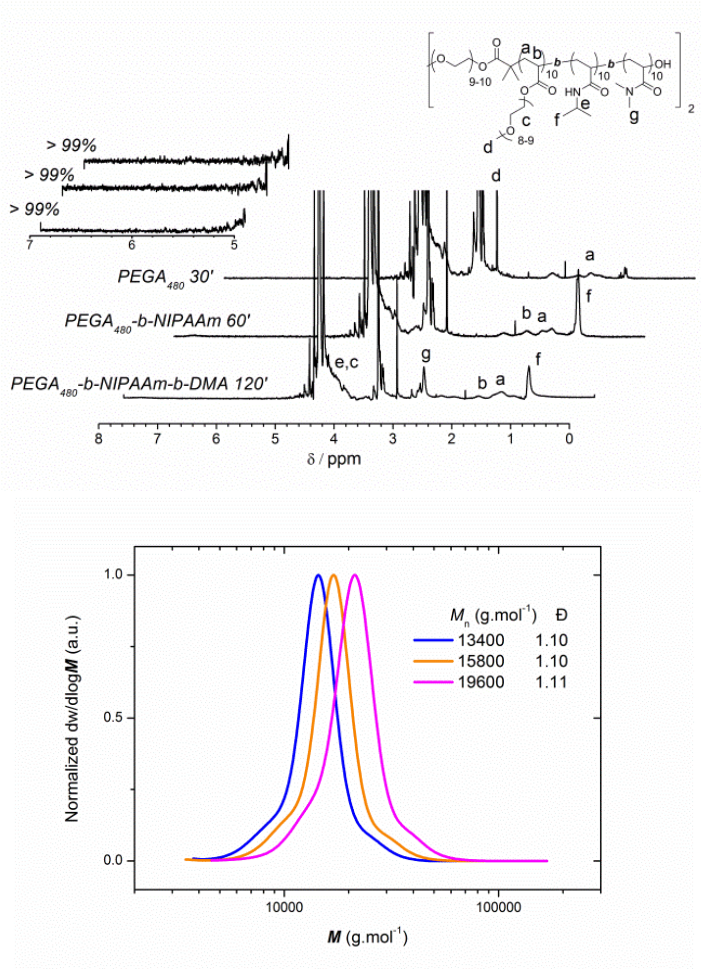


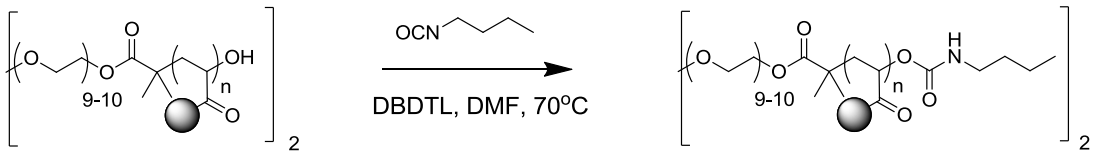
Figure 3.11. Monitoring the chain extension of poly[poly(ethylene glycol) methyl ether acrylate] in H_2O at 0°C upon sequential addition of *N*-isopropylacrylamide and *N*,*N*-dimethylacrylamide by ^{1}H NMR (D_2O, 250 MHz, top). SEC traces (DMF eluent, bottom) of multiblock copolymer PDMA$_{10}$-*b*-PNIPAAm$_{10}$-*b*-PPEGA$_{480,10}$-*b*-PEG-*b*-PPEGA$_{480,10}$-*b*-PNIPAAm$_{10}$-*b*-PDMA$_{10}$.

More importantly, the DMA$_{10}$-*b*-NIPAAm$_{10}$-*b*-PEGA$_{480,10}$-*b*-PEG-*b*-PEGA$_{480,10}$-*b*-NIPAAm$_{10}$-*b*-DMA$_{10}$ heptablock copolymer presented excellent control over the molecular weight distributions for the final material (*Đ*< 1.11, Figure 3.11), while high monomer conversions were attained for each individual block (> 99 % by ^{1}H NMR), prior to addition of the next monomer. Evidence of shoulder peaks can be observed in the SEC traces at high molecular weights (ascribed to the presence of diacrylates in the PEGA$_{480}$).[76] Tailing at low molecular weight can be attributed to the limited, yet visible, extend of contamination with mono-functional initiator traces considering the differences in M_p (8000 g.mol^{-1} and 14500

g.mol^{-1} for the first block). It should be noted that such high detail in our system is visible due to the narrow molecular weight distributions. However, the successful integration of three different monomeric moieties highlights the high robustness and versatility of the polymerisation technique.

3.2.2.4 Exploiting the hydrolysis of the *α,ω*-Br chain ends

When the desired polymer composition is obtained and no additional monomer is injected, the halogen chain ends were left to hydrolyse[9, 51] (over at least 8 hours) in the aqueous solution, resulting in dihydroxyl functional *α,ω*-end groups. So far, the unavoidable termination *via* hydrolysis has been considered as a limitation of the polymerisations in aqueous media as the resulting macrodiol cannot re-initiate polymerisation (typically after a few hours).[10] However, during this investigation the substitution of the *α,ω*-Br by water to form nucleophilic *α,ω*-OH enables the introduction of additional functionalities *via* reaction with monoisocyanates to the polymer end groups.[76, 77]



Scheme 3.6. Hydrophobic modification of in situ generated *α,ω*-telechelic diol with n-butyl isocyanate.

The post-polymerisation modification is carried out in a dry organic solvent, avoiding the presence of air and residual water, utilising *n*-butyl isocyanate as the selected end-capping moiety (Scheme 3.6). After lyophilisation, the successful modification of the copolymer is examined by ^{1}H NMR. The presence of butyl *α,ω*-chain ends is highlighted by the appearance of peaks at 2.17, 1.48, 1.17 and 0.87 ppm (Figure 3.12).

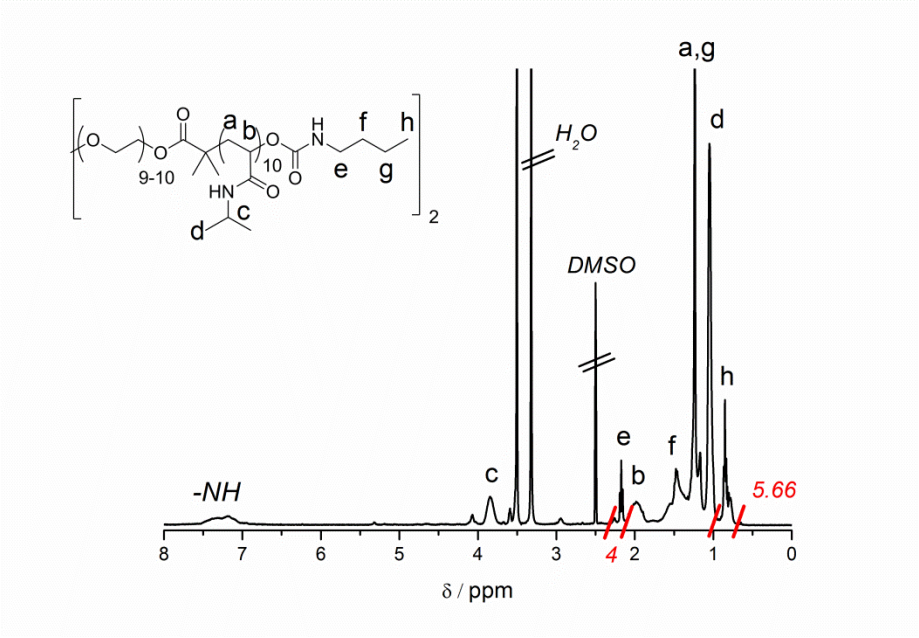


Figure 3.12. ^{1}H NMR (d_6-DMSO, 400 MHz) of *n*-butyl isocyanate modified poly(*N*-isopropylacrylamide)$_{10}$-*b*-poly(ethylene glycol)-*b*-poly(*N*-isopropylacrylamide)$_{10}$.

Moreover, the comparison of the integration of the peaks at 2.17 ppm (HN-C***H***$_2$-CH$_2$-CH$_2$-CH$_3$) and 0.87 ppm (HN-CH$_2$-CH$_2$-CH$_2$-C***H***$_3$) reveals 94 % end group fidelity by ^{1}H NMR, which implies that 94 % of the chains were hydroxyl terminated prior to functionalisation (assuming all chains were *α,ω*–OH terminated). The remaining polymer chains are potentially terminated *via* combination, as noticed in previously reported studies.[37]

3.2.2.5 Testing the copolymers thermo-responsive behaviours

The preparation of multiblock copolymers with well-defined molecular composition allows for tuning the cloud point of PNIPAAm. Using the bi-functional PEG based initiator, macro-diols containing secondary and tertiary acrylamides and/or acrylates were prepared. The LCST of NIPAAm based compounds has been widely studied,[49, 50] and implemented into the design of thermo-responsive "smart" materials.[78] The copolymerisation of the thermo-responsive NIPAAm (LCST ~ 32-35°C) with a hydrophilic 'spacer' should increase the

cloud point temperature (T_{cp}) of the macrodiol, compared to PNIPAAm with a similar molecular weight (T_{cp}~ 41°C, Figure 3.13). In order to verify this, the influence of the molecular weight of poly(NIPAAm) on the T_{cp} was investigated. In this work, the cloud point temperature is extracted from the positive curvature point of the recorded turbidimetry by UV-Vis NIR spectroscopy at a specific wavelength (λ=650 nm, see section 3.4.7 for details).

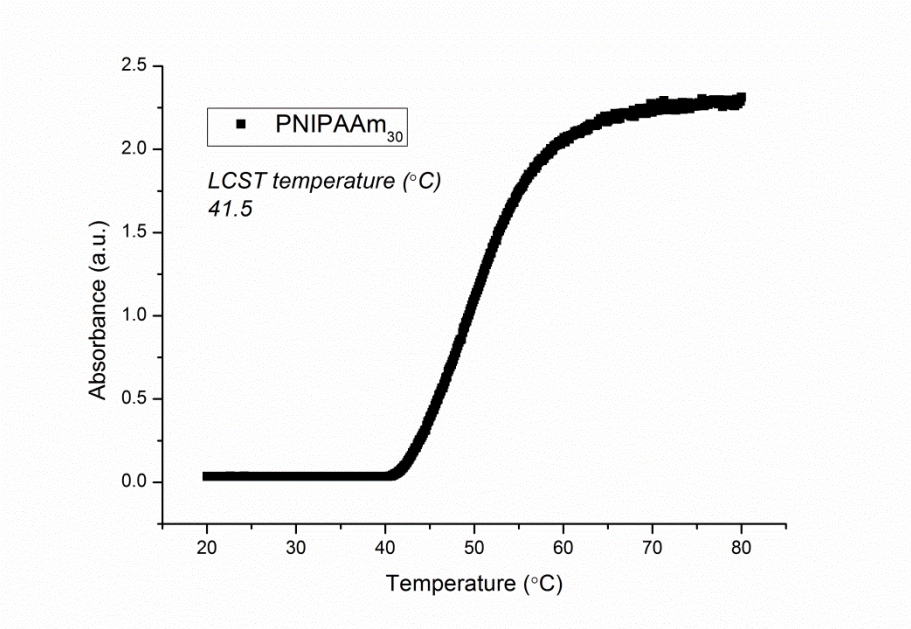


Figure 3.13. Cloud point recording of poly(*N*-isopropylacrylamide)$_{30}$ initiated by 3-dihydroxypropyl 2-bromo-2-methylpropanoate in H_2O.

The influence of the PNIPAAm$_n$-*b*-PEG-*b*-PNIPAAm$_n$ (co)polymers (10 < n < 160) molecular weights on the LCST transition is shown in figure 3.13 and table 3.2. In order to have a more accurate understanding of the system, one has to take into account the influence of the sample concentration and the end group functionality (particularly for low molecular weight polymers) which can further affect the LCST transition.[79-81] An increase in molecular weight of PNIPAAm block resulted in a decrease of T_{cp} (71.3 – 41.2 °C).

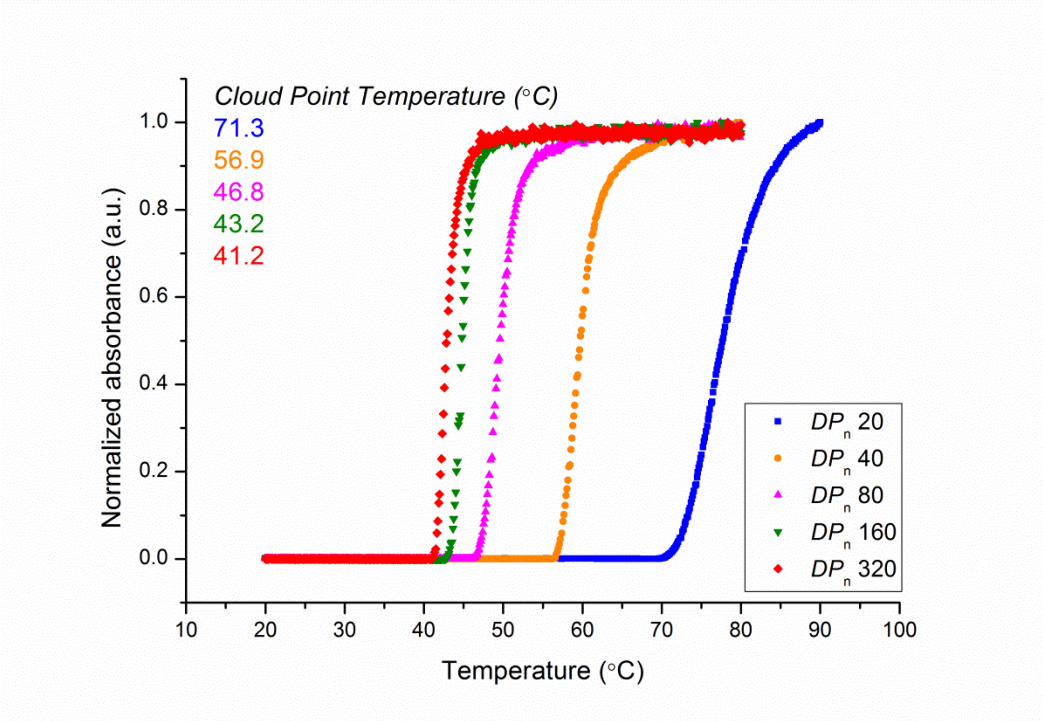


Figure 3.14. Cloud point recording of poly(*N*-isopropylacrylamide)-*b*-poly(ethylene glycol)-*b*-poly(*N*-isopropylacrylamide) in H_2O with different degrees of polymerisation (1 $mg.mL^{-1}$ solution).

Furthermore, a decrease of the polymer solution concentration in water showed an increase in T_{cp} for all DP_ns investigated (Figure 3.15). Those evolutions of the LCST transition are common for homo and hetero-telechelic PNIPAAms of similar molar mass.[79]

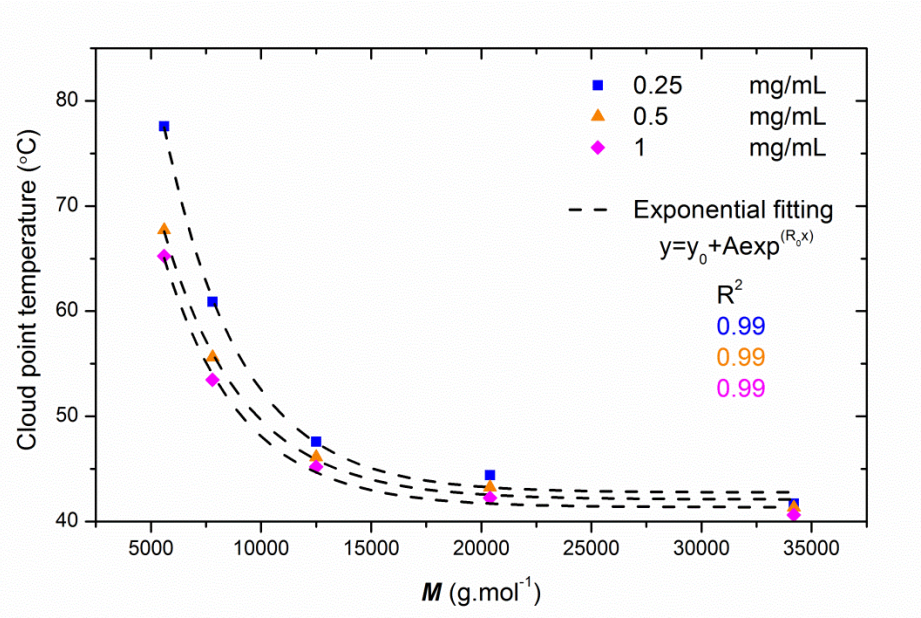


Figure 3.15. Evolution of the cloud point temperature of poly(*N*-isopropylacrylamide)-*b*-poly(ethylene glycol)-*b*-poly(*N*-isopropylacrylamide) in H_2O as a function of the observed molecular weight (SEC, DMF eluent) and the solution concentration.

Subsequently, the influence of the presence of co-monomers on T_{cp} was investigated. Considering the high tolerance of our system towards acrylates and acrylamides, the thermo-responsive and/or hydrophilic properties of each monomer were combined, as previously discussed, in the same polymer chain. Thus, the considerable difference in thermal properties of DEA (theoretical LCST ~ 33°C)[82] and DMA (no LCST between 0-100°C)[83, 84] should have opposite effects on the LCST transition when included in the overall copolymer composition.

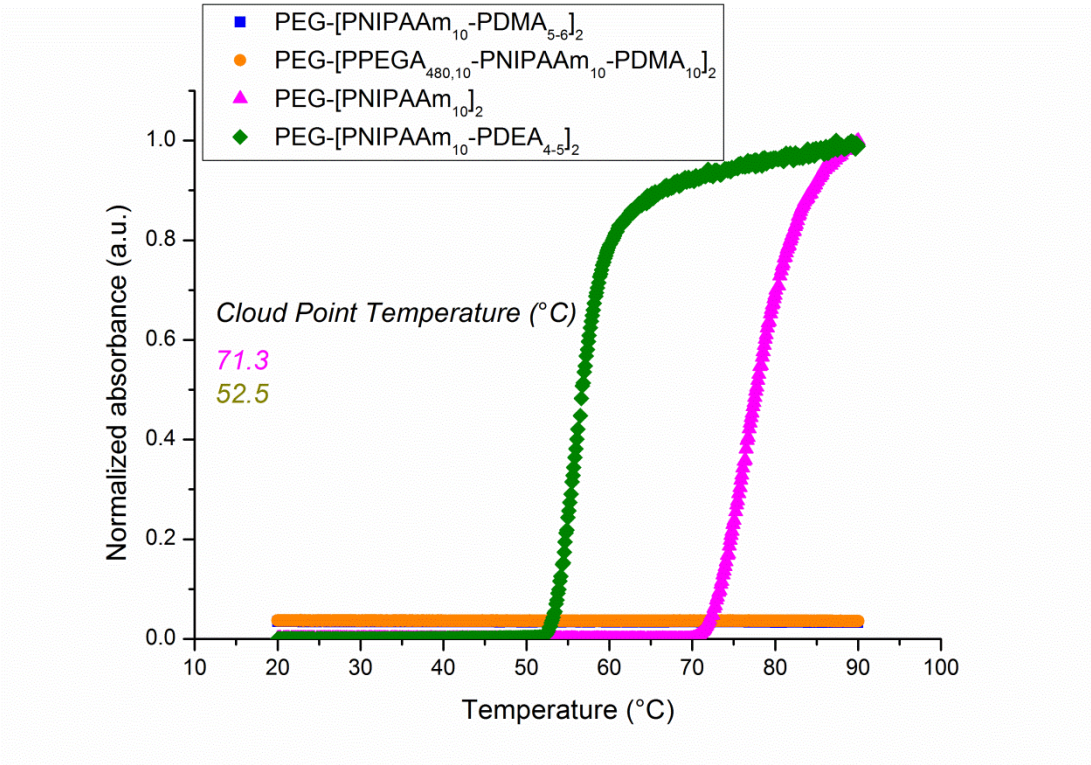


Figure 3.16. Modification of the cloud point temperature in H_2O of a poly(*N*-isopropylacrylamide)-*b*-poly(ethylene glycol)-*b*-poly(*N*-isoproylacrylamide) copolymer upon incorporation of additional backbone functionality.

The turbidimetry curves highlight the effect of both co-monomers on the LCST transition temperature (Figure 3.16, Table 3.2 entries 6-8). The incorporation of DEA as a co-monomer is expected to result in a decrease of T_{cp}. Indeed, the overall cloud point of a $PDEA_{4\text{-}5}$-*b*-$PNIPAAm_{10}$-*b*-PEG-*b*-$PNIPAAm_{10}$-*b*-$PDEA_{4\text{-}5}$ decreases from 71.3 °C ($PNIPAAm_{10}$-*b*-PEG-*b*-$PNIPAAm_{10}$) to 52.5 °C. Thus, it is shown that the composition of the copolymer can have a significant impact on T_{cp}. The incorporation of DMA into the (co)polymer is expected to increase the overall LCST. Within the limits of our instruments (5 °C < *T* < 90 °C), the temperature transition could not be observed, suggesting an increase of the LSCT beyond our upper temperature limit. Nevertheless, one could tune the stimuli-responsive properties of a copolymer by simple addition of a co-monomer, depending on the final application of the supramolecular structure.

Table 3.2. Observed cloud point temperature for poly(*N*-isopropylacrylamide) based copolymers.

Entry	Copolymer	M_n (g.mol^{-1})[a]	$Đ$ [a]	Conc. (mg/mL)	T_{cp} (°C)[b]
1	$PNIPAAm_{30}$	6100	1.14	1	41
2	$PNIPAAm_{10}$-*b*-PEG-*b*-$PNIPAAm_{10}$	5600	1.08	1	71.3
3	$PNIPAAm_{10}$-*b*-PEG-*b*-$PNIPAAm_{10}$	5600	1.08	0.5	73.9
4	$PNIPAAm_{10}$-*b*-PEG-*b*-$PNIPAAm_{10}$	5600	1.08	0.25	77.6
5	butyl-$PNIPAAm_{20}$-*b*-PEG-*b*-$PNIPAAm_{20}$-butyl	n/a	n/a	1	48.1
6	$PDMA_{5-6}$-*b*-$PNIPAAm_{10}$-PEG-$PNIPAAm_{10}$-*b*-$PDMA_{5-6}$	7900	1.09	1	n/a
7	$PDEA_{4-5}$-*b*-$PNIPAAm_{10}$-PEG-$PNIPAAm_{10}$-*b*-$PDEA_{4-5}$	7300	1.13	1	52.5
8	$PDMA_{5-6}$-*b*-$PNIPAAm_{10}$-*b*-$PPEGA_{480,10}$-*b*-PEG-*b*-$PPEGA_{480,10}$-*b*-$PNIPAAm_{10}$-*b*-$PDMA_{5-6}$	19600	1.11	1	n/a
9	$PNIPAAm_{20}$-*b*-PEG-*b*-$PNIPAAm_{20}$	7800	1.11	1	56.9
10	$PNIPAAm_{40}$-*b*-PEG-*b*-$PNIPAAm_{40}$	12500	1.14	1	46.8
11	$PNIPAAm_{80}$-*b*-PEG-*b*-$PNIPAAm_{80}$	20400	1.16	1	43.2
12	$PNIPAAm_{160}$-*b*-PEG-*b*-$PNIPAAm_{160}$	34200	1.19	1	41.2

[a] Obtained by SEC (DMF + 5mM NH_4BH_4) over PMMA standards; [b] Extracted from the positive curvature point of the recorded turbidity curve.

Following successful addition of monoisocyanates to the *α*- and *ω*-chain ends of the (co)polymer, the effect on T_{cp} was investigated. The change in the hydrophobicity of the

polymer end groups was expected to decrease the T_{cp} of the PNIPAAm$_{10}$-*b*-PEG-*b*-PNIPAAm$_{10}$ triblock copolymer.

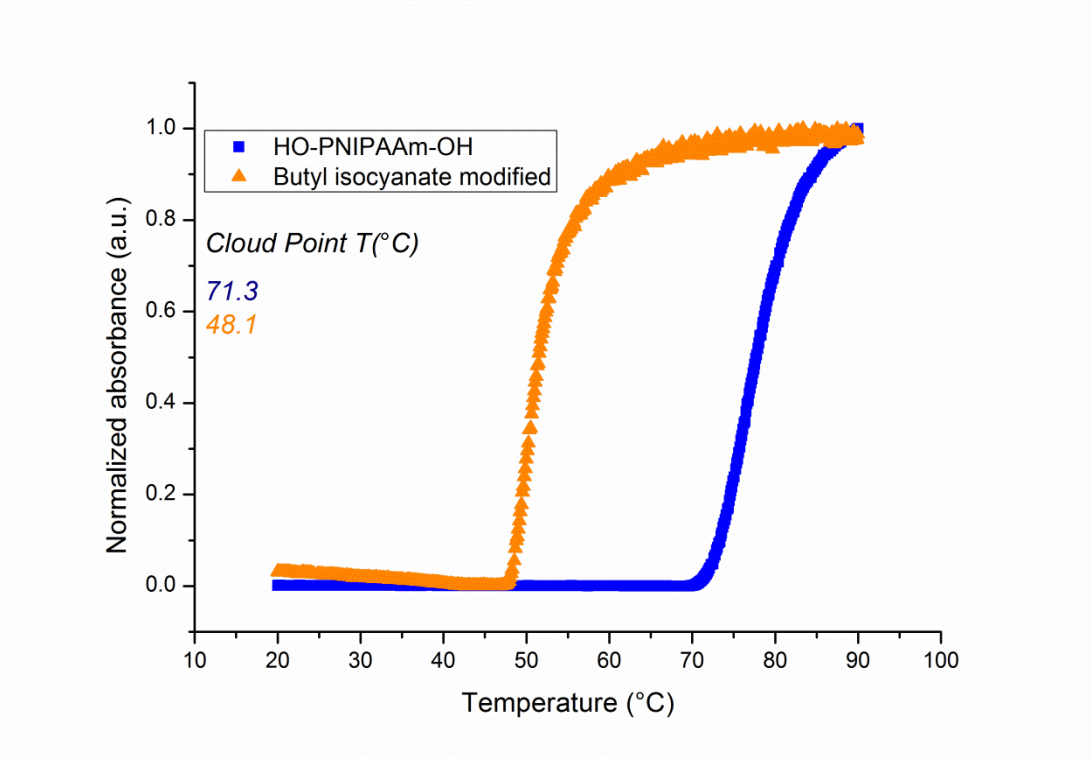


Figure 3.17. Modification of the cloud point temperature in H_2O of the hydrophobically modified poly(*N*-isopropylacrylamide)$_{101}$-*b*-poly(ethylene glycol)-*b*-poly(*N*-isopropylacrylamide)$_{10}$ in H_2O.

The T_{cp} of a hydroxyl-terminated PNIPAAm$_{10}$-*b*-PEG-*b*-PNIPAAm$_{10}$ was recorded at 71.3°C in water prior to modification. The modification of the chain ends with butyl isocyanate resulted in a decrease of T_{cp} to 48.1°C (Figure 3.17, Table 3.2 entry 5). This major decrease in T_{cp} (23.2°C) for the modified copolymer is more pronounced than previously reported for a non-telechelic PNIPAAm, modified *via* CuAAC post polymerisation[85] (> 5°C) and is believed to be due to the telechelic nature of our materials and thus the introduction of two functionalities at the polymer chain ends. It should be noted that the presence of multiple hydrophobic chain ends favours the phase separation of the copolymer from the solvent, inducing a significant decrease of T_{cp}.[86, 87] Thus, the

introduction of two hydrophobes instead of one induces a poorer miscibility of the copolymer in water, and a reduction of the copolymer mixing entropy *via* self-assembly (Appendix B), which increases the local copolymer concentration.[88]

3.3 Conclusions

In this chapter, the synthesis of *α,ω*-hydroxyl functionalized multiblock copolymers utilising a diversity of hydrophilic and/or thermo-responsive monomers including $PEGA_{480}$, NIPAAm, DEA and DMA was investigated. Polymerisations were performed in aqueous and aqueous/organic mixtures, employing two different types of bi-functional initiators. Upon careful optimisation of the reaction conditions, narrow dispersed ($Đ$ < 1.15) block copolymers were obtained in a near quantitative manner (>99% conversion by ^{1}H NMR upon each monomer addition). Noteworthy, the synthesis of a well-defined heptablock copolymer consisting of both acrylamides and acrylates could also be achieved within only two hours of overall reaction time without any need for purification between the iterative additions. More importantly, hydrolysis of the polymer end groups after polymerisation was exploited to perform hydrophobic end group modification *via* isocyanate end-capping. Subsequently, the effect of the bi-functional initiator, multiblock composition and end group modification on the (co)polymer cloud point temperature was investigated in detail, paving the way for the rapid and facile synthesis of "smart" materials.

3.4 Experimental

3.4.1 Materials

Previously used materials can be found in section 2.4.1.

N,*N*-dimethylacrylamide (DMA, 99%, Sigma-Aldrich), *N*,*N*-diethylacrylamide (DEA, 99%, Sigma-Aldrich), *n*-butyl isocyanate (>98%, Sigma-Aldrich), water (HPLC grade, VWR) were used as received without further purification. Cuprisorb™ resin was purchased from Seachem. Cu(I)Br (CuBr, 97%, Sigma-Aldrich) was purified according to the method of Keller and Wycoff,[89] by washing sequentially with acetic acid glacial and ethanol and dried over reduced pressure. *N*-isopropylacrylamide (NIPAAm, 97%, Sigma-Aldrich) was recrystallized three times from *n*-hexane and dried over reduced pressure prior to use. 3-dihydroxypropyl 2-bromo-2-methylpropanoate was synthesized according to a reported procedure.[16]

3.4.2 Characterisation

^{1}H, ^{13}C NMR spectra were recorded on Bruker ACF-250, DPX-300 and DPX-400 spectrometers using deuterated solvents obtained from Sigma-Aldrich.

DMF SEC traces were obtained on a Varian 390-LC system using a DMF (+ 5 mM NH_4BH_4) eluent at 50°C, equipped with refractive index, UV and viscometry detectors, 2 × PLgel 5 mm mixed D columns (300 × 7.5 mm), 1 × PLgel 5 mm guard column (50 × 7.5 mm) and autosampler. Narrow linear poly(methyl methacrylate) standards in range of 200 to 1.0×10^6 g·mol^{-1} were used to calibrate the system. All samples were passed through 0.45 µm PTFE filter before analysis. Cloud point temperatures were recorded on an Agilent Technologies Cary 60 UV-Vis using a cuvette with 1cm path length. Dynamic light scattering (DLS) experiment were carried out at 25°C on a MALVERN Zetasizer instrument (backscattering angle 173°C) using a plastic cuvette with 1 cm path length.

3.4.3 Monitoring the disproportionation of [Cu^{I}(Me_6-TREN)Br] in IPA/H_2O 50% *v/v*

The theoretical disproportionation curve was obtained by preparing a solution of $Cu(II)Br_2$ (91.48 mg, 0.41 mmol) in the presence of Me_6-TREN (109.5 µL, 0.5 eq.) in IPA/H_2O 50 % *v/v*, in a volumetric flask (25 mL ± 0.04 mL). The main solution was diluted in five concentrations (diluted 50 to 10 times) using volumetric flasks (5 mL ± 0.025 mL). Disproportionation was performed by adding Cu(I)Br (9.4 mg, 6.5 10^{-5} mol) to a solution of solvent (2 mL) and Me_6-TREN (9 µL, 0.5 eq.), which was left to stir and deoxygenate with nitrogen for 15 minutes. Subsequently, the solution was filtered under nitrogen to remove any Cu(0) particles, and the filtrate diluted 10 times using a volumetric flask (5 mL ± 0.025 mL). UV-Vis NIR spectrum was recorded using a quartz cuvette (path length 1 cm).

3.4.4 Initiator synthesis

Refer to sections 2.4.3.1 for ethylene bis(2-bromoisobutyrate)

3.4.4.1 Synthesis of poly(ethylene glycol) bis(2-bromoisobutyrate)

Poly(ethylene glycol) (av. M_n = 1000 g.mol^{-1}, 15 g, 15 mmol) was charged in a 500 mL three neck RB flask equipped with a dropping funnel, magnetic stirring bar and rubber septa and left to deoxygenate under nitrogen for 30 mins. Anhydrous toluene (300 mL) was canulated into the flask and the mixture left to stir for 5 mins. Subsequently, 50 mL of solvent was distilled under reduced pressure. Triethylamine (5.2 mL, 2.5 eq.) was added to the solution *via* a deoxygenated syringe and the mixture placed in an ice bath. α-bromoisobutyryl bromide (4.6 mL, 2.5 eq.) was added dropwise *via* the dropping funnel. Upon complete addition, the mixture was left to stir at 0°C for 30 minutes and at ambient temperature overnight.

The mixture was filtered, so as to remove the amine salt and the volatiles removed by rotary evaporation. The solid was dissolved in dichloromethane (150 mL) and washed three times

with a saturated solution of Na_2CO_3 (2* 75 mL). The organic phase was dried over $MgSO_4$ before the volatiles were removed by rotary evaporation to yield a light yellow liquid. The solid was dissolved in THF and precipitated twice in cold petroleum ether (60-80°C) to yield a light yellow solid (15.4 g, 84 % yield).

^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 4.33 (t, 4H, J_1=9.6 Hz, J_2=4.9Hz, CO-O-C***H***$_2$-CH_2), 3.75 (t, 4H, J_1=9.6 Hz, J_2=4.9Hz, CO-O-CH_2-C***H***$_2$), 3.65 (s, 74H, -O-C***H***$_2$-C***H***$_2$) and 1.95 (s, 12H, -(C***H***$_3$)$_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 70.5, 68.7, 65.1 and 30.7. FT-IR (ν, cm^{-1}): 3000 (C-H stretch) 1750 (O-CO-R), 1380 (-(CH_3)$_2$), 1300 (CH stretch), 1200 (CH stretch). HRMS (ESI, m/z, Da): [2M + Na^+] 621.9 (*DP_n* 18, *621.2 Th*).

3.4.5 Polymer synthesis

3.4.5.1 Polymerisation in binary alcoholic mixtures, IPA/H_2O 50% *v/v*

This generic procedure is adapted from the Zhang *et. al.* procedure[37] to yield telechelic polymers in a solvent/water system, where the [DP_n]:[Cu(I)Br]:[ligand] ratios can be modified. To an oven dried Schlenk tube fitted with a magnetic stirring bar and rubber septum was added H_2O (1.5 mL), Me_6-TREN (29.5 µL, 0.4 eq.) and Cu(I)Br (31.8 mg, 0.8 eq.). The solution was left to deoxygenate for 20 minutes with nitrogen and to stir for an extra 10 minutes. In a vial fitted with a rubber septum and magnetic stirring bar was charged with ethylene bis(2-bromoisobutyrate) (100 mg, 0.28 mmol), $PEGA_{480}$ (978 µL, 8 eq.) and IPA:H_2O 4:1 (2 mL). The mixture was left to stir until complete dissolution of the monomer (typically 2 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the Schlenk tube and the reaction was left to polymerise at 0°C.

3.4.5.2 Polymerisation in aqueous medium and sequential additions *in situ*

In this generic procedure for NIPAAm (DP_n=20), the nature of the monomer and [DP_n]:[Cu(I)Br]:[Me_6-TREN] ratios can be modified, whilst the monomer concentration remains unchanged (20% *w/w*). To an oven dried Schlenk tube fitted with a magnetic stirring bar and rubber septum was added H_2O (1.5 mL), Me_6-TREN (13 µL, 0.6 eq.) and Cu(I)Br (9.4 mg, 0.8 eq.). The solution was left to deoxygenate with nitrogen for 20 minutes and to stir for an extra 10 minutes. In a vial fitted with a rubber septum and magnetic stirring bar was charged with poly(ethylene glycol) bis(2-bromoisobutyrate) (100 mg, 8.1 10^{-5} mol), NIPAAm (185 mg, 20 eq.) and H_2O (1.5 mL). The mixture was left to stir until complete dissolution of the monomer (typically 2 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the Schlenk tube and the reaction was left to polymerise at 0°C.

Sequential addition was performed by cannulating a pre-deoxygenated solution of monomer and solvent (20 % *w/w*) into the reaction vessel at quantitative conversion of the previous block (>99 % by ^{1}H NMR).

3.4.6 Hydrophobic modification *via n*-butyl isocyanate end-capping

α,ω-Hydroxyl terminated poly(NIPAAm) (M_n= 5600 g.mol^{-1}, 50 mg, 8.9 10^{-6} mol) was added to a 50 mL RB flask equipped with a magnetic stirring bar and a rubber septum. The polymer was dried under vacuum at 70°C overnight before anhydrous DMF (10 mL) was added under nitrogen flow. Butyl isocyanate (40 µL, 40 eq.) and dibutyltin dilaureate (3 drops) were added *via* a deoxygenated syringe. The reaction mixture was placed in an oil bath at 60°C and left to stir for 9h. Following the reaction, the solution was dialyzed over

deionized water (MWCO 3.5 kDa) for one week. The success of the functionalisation of the hydroxyl end groups was assessed by ^{1}H NMR and COSY (See Appendix B for COSY).

3.4.7 Cloud point recording by UV-Vis spectroscopy

A solution of 1 mg/mL of (co)polymer in deionised water was prepared and left to stir for 2 hours at ambient temperature. Subsequently 1 mL of the solution was placed in a plastic cuvette and left to equilibrate at 20°C for 5 minutes into the UV-Vis spectrometer. A temperature ramp from 20°C to 90°C was then applied with a gradient of 1°C/min and the absorbance recorded at λ=650 nm.

The cloud point temperature was then extracted from positive curvature point of the recorded curve.

3.5 References

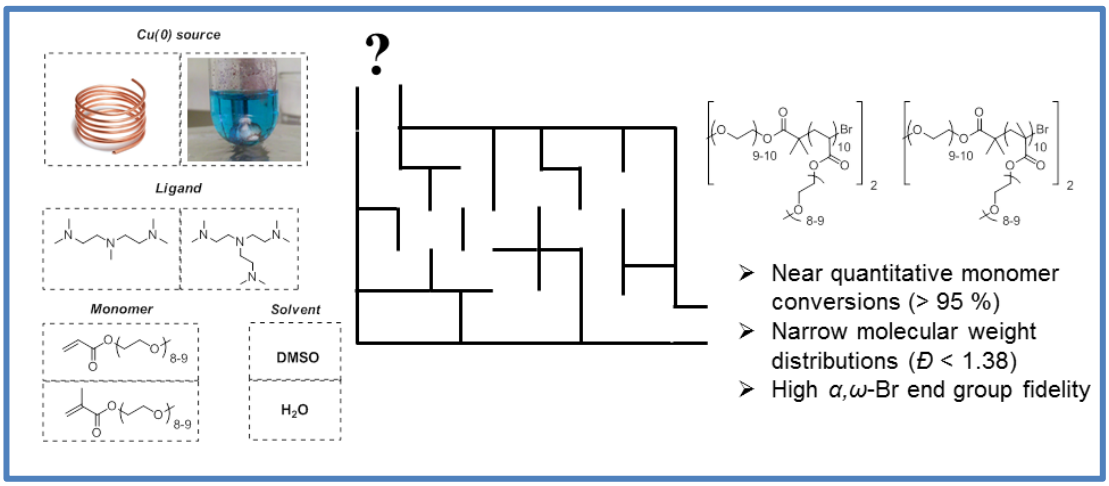
1. H. Feil, Y. H. Bae, J. Feijen and S. W. Kim, *Macromolecules*, 1992, **25**, 5528-5530.
2. F. D. Jochum, P. J. Roth, D. Kessler and P. Theato, *Biomacromolecules*, 2010, **11**, 2432-2439.
3. J. E. Glass, *Polymers in aqueous media: performance through association*, American Chemical Society, 1989.
4. M. D. C. Topp, P. J. Dijkstra, H. Talsma and J. Feijen, *Macromolecules*, 1997, **30**, 8518-8520.
5. F. J. Xu, J. Li, S. J. Yuan, Z. X. Zhang, E. T. Kang and K. G. Neoh, *Biomacromolecules*, 2007, **9**, 331-339.
6. T. Koga and F. Tanaka, *Macromolecules*, 2010, **43**, 3052-3060.
7. M. A. Winnik and A. Yekta, *Curr. Opin. Colloid Interface Sci.*, 1997, **2**, 424-436.
8. R. K. Iha, K. L. Wooley, A. M. Nyström, D. J. Burke, M. J. Kade and C. J. Hawker, *Chem. Rev.*, 2009, **109**, 5620-5686.
9. J. T. Rademacher, M. Baum, M. E. Pallack, W. J. Brittain and W. J. Simonsick, *Macromolecules*, 1999, **33**, 284-288.
10. F. Alsubaie, A. Anastasaki, P. Wilson and D. Haddleton, *Polym. Chem.*, 2015, **6**, 406-417.
11. B. Boutevin, G. David and C. Boyer, in *Oligomers - Polymer Composites - Molecular Imprinting*, Springer Berlin Heidelberg, 2007, vol. 206, pp. 31-135.
12. C. J. Hawker, A. W. Bosman and E. Harth, *Chem. Rev.*, 2001, **101**, 3661-3688.
13. G. Moad, E. Rizzardo and S. H. Thang, *Aust. J. Chem.*, 2012, **65**, 985-1076.
14. M. Kamigaito, T. Ando and M. Sawamoto, *Chem. Rev.*, 2001, **101**, 3689-3746.
15. K. Matyjaszewski and J. Xia, *Chem. Rev.*, 2001, **101**, 2921-2990.

16. S. Perrier, S. P. Armes, X. S. Wang, F. Malet and D. M. Haddleton, *J. Polym. Sci., Part A: Polym. Chem.*, 2001, **39**, 1696-1707.
17. W. A. Braunecker, N. V. Tsarevsky, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2009, **42**, 6348-6360.
18. N. V. Tsarevsky, T. Pintauer and K. Matyjaszewski, *Macromolecules*, 2004, **37**, 9768-9778.
19. M. Teodorescu and K. Matyjaszewski, *Macromolecules*, 1999, **32**, 4826-4831.
20. K. Matyjaszewski, *Macromolecules*, 2012, **45**, 4015-4039.
21. N. H. Nguyen, J. Kulis, H.-J. Sun, Z. Jia, B. van Beusekom, M. E. Levere, D. A. Wilson, M. J. Monteiro and V. Percec, *Polym. Chem.*, 2013, **4**, 144-155.
22. N. H. Nguyen, C. Rodriguez-Emmenegger, E. Brynda, Z. Sedlakova and V. Percec, *Polym. Chem.*, 2013, **4**, 2424-2427.
23. N. H. Nguyen, B. M. Rosen, X. Jiang, S. Fleischmann and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 5577-5590.
24. G. Lligadas and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2008, **46**, 2745-2754.
25. W. Jakubowski, K. Min and K. Matyjaszewski, *Macromolecules*, 2005, **39**, 39-45.
26. J. Pietrasik, H. Dong and K. Matyjaszewski, *Macromolecules*, 2006, **39**, 6384-6390.
27. K. Matyjaszewski, W. Jakubowski, K. Min, W. Tang, J. Huang, W. A. Braunecker and N. V. Tsarevsky, *P. Natl. Acad. Sci. USA.*, 2006, **103**, 15309-15314.
28. A. J. D. Magenau, N. C. Strandwitz, A. Gennaro and K. Matyjaszewski, *Science*, 2011, **332**, 81-84.
29. Y. Zhang, Y. Wang and K. Matyjaszewski, *Macromolecules*, 2011, **44**, 683-685.
30. C.-H. Peng, M. Zhong, Y. Wang, Y. Kwak, Y. Zhang, W. Zhu, M. Tonge, J. Buback, S. Park, P. Krys, D. Konkolewicz, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 3803-3815.
31. Y. Wang, M. Zhong, W. Zhu, C.-H. Peng, Y. Zhang, D. Konkolewicz, N. Bortolamei, A. A. Isse, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 3793-3802.
32. M. Zhong, Y. Wang, P. Krys, D. Konkolewicz and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 3816-3827.
33. D. Konkolewicz, P. Krys, J. R. Góis, P. V. Mendonça, M. Zhong, Y. Wang, A. Gennaro, A. A. Isse, M. Fantin and K. Matyjaszewski, *Macromolecules*, 2014, **47**, 560-570.
34. D. Konkolewicz, Y. Wang, P. Krys, M. Zhong, A. A. Isse, A. Gennaro and K. Matyjaszewski, *Polym. Chem.*, 2014, **5**, 4396-4417.
35. V. Percec, T. Guliashvili, J. S. Ladislaw, A. Wistrand, A. Stjerndahl, M. J. Sienkowska, M. J. Monteiro and S. Sahoo, *J. Am. Chem. Soc.*, 2006, **128**, 14156-14165.
36. B. M. Rosen and V. Percec, *Chem. Rev.*, 2009, **109**, 5069-5119.
37. Q. Zhang, P. Wilson, Z. Li, R. McHale, J. Godfrey, A. Anastasaki, C. Waldron and D. M. Haddleton, *J. Am. Chem. Soc.*, 2013, **135**, 7355-7363.
38. V. Percec, A. V. Popov, E. Ramirez-Castillo, M. Monteiro, B. Barboiu, O. Weichold, A. D. Asandei and C. M. Mitchell, *J. Am. Chem. Soc.*, 2002, **124**, 4940-4941.
39. X. Leng, N. H. Nguyen, B. van Beusekom, D. A. Wilson and V. Percec, *Polym. Chem.*, 2013, **4**, 2995-3004.
40. V. Percec, A. V. Popov, E. Ramirez-Castillo and O. Weichold, *J. Polym. Sci., Part A: Polym. Chem.*, 2003, **41**, 3283-3299.
41. J. Ye and R. Narain, *J. Phys. Chem. B*, 2009, **113**, 676-681.
42. N. H. Nguyen, B. M. Rosen and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 1752-1763.

43. A. Anastasaki, A. J. Haddleton, Q. Zhang, A. Simula, M. Droesbeke, P. Wilson and D. M. Haddleton, *Macromol. Rapid Commun.*, 2014, **35**, 965-970.
44. S. R. Samanta, V. Nikolaou, S. Keller, M. J. Monteiro, D. A. Wilson, D. M. Haddleton and V. Percec, *Polym. Chem.*, 2015, **6**, 2084-2097.
45. Q. Zhang, Z. Li, P. Wilson and D. M. Haddleton, *Chem. Commun.*, 2013, **49**, 6608-6610.
46. C. Waldron, Q. Zhang, Z. Li, V. Nikolaou, G. Nurumbetov, J. Godfrey, R. McHale, G. Yilmaz, R. K. Randev, M. Girault, K. McEwan, D. M. Haddleton, M. Droesbeke, A. J. Haddleton, P. Wilson, A. Simula, J. Collins, D. J. Lloyd, J. A. Burns, C. Summers, C. Houben, A. Anastasaki, M. Li, C. R. Becer, J. K. Kiviaho and N. Risangud, *Polym. Chem.*, 2014, **5**, 57-61.
47. American Cyanamid Company, Brochure IC3-1354-500-4/63 on "*N*-isopropylacrylamide".
48. J. S. Scarpa, D. D. Mueller and I. M. Klotz, *J. Am. Chem. Soc.*, 1967, **89**, 6024-6030.
49. M. Heskins and J. E. Guillet, *J. Macromol. Sci. Chem.*, 1968, **2**, 1441-1455.
50. H. G. Schild, *Prog. Polym. Sci.*, 1992, **17**, 163-249.
51. Y. Xia, X. Yin, N. A. D. Burke and H. D. H. Stöver, *Macromolecules*, 2005, **38**, 5937-5943.
52. M. Ito and T. Ishizone, *J. Polym. Sci., Part A: Polym. Chem.*, 2006, **44**, 4832-4845.
53. H. G. Schild, M. Muthukumar and D. A. Tirrell, *Macromolecules*, 1991, **24**, 948-952.
54. D. Dhara and P. R. Chatterji, *Journal of Macromolecular Science, Part C*, 2000, **40**, 51-68.
55. R. Freitag and F. Garret-Flaudy, *Langmuir*, 2002, **18**, 3434-3440.
56. D. Roy, J. N. Cambre and B. S. Sumerlin, *Prog. Polym. Sci.*, 2010, **35**, 278-301.
57. J.-F. Lutz, Ö. Akdemir and A. Hoth, *J. Am. Chem. Soc.*, 2006, **128**, 13046-13047.
58. I. Dimitrov, B. Trzebicka, A. H. E. Müller, A. Dworak and C. B. Tsvetanov, *Prog. Polym. Sci.*, 2007, **32**, 1275-1343.
59. N. S. Ieong, M. Hasan, D. J. Phillips, Y. Saaka, R. K. O'Reilly and M. I. Gibson, *Polym. Chem.*, 2012, **3**, 794-799.
60. B. A. Wolf, *Pure Appl. Chem.*, 1985, **57**, 323-336.
61. G. Gody, T. Maschmeyer, P. B. Zetterlund and S. Perrier, *Nat. Commun.*, 2013, **4**.
62. G. Gody, T. Maschmeyer, P. B. Zetterlund and S. Perrier, *Macromolecules*, 2014, **47**, 3451-3460.
63. J. Chiefari, J. Jeffery, R. T. A. Mayadunne, G. Moad, E. Rizzardo and S. H. Thang, *Macromolecules*, 1999, **32**, 7700-7702.
64. M. C. Grady, W. J. Simonsick and R. A. Hutchinson, *Macromol. Symp.*, 2002, **182**, 149-168.
65. L. Martin, G. Gody and S. Perrier, *Polym. Chem.*, 2015, **6**, 4875-4886.
66. A. Anastasaki, V. Nikolaou, G. S. Pappas, Q. Zhang, C. Wan, P. Wilson, T. P. Davis, M. R. Whittaker and D. M. Haddleton, *Chem. Sci.*, 2014, **5**, 3536-3542.
67. A. H. Soeriyadi, C. Boyer, F. Nyström, P. B. Zetterlund and M. R. Whittaker, *J. Am. Chem. Soc.*, 2011, **133**, 11128-11131.
68. C. Boyer, A. H. Soeriyadi, P. B. Zetterlund and M. R. Whittaker, *Macromolecules*, 2011, **44**, 8028-8033.
69. S. Saeki, N. Kuwahara, M. Nakata and M. Kaneko, *Polymer*, 1976, **17**, 685-689.
70. D. G. Lessard, M. Ousalem, X. X. Zhu, A. Eisenberg and P. J. Carreau, *J. Polym. Sci., Part B: Polym. Phys.*, 2003, **41**, 1627-1637.
71. F. Fischer, D. Zufferey and R. Tahoces, *Polym. Int.*, 2011, **60**, 1259-1262.
72. A. Anastasaki, C. Waldron, P. Wilson, R. McHale and D. M. Haddleton, *Polym. Chem.*, 2013, **4**, 2672.
73. R. O. R. Costa and R. F. S. Freitas, *Polymer*, 2002, **43**, 5879-5885.

74. F. M. Winnik, M. F. Ottaviani, S. H. Bossmann, M. Garcia-Garibay and N. J. Turro, *Macromolecules*, 1992, **25**, 6007-6017.
75. J. H. Truelsen, J. Kops, W. Batsberg and S. P. Armes, *Macromol. Chem. Phys.*, 2002, **203**, 2124-2131.
76. A. Simula, G. Nurumbetov, A. Anastasaki, P. Wilson and D. M. Haddleton, *Eur. Polym. J.*, 2014, **62**, 294-303.
77. F. Biedermann, E. A. Appel, J. s. del Barrio, T. Gruendling, C. Barner-Kowollik and O. A. Scherman, *Macromolecules*, 2011, **44**, 4828-4835.
78. D. J. Phillips and M. I. Gibson, *Chem. Commun.*, 2012, **48**, 1054-1056.
79. Z. Li, Y.-H. Kim, H. Min, C.-K. Han and K. Huh, *Macromol. Res.*, 2010, **18**, 618-621.
80. P. J. Roth, F. D. Jochum, F. R. Forst, R. Zentel and P. Theato, *Macromolecules*, 2010, **43**, 4638-4645.
81. S. Furyk, Y. Zhang, D. Ortiz-Acosta, P. S. Cremer and D. E. Bergbreiter, *J. Polym. Sci., Part A: Polym. Chem.*, 2006, **44**, 1492-1501.
82. I. Idziak, D. Avoce, D. Lessard, D. Gravel and X. X. Zhu, *Macromolecules*, 1999, **32**, 1260-1263.
83. K. Pagonis and G. Bokias, *Polymer*, 2004, **45**, 2149-2153.
84. A. J. Convertine, B. S. Lokitz, Y. Vasileva, L. J. Myrick, C. W. Scales, A. B. Lowe and C. L. McCormick, *Macromolecules*, 2006, **39**, 1724-1730.
85. A. Narumi, K. Fuchise, R. Kakuchi, A. Toda, T. Satoh, S. Kawaguchi, K. Sugiyama, A. Hirao and T. Kakuchi, *Macromol. Rapid Commun.*, 2008, **29**, 1126-1133.
86. P. Kujawa and F. M. Winnik, *Macromolecules*, 2001, **34**, 4130-4135.
87. P. Kujawa, H. Watanabe, F. Tanaka and F. M. Winnik, *Eur. Phys. J. E*, 2005, **17**, 129-137.
88. P. Kujawa, F. Segui, S. Shaban, C. Diab, Y. Okada, F. Tanaka and F. M. Winnik, *Macromolecules*, 2005, **39**, 341-348.
89. R. N. Keller, H. D. Wrcoff and L. E. Marchi, in *Inorg. Synth.*, John Wiley & Sons, Inc., 2007, pp. 1-4.

The importance of ligand, solvent and Cu(0) source on the efficient (co)polymerisation of polyether acrylates and methacrylates in aqueous and organic media



The synthesis of well-defined telechelic polyacrylates and polymethacrylates in organic and aqueous media via Cu(0)-mediated reversible-deactivation radical polymerisation is investigated. Poly(ethylene glycol) methyl ether acrylate ($PEGA_{480}$) and poly(ethylene glycol) methyl ether methacrylate ($PEGMA_{475}$) are used as exemplar monomers to determine the optimum polymerisation conditions for the rapid, controlled and quantitative production of both homopolymers and block copolymers. The effect of the copper source (i.e. Cu(0)-wire or Cu(0) particles), the ligand (e.g. Me_6-TREN or PMDETA) and the solvent (e.g. H_2O or DMSO) on the polymerisation of acrylates and methacrylates has been evaluated. Under carefully optimized conditions, narrowly distributed polymethacrylates homopolymers can be obtained in a quantitative manner (> 98% conversion) within 30 min of polymerisation with very high end-group fidelity, exemplified by in situ chain extensions; hence highlighting the importance of the appropriate combination of the monomer with a compatible ligand, copper source, solvent and polymerisation technique.

.

4.1 Introduction

In chapter 3, the versatility of Cu(0)-mediated polymerisation in aqueous media to yield well-defined telechelic macromolecules was discussed. The complete pre-disproportionation of [Cu^{I}(Me_6-TREN)Br] in water into Cu(0) particles and [Cu^{II}(Me_6-TREN)Br]Br was exploited prior to monomer and initiator addition to yield bi-functional polyacrylates and polyacrylamides with unprecedented control over the MWD.[1] More importantly, the α,ω-Br chain ends could be retained within the time scale of polymerisation to yield multiblock copolymers with high tolerance over the backbone functionality.[2] Subsequently, the halide end groups undergo hydrolysis, yielding stimuli-responsive diols *in situ*.[3] This robust tool completed previous investigations on the design of functional telechelics in organic solvents (*e.g.* DMSO, IPA) utilising Cu(0)-wire as a primary copper source. [4]

However, the majority of the aforementioned reports are associated with the polymerisation of monomers with high k_p such as acrylates and acrylamides, whilst reports on the polymerisation of monomers with lower k_p (*e.g.* methacrylates) are more limited in aqueous media.[5, 6] In addition, although Me_6-TREN is probably the most commonly employed ligand, the importance of using the appropriate ligand that matches with the activity of the monomer is not often discussed in Cu(0)-mediated polymerisation. Moreover, although both the organic SET-LRP protocol (using Cu(0)-wire) and the aqueous SET-LRP approach (utilising Cu(0) particles obtained *via* pre-disproportionation) have attracted considerable attention, a direct comparison of these two protocols is not yet available.

4.1.1 Matching the activity of ligand and monomers in copper catalysed reactions

One of the most advantageous features of TMM-LRP lies in the ability of tuning the catalyst, whereby the selectivity between activation and deactivation processes is adapted depending on the ligand employed.[7] Indeed, numerous optimisations have been conducted in ATRP in the selection of active/inactive ligands to successfully mediate the polymerisation of a wide range of monomer moieties (*e.g.* methacrylates, acrylates, acrylamides, methacrylamides, styrene, vinyl halide and vinyl esters).[8] A catalyst which would preferentially display greater stabilisation in the highest oxidation state (Cu^{II}) would be described as active. *N*-containing σ-donor ligands (Me_6-TREN, PMDETA, Cyclam) are commonly described as active catalysts, whilst achieving good control over the polymerisation of high k_p monomers (*e.g.* acrylates, acrylamides).[9-14] Additionally, π-orbital containing ligands (*e.g.* bipyridine, pyridine-imines) can preferentially stabilise the metal on its transitional state (Cu^{I}) *via* back donation into low lying π*-orbitals, hence yielding catalysts ascribed as less active. Such ligands achieve better control over the polymerisation of low k_p monomers (*e.g.* methacrylates, styrene),[15-17] though some exceptions are noticeable. HMTETA and TPMA for example, can successfully mediate the polymerisation of methacrylates in aqueous and organic media despite being considered as active ligands (figure 4.1).[18, 19]

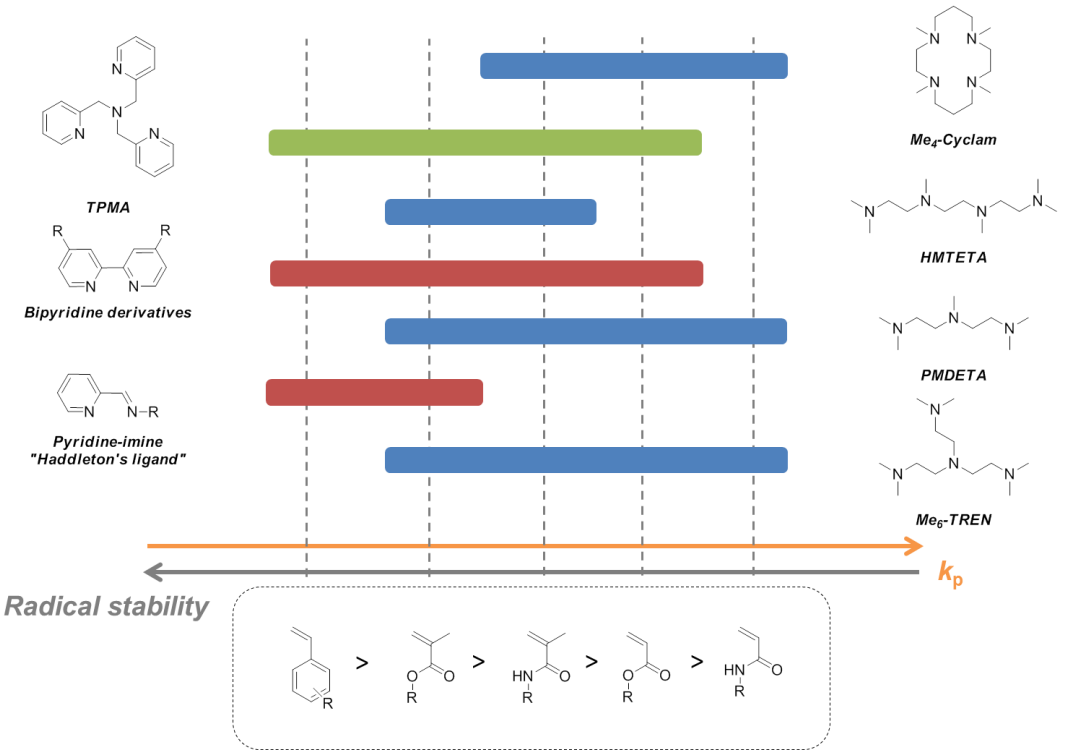
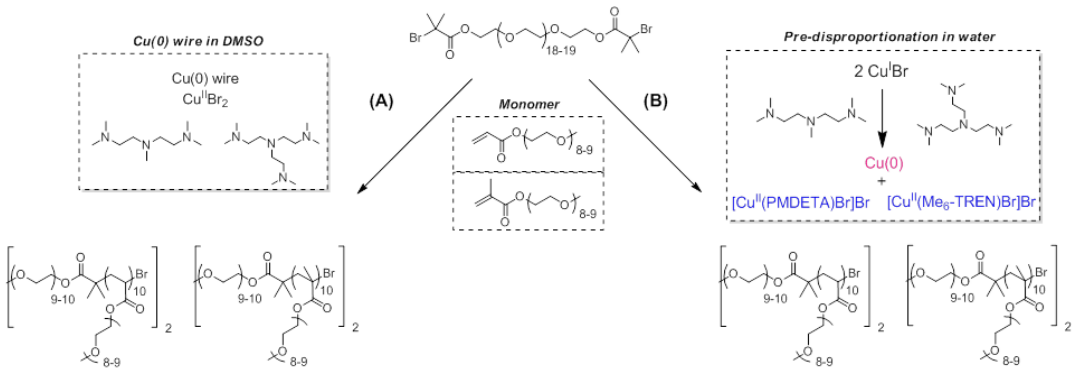


Figure 4.1. Representative scheme of ligand and monomer combination in ATRP. The length of the bars represents successful ligand/monomer combinations. Ligands are σ-donors (blue), π-acceptors (red), or both (green).

An unsuccessful combination of catalyst and monomer results in undesired termination events at the early stage of the polymerisation, exemplified by broad distributions and/or loss of halide chain end fidelity.[20] However, selecting a catalyst that displays a high activation/deactivation ratio (for a selected initiator) would be ideal to achieve good control over the polymerisation. Furthermore, a high rate of deactivation is necessary in order to provide polymers with low dispersity values and high retention of the chain ends. It should be noted that the nature of the initiating species also has an extensive influence on the control,[21-23] albeit it will not be investigated in this contribution.

In this chapter, an investigation of the polymerisation of acrylates and methacrylates in organic and aqueous media is presented. Poly(ethylene glycol) methyl ether acrylate (av.

M_n= 480 g.mol^{-1}, $PEGA_{480}$) and poly(ethylene glycol) methyl ether methacrylate (av. M_n= 475 g.mol^{-1}, $PEGMA_{475}$) have been utilised as exemplar monomers in order to assess the optimum Cu(0)-mediated polymerisation conditions to synthesise well-defined acrylic and methacrylic materials (scheme 4.1.). Both Cu(0)-wire and Cu(0) particles are employed as the Cu(0) source, highlighting the potential and limitations of each technique. The effect of the disproportionation reaction on the polymerisation rate and control over the MWDs has also been studied in DMSO and water, dictating the optimal polymerisation protocol depending on the solvent employed. The role of two ligand structures (*e.g.* Me_6-TREN, PMDETA) on the retention of MWDs and end-group(s) fidelity has also been investigated, revealing significant variations for different monomers and protocols used. Finally, kinetic experiments have been used to assess the "*livingness*" of each system while *in situ* chain extensions have also been conducted as an indirect measurement of the end-group fidelity of the homopolymers.



Scheme 4.1. Synthetic route to yield telechelic poly[poly(ethylene glycol) methyl ether acrylate] and poly[poly(ethylene glycol) methyl ether methacrylate] by Cu(0)-mediated reversible-deactivation radical polymerisation using (A) Cu(0)-wire in DMSO and/or (B) pre-disproportionation of CuBr in water under the presence of Me_6-TREN or PMDETA ligand.

4.2 Results and discussions

In order to achieve a thorough investigation of the (co)polymerisation of acrylic and methacrylic moieties in both DMSO and water, it would be preferred to have an initiator that would achieve good solubility in both solvents. Consequently, we decided to synthesise a bi-functional initiator derived from PEG (M_n= 1000 g.mol^{-1}), *via* esterification of the hydroxyl end groups (see sections 3.2.1.1 and 3.4.4.1).

It is important to stress that the initiation efficiency of this initiator is expected to be lower whilst polymerising methacrylates, compared to the acrylates,[23] which would induce broader MWD and poorer agreement between theoretical and observed MW. Nevertheless, optimisation of the initiator structure will not be the subject of this chapter.

4.2.1 Polymerisations in DMSO

The polymerisation of $PEGA_{480}$ and $PEGMA_{475}$ were initially assessed in DMSO using the tetradentate *N*-donor ligand, Me_6-TREN, Cu(0)-wire and poly(ethylene glycol) bis(2-bromoisobutyrate) initiator (section 3.2.1.1). The kinetic experiments for the Cu(0)-wire mediated polymerisation of $PEGA_{480}$ and $PEGMA_{475}$ are shown in figures 4.2 and 4.3. Polymerisation of $PEGA_{480}$ proceeds relatively fast, with quantitative or near quantitative conversion achieved within 5 hours (> 98%), as determined by ^{1}H NMR (figure 4.2.D). Monomer conversion is calculated by comparing the monomer vinyl peaks (δ= 5.5-6.5 ppm) to the polymer –C$\boldsymbol{H}_3$ pendant group (δ= 3.3 ppm). The kinetic experiments revealed a linear evolution of number average molecular weight (M_n) with conversion and narrow MWD, associated with the "*living*" nature of the polymerisation, with good agreement between the

theoretical and experimental molecular weights (figure 4.2.A-B). The linear increment of $\ln([M]_0/[M]_n)$ with time was maintained throughout polymerisation, highlighting a constant radical concentration, even when the polymerisation reaches near quantitative conversion (figure 4.2.C). Importantly, SEC chromatograms reveal a mono-modal polymer peak distribution shifting to higher molecular weights throughout the polymerisation, whilst the molecular weight distributions are slightly reduced during the reaction with a final dispersity value of $Đ$= 1.08 (figure 4.2.E). A shoulder at high MW is observed, similarly as in section 2.2.2, which could be due to termination of the polyacrylate *via* β-scission and/or branching as well as undesired diacrylate impurities in the monomer.

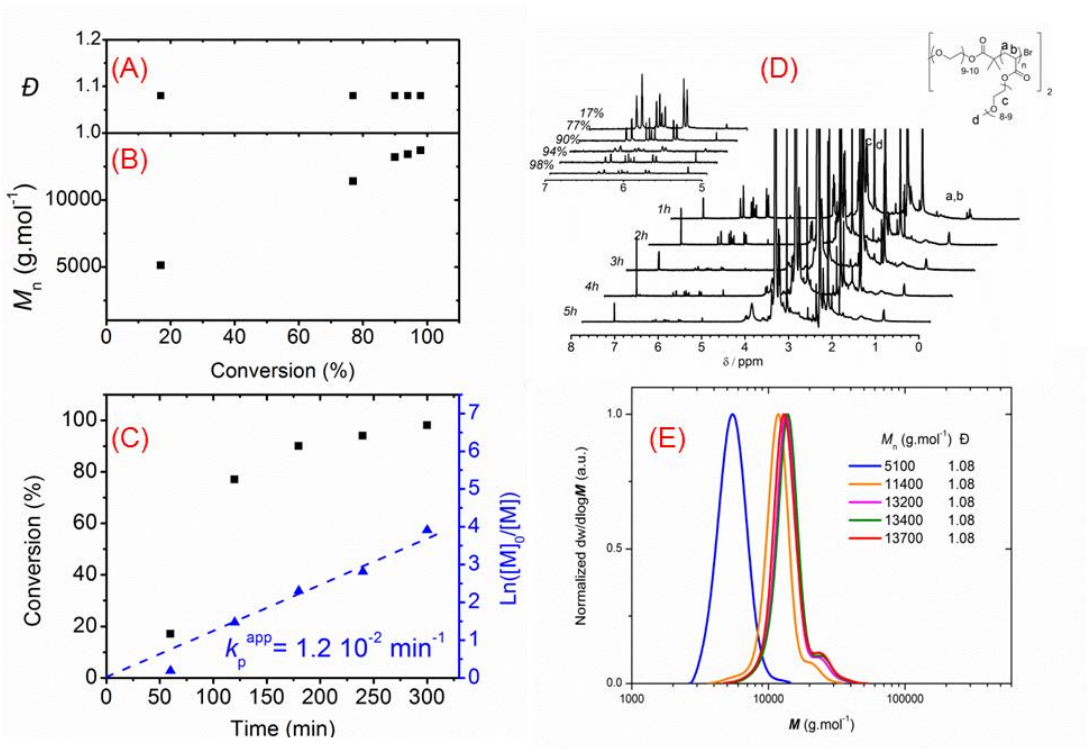


Figure 4.2. Monitoring the polymerisation of $PEGA_{480}$ with Me_6-TREN ligand in DMSO (50 % *v/v*) at 25°C by ^{1}H NMR (250 MHz, $CDCl_3$, D) and SEC (DMF eluent, E); [I]:[M]:[Me_6-TREN]:[$Cu^{II}Br_2$]= 1:20:0.18:0.05 and 5 cm Cu(0) wire.

Subsequently, the polymerisation of $PEGMA_{475}$ was conducted under identical conditions ([I]:[M]:[Me_6-TREN]:[$Cu^{II}Br_2$]= 1:20:0.18:0.05 and 5 cm Cu(0) wire) in order to achieve a

direct comparison (figure 4.3). A reduced apparent rate of polymerisation is observed (k_p^{app}= 4.9 10^{-3} min^{-1} versus k_p^{app}= 1.2 10^{-2} $min^{-1}$for $PEGA_{480}$) with 76% conversion achieved (as opposed to 98% for $PEGA_{480}$) over the same time scale (5 hours). It is important to notice that although samples were also taken up to 11 hours of polymerisation of $PEGMA_{475}$, the monomer conversion remained unchanged, suggesting that significant termination events occur after 5 hours. Nevertheless, the polymerisation seems to fulfil the criteria of a controlled/"*living*" system up to 5 h with $\ln([M]_0/[M]_n)$ increasing linearly with time and SEC analysis revealing a linear increase of M_n with increasing conversion. However, slightly broader MWD ($Đ$= 1.22, figure 4.3.E) are detected, as opposed to the acrylate analogue ($Đ$= 1.08) when this monomer/solvent/ligand/catalyst combination is employed. Moreover, no apparent high MW shoulder is noticeable, which would contradict the hypothesis of impurities in the monomer, as similar tailing would be observed, regardless of the broader MWD. Further discussions on termination will be provided in section 4.2.2.

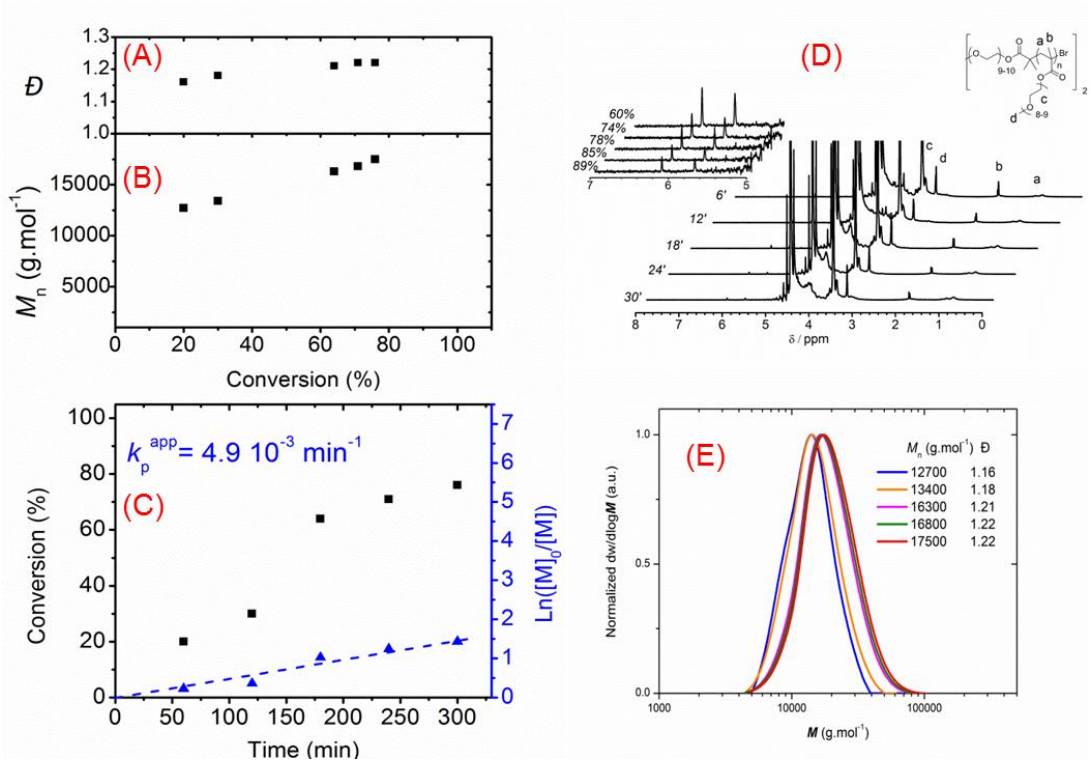


Figure 4.3. Monitoring the polymerisation of $PEGMA_{475}$ with Me_6-TREN ligand in DMSO (50 % *v/v*) at 25°C by ^1H NMR (250 MHz, $CDCl_3$, D) and SEC (DMF eluent, E); [I]:[M]:[Me_6-TREN]:[$Cu^{II}Br_2$]= 1:20:0.18:0.05 and 5 cm Cu(0) wire.

Unfortunately, the kinetic experiments do not give an insight of the *α,ω*-Br end groups fidelity that is essential for the synthesis of block copolymers and post-polymerisation modifications. In addition, considering the high molecular weight of the polymers (in addition to the oligomeric nature of the monomers), a combination of NMR and MALDI-ToF MS analyses is not possible. Consequently, chain extensions have been performed as an alternative indirect assessment of the halide chain end fidelity *via* injection of a second aliquot of deoxygenated monomer *in situ*, at high monomer conversion of the first block. In the case of $PEGA_{480}$ (98% conversion in 5 hours) a significant shift towards higher molecular weights is noticeable in SEC analysis upon addition of the second aliquot of $PEGA_{480}$, whilst the low dispersity values are maintained (*Đ*= 1.1, after 15 hours, figure 4.4). Symmetrical SEC traces are maintained, highlighting the good control over the polymerisation and chain extension, though tailing at high MWD can be observed for $PPEGA_{480}$ chromatograms, possibly due to the presence of trace quantities of diacrylates in the monomers.[4] As such, high end group fidelity is evident during the polymerisation of $PEGA_{480}$ when Me_6-TREN/DMSO/Cu(0) wire are utilised.

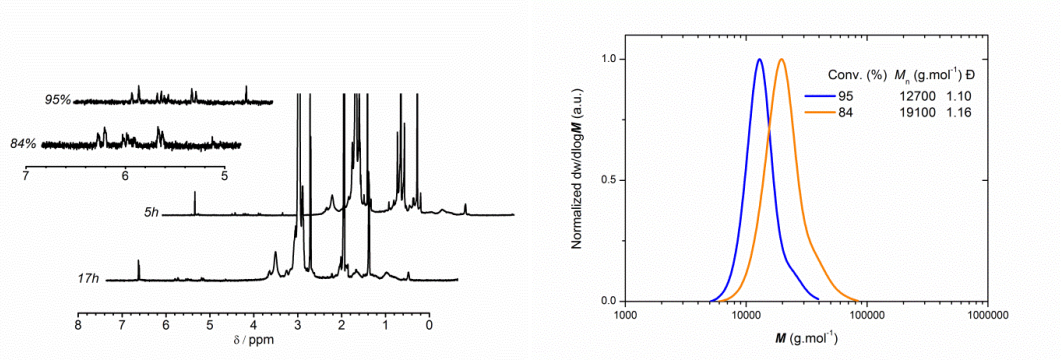


Figure 4.4. Monitoring the chain extension of poly[poly(ethylene glycol) methyl ether acrylate] with $PEGA_{480}$ in DMSO with Me_6-TREN ligand at 25°C, by ^1H NMR ($CDCl_3$, 250 MHz, left) and SEC (DMF eluent, right).

On the contrary, in the case of $PEGMA_{475}$ the cessation of the polymerisation after 5 hours suggests poor end-group fidelity. In order to verify this and despite the limited conversion (76% by ^{1}H NMR) a second aliquot of monomer was added. However, no monomer consumption was detected by ^{1}H NMR and no shift is observed by SEC (data not shown) suggesting that, under these conditions, the end-group fidelity has been compromised. This poor end group fidelity in combination with the increase in the dispersity values could be attributed to the limited ability of the [Cu^{II}(Me_6-TREN)Br]Br complex to successfully deactivate a propagating tertiary radical, leading to pronounced termination events.[7, 24] Similar behaviours have been observed in classical ATRP in organic solvents when too active ligands (high k_{act} and low k_{deact}) are employed to polymerise styrene or methacrylates.[7]

However, the copper/ligand catalyst can be modified in order to tune the rate of deactivation of a growing polymer chain and therefore limit the probability of termination events.[20] The commercially available, *N*-donor tridentate ligand PMDETA has been studied in several ATRP processes for the polymerisation of a range of monomers, due to its high activity and relatively low cost.[10, 25] More importantly, the [Cu^{II}(PMDETA)Br]Br complex is reported to have a greater ability to deactivate radicals (higher k_{deact}) compared to [Cu^{II}(Me_6-TREN)Br]Br.[25] Furthermore, PMDETA is known to promote the rapid disproportionation of [Cu^{I}(PMDETA)Br] in polar media[26-29] (figure 4.5), which is key for generation of active Cu(0) particles and [Cu^{II}(PMDETA)Br]Br deactivator throughout the polymerisation.

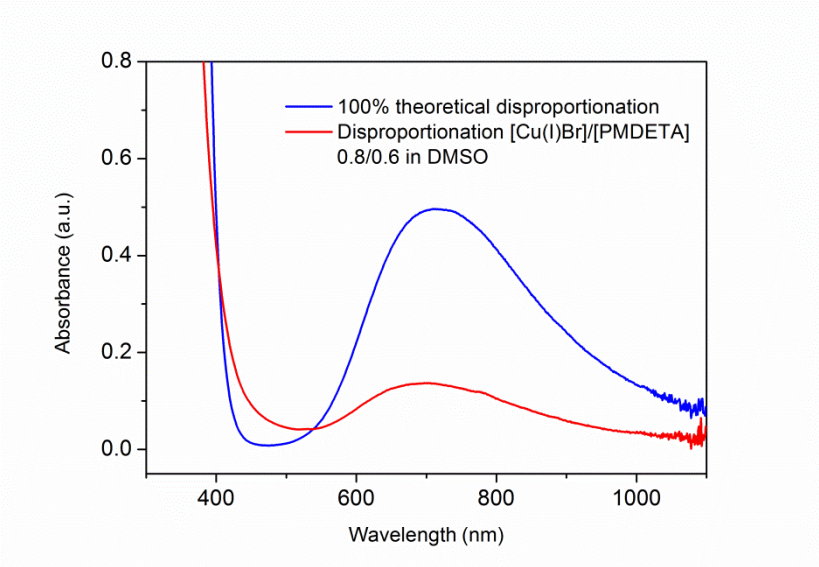


Figure 4.5. Monitoring the disproportionation of Cu(I)Br in the presence of PMDETA in DMSO.

Thus, the polymerisation of $PEGA_{480}$ and $PEGMA_{475}$ were subsequently conducted using PMDETA in place of Me_6-TREN (figures 4.6 and 4.7). The use of the tridentate ligand has a significant effect on the rate of polymerisation of the hydrophilic acrylate as manifested by a significant reduction in the polymerisation rate (k_p^{app}= 4.3 10^{-3} min^{-1} *vs* k_p^{app}= 1.2 10^{-2} min^{-1} with Me_6-TREN, table 4.1 entries 2 and 1). Nevertheless, a high monomer conversion is reached (94% by ^{1}H NMR, table 4.1 entry 2) after 11 hours, with linear evolution of molecular weight over conversion and narrow MWDs retained ($Đ$< 1.08, figure 4.6.E).

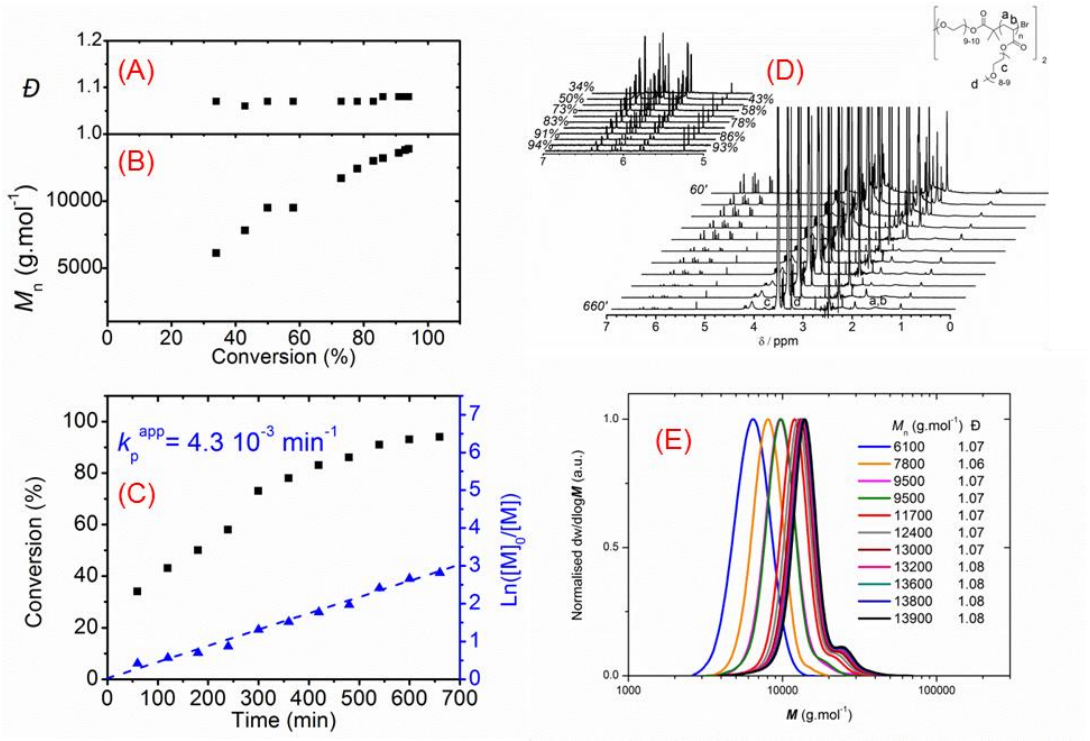


Figure 4.6. Monitoring the polymerisation of $PEGA_{480}$ with PMDETA ligand in DMSO (50 % *v/v*) at 25°C by ^{1}H NMR (250 MHz, $CDCl_3$, D) and SEC (DMF eluent, E); [I]:[M]:[PMDETA]:[$Cu^{II}Br_2$]= 1:20:0.18:0.05 and 5 cm Cu(0) wire.

Pleasingly, in the case of $PEGMA_{475}$ a reverse scenario is observed and an enhanced polymerisation rate is evident (k_p^{app}= 1.3 10^{-2} min^{-1} *vs* k_p^{app}= 4.9 10^{-3} min^{-1} for Me_6-TREN, table 4.1 entries 4 and 3) whilst relatively narrow MWDs are also obtained (*Đ*< 1.27, figure 4.7.E), even at near quantitative conversions (> 98%, table 4.1 entry 4). It should be noted that the polymerisation of $PEGMA_{475}$ in the presence of PMDETA is even faster than the polymerisation of $PEGA_{480}$ (a higher k_p monomer) under the given conditions.

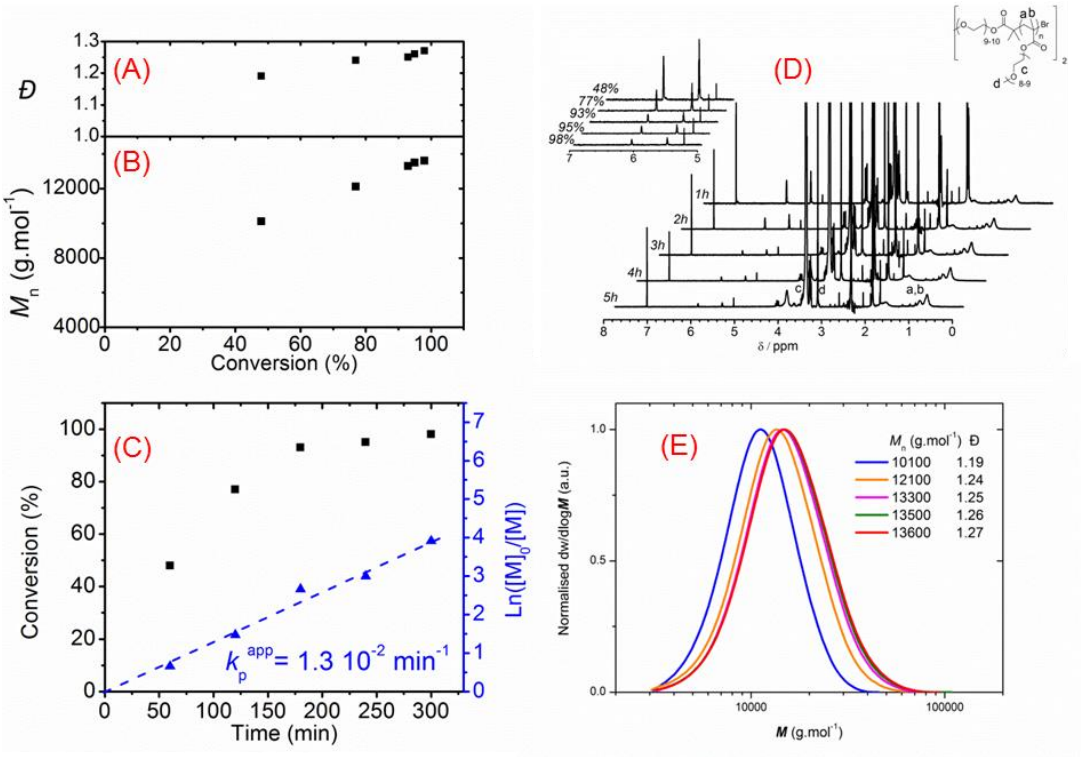


Figure 4.7. Monitoring the polymerisation of $PEGMA_{475}$ with PMDETA ligand in DMSO (50 % *v/v*) at 25°C by ^{1}H NMR (250 MHz, $CDCl_3$, D) and SEC (DMF eluent, E); [I]:[M]:[PMDETA]:[$Cu^{II}Br_2$]= 1:20:0.18:0.05 and 5 cm Cu(0) wire.

Considering the high monomer conversions obtained for the polymerisation of $PEGA_{480}$ with PMDETA, chain extension should be possible. Interestingly, poorer yield (74% *vs* 84% with Me_6-TREN after 15 hours, figure 4.8) and slightly broader MWDs (*Đ*= 1.17 *vs Đ*= 1.08 with Me_6-TREN) are obtained, suggesting that Me_6-TREN is a better alternative to yield good acrylic based block copolymers.

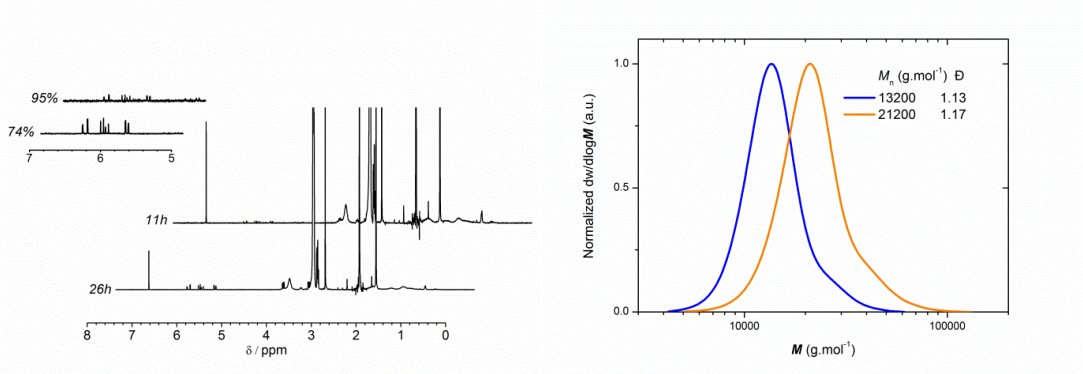


Figure 4.8. Monitoring the chain extension of poly[poly(ethylene glycol) methyl ether acrylate] with $PEGA_{480}$ in DMSO with PMDETA ligand at 25°C, by ^{1}H NMR ($CDCl_3$, 250 MHz, left) and SEC (DMF eluent, right).

However, the use of the tridentate ligand for the chain extension of $PEGMA_{475}$ was not successful, as only 20% conversion is attained for the second block (after 15 hours, figure 4.9), suggesting that a significant loss of end-group fidelity occurs with this system.

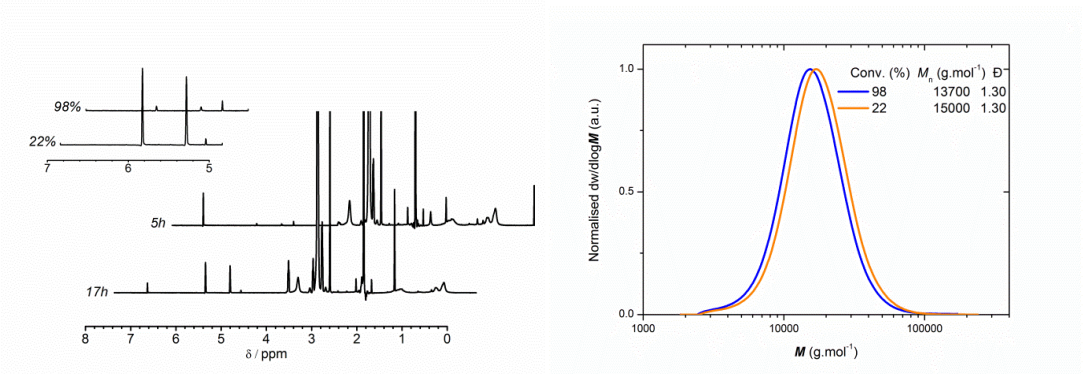


Figure 4.9. Monitoring the chain extension of poly[poly(ethylene glycol) methyl ether methacrylate] with $PEGMA_{475}$ in DMSO with PMDETA ligand at 25°C, by ^{1}H NMR ($CDCl_3$, 250 MHz, left) and SEC (DMF eluent, right).

Nevertheless, it is clear that the use of a more deactivating ligand has a prominent effect on the polymerisation of acrylates and methacrylates in DMSO when Cu(0)-wire is employed as the desired copper source. PMDETA appears to be a better ligand for methacrylates, resulting in an increase in the polymerisation rate and monomer conversions obtained; whilst

acrylates exhibit a decrease on the polymerisation rate, accompanied by poorer conversions and slightly higher dispersity values. Likewise, Me_6-TREN better supports the polymerisation of acrylates yielding materials with narrow MWDs, high conversion and high end-groups fidelity, whilst methacrylates are found to be significantly slower with limited conversions (~ 76% even when the reaction was left overnight) and lower retention of α,ω-Br chain-ends functionality.

Table 4.1. Solvent and ligand influence on the Cu(0)-wire mediated polymerisation of $PEGA_{480}$ and $PEGMA_{475}$ in DMSO.

Copper source	Monomer	Ligand	Time (min)	Conv. (%)[a]	M_n^{Exp} (g.mol^{-1})[b]	$Đ$ [b]	k_p^{app} (min^{-1})
Cu(0)-wire	$PEGA_{480}$	Me_6-TREN	300	98	13700	1.08	$1.2\ 10^{-2}$
Cu(0)-wire	$PEGA_{480}$	PMDETA	660	94	13900	1.08	$4.3\ 10^{-3}$
Cu(0)-wire	$PEGMA_{475}$	Me_6-TREN	300	76	17500	1.22	$4.9\ 10^{-3}$
Cu(0)-wire	$PEGMA_{475}$	PMDETA	300	98	13600	1.27	$1.3\ 10^{-2}$

[a] Determined by ^1H NMR (250 MHz, $CDCl_3$). [b] Determined by SEC (DMF + 5 mM NH_4BH_4) using PMMA standards.

4.2.2 Polymerisations in water

The aforementioned study on the influence of monomer and ligand composition on the polymerisation of hydrophilic (meth)acrylates in DMSO when Cu(0)-wire was employed as the copper source suggests a preference of acrylates to be better polymerised with Me_6-TREN and methacrylates with PMDETA. Nevertheless, the inefficient chain extension for the methacrylate encouraged us to seek for a better alternative. Hence, we decided to explore the effect of the solvent composition on the control over the polymerisation. Water was selected as the solvent for the polymerisation of the hydrophilic (meth)acrylate polymers. The incorporation of water in the system has been shown to accelerate the rate of polymerisation in ATRP-type systems, providing access to a wide range of (co)polymers in limited period of time with good control over the MWD.[30, 31] Functional polymethacrylates have been successfully synthesised in aqueous medium through the use of a transition-metal catalyst, with good retention of chain-end(s) fidelity and relatively low dispersity values at high monomer conversions. However, the majority of ligands employed do not promote disproportionation and therefore are not of interest for this current study.[11, 18]

In order to achieve a direct comparison with the previously used system, the same primary copper source (*e.g.* Cu(0)-wire) was also employed to assess the polymerisation of $PEGA_{480}$ in water. However, limited monomer conversions were attained over a comparable time scale (48% in 5h, table 4.2, entry 6), accompanied by a significant increase in MWD is ($Đ$< 1.37, figure 4.10), indicating that Cu(0)-wire is not best suited for polymerisations in water under the previously employed conditions (solvent 50% *v/v* at 25°C; [I]:[M]:[Me_6-TREN]:[$Cu^{II}Br_2$]= 1:20:0.18:0.05 and 5 cm Cu(0) wire).

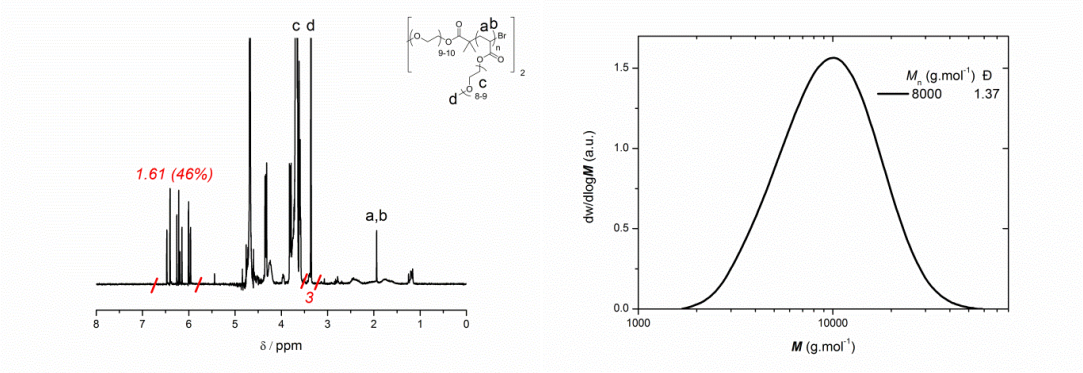


Figure 4.10. Monitoring the polymerisation of $PEGA_{480}$ in H_2O with Me_6-TREN ligand after 300 minutes at 25°C, by ^1H NMR (D_2O, 250 MHz, left) and SEC (DMF eluent, right).

Recently, the rapid disproportionation of [Cu^I(Me_6-TREN)Br] in water prior to polymerisation to generate active Cu(0) particles and [Cu^{II}(Me_6-TREN)Br]Br deactivator *in situ* has been used to yield functional hydrophilic polyacrylamides and polyacrylates.[1] The temperature of the reaction was reduced to 0°C, as this has been previously demonstrated to enhance the halogen end group(s) fidelity and narrow MWD when higher molecular weights are targeted.[1, 2] When the disproportionation was allowed to occur quantitatively in pure water prior the addition of the monomer and initiator ([I]:[M]:[Me_6-TREN]:[Cu^IBr]= 1:20:0.6:0.8, 20 % *v/v* monomer in water at 0°C), the kinetics of $PEGA_{480}$ revealed an enhanced apparent rate of polymerisation (k_p^{app}= 2.1 10^{-1} min^{-1}, table 4.2 entry 2), compared to the DMSO system (k_p^{app}=1.2 10^{-2} min^{-1}, table 4.1 entry 1). Furthermore, good linear evolution of molecular weight *vs.* monomer conversion highlights the good "*living*" behaviour of the system, whilst quantitative monomer conversions and narrow MWDs ($Đ$<1.12, figure 4.11.E) are attained within 30 minutes. It is important to notice that no apparent shoulder at high MW is observed for the polymerisation of $PEGA_{480}$ at lower temperature (0°C compared to 25°C, see section 4.2.1). This would favour a hypothesis of undesired termination of the polyacrylate *via* β-scission and/or branching, as the extent of termination would be diminished at lower temperatures. The comparison of the two

techniques contradicts the mode of termination hypothesised in chapter 2 (see section 2.2.2), wherein the presence of diacrylates in the monomer was responsible for a shoulder at high MW.

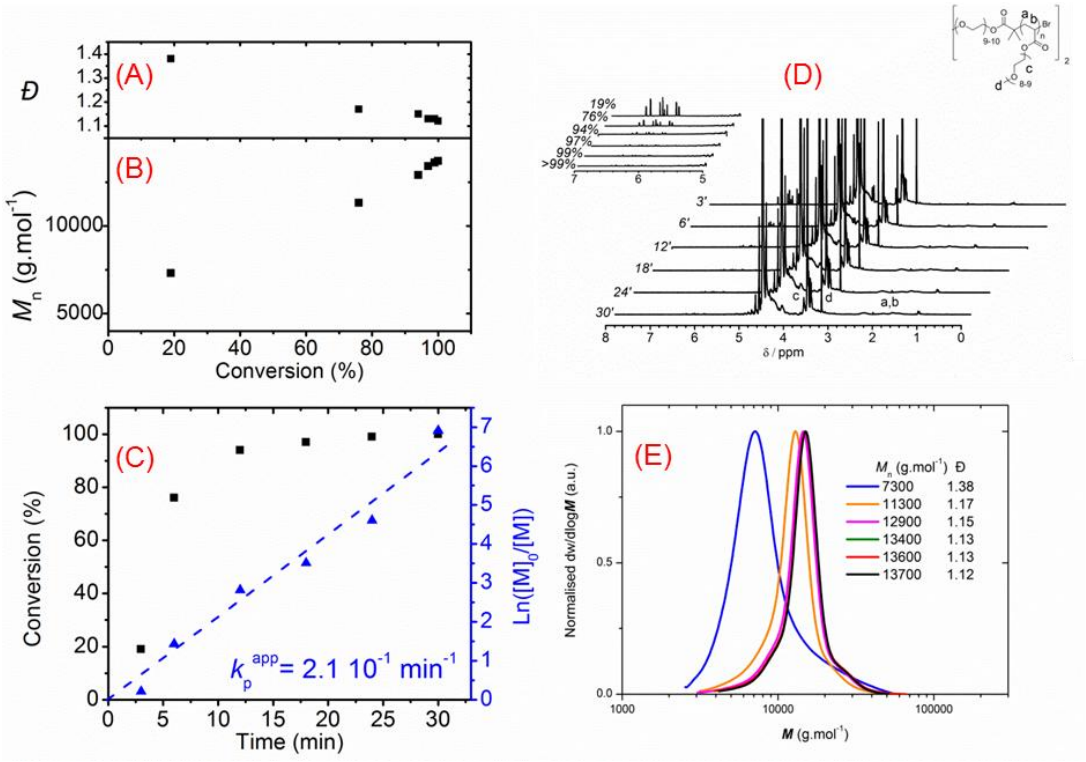


Figure 4.11. Monitoring the polymerisation of $PEGA_{480}$ with Me_6-TREN ligand in water at 0°C C by ^1H NMR (250 MHz, D_2O, D) and SEC (DMF eluent, E); [I]:[M]:[Me_6-TREN]:[Cu^IBr]= 1:20:0.6:0.8, 20 % *v/v* monomer in water.

Pleasingly, chain extension can be performed on $PPEGA_{480}$ with an additional aliquot of $PEGA_{480}$, resulting in well-defined polyacrylates with narrow MWDs (*Đ*~ 1.12, figure 4.12), even when the reaction reached quantitative conversion. Impressively, the chain extension occurred in a quantitative manner within 1 hour, further highlighting the ideal combination of an acrylate with Me_6-TREN under aqueous conditions (and pre-disproportionation of [$Cu^I(Me_6$-TREN)Br]).

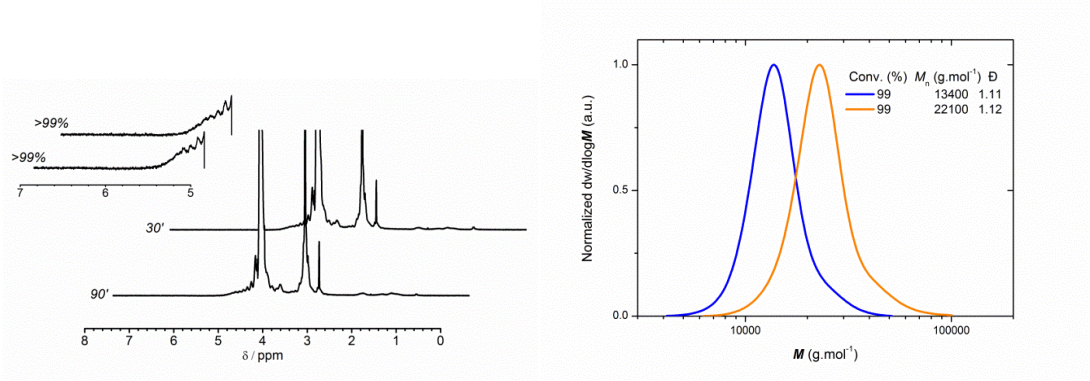


Figure 4.12. Monitoring the chain extension of poly[poly(ethylene glycol) methyl ether acrylate] with $PEGA_{480}$ in H_2O with Me_6-TREN ligand at 0°C, by ^1H NMR (D_2O, 250 MHz, left) and SEC (DMF eluent, right).

However, this robust tool has not yet been exploited for the formation of polymethacrylates; it therefore becomes of interest to test the versatility of the efficient synthetic process towards more propagating radicals. The polymerisation of $PEGMA_{475}$ was first attempted using Me_6-TREN ligand in order to compare its reactivity to the acrylate. Although relative fast polymerisation rates were maintained (k_p^{app}= 8.1 10^{-2} min^{-1}, table 4.2 entry 4) achieving 89% conversion in 30 minutes, the experimental molecular weight is significantly higher than the theoretical value (M_n^{SEC}= 25800 g.mol^{-1}; M_n^{Th}= 10725 g.mol^{-1}), whilst the MWDs are very broad ($Đ$> 1.7, figure 4.13.E) for a RDRP system, suggesting significant loss of control. This result underlines again the poor ability of the [Cu^{II}(Me_6-TREN)Br]Br to successfully end-cap a tertiary propagating radical. In this case, *in situ* chain extension experiments were not attempted due to the poor control obtained during the formation of the macroinitiator.

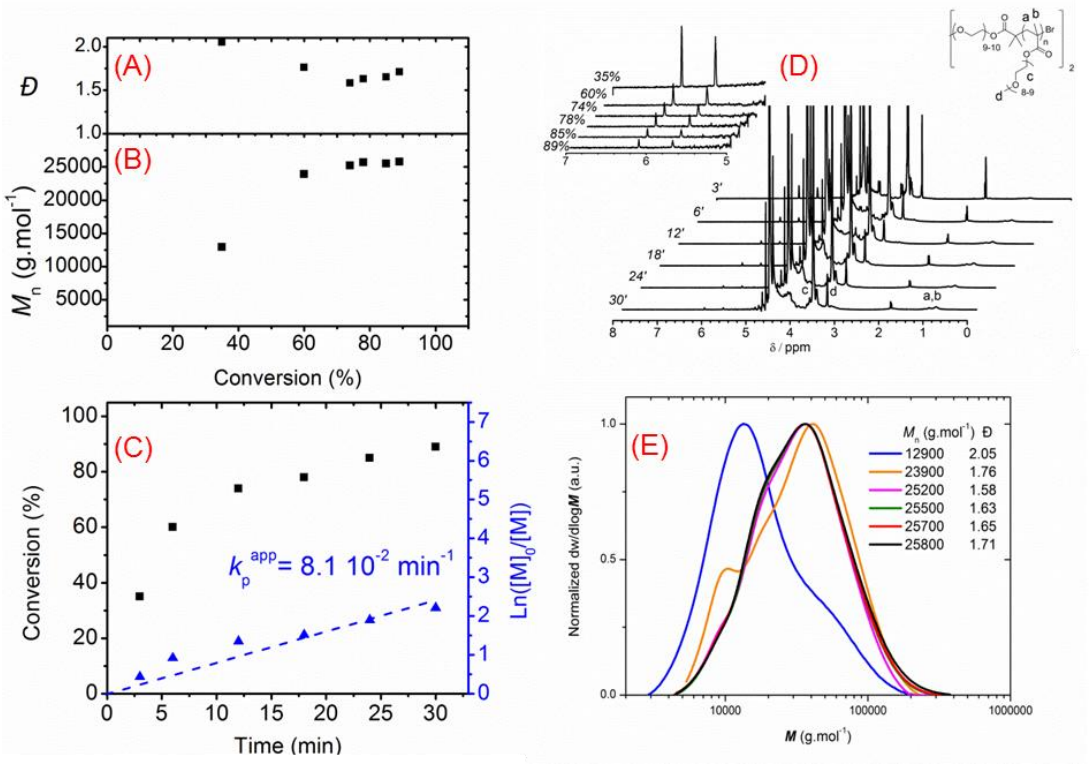


Figure 4.13. Monitoring the polymerisation of $PEGMA_{475}$ with Me_6-TREN ligand in water at 0°C by ^{1}H NMR (250 MHz, D_2O, D) and SEC (DMF eluent, E); [I]:[M]:[Me_6-TREN]:[Cu^IBr]= 1:20:0.6:0.8, 20 % *v/v* monomer in water.

Inspired by the initial findings in DMSO, the tridentate ligand PMDETA was utilised to form the catalytic system, in an attempt to improve the synthesis of polymethacrylate (co)polymers. The extent of disproportionation of the [Cu^I(PMDETA)Br] complex in water was first assessed by UV-Vis NIR spectroscopy, revealing a fast and complete formation of Cu(0) and $Cu^{II}Br_2$/PMDETA complexes (figure 4.14).

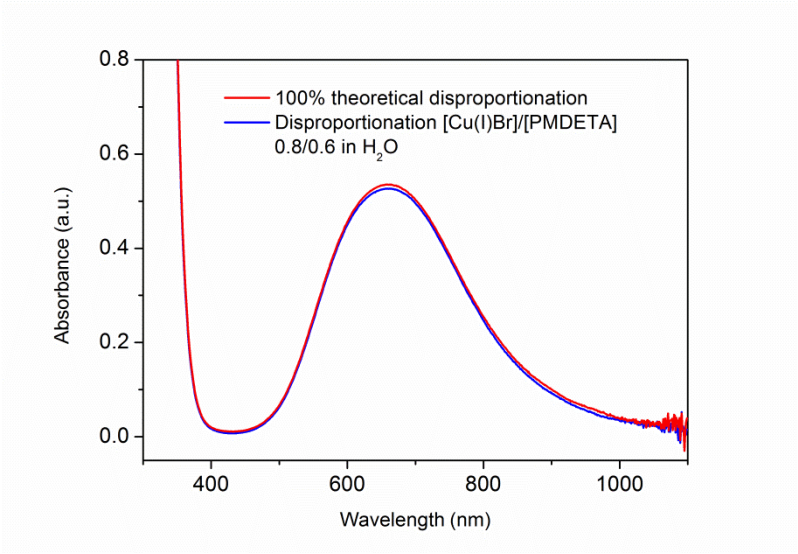


Figure 4.14. Monitoring the disproportionation of Cu(I)Br in the presence of PMDETA in water by UV-Vis.

The quantitative formation of the catalytic system was followed by the addition of $PEGA_{480}$ and initiator ([I]:[M]:[PMDETA]:[$Cu^{I}Br$]= 1:20:0.6:0.8, 20 % *v/v* monomer in water; figure 4.15) and the kinetics of the reaction (monitored by ^{1}H NMR and SEC) were found to disobey the typical linear first order kinetics. This observation could be due to the tridentate nature of the ligand. Indeed, the presence of a lone site in the deactivating complex [Cu^{II}(PMDETA)Br]Br could allow the introduction of hydroxyl groups to form [Cu^{II}(PMDETA)OHBr]Br^{-},[26, 27] in aqueous medium, inducing more termination events at the early stage of the polymerisation *via* -OH end capping of the propagating radical. Nevertheless, high conversions could be obtained (> 95%, table 4.2 entry 3) and the MWDs remained as narrow as $Đ$= 1.14 (figure 4.15.E).

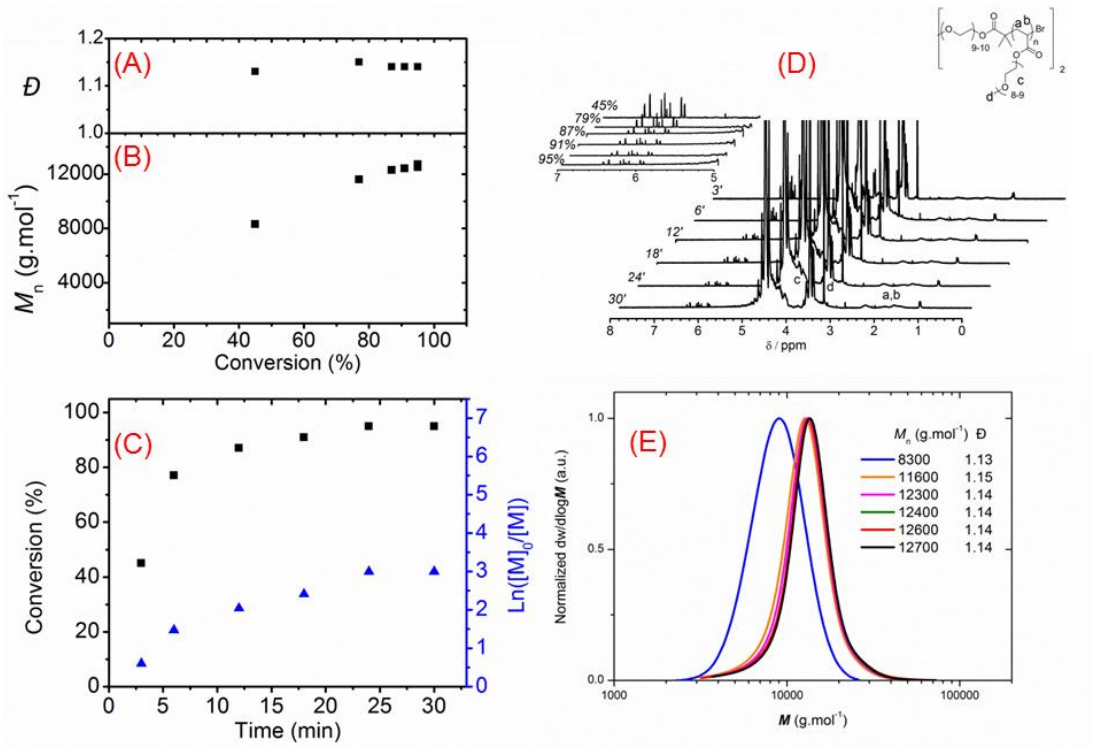


Figure 4.15. Monitoring the polymerisation of $PEGA_{480}$ with PMDETA ligand in water at 0°C by ^1H NMR (250 MHz, D_2O, D) and SEC (DMF eluent, E); [I]:[M]:[PMDETA]:[Cu^{I}Br]= 1:20:0.6:0.8, 20 % *v/v* monomer in water.

However, when chain extensions experiments were performed with the acrylate based macroinitiator, only 10% of monomer consumption was attained (after 1 hour, figure 4.16). The inefficient chain extension of $PPEGA_{480}$ strongly suggests a significant loss of halide end groups under these conditions, further confirming the unusual trend in the kinetic experiments and despite the low dispersity values of the macroinitiator. Thus, the polymerisation of $PEGA_{480}$ in water appears to be less tolerant to the ligand choice as opposed to the DMSO system where chain extensions with PMDETA could be successfully performed.

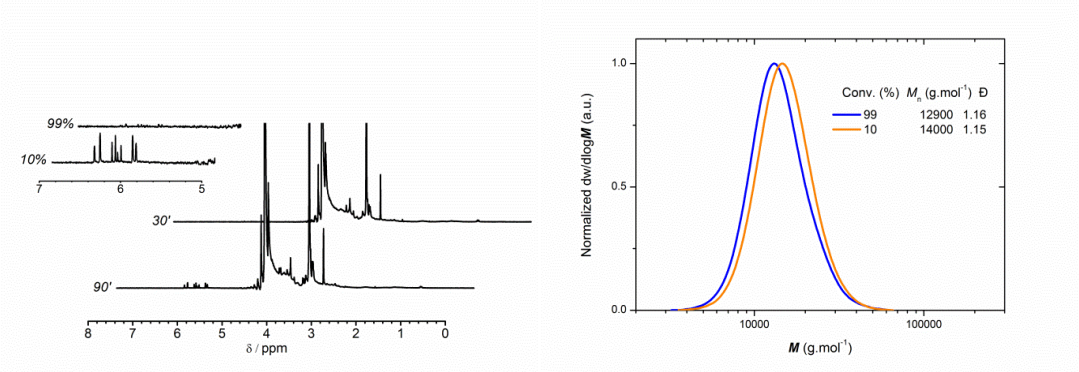


Figure 4.16. Monitoring the chain extension of poly[poly(ethylene glycol) methyl ether acrylate] with $PEGA_{480}$ in H_2O with PMDETA ligand at 0°C, by ^1H NMR (D_2O, 250 MHz, left) and SEC (DMF eluent, right).

Subsequently, the polymerisation of PEGMA utilising PMDETA was studied, revealing an enhanced control over the polymerisation. Indeed, an acceleration of the rate of polymerisation (k_p^{app}= 1.3 10^{-1} min^{-1} *vs* k_p^{app}= 8.1 10^{-2} min^{-1} with Me_6-TREN) and an improved control over the MWD (*Đ*= 1.38, figure 4.17.E *vs* *Đ*= 1.7 with Me_6-TREN) are observed. Pleasingly, near quantitative monomer conversions are obtained (98% by ^1H NMR, table 4.2 entry 5 *vs* 89% with Me_6-TREN, table 4.2 entry 4), further highlighting the beneficial use of PMDETA to synthesise well-defined $PPEGMA_{475}$.

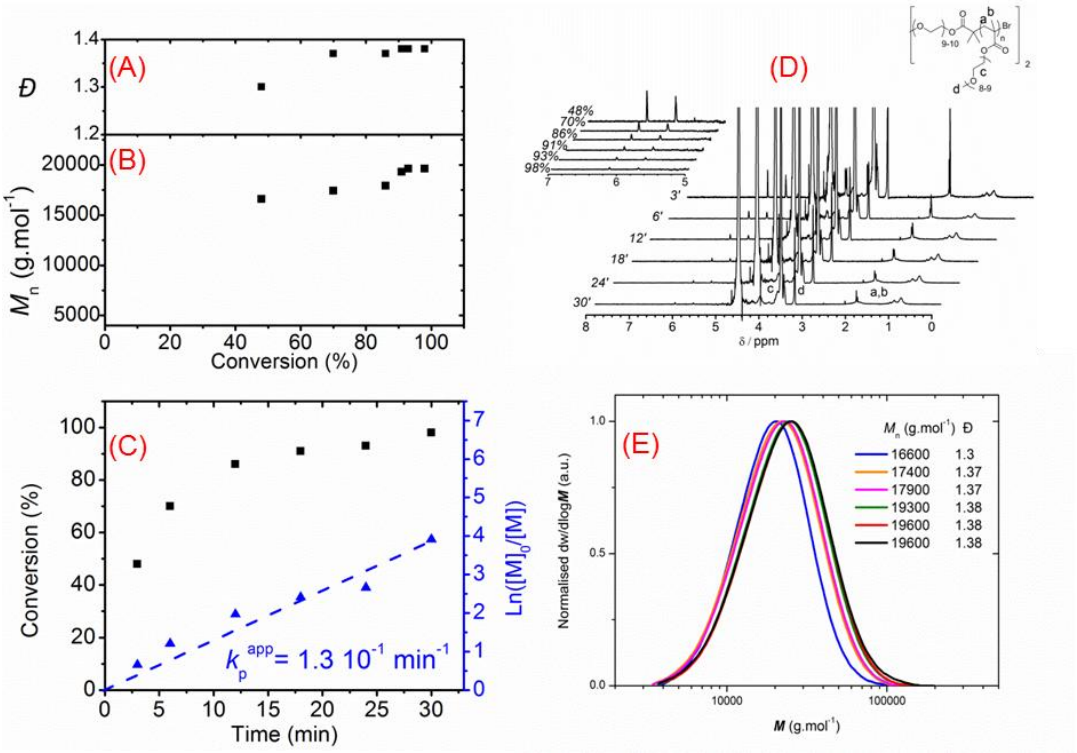


Figure 4.17. Monitoring the polymerisation of $PEGMA_{475}$ with PMDETA ligand in water at 0°C by ^{1}H NMR (250 MHz, D_2O, D) and SEC (DMF eluent, E); [I]:[M]:[PMDETA]:[Cu^{I}Br]= 1:20:0.6:0.8, 20 % *v/v* monomer in water.

Nevertheless, although a deviation of the experimental molecular weight (M_n^{SEC}= 19600 g.mol^{-1}) from the theoretical values (M_n^{Th}= 10500 g.mol^{-1}) is observed, *in situ* chain extension were also attempted. Interestingly, a complete shift towards higher molecular weights is observed in SEC, without compromising the final dispersity values (*Đ*= 1.38) for $PPEGMA_{475}$. Moreover, high conversion of the second monomer aliquot was obtained (95% by ^{1}H NMR after 1 hour, figure 4.18) within 1 hour.

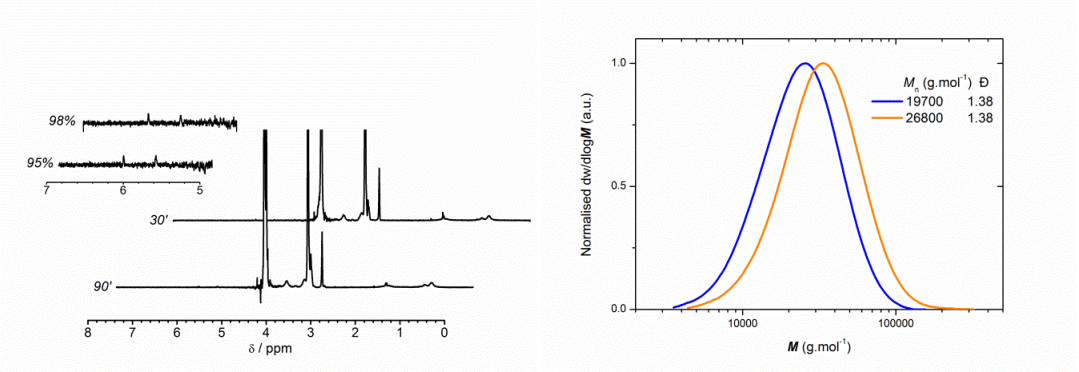


Figure 4.18. Monitoring the chain extension of poly[poly(ethylene glycol) methyl ether methacrylate] with $PEGMA_{475}$ in H_2O with PMDETA ligand at 0°C, by ^1H NMR (D_2O, 250 MHz, left) and SEC (DMF eluent, right).

Thus, it has been determined that utilising the pre-disproportionation of [Cu^I(L)Br] to yield Cu(0) particles and [Cu^{II}(L)Br]Br deactivator (whereby L is Me_6-TREN or PMDETA) followed by monomer and initiator *in situ* is a useful method to yield well-defined poly(meth)acrylate (co)polymers. However, we were also intrigued to understand the effect of the solvent on the control over the polymerisation. In order to investigate this, [Cu^I(Me_6-TREN)Br] was disproportionated in DMSO under identical conditions to yield the catalytic system *in situ* prior to polymerisation ([I]:[M]:[Me_6-TREN]:[Cu^IBr]= 1:20:0.6:0.8, 20 % *v/v* monomer in solvent), though UV-Vis NIR analysis revealed limited yield (figure 4.19).

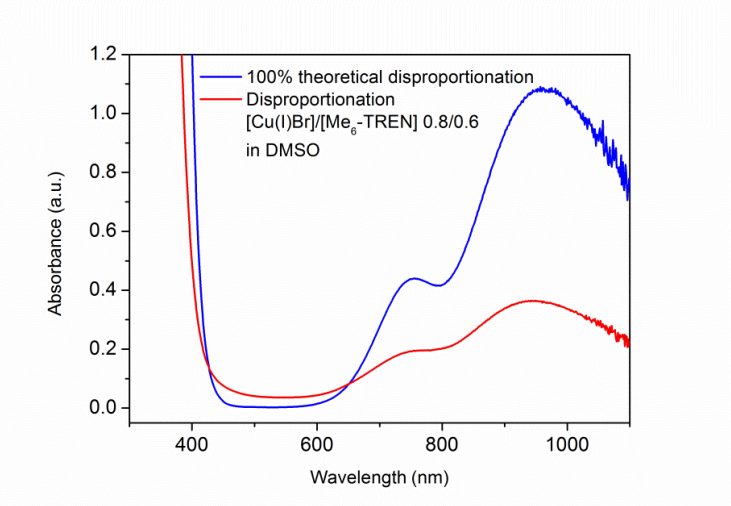


Figure 4.19. Monitoring the disproportionation of Cu(I)Br in the presence of Me_6-TREN in DMSO by UV-Vis.

However, the polymerisation of $PEGA_{480}$ yielded poor monomer conversions over a comparable timescale (48% in 30 minutes, table 4.2 entry 1), and low dispersity values were obtained ($Đ$= 1.05, figure 4.20).

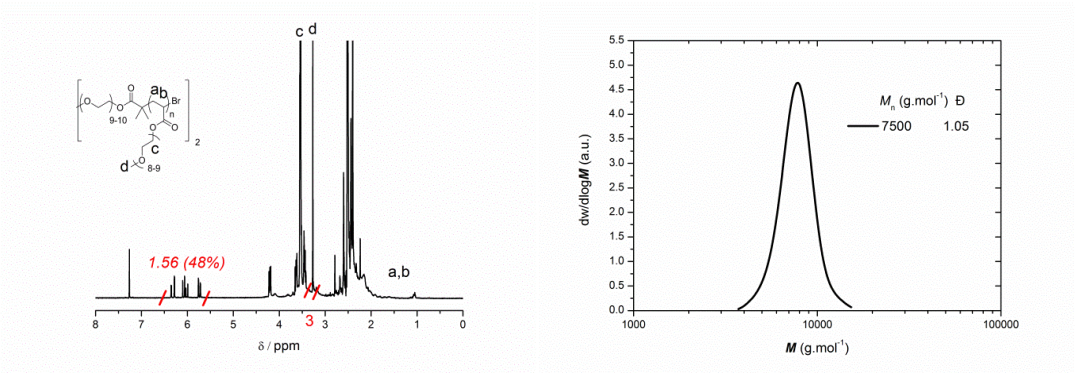


Figure 4.20. Monitoring the polymerisation of $PEGMA_{475}$ methacrylate in DMSO with Me_6-TREN ligand after 30 minutes at 0°C, by ^1H NMR ($CDCl_3$, 250 MHz) and SEC (DMF eluent).

Therefore, it is concluded that utilising the pre-disproportionation approach for the preparation of well-defined (co)polymers with almost quantitative conversions is only possible in solvents that significantly promote the rapid and complete disproportionation of

the [Cu^{I}(L)Br] complex, such as water. More importantly, any deviation from the proposed conditions results in inefficient formation of a macroinitiator, compromising the formation of well-defined block copolymers *in situ*.

Table 4.2. Solvent, ligand and copper source influence on the Cu(0)-mediated polymerisation of $PEGA_{480}$ and $PEGMA_{475}$ in water and DMSO.

Solvent	Copper source	Monomer	Ligand	Time (min)	Conv. (%)[a]	M_n^{Exp} (g.mol^{-1})[b]	$Đ$ [b]	k_p^{app} (min^{-1})
DMSO	Pre disp. Cu(I)Br	$PEGA_{480}$	Me_6-TREN	30	48	7500	1.05	n/a
H_2O	Pre disp. Cu(I)Br	$PEGA_{480}$	Me_6-TREN	30	> 99	13700	1.12	2.1 10^{-1}
H_2O	Pre disp. Cu(I)Br	$PEGA_{480}$	PMDETA	30	95	12700	1.14	n/a
H_2O	Pre disp. Cu(I)Br	$PEGMA_{475}$	Me_6-TREN	30	89	25800	1.71	8.1 10^{-2}
H_2O	Pre disp. Cu(I)Br	$PEGMA_{475}$	PMDETA	30	98	19600	1.38	1.3 10^{-1}
H_2O	Cu(0)-wire	$PEGA_{480}$	Me_6TREN	300	48	8000	1.37	n/a

[a] Determined by ^{1}H NMR (250 MHz, $CDCl_3$ or D_2O for polymerisation in DMSO and H_2O respectively). [b] Determined by SEC (DMF + 5 mM NH_4BH_4) using PMMA standards.

4.3 Conclusions

In this chapter, a comprehensive study on the formation of polyether containing acrylates and methacrylates in both DMSO and water is reported, utilising two different polymerization protocols. It has been found that the combination of the monomer structure with the appropriate ligand, Cu(0)-source, solvent and polymerisation method is essential for the retention of the halide end-group fidelity. Moreover, the thorough investigation of the effect of each component revealed that a non-adapted combination would be deleterious for the "*living*" character of the polymerisation, the rate, the chain ends retention and molecular weight distribution. In the case of DMSO, the polymerisation of $PEGA_{480}$ with Cu(0)-wire reaches full conversion within 5 hours with low dispersity values ($Đ$~ 1.1) and good end-group(s) fidelity, as exemplified by *in situ* chain extension when Me_6-TREN is employed as the ligand. Under identical conditions, the polymerisation of the methacrylate analogue, $PEGMA_{475}$, results in broader MWDs ($Đ$= 1.22) and lower conversions (76% after 5 hours) whilst the end-group(s) fidelity is significantly compromised. Interestingly, adapting the ligand from Me_6-TREN to PMDETA accelerates the polymerisation of $PEGMA_{475}$, although the end-group fidelity is still poor; whilst the polymerisation of the acrylate analogue $PEGA_{480}$, compromises both rate of polymerisation and chain ends retention. In order to further enhance the α,ω-Br end-groups fidelity and the rate of polymerisation, water was subsequently employed as the solvent, exploiting the *in situ* pre-disproportionation of $[Cu^{I}(L)Br]$ prior to addition of the monomer and initiator. When Me_6-TREN is selected as a ligand, the quantitative synthesis of well-defined $PPEGA_{480}$ based diblock copolymers is facilitated within 90 minutes ($Đ$= 1.14). Conversely, the polymerisation of $PEGMA_{475}$ in similar conditions reveals a loss of control ($Đ$> 1.7) which suggests that the careful selection of the ligand is of upmost importance for an effective polymerization. In order to verify this, PMDETA is used under identical conditions, yielding polymethacrylates with quite narrow

MWDs (*Đ*= 1.38) and high end-group(s) fidelity even at quantitative conversions. However, when PMDETA is utilised for the polymerization of $PEGA_{480}$, poor end group fidelity is manifested by *in situ* chain extension, further highlighting the crucial selection of the (co)polymerisation conditions for each monomer.

4.4 Experimental

4.4.1 Materials

Previously used materials can be found in sections 2.4.1 and 3.4.1.

Poly(ethylene glycol) methyl ether methacrylate ($PEGMA_{475}$, 98%, Sigma-Aldrich, av. M_n = 475 $g.mol^{-1}$ was used as received without purification. *N,N,N',N'',N''*-Pentamethyldiethylenetriamine (PMDETA, 98%, Sigma-Aldrich) was distilled under reduced pressure (55°C, 10^{-1} mbar), deoxygenated and stored at 4°C under nitrogen prior to use.

4.4.2 Characterisation

^{1}H, ^{13}C NMR spectra were recorded on Bruker ACF-250 and DPX-300 spectrometers using deuterated solvents obtained from Sigma-Aldrich.

DMF SEC traces were obtained on a Varian 390-LC system using a DMF (+ 5 mM NH_4BH_4) eluent at 50°C, equipped with refractive index, UV and viscometry detectors, 2 × PLgel 5 mm mixed D columns (300 × 7.5 mm), 1 × PLgel 5 mm guard column (50 × 7.5 mm) and autosampler. Narrow linear poly(methyl methacrylate) standards in range of 200 to 1.0×10^{6} $g \cdot mol^{-1}$ were used to calibrate the system. All samples were passed through 0.45

µm PTFE filter before analysis. UV-Vis NIR spectra were obtained on an Agilent Technologies Cary 60 UV-Vis spectrometer using a quartz cuvette with 1cm path length at 20°C.

4.4.3 Cu(0)-mediated polymerisation in DMSO.

This procedure for the polymerisation of $PEGA_{480}$ with Me_6-TREN in DMSO can be adapted for all polymerisations utilising Cu(0)-wire as a primary copper source.

In an oven dried Schlenk tube were added poly(ethylene glycol) bis(2-bromoisobutyrate) (0.7 g, 0.57 mmol), copper(II) bromide (6.4 mg, 0.05 eq.), $PEGA_{480}$ (5.0 mL, 20 eq.), DMSO (5 mL). The stirring bar with the pre-activated copper wire was then added and the Schlenk tube was sealed with a rubber septum. The reaction was kept stirring and deoxygenated with nitrogen for 10 min. Me_6-TREN (27.5 µL, 0.18 eq.) was injected *via* a deoxygenated microsyringe and the reaction was left to polymerize at 25°C.

Sequential additions were performed as followed. A vial fitted with a rubber septum and magnetic stirring bar was charged with monomer ($PEGA_{480}$ or $PEGMA_{475}$ respectively, 20 eq.) and DMSO (5 mL). The mixture was left to stir until complete dissolution of the monomer (typically 1 minute) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the reaction vessel upon near quantitative conversion of the first block (>95 % by ^{1}H NMR, unless stated otherwise) and the reaction was left to stir at 25°C.

4.4.4 Monitoring the disproportionation of Cu(I)Br in the presence of ligand in DMSO or water.

This generic procedure to monitor the extent of disproportionation of [Cu^I(PMDETA)Br] in DMSO can be adapted in different solvents, whilst utilising various ligands.

The theoretical disproportionation curve was obtained by preparing a solution of Cu(II)Br_2 (10.8 mg, 4.8 10^{-5} mol) in the presence of PMDETA (11.5 µL) in DMSO. Disproportionation was performed by adding Cu(I)Br (14 mg, 9.7 10^{-5} mol) to a solution of solvent (2 mL) and PMDETA (11.5 µL, 0.75 eq.), which was left to stir and deoxygenate with nitrogen for 15 minutes. Subsequently, the solution was filtered under nitrogen to remove any Cu(0) particles. UV-Vis NIR spectrum was recorded using a quartz cuvette (path length 1 cm).

4.4.5 Disproportionation of Cu(I)Br in the presence of ligand to catalyse the polymerisation of (meth)acrylic monomers in H_2O.

This procedure for the polymerisation of $PEGA_{480}$ with Me_6-TREN in water can be adapted for all polymerisations utilising the pre-disproportionation of a [Cu^I(L)X] complex, where L is a *N*-containing ligand (Me_6-TREN, PMDETA), to yield the catalytic system.

To an oven dried Schlenk tube fitted with a magnetic stirring bar and rubber septum was added H_2O (2 mL), Me_6-TREN (52 µL, 0.6 eq.) and Cu(I)Br (37.5 mg, 0.8 eq.). The solution was left to deoxygenate with nitrogen for 20 minutes and to stir for an extra 10 minutes. A vial fitted with a rubber septum and magnetic stirring bar was charged with poly(ethylene glycol) bis(2-bromoisobutyrate) (400 mg, 0.33 mmol), $PEGA_{480}$ (2.87 mL, 20 eq.) and H_2O (10 mL). The mixture was left to stir until complete dissolution of the monomer (typically 2 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the Schlenk tube and the reaction was left to polymerise at 0°C.

Sequential additions were performed as followed. A vial fitted with a rubber septum and magnetic stirring bar was charged with monomer ($PEGA_{480}$ or $PEGMA_{475}$ respectively, 20

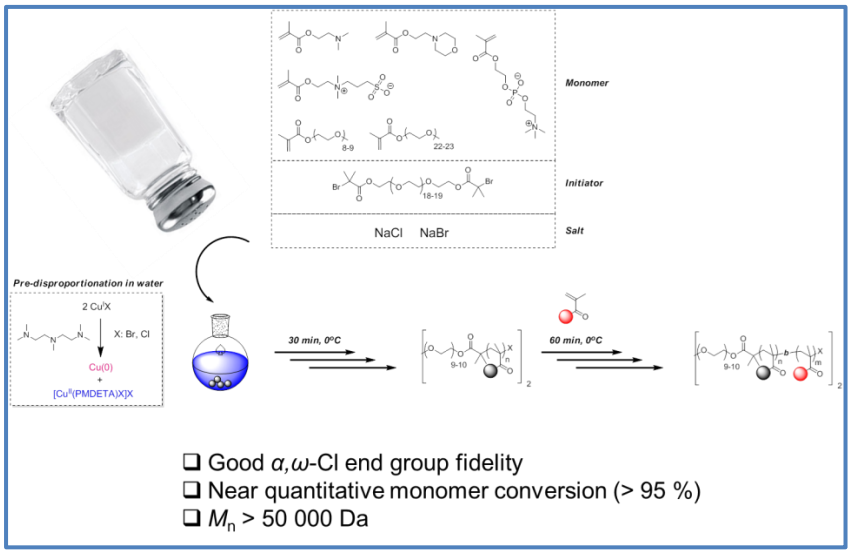
eq.) and H_2O (10 mL). The mixture was left to stir until complete dissolution of the monomer (typically 1 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the reaction vessel upon 30 minutes of polymerisation and the reaction was left to stir at 0°C.

4.5 References

1. Q. Zhang, P. Wilson, Z. Li, R. McHale, J. Godfrey, A. Anastasaki, C. Waldron and D. M. Haddleton, *J. Am. Chem. Soc.*, 2013, **135**, 7355-7363.
2. F. Alsubaie, A. Anastasaki, P. Wilson and D. M. Haddleton, *Polym. Chem.*, 2015, **6**, 406-417.
3. A. Simula, V. Nikolaou, A. Anastasaki, F. Alsubaie, G. Nurumbetov, P. Wilson, K. Kempe and D. M. Haddleton, *Polym. Chem.*, 2015, **6**, 2226-2233.
4. A. Simula, G. Nurumbetov, A. Anastasaki, P. Wilson and D. M. Haddleton, *Eur. Polym. J.*, 2014, **62**, 294-303.
5. N. H. Nguyen, X. Leng and V. Percec, *Polym. Chem.*, 2013, **4**, 2760-2766.
6. N. H. Nguyen, X. Leng, H.-J. Sun and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2013, **51**, 3110-3122.
7. W. Tang, Y. Kwak, W. Braunecker, N. V. Tsarevsky, M. L. Coote and K. Matyjaszewski, *J. Am. Chem. Soc.*, 2008, **130**, 10702-10713.
8. K. Matyjaszewski, *Macromolecules*, 2012, **45**, 4015-4039.
9. J. Xia, S. G. Gaynor and K. Matyjaszewski, *Macromolecules*, 1998, **31**, 5958-5959.
10. J. Xia and K. Matyjaszewski, *Macromolecules*, 1997, **30**, 7697-7700.
11. X. S. Wang, S. F. Lascelles, R. A. Jackson and S. P. Armes, *Chem. Commun.*, 1999, 1817-1818.
12. J. T. Rademacher, M. Baum, M. E. Pallack, W. J. Brittain and W. J. Simonsick, *Macromolecules*, 1999, **33**, 284-288.
13. M. Teodorescu and K. Matyjaszewski, *Macromolecules*, 1999, **32**, 4826-4831.
14. Č. r. Koňák, B. Ganchev, M. Teodorescu, K. Matyjaszewski, P. Kopečková and J. Kopeček, *Polymer*, 2002, **43**, 3735-3741.
15. J.-S. Wang and K. Matyjaszewski, *J. Am. Chem. Soc.*, 1995, **117**, 5614-5615.
16. D. M. Haddleton, C. B. Jasieczek, M. J. Hannon and A. J. Shooter, *Macromolecules*, 1997, **30**, 2190-2193.
17. T. E. Patten, J. Xia, T. Abernathy and K. Matyjaszewski, *Science*, 1996, **272**, 866-868.
18. X. S. Wang and S. P. Armes, *Macromolecules*, 2000, **33**, 6640-6647.
19. A. Simakova, S. E. Averick, D. Konkolewicz and K. Matyjaszewski, *Macromolecules*, 2012, **45**, 6371-6379.
20. N. V. Tsarevsky, W. A. Braunecker, A. Vacca, P. Gans and K. Matyjaszewski, *Macromol. Symp.*, 2007, **248**, 60-70.
21. M. Kamigaito, T. Ando and M. Sawamoto, *Chem. Rev.*, 2001, **101**, 3689-3746.
22. K. Matyjaszewski and J. Xia, *Chem. Rev.*, 2001, **101**, 2921-2990.
23. W. Tang and K. Matyjaszewski, *Macromolecules*, 2007, **40**, 1858-1863.
24. H. Bergenudd, G. Coullerez, M. Jonsson and E. Malmström, *Macromolecules*, 2009, **42**, 3302-3308.

25. K. Matyjaszewski, B. Göbelt, H.-j. Paik and C. P. Horwitz, *Macromolecules*, 2001, **34**, 430-440.
26. N. Navon, G. Golub, H. Cohen, P. Paoletti, B. Valtancoli, A. Bencini and D. Meyerstein, *Inorg. Chem.*, 1999, **38**, 3484-3488.
27. T. Pintauer and K. Matyjaszewski, *Coord. Chem. Rev.*, 2005, **249**, 1155-1184.
28. W. A. Braunecker, N. V. Tsarevsky, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2009, **42**, 6348-6360.
29. E. Kimura, T. Koike, M. Kodama and D. Meyerstein, *Inorg. Chem.*, 1989, **28**, 2998-3001.
30. M. Horn and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 3350-3357.
31. N. H. Nguyen, J. Kulis, H.-J. Sun, Z. Jia, B. van Beusekom, M. E. Levere, D. A. Wilson, M. J. Monteiro and V. Percec, *Polym. Chem.*, 2013, **4**, 144-155.

The importance of external halide salt for the Cu(0)-mediated (co)polymerisation of methacrylic monomers in water



The polymerisation of methacrylic, water soluble and zwitterionic monomers is assessed by Cu(0)-mediated polymerisation in water. The pre-disproportionation of [Cu^{I}(PMDETA)Cl] in water prior to initiator and monomer addition is exploited to yield well-defined polymethacrylates with quantitative monomer conversions in 30 minutes. Subsequently, the addition of supplementary halide salt (NaCl, 1M) enabled the synthesis of various molecular weight poly[poly(ethylene glycol) methyl ether methacrylate] ($PEGMA_{475}$) (DP_n=10-80) with narrow molecular weight distributions (MWD, Đ< 1.3). More importantly, the block copolymerisation of 2-dimethylaminoethyl methacrylate (DMAEMA), 2-morpholinoethyl methacrylate (MEMA), [2-(methacryloyloxy)ethyl]dimethyl-(3-sulfopropyl)ammonium hydroxide (SBMA) and 2-methacryloyloxyethyl phosphorylcholine (MPC) with $PEGMA_{475}$ was successful in aqueous medium without the need of purification steps. Moreover, good control was still retained, reciprocated by quantitative monomer conversions and moderate MWD (Đ< 1.6).

.

5.1 Introduction

In chapter 4, the importance in the selection of ligand and copper source was highlighted whilst engaging Cu(0)-mediated polymerisation in organic and aqueous media. The association of kinetic experiments with *in situ* chain extensions highlighted the effect of ligand (tridentate and tetradentate, *i.e.* PMDETA and Me_6-TREN), solvent (DMSO and water) and copper source (Cu(0)-wire and *in situ* generated Cu(0)-particles) on the control over the (co)polymerisation of $PEGA_{480}$ and $PEGMA_{475}$. It came to light that methacrylic block copolymers could be attained whilst exploiting the pre-disproportionation of [Cu^{I}(PMDETA)Br] prior to initiator and monomer addition in water, with good control over the MWD ($Đ$< 1.38) at near quantitative monomer conversion.[1]

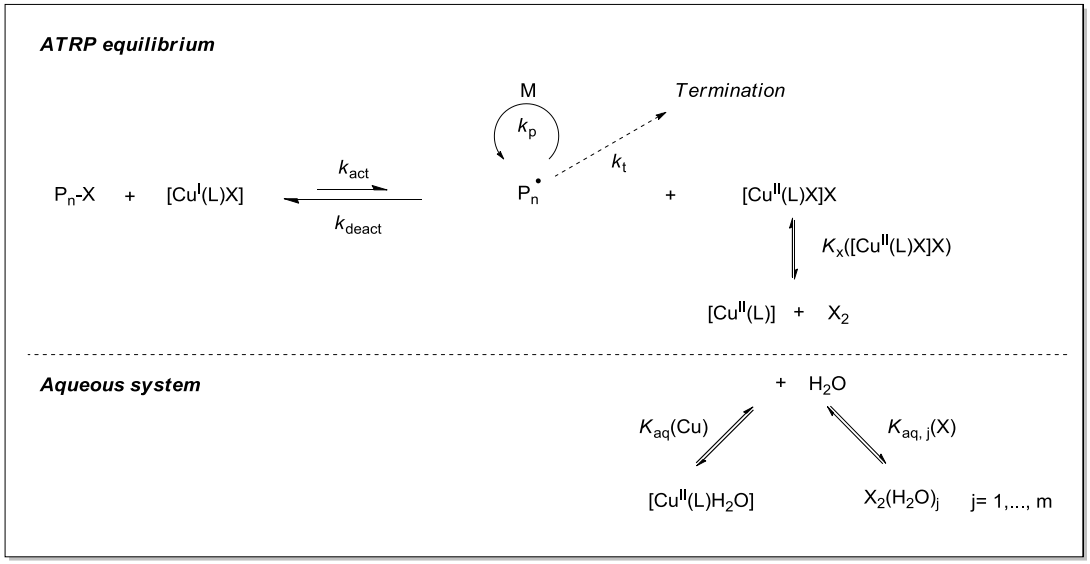
However, the current literature lacks scope with respect to functional methacrylates, which stimulates the investigations reported within this chapter. Hence, the focus will be on (co)polymerising monomers such as 2-dimethylaminoethyl methacrylate (DMAEMA), which finds great interest in targeted delivery of DNA.[2, 3] This monomer could be easily polymerised by standard copper-mediated polymerisation in organic media (utilising Cu(I)X or Cu(0) as the primary copper source),[4-7] though a few reports are present in water.[8] 2-morpholinoethyl methacrylate (MEMA) would be a monomer of interest due the high solubility of the side chain in several solvents, providing access to schizophrenic architectures,[9-11] *i.e.* micelles and vesicles which can re-arrange depending on the dispersing solvent employed. Nevertheless, the design of such "smart" materials could only be possible with good control over both MWD and end group fidelity.

5.1.1 Halogen exchange in copper-mediated polymerisations

One of the advantageous features of copper-mediated RDRP is the ability to tune the catalyst depending on monomer activity. In section 4.1.1, the design of a suitable ligand/monomer pair was presented, highlighting the importance of matching activities to retain good control over the polymerisation and perhaps more importantly, end group(s) fidelity. Numerous investigations have also been conducted to adapt the nature of the halogen in the copper complex catalyst to enhance the control over the polymerisation of monomers with different activities *i.e.* low k_p methacrylates and high k_p acrylates. For instance, it has been reported that utilising a copper chloride initiator/catalyst system would be beneficial to mediate the polymerisation of methacrylates,[12] whilst a copper bromide initiator/catalyst system would be best suited for the polymerisation of acrylates. Indeed, adapting the strength of the C-X bond (where X is an halogen) depending on the initiator/monomer employed has a great influence on experimental molecular weights and MWD,[12, 13] as tuning the lability of the C-X bond influences the (re)-initiation steps.[14] Interestingly, when cross propagation could be an issue, *i.e.* chain extending from a polyacrylate or using an unsuitable initiator, one of the strategies to yield well-defined polymethacrylates is to utilise a halogen exchange process, whereby the initiating alkyl halide would bear a weak C-Br and copper chloride would generate a catalyst.[13, 15-18] Hence, fast initiation, activation[19] and enhanced control over the targeted MW are provided, in addition to narrow MWD.[20]

5.1.2 Influence of external halides in aqueous medium

The introduction of water in copper-mediated RDRP results in faster polymerisations, albeit with poorer control usually achieved for a wide variety of polymers.[21] Indeed, dissociation and/or denaturation of the $[Cu^{II}(L)X]X$ (X an halogen) complex in water[22-27] is suggested to induce undesired terminations events, reciprocated by broader distributions and loss of halide end group fidelity.[28]



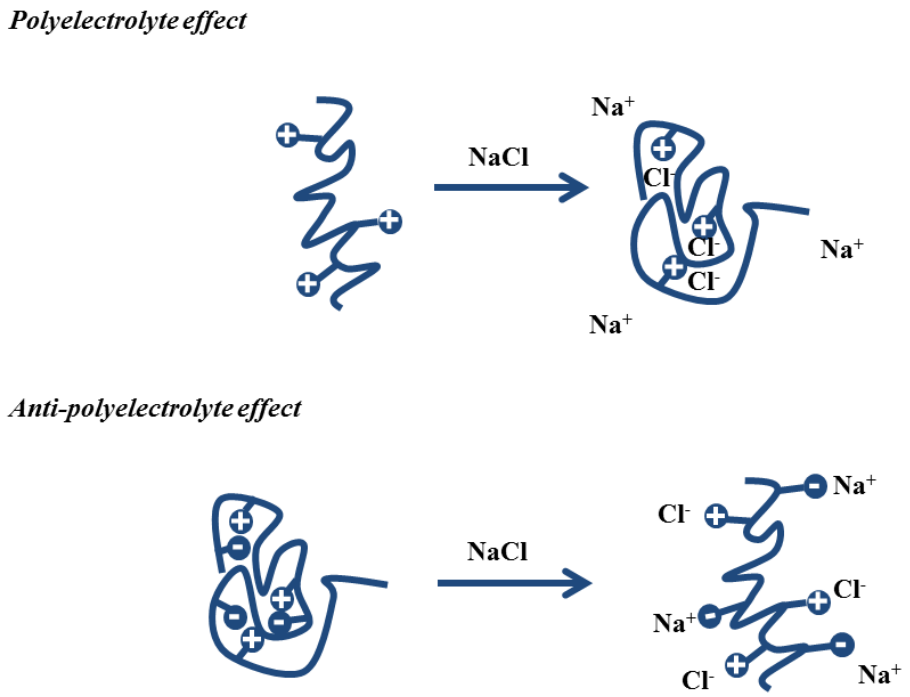
Scheme 5.1. Proposed ATRP equilibrium in aqueous medium, according to Matyjaszewski *et al.*[29] $K_x([Cu^{II}(L)X]X]$ is the rate of association of the $[Cu^{II}(L)]$ complex to halides (or stability constant), $K_{aq}(L)$ is the rate of association of a water molecule to a copper complex and $K_{aq,j}(X)$ is the rate of halide association to j (an integer) water molecule(s).

This can be circumvented by the introduction of larger amounts of deactivating species, or *via* a supplementary halide source. Salts, *e.g.* TEABr, NaBr have been utilised as an external source of halides to diminish the denaturation of $[Cu^{II}(L)X]X$ complexes in water.[29] This resulted in enhanced control over the MWD, as well as the end-group fidelity. As such, poly(meth)acrylates could be generated with low dispersity values ($1.15 < Đ < 1.5$) at various monomer conversions (50-90 %).[30-32] More importantly, the halide chain end could be

retained, as exemplified by chain extensions experiments, yielding well-defined block copolymers.[30] However, the presence of supplementary halide source would also result in slower polymerisation rates, ascribed to the increase in the rate of deactivation.[29]

5.1.3 Motivation: towards zwitterionic copolymers in aqueous medium

Zwitterionic polymers are interesting for a wide range of applications, including anti-fouling, bio-conjugation, water treatment and formulation in personal care products.[33, 34] One of the most attractive features of polyzwitterions is their unique and variable behaviour in aqueous solution, usually different from polyelectrolytes. Typically, a polyelectrolyte occupies a large volume when dispersed in aqueous solution. This volume can be reduced by the introduction of additional salts (*e.g.* NaCl), a phenomenon referred to as the *polyelectrolyte effect*, *i.e*. chain contraction. However, polyzwitterions display the opposite behaviour in aqueous solutions, *i.e.* chain expansion upon addition of external low MW electrolyte, or *anti-polyelectrolyte effect* (scheme 5.2).[35]



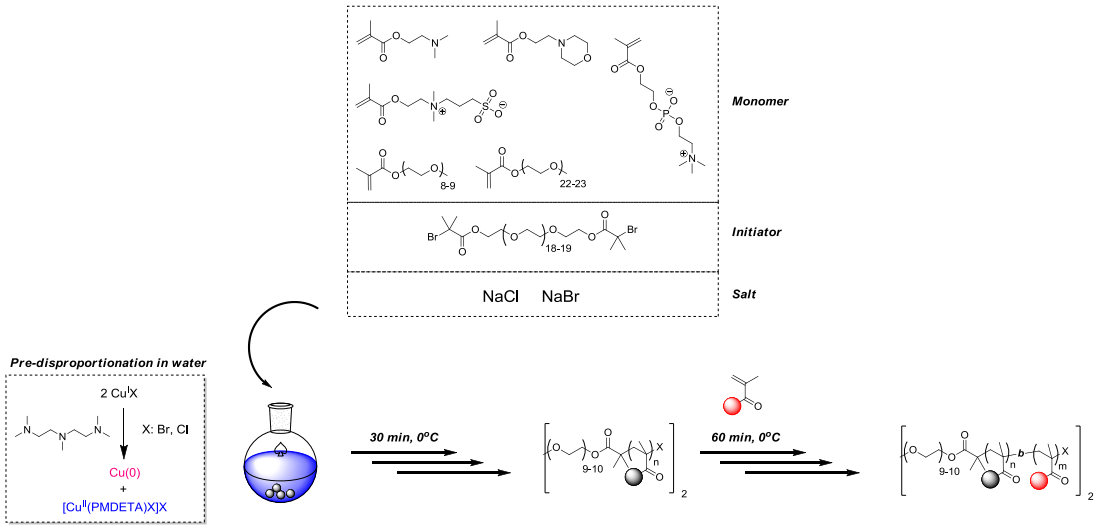
Scheme 5.2. Polyelectrolyte and anti-polyelectrolyte effects. According to Lowe and McCormick.[35]

The interesting insolubility of several polyzwitterions (*e.g.* polymeric betaines) in pure water can thus be altered by the introduction of salts or co-solvents,[36-39] allowing the formation of sophisticated architectures. The limited solubility of polyzwitterions in organic media, usually restricted to highly *H*-bond donating solvents (*e.g.* alcohols, fluorinated solvents) can vary depending on the nature of the zwitterion, as phosphobetaines typically show greater solvability in both organic and aqueous media than sulfobetaines.

The synthesis of zwitterionic polymers has received extensive attention by RDRP techniques, to control both MWD and architectures. Two different approaches are usually conducted, the first being the synthesis of an uncharged polymer (*e.g.* PDMAEMA) which will become zwitterionic upon post-polymerisation modifications.[33, 40, 41] The second route is the direct polymerisation of a zwitterionic monomer, though several solubility issues can

arise, as previously described. RAFT has been the polymerisation tool of choice to yield well-defined polyzwitterions, due the extensive tolerance to various solvent mixtures.[42-44] However, TMM-RDRP has proved to be a robust process to (co)polymerise sulfobetaines, phosphobetaines and carboxybetaines.[45, 46] Interestingly, Cu(0)-mediated RDRP has not been extensively employed to yield functional charged copolymers, especially in aqueous media.[7, 47]

In this chapter, the pre-disproportionation of [Cu^{I}(PMDETA)X] (where X is an halogen) is exploited to assess the (co)polymerisation of water soluble methacrylic monomers, namely poly(ethylene glycol) methyl ether methacrylate (av. M_n= 475 g.mol^{-1}, $PEGMA_{475}$; av. M_n= 1100 g.mol^{-1}, $PEGMA_{1100}$), DMAEMA, MEMA, [2-(methacryloyloxy)ethyl]dimethyl-(3-sulfopropyl)ammonium hydroxide (SBMA) and 2-methacryloyloxyethyl phosphorylcholine (MPC) in aqueous medium (scheme 5.3). The effect of the nature of the copper source (*e.g.* CuBr, CuCl), in addition of the influence of the addition of external halide salt (*e.g.* NaBr, NaCl) are investigated to yield well-defined copolymers with moderate dispersity values (*Đ*< 1.6) and high chain end(s) fidelity, even at near quantitative monomer conversion.



Scheme 5.3. Cu(0)-mediated polymerisation of functional methacrylates in water in the presence of salt.

5.2 Results and discussions

5.2.1 Enhancing the control over the polymerisation of PEGMA *via* an external halide source

The bi-functional initiator, poly(ethylene glycol) bis(2-bromoisobutyrate) (see sections 4.2.1, 3.2.1.1 and 3.4.4.1) has been selected as the initiating species, for comparison purposes with investigations in chapter 4. A first strategy to improve the control over the polymerisation of $PEGMA_{475}$ would be to increase the [ligand]:[CuBr] ratio, as previously reported in the case of acrylates and acrylamides.[48] Consequently, the synthesis of $PPEGMA_{475}$ was assessed by Cu(0)-mediated polymerisation in water ([I]:[M]:[PMDETA]:[CuBr]= 1:DP_n:0.6:1.1, 20% *v/v* monomer in water), as opposed to ([I]:[M]:[PMDETA]:[CuBr]= 1:DP_n:0.6:0.8, 20% *v/v* monomer in water, see section 4.2.2). Good control over the polymerisation can be retained, exemplified by the quantitative monomer conversion and narrow distributions obtained in 30 minutes ($Đ$< 1.38, figure 5.1), though a significant deviation between theoretical and measured experimental molecular weight is noticeable (M_n^{th} = 10725 g.mol^{-1}; M_n^{exp} = 22600 g.mol^{-1}), which could be due to a limited initiator efficiency.

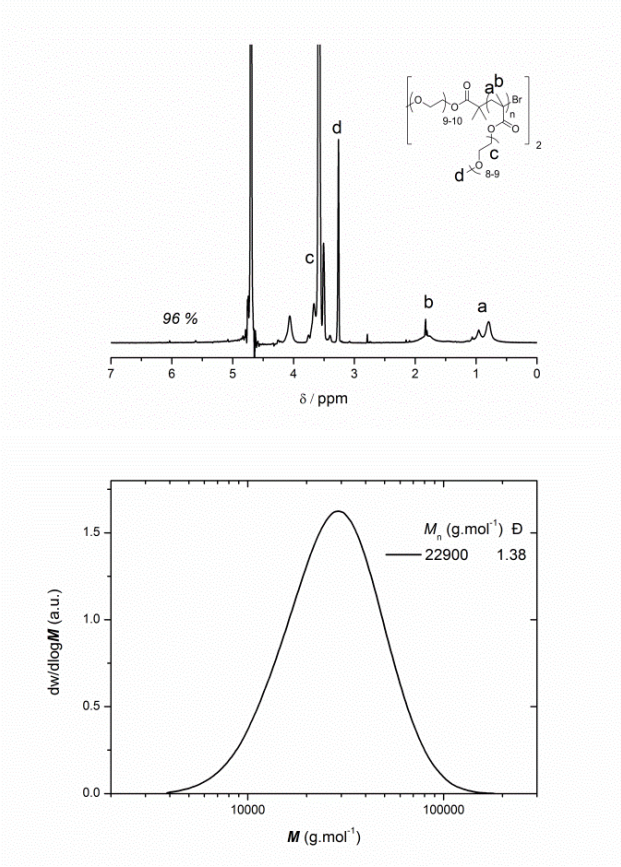


Figure 5.1. Monitoring the polymerisation of $PEGMA_{475}$ in water ([I]:[M]:[PMDETA]:[CuBr]= 1:20:0.6:1.1, 20% *v/v* monomer in water) at 0°C by ^1H NMR (D_2O, 400 MHz, left) and SEC (DMF eluent, right).

Although changing the [ligand]:[CuBr] ratio from 0.6:0.8 to 0.6:1.1 has no particular effect on low DP_n, it would be of interest to test the effect on higher targeted MW. Thus, similar reaction conditions were employed to polymerise $PEGMA_{475}$ with higher DP_n ([I]:[M]:[PMDETA]:[CuBr]= 1:40:0.6:1.1, 20% *v/v* monomer in water). Unfortunately, a loss of control arises, reciprocated by tailing at low molecular weight on the SEC traces (*Đ*~ 1.47, figure 5.2).

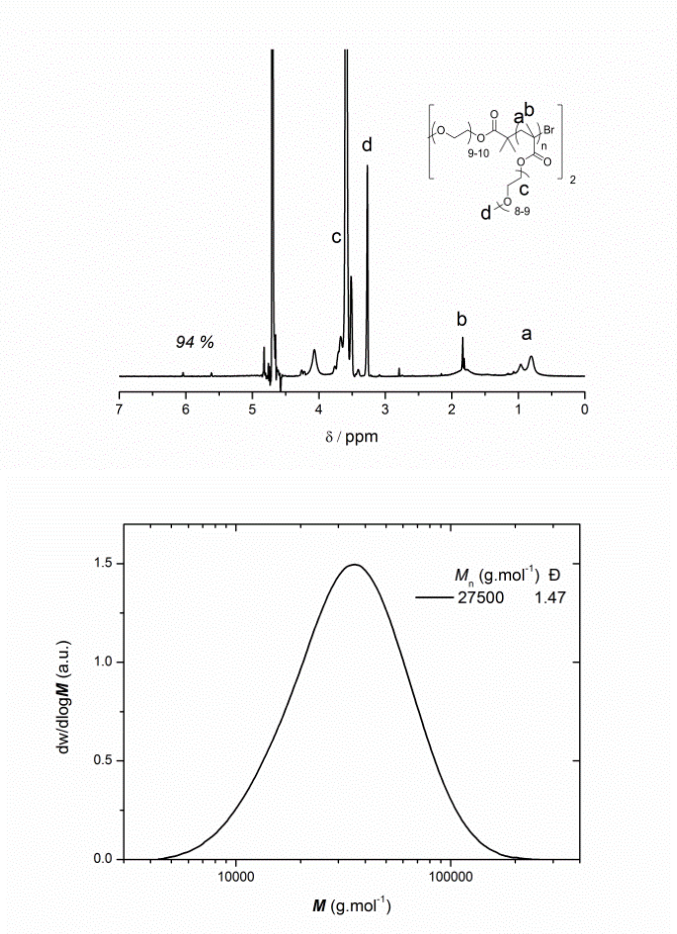


Figure 5.2. Monitoring the polymerisation of $PEGMA_{475}$ in water ([I]:[M]:[PMDETA]:[CuBr]= 1:40:0.6:1.1, 20% *v/v* monomer in water) at 0°C by ^{1}H NMR (D_2O, 400 MHz, left) and SEC (DMF eluent, right).

The poor control could be due to the weak nature of the C-Br bond, which in addition to the use of low k_p monomers (*e.g.* methacrylates), introduces more termination events, as commonly seen in classical ATRP conditions.[49] Consequently, it was decided to investigate the nature of the carbon-halogen bond, *via* halogen exchange using a CuCl derived catalyst. The extent of disproportionation was tested in the presence of PMDETA, to ensure a quantitative formation of Cu(0) particles and $[Cu^{II}(PMDETA)Cl]Cl$ prior to initiator and monomer addition. Pleasingly, changing the nature of the copper salt does not affect the quantitative yield of disproportionation, as confirmed by UV-Vis spectroscopy (figure 5.3).

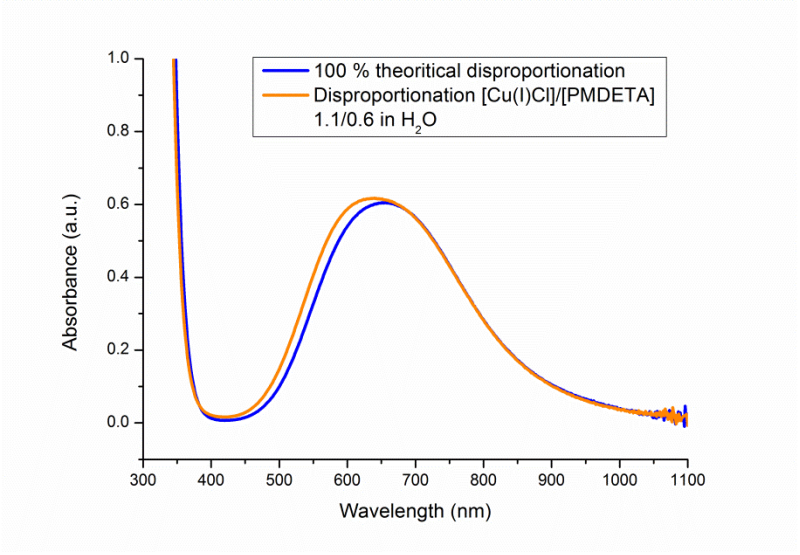


Figure 5.3. Monitoring the disproportionation of Cu(I)Cl in the presence of PMDETA in water.

Subsequently, $PEGMA_{475}$ was polymerised under comparable reaction conditions ([I]:[M]:[PMDETA]:[CuCl]= 1:20:0.6:1.1, 20% *v/v* monomer in water), albeit a loss of control was unexpectedly observed (figure 5.4), with a significant deviation of MWD observed by SEC.

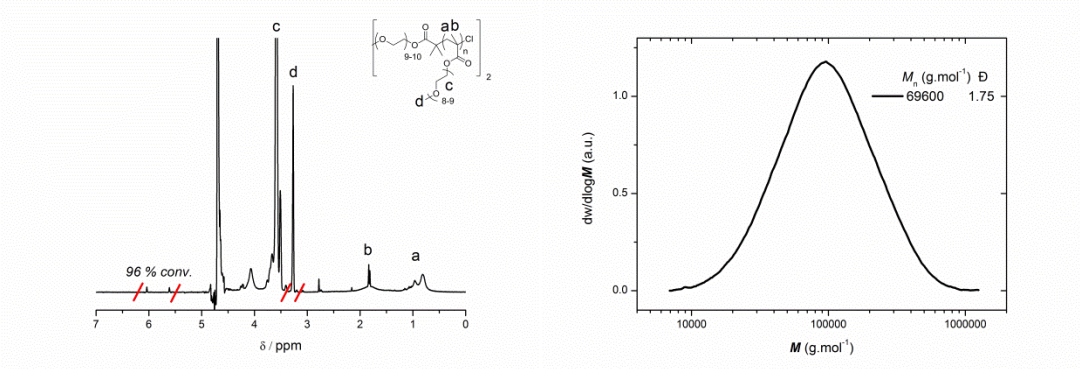


Figure 5.4. Monitoring the polymerisation of $PEGMA_{475}$ in water ([I]:[M]:[PMDETA]:[CuCl]= 1:20:0.6:1.1, 20% *v/v* monomer in water) at 0°C by ^{1}H NMR (D_2O, 400 MHz, left) and SEC (DMF eluent, right).

The large dispersity values indicate that termination events remain prevalent in the halogen exchange system, which is attributable to inefficient deactivation due to dissociation of the deactivating complex ([Cu^{II}(PMDETA)Cl]Cl).

5.2.2 Addition of external halide salt

It has been suggested that the addition of external halide salts can improve the control of polymerisation by reducing the extent of deactivator complex dissociation, as previously reported.[30] Hence the polymerisation of $PEGMA_{475}$ ([I]:[M]:[PMDETA]:[CuBr]= 1:20:0.6:1.1, 20% *v/v* monomer in water) was first conducted with an external halide source NaBr (1M), utilising the pre-disproportionation of [Cu^{I}(PMDETA)Br]Br prior to initiator and monomer addition, as moderate control could be attained with a bromide containing initiator/catalyst system. Pleasingly, the presence of the salt directly enhanced the control over the polymerisation, as evidenced by narrow MWD in SEC ($Đ$< 1.17, figure 5.5). Although the quantity of salt present in the reaction medium is greater than in previous reports, the presence of the salt did not lowered the speed of the polymerisation (as opposed to previous investigations),[30, 49, 50] as near quantitative monomer conversions could still be attained within 30 minutes (table 5.1 entry 3).

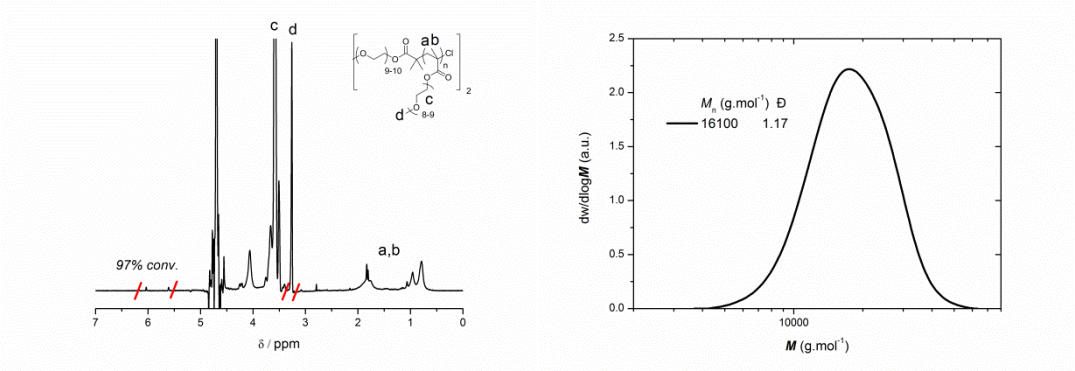


Figure 5.5. Monitoring the polymerisation of $PEGMA_{475}$ in water ([I]:[M]:[PMDETA]:[CuBr]= 1:20:0.6:1.1, 20% *v/v* monomer in water) with NaBr (1M) at 0°C by ^{1}H NMR (D_2O, 400 MHz, left) and SEC (DMF eluent, right).

Although a significant reduction of the dispersity values is observed, the asymmetrical shape of the SEC trace does not suggest a satisfactory control over the polymerisation. Consequently, it was decided to test the influence of the nature of the halide salt (*e.g.* NaCl, NaBr), as well as the nature of the initiator/catalyst system (*e.g.* CuCl or CuBr based complex) on the control over the polymerisation of $PEGMA_{475}$. The polymerisation of $PEGMA_{475}$ was conducted under similar reaction conditions ([I]:[M]:[PMDETA]:[CuBr]= 1:20:0.6:1.1, 20% *v/v* monomer in water), albeit the salt was changed from NaBr to NaCl (1M). Although the monomer conversion remains unaffected (97% by ^{1}H NMR, table 5.1 entry 4), an asymmetrical SEC trace is observed with higher dispersity values (*Đ*< 1.28, figure 5.6 left), thus suggesting that adapting the nature of the halide salt is not sufficient to sustain good control over the polymerisation when utilising a bromide based initiator/catalyst system. Similar results are obtained when the pre-disproportionation of [Cu^I(PMDETA)Cl] is exploited prior to initiator and $PEGMA_{475}$ addition ([I]:[M]:[PMDETA]:[CuCl]= 1:20:0.6:1.1, 20% *v/v* monomer in water), in the presence of NaBr (1M), as evidenced by asymmetrical SEC traces with low dispersity values (*Đ*< 1.22, figure 5.6 right).

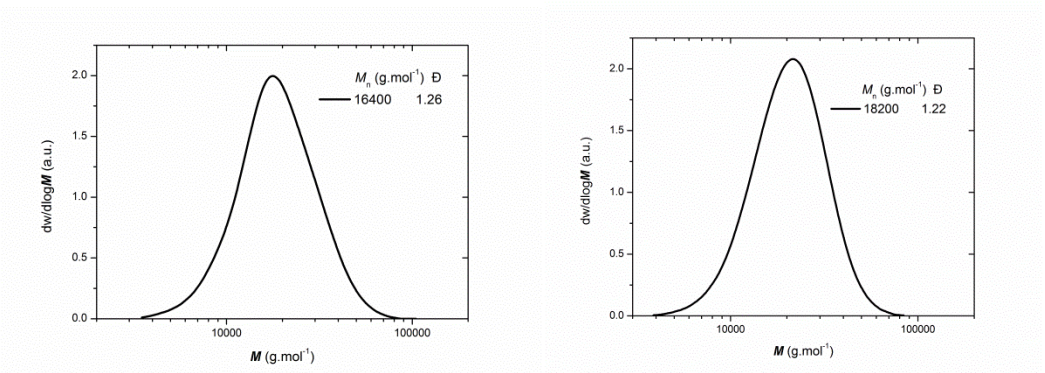


Figure 5.6. Monitoring the polymerisation of $PEGMA_{475}$ in water ([I]:[M]:[PMDETA]:[CuBr]= 1:20:0.6:1.1, 20% *v/v* monomer in water) with NaCl (1M) at 0°C (left) and $PEGMA_{475}$ in water ([I]:[M]:[PMDETA]:[CuCl]= 1:20:0.6:1.1, 20% *v/v* monomer in water) with NaBr (1M) by SEC (DMF eluent, right).

The unexpected shape of the SEC traces, in addition to a slight broadening of the MWD could be attributed to unsatisfactory halogen exchange throughout polymerisation when utilising mixed halides as the initiator/catalyst system and salt (see section 5.1.1.).[15, 20]

Consequently, a chloride salt (NaCl, 1M) was added to the reaction medium ([I]:[PEGMA$_{475}$]:[PMDETA]:[CuCl]= 1:20:0.6:1.1, 20% *v/v* monomer in water), directly enhancing the control over the polymerisation, as evidenced by symmetrical SEC traces with narrow MWD (*Đ*< 1.20, table 1 entry 7) even at high monomer conversions (> 99 % by ^{1}H NMR). More importantly, this level of control could be expanded to a variety of targeted DP_ns for PPEGMA$_{475}$ (DP_n=10-160, table 5.1), whilst the dispersity values would remain low for DP_n< 80 (*Đ*< 1.3, figure 5.7) and the monomer conversion quantitative within 30 minutes. It thus comes to light that utilising a chloride containing deactivating complex as well as a chloride based salt could achieve better control for the Cu(0)-mediated polymerisation of PEGMA$_{475}$ in water.

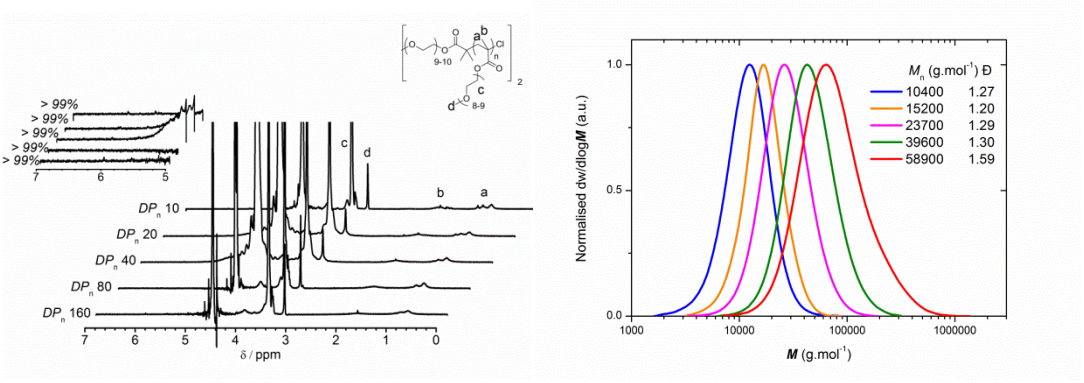


Figure 5.7. Monitoring the polymerisation of various DP_n of PEGMA$_{475}$ in water ([I]:[M]:[PMDETA]:[CuCl]= 1:DP_n:x:y, 20% *v/v* monomer in water) (x=0.6-0.8), (y= 1.1-1.6) under the presence of NaCl at 0°C by ^{1}H NMR (D_2O, 250 MHz, left) and SEC (DMF eluent, right).

For DP_n= 80-160, the concentration of halide salt had to be increased from 1M to 3M to retain symmetrical SEC traces with narrow MWD (*Đ*< 1.3); though limitations are evident for higher targeted DP_n (DP_n> 160), as the loss of control is revealed by a broadening of the

MWD (*Đ*~ 1.59). Pleasingly, when $PEGMA_{1100}$ is employed as a monomer to target comparable molecular weights (M_n> 50000 $g.mol^{-1}$), narrow MWD are observed at quantitative monomer conversion (*Đ*< 1.39, figure 5.8). However, longer reaction times are necessary (2 hours as opposed to 30 minutes).

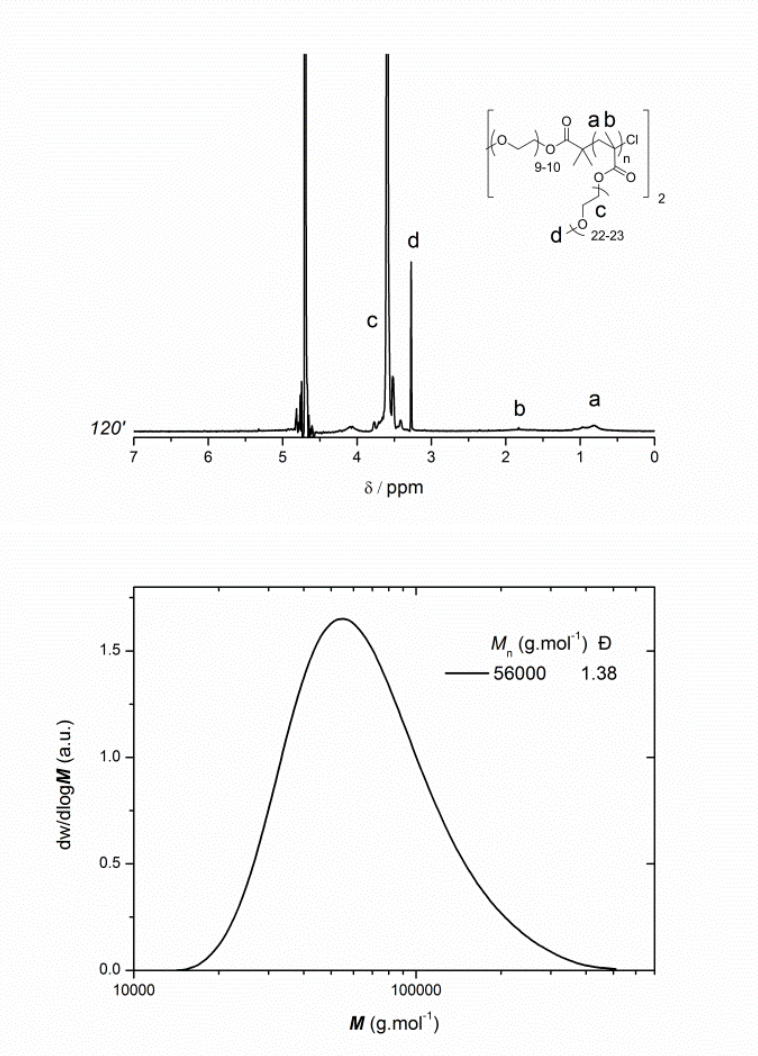


Figure 5.8. Monitoring the polymerisation of $PEGMA_{1100}$ in water ([I]:[M]:[PMDETA]:[CuCl]= 1:60:0.6:1.1, 20% *v/v* monomer in water) under the presence of salt (NaCl, 3M) at 0°C by ^1H NMR (D_2O, 400 MHz, left) and SEC (DMF eluent, right).

The high molecular weight attained in addition to the good control over the MWD allows the polymer to be a candidate for bio-conjugation purposes.[51, 52]

Table 5.1. Influence of salt content on the polymerisation of $PEGMA_{475}$ with various DP_n.

Entry	$PEGMA_{475}$ DP_n	[I]:[PMDETA]:[CuX] X: Br, Cl	Conc. Salt	Conv. (%)[a]	M_n ($g.mol^{-1}$)[b]	M_w/M_n [b]
1	10	1: 0.6: 1.1; CuCl	1M, NaCl	> 99	10400	1.27
2	20	1: 0.6: 1.1; CuBr	n/a	96	22900	1.38
3	20	1: 0.6: 1.1; CuBr	1M, NaBr	97	16100	1.17
4	20	1: 0.6: 1.1; CuBr	1M, NaCl	97	16400	1.26
5	20	1: 0.6: 1.1; CuCl	n/a	96	69600	1.75
6	20	1: 0.6: 1.1; CuCl	1M, NaBr	99	18200	1.22
7	20	1: 0.6: 1.1; CuCl	1M; NaCl	> 99	15200	1.20
8	40	1: 0.6: 1.1; CuBr	n/a	94	27500	1.47
9	40	1: 0.6: 1.1; CuCl	1M, NaCl	> 99	23700	1.29
10	80	1: 0.8: 1.6; CuCl	3M, NaCl	> 99	39600	1.30
11	160	1: 0.8: 1.6; CuCl	3M, NaCl	> 99	58900	1.59

[a] Obtained by ^1H NMR (D_2O, 250 MHz); [b] extracted from SEC analysis (DMF eluent, PMMA standards).

The previous experiments do not give a clear insight into the α,ω-Cl chain end fidelity, which is necessary for the synthesis of functional block copolymers. Consequently, *in situ* addition of a second aliquot of monomer was performed to indirectly assess the end group fidelity. $PPEGMA_{475}$ was tested as an exemplar macroinitiator, with $PEGMA_{475}$ (targeted DP_n= 40) added upon high conversion of the first block (97 % by ^{1}H NMR). The high retention of the halogen chain ends is confirmed by the shift in SEC towards higher MW, with quantitative consumption of the second monomer aliquot, whilst the MWD remained moderate ($Đ$< 1.41, figure 5.9). A slight broadening of the MWD can be observed, as the concentration of NaCl was kept the same for both targeted DP_ns, though the SEC traces remain symmetrical.

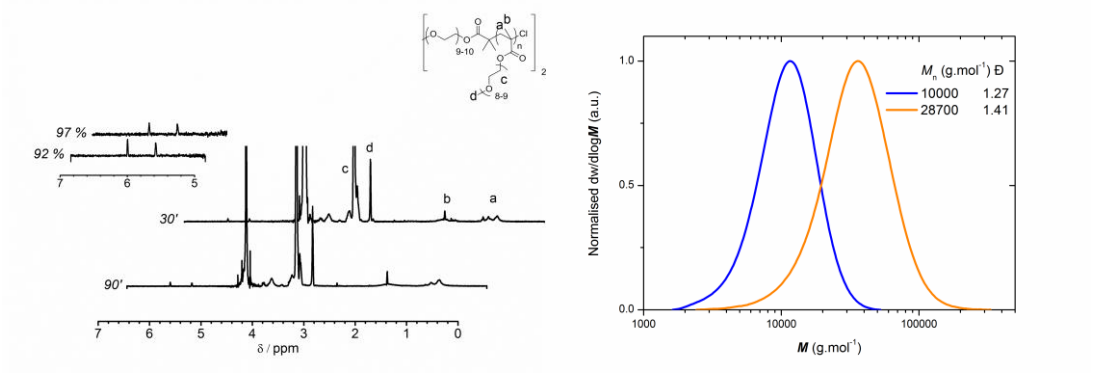


Figure 5.9. Monitoring the chain extension of $PPEGMA_{475}$ with $PEGMA_{475}$ in water ([I]:[M]:[PMDETA]:[CuCl]= 1:40:0.6:1.1, 20% *v/v* monomer in water) under the presence of NaCl (1M) at 0°C by ^{1}H NMR (D_2O, 250 MHz, left) and SEC (DMF eluent, right).

5.2.3 Expanding the scope of hydrophilic monomers

The scope of polymerisable methacrylates was further expanded, with MEMA utilised as one of the building block of a pentablock copolymer. It should be emphasised that the presence of a supplementary halide salt is necessary to retain the control over the formation of a well-defined copolymer. Indeed, it is clear that the halogen chain ends, as well as the narrow MWD cannot be retained for the polymerisation of $PMEMA_{10}$-*b*-PEG-*b*-$PMEMA_{10}$

in the absence of salt, reciprocated by broad MWD in SEC ($Đ$~ 3.1, figure 5.10) and poor agreement between theoretical and experimental molecular weights (M_n^{th} = 5210 g.mol^{-1}; M_n^{exp} = 8100 g.mol^{-1}).

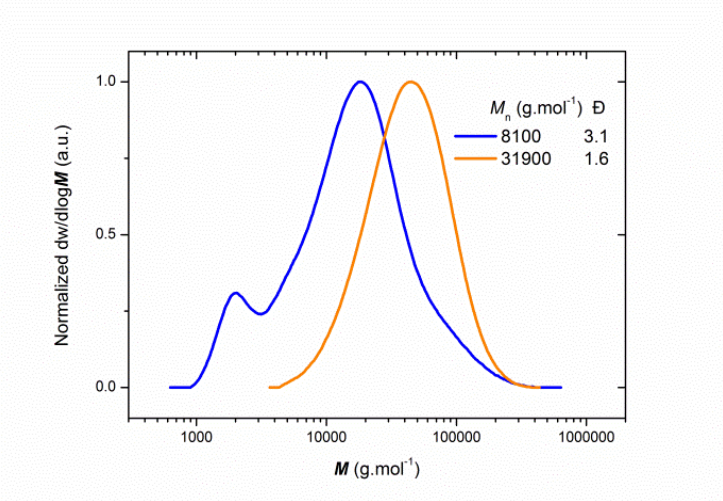


Figure 5.10. Monitoring the chain extension of PMEMA with PEGMA$_{475}$ in water ([I]:[M]:[PMDETA]:[CuCl]= 1:20:0.6:1.1, 20% *v/v* monomer in water) without the presence of NaCl (1M) at 0°C by SEC (DMF eluent, bottom).

However, the addition of NaCl (up to 1M concentration) allows good retention of the α,ω-Cl end groups throughout polymerisation, even at high monomer conversion. This is confirmed upon sequential addition of an aliquot of deoxygenated PEGMA$_{475}$ solution, inducing a complete shift towards higher MW in SEC, whilst the MWD remain narrow ($Đ$< 1.28, figure 5.11). The reduction of the MWD could be induced by a better solubility of the copolymer in the SEC eluent.

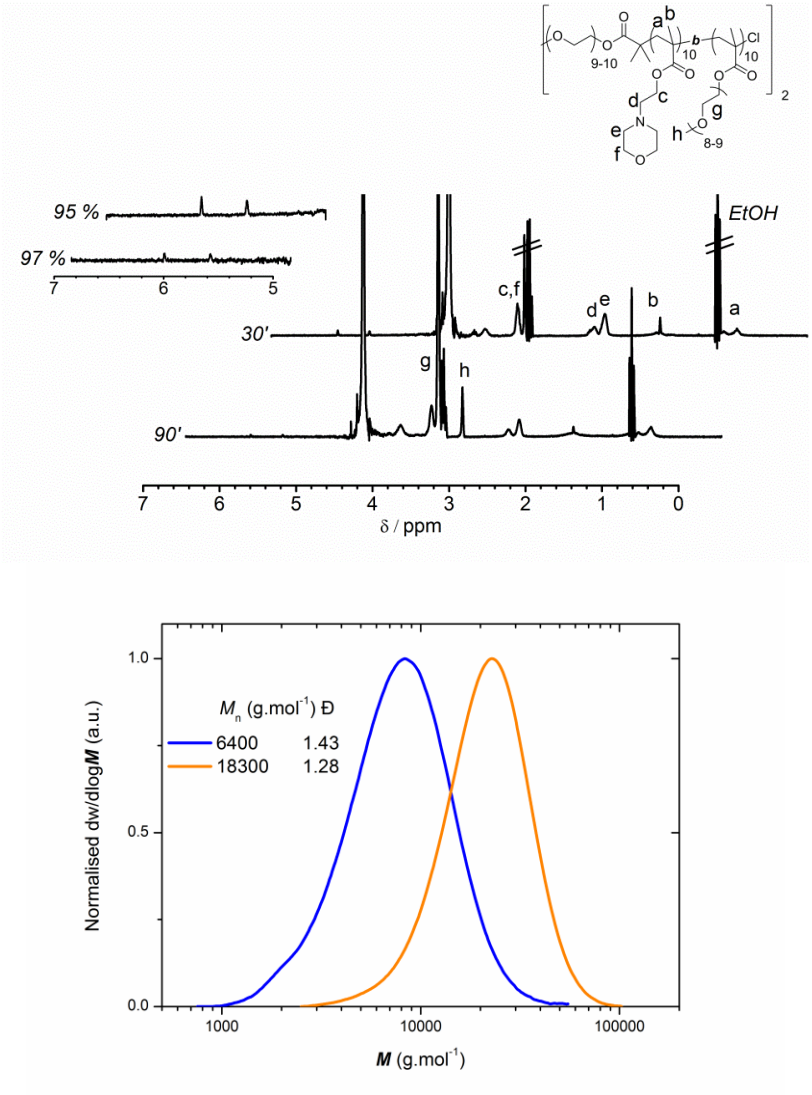


Figure 5.11. Monitoring the chain extension of PMEMA with $PEGMA_{475}$ in water ([I]:[M]:[PMDETA]:[CuCl]= 1:20:0.6:1.1, 20% *v/v* monomer in water) with the presence of NaCl (1M) at 0°C by ^{1}H NMR (D_2O, 250 MHz, top) and SEC (DMF eluent, bottom).

The importance over the presence of a halide salt is further exploited for the copolymerisation of DMAEMA, SBMA and MPC with $PEGMA_{475}$ respectively. In the case of DMAEMA, a second monomer aliquot is added at 75% conversion (by ^{1}H NMR in 30 minutes figure 5.12) of the first block to avoid extensive hydrolysis of the unreacted monomer, hence affecting the integrity of the block copolymer.[53] Nevertheless, good

retention of the halide chain ends is observed, as evidenced by a shift towards higher MWD in SEC, accompanied by a reduction of the dispersity value (*Đ*< 1.37).

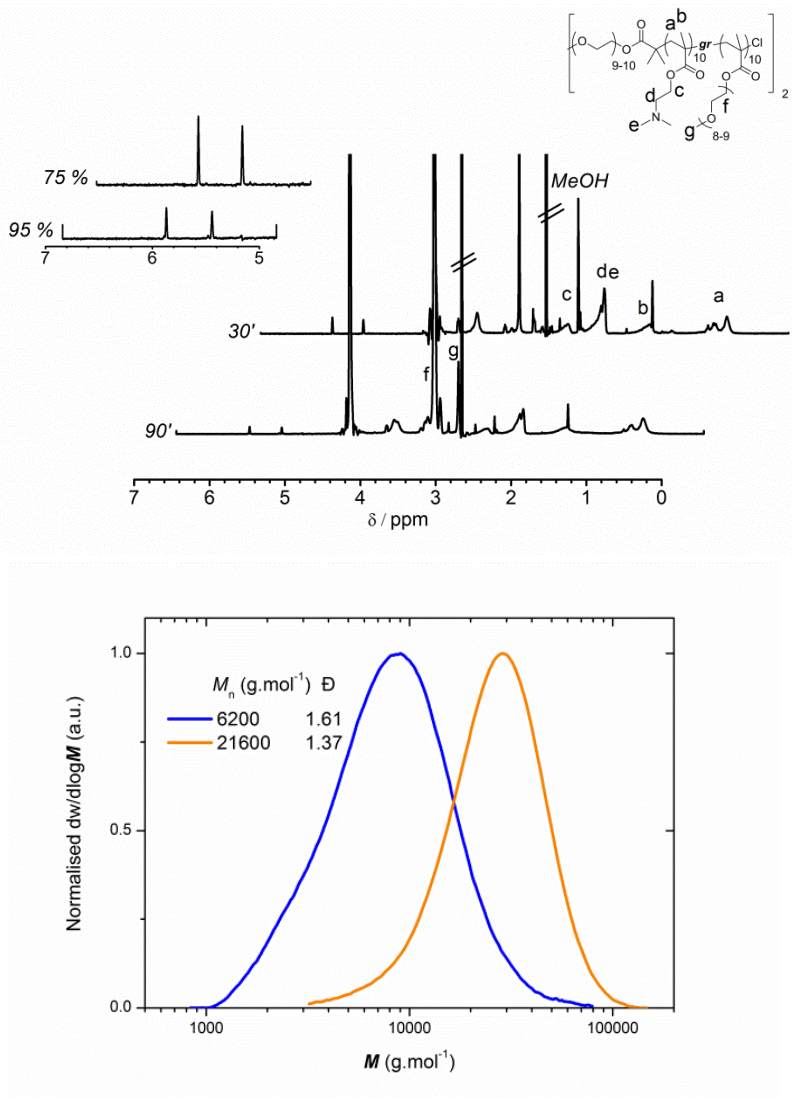


Figure 5.12. Monitoring the chain extension of PDAEMA with $PEGMA_{475}$ in water ([I]:[M]:[PMDETA]:[CuCl]= 1:20:0.6:1.1, 20% *v/v* monomer in water) under the presence of salt (NaCl, 1M) at 0°C by ^{1}H NMR (D_2O, 400 MHz, left) and SEC (DMF eluent, right).

5.2.4 Polymerisation of zwitterionic monomers in aqueous medium

The polymerisation of zwitterionic monomers has proved to be problematic, mainly due to the limited solubility in organic solvents (and mixtures) in addition to spontaneous polymerisation in water.[45] A few reports deal with the polymerisation of SBMA and MPC under copper-mediated conditions in aqueous medium, it was therefore interesting to test the versatility of Cu(0)-mediated RDRP in water with zwitterionic monomers.

Pleasingly, previously reported issues on zwitterions polymerisation are not present upon the addition of salt and co-solvent, allowing good control over the polymerisation of SBMA under similar reaction conditions ([I]:[M]:[PMDETA]:[CuCl]= 1:20:0.6:1.1, 20% *v/v* monomer in EtOH/H_2O 25% *v/v*). The presence of a co-solvent allows better solubility of the zwitterionic monomer and polymer, which allows good polymerisation with high conversions (> 98 % by ^{1}H NMR) and moderate MWD ($Đ$< 1.43, figure 5.14).

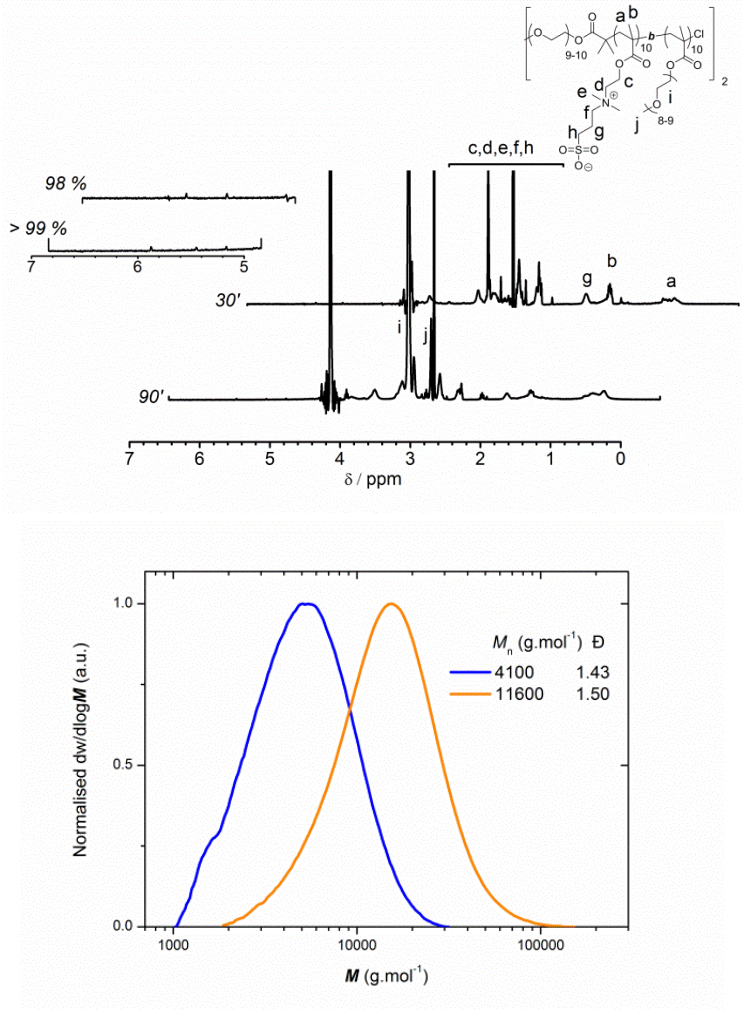


Figure 5.14. Monitoring the chain extension of PSBMA with $PEGMA_{475}$ in water ([I]:[M]:[PMDETA]:[CuCl]= 1:20:0.6:1.1, 20% *v/v* monomer in water) under the presence of salt (NaCl, 1M) at 0°C by ^{1}H NMR (D_2O, 400 MHz) and SEC (0.1M $NaNO_3$ eluent).

More importantly, a sequential addition of a deoxygenated aliquot of $PEGMA_{475}$ revealed a complete shift towards higher MWD in SEC, whilst retaining moderate MWD ($Đ$< 1.50). This clearly indicates a high halide end group fidelity when SBMA is polymerised under Cu(0)-mediated RDRP in aqueous medium.

Similarly, the polymerisation of a second zwitterion, MPC, was tested under similar reaction conditions, though the co-solvent had to be adapted ([I]:[M]:[PMDETA]:[CuCl]= 1:20:0.6:1.1, 20% *v/v* monomer in IPA/H_2O 25% *v/v*), according to previous reports.

Pleasingly, a comparable level of control was attained whilst polymerising MPC in aqueous medium, reciprocated by near quantitative monomer conversions (> 96 % by ^{1}H NMR) and moderate dispersity values ($Đ$< 1.7, figure 5.15).

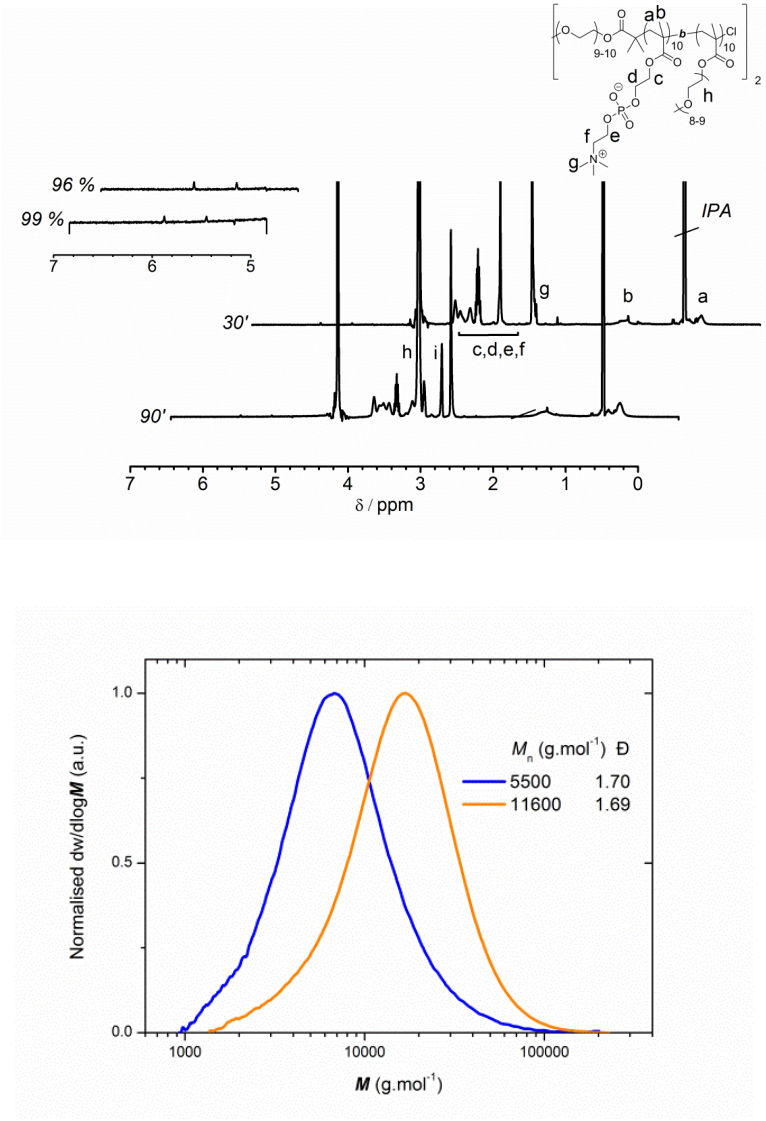


Figure 5.15. Monitoring the chain extension of PMPC with $PEGMA_{475}$ in water ([I]:[M]:[PMDETA]:[CuCl]= 1:10:0.6:1.1, 20% *v/v* monomer in water) under the presence of NaCl (1M) at 0°C by SEC (0.1M $NaNO_3$ eluent).

The high retention of the halide chain ends allows good chain extension from zwitterionic macromonomer moieties, despite a moderate control over the MWD. This further expands the scope of monomer moieties accessible by Cu(0)-mediated polymerisation in aqueous

media. Indeed, to the best of our knowledge, this is the first report of an homogenous block copolymerisation of SBMA and MPC in aqueous media whilst utilising Cu(0) as the primary copper source.

5.3 Conclusions

In this chapter, the copolymerisation of water soluble and zwitterionic methacrylates was presented. The versatility of the pre-disproportionation of [Cu^{I}(PMDETA)Cl] prior to initiator and monomer addition was further expanded by addition of an halide salt, providing access to high molecular weight homopolymers and block copolymers with near quantitative conversion for each block and narrow MWD ($Đ$~ 1.3). Furthermore, the presence of the halide salt proved to be of upmost importance for the successful Cu(0)-mediated block copolymerisation of zwitterionic moieties in aqueous solution, whilst retaining good control ($Đ$< 1.3).

5.4 Experimental

5.4.1 Materials

Previously employed materials can be found in sections 2.4.1, 3.4.1 and 4.4.1.

Poly(ethylene glycol) methyl ether methacrylate ($PEGMA_{1100}$, 98%, Sigma-Aldrich, av. M_n = 1100 $g.mol^{-1}$), 2-morpholinoethyl methacrylate (MEMA, 95%, Sigma-Aldrich), copper(II) chloride ($Cu^{II}Cl_2$, 97%, Sigma-Aldrich), 1,3-Propanesultone (97%, Fisher Scientific), 2-isopropanol (IPA, reagent grade, VWR), methanol (MeOH, reagent grade, VWR), ethanol (EtOH, reagent grade, Sigma-Aldrich) and water (HPLC grade, VWR) were used as received without further purification. 2-dimethylaminoethyl methacrylate (DMAEMA, 98%,

Sigma-Aldrich) was passed twice through basic alumina, deoxygenated and stored under nitrogen at 4°C. 2-Methacryloyloxyethyl phosphorylcholine (MPC) was kindly donated by Biocompatibles UK.

Copper(I) chloride (CuCl, 97%, Sigma-Aldrich) was purified by the method of Keller and Wycoff,[54] by washing five times with acetic acid glacial, rinsed with ethanol and diethyl ether and dried over reduced pressure overnight.

5.4.2 Characterisation

^{1}H, ^{13}C NMR spectra were recorded on Bruker ACF-250, DPX-300, DPX-400 and DPX-500 spectrometers using deuterated solvents obtained from Sigma-Aldrich.

DMF SEC traces were obtained on a PL-GPC50 system using a DMF (+ 0.1M LiBr) eluent at 50°C, equipped with refractive index and UV detectors, 2 × PLgel 5 mm mixed D columns (300 × 7.5 mm), 1 × PLgel 5 mm guard column (50 × 7.5 mm) and autosampler. Narrow linear poly(methyl methacrylate) standards in range of 200 to 1.0×10^{6} g·mol^{-1} were used to calibrate the system. All samples were passed through 0.45 µm PTFE filter before analysis.

Aqueous SEC traces were obtained on a PL-GPC50 system using a buffer (0.1M $NaNO_3$, pH 7.4) eluent at 30°C, equipped with a refractive index detector, two PLaquagel-OH 30 (300 × 7.5 mm), PLaquagel guard (50 × 7.5 mm) and autosampler. Narrow linear poly(ethylene oxide) standards in range of 200 to 1.3×10^{5} g.mol^{-1} were used to calibrate the system. All samples were passed through 0.22 µm PTFE filter before analysis.

5.4.3 Synthesis of initiators

See section 3.4.3

5.4.4 Synthesis of monomers

5.4.4.1 Synthesis of [2-(methacryloyloxy)ethyl]dimethyl-(3-sulfopropyl)ammonium hydroxide

To a 250 mL RB flask was added 2-dimethylaminoethyl methacrylate (6.4 mL, 38.1 mmol) and diethyl ether (40 mL). 1,3-Propanesultone (4.6 g, 1 eq) was added dropwise to the solution and the mixture was left to stir overnight under nitrogen at ambient temperature. The resulting white precipitate was filtered, washed with diethyl ether and dried overnight over reduced pressure. A white solid was obtained (6.25 g, 58 % yield).

^{1}H NMR (D_2O, 500 MHz): 6.11-5.73 (2H, d, C***H***$_2$=C(CH_3)), 4.55 (2H, m, O-CH_2-C***H***$_2$), 3.74 (2H, m, O-C***H***$_2$-CH_2), 3.53 (2H, m, $N^+(CH_2)_2$-C***H***$_2$-), 3.17 (6H, s, N^+(C***H***$_2$)$_2$), 2.93 (2H, m, -C***H***$_2$-SO_3^-), 2.22 (2H, m, CH_2-C***H***$_2$-CH_2-SO_3^-) and 1.89 (s, 3H, CH_2=C(C***H***$_3$)). ^{13}C NMR (D_2O, 125 MHz): 168 (***C***=O), 135 (***C***(CH_3)=CH_2), 127 (***C***H_2=C(CH_3)), 63 (N(CH_3)$_2$***C***H_2-), 62 (O-CH_2-***C***H_2), 58 (O-***C***H_2-CH_2), 51 (N(***C***H_3)$_2$), 47 (***C***H_2-SO_3^-), 18 (CH_2-***C***H_2-CH_2-SO_3^-) and 17 ((***C***H_3)C=CH_2). HRMS (ESI, m/z, Da): [M+Na^+] 302.2 (*302.1 Th*).

5.4.5 Monitoring the disproportionation of [Cu^I(PMDETA)Cl] in water

The theoretical disproportionation curve was obtained by preparing a solution of $Cu^{II}Cl_2$ (10.8 mg, 4.8 10^{-5} mol) in the presence of PMDETA (11.5 µL) in H_2O. Disproportionation was performed by adding Cu(I)Cl (14 mg, 9.7 10^{-5} mol) to a solution of solvent (2 mL) and PMDETA (11.5 µL, 0.75 eq.), which was left to stir and deoxygenate with nitrogen for 15

minutes. Subsequently, the solution was filtered under nitrogen to remove any Cu(0) particles. UV-Vis spectrum was recorded using a quartz cuvette (path length 1 cm).

5.4.6 Disproportionation of [Cu^{I}(PMDETA)Br] to catalyse the polymerisation of $PEGMA_{475}$ in water

Please refer to section 4.4.5

5.4.7 Disproportionation of [Cu^{I}(PMDETA)Br] to catalyse the polymerisation of $PEGMA_{475}$ in water in the presence of salt

The nature of the salt can also be changed from NaBr to NaCl.

To an oven dried Schlenk tube fitted with a magnetic stirring bar and rubber septum was added H_2O (2 mL), PMDETA (20.5 μL, 0.6 eq.) and Cu(I)Br (28.1 mg, 1.1 eq.). The solution was left to deoxygenate for 20 minutes and to stir for an extra 10 minutes. A vial fitted with a rubber septum and magnetic stirring bar was charged with poly(ethylene glycol) bis(2-bromoisobutyrate) (200 mg, 0.16 mmol), $PEGMA_{475}$ (1.44 mL, 10 eq.), NaBr (617 mg, 1M) and H_2O (4 mL). The mixture was left to stir until complete dissolution of the monomer (typically 2 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the Schlenk tube and the reaction was left to polymerise at 0°C.

5.4.8 Disproportionation of [Cu^{I}(PMDETA)Cl] to catalyse the polymerisation of $PEGMA_{475}$ in water

This procedure to target DP_n= 20 can be adapted to higher DP_ns, whilst retaining similar monomer concentration (20 % *v/v*).

To an oven dried Schlenk tube fitted with a magnetic stirring bar and rubber septum was added H_2O (2 mL), PMDETA (20.5 μL, 0.6 eq.) and Cu(I)Cl (17.5 mg, 1.1 eq.). The solution was left to deoxygenate for 20 minutes and to stir for an extra 10 minutes. A vial fitted with a rubber septum and magnetic stirring bar was charged with poly(ethylene glycol) bis(2-bromoisobutyrate) (200 mg, 0.16 mmol), $PEGMA_{475}$ (1.44 mL, 20 eq.) and H_2O (4 mL). The mixture was left to stir until complete dissolution of the monomer (typically 2 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the Schlenk tube and the reaction was left to polymerise at 0°C.

5.4.9 Disproportionation of [Cu^I(PMDETA)Cl] to catalyse the polymerisation of $PEGMA_{475}$ in the presence of salt.

This procedure for [I]:[M]:[PMDETA]:[CuCl]= 1:10:0.6:1.1, 20% *v/v* monomer in water can be adapted for higher DP_n, whilst retaining similar monomer concentration (20 % *v/v*). Moreover, the [PMDETA]:[CuCl] ratios can be adapted from 0.6:1.1 to 0.8:1.6. The concentration of salt is also changed from 1M to 3M.

To an oven dried Schlenk tube fitted with a magnetic stirring bar and rubber septum was added H_2O (2 mL), PMDETA (41 μL, 0.6 eq.) and Cu(I)Cl (35.1 mg, 1.1 eq.). The solution was left to deoxygenate for 20 minutes and to stir for an additional 10 minutes. A vial fitted with a rubber septum and magnetic stirring bar was charged with poly(ethylene glycol) bis(2-bromoisobutyrate) (400 mg, 0.32 mmol), $PEGMA_{475}$ (1.44 mL, 10 eq.), NaCl (350 mg, 1M) and H_2O (4 mL). The mixture was left to stir until complete dissolution of the monomer (typically 2 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the Schlenk tube and the reaction was left to polymerise at 0°C.

Sequential additions were performed as followed. A vial fitted with a rubber septum and magnetic stirring bar was charged with monomer ($PEGMA_{475}$, 40 eq.), NaCl (234 mg, 1M) and H_2O (4 mL). The mixture was left to stir until complete dissolution of the monomer (typically 1 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the reaction vessel upon 30 minutes of polymerisation and the reaction was left to stir at 0°C.

5.4.10 Disproportionation of [Cu^I(PMDETA)Cl] to catalyse the polymerisation of $PEGMA_{1100}$ in the presence of salt

To an oven dried Schlenk tube fitted with a magnetic stirring bar and rubber septum was added H_2O (2 mL), PMDETA (5 µL, 0.6 eq.) and Cu(I)Cl (6.5 mg, 1.6 eq.). The solution was left to deoxygenate for 20 minutes and to stir for an extra 10 minutes. A vial fitted with a rubber septum and magnetic stirring bar was charged with poly(ethylene glycol) bis(2-bromoisobutyrate) (50 mg, 4.10^{-5} mol), $PEGMA_{1100}$ (2.7 g, 60 eq.), NaCl (2.1 g, 3M) and H_2O (10 mL). The mixture was left to stir until complete dissolution of the monomer (typically 2 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the Schlenk tube and the reaction was left to polymerise at 0°C.

5.4.11 Disproportionation of [Cu^I(PMDETA)Cl] to catalyse the polymerisation of MEMA in the presence of salt

To an oven dried Schlenk tube fitted with a magnetic stirring bar and rubber septum was added H_2O (2 mL), PMDETA (20.5 µL, 0.6 eq.) and Cu(I)Cl (17.5 mg, 1.1 eq.). The solution was left to deoxygenate for 20 minutes and to stir for an extra 10 minutes. A vial fitted with a rubber septum and magnetic stirring bar was charged with poly(ethylene glycol)

bis(2-bromoisobutyrate) (200 mg, 0.16 mmol), MEMA (650 mg, 20 eq.), NaCl (350 mg, 1M) and EtOH/H_2O 25% *v/v* (4 mL). The mixture was left to stir until complete dissolution of the monomer (typically 2 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the Schlenk tube and the reaction was left to polymerise at 0°C.

Sequential addition was performed in a vial fitted with a rubber septum and magnetic stirring bar charged with monomer ($PEGMA_{475}$, 20 eq.), NaCl (234 mg, 1M) and H_2O (4 mL). The mixture was left to stir until complete dissolution of the monomer (typically 1 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the reaction vessel upon 30 minutes of polymerisation and the reaction was left to stir at 0°C.

5.4.12 Disproportionation of [Cu^I(PMDETA)Cl] to catalyse the polymerisation of DMAEMA in the presence of salt

To an oven dried Schlenk tube fitted with a magnetic stirring bar and rubber septum was added H_2O (2 mL), PMDETA (20.5 µL, 0.6 eq.) and Cu(I)Cl (17.5 mg, 1.1 eq.). The solution was left to deoxygenate for 20 minutes and to stir for an extra 10 minutes. A vial fitted with a rubber septum and magnetic stirring bar was charged with poly(ethylene glycol) bis(2-bromoisobutyrate) (200 mg, 0.16 mmol), DMAEMA (550 µL, 20 eq.), NaCl (350 mg, 1M) and MeOH/H_2O 50% *v/v* (4 mL). The mixture was left to stir until complete dissolution of the monomer (typically 2 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the Schlenk tube and the reaction was left to polymerise at 0°C.

Sequential addition was performed as follows. A vial fitted with a rubber septum and magnetic stirring bar was charged with monomer ($PEGMA_{475}$, 20 eq.), NaCl (234 mg, 1M) and H_2O (4 mL). The mixture was left to stir until complete dissolution of the monomer (typically 1 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was

cannulated into the reaction vessel upon 30 minutes of polymerisation and the reaction was left to stir at 0°C.

5.4.13 Disproportionation of [Cu^{I}(PMDETA)Cl] to catalyse the polymerisation of SBMA in the presence of salt

To an oven dried Schlenk tube fitted with a magnetic stirring bar and rubber septum was added H_2O (2 mL), PMDETA (20.5 μL, 0.6 eq.) and Cu(I)Cl (17.5 mg, 1.1 eq.). The solution was left to deoxygenate for 20 minutes and to stir for an extra 10 minutes. A vial fitted with a rubber septum and magnetic stirring bar was charged with poly(ethylene glycol) bis(2-bromoisobutyrate) (200 mg, 0.16 mmol), SBMA (0.91 g, 20 eq.), NaCl (350 mg, 1M) and MeOH/H_2O 50 % *v/v* (4 mL). The mixture was left to stir until complete dissolution of the monomer (typically 2 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the Schlenk tube and the reaction was left to polymerise at 0°C.

Sequential addition was performed as follows. A vial fitted with a rubber septum and magnetic stirring bar was charged with monomer ($PEGMA_{475}$, 20 eq.), NaCl (234 mg, 1M) and H_2O (4 mL). The mixture was left to stir until complete dissolution of the monomer (typically 1 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the reaction vessel upon 30 minutes of polymerisation and the reaction was left to stir at 0°C.

5.4.14 Disproportionation of [Cu^{I}(PMDETA)Cl] to catalyse the polymerisation of MPC in the presence of salt

To an oven dried Schlenk tube fitted with a magnetic stirring bar and rubber septum was added H_2O (2 mL), PMDETA (20.5 μL, 0.6 eq.) and Cu(I)Cl (17.5 mg, 1.1 eq.). The solution was left to deoxygenate for 20 minutes and to stir for an extra 10 minutes. A vial fitted with a rubber septum and magnetic stirring bar was charged with poly(ethylene glycol) bis(2-bromoisobutyrate) (200 mg, 0.16 mmol), MPC (0.96 g, 20 eq.), NaCl (350 mg, 1M) and IPA/H_2O 50% *v/v* (4 mL). The mixture was left to stir until complete dissolution of the monomer (typically 2 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the Schlenk tube and the reaction was left to polymerise at 0°C.

Sequential addition was performed as follows. A vial fitted with a rubber septum and magnetic stirring bar was charged with monomer ($PEGMA_{475}$, 20 eq.), NaCl (234 mg, 1M) and H_2O (4 mL). The mixture was left to stir until complete dissolution of the monomer (typically 1 minutes) and deoxygenated with nitrogen for 10 minutes. The solution was cannulated into the reaction vessel upon 30 minutes of polymerisation and the reaction was left to stir at 0°C.

5.5 References

1. A. Simula, V. Nikolaou, F. Alsubaie, A. Anastasaki and D. M. Haddleton, *Polym. Chem.*, 2015, **6**, 5940-5950.
2. J.-Y. Cherng, P. van de Wetering, H. Talsma, D. A. Crommelin and W. Hennink, *Pharm. Res.*, 1996, **13**, 1038-1042.
3. P. van de Wetering, J. Y. Cherng, H. Talsma, D. J. A. Crommelin and W. E. Hennink, *J. Controlled Release*, 1998, **53**, 145-153.
4. X. Zhang and K. Matyjaszewski, *Macromolecules*, 1999, **32**, 1763-1766.
5. R. A. Young, E. L. Malins and C. R. Becer, *Aust. J. Chem.*, 2012, **65**, 1132-1138.
6. G. Lu, Y. Li, B. Dai, C. Xu and X. Huang, *J. Polym. Sci., Part A: Polym. Chem.*, 2013, **51**, 1880-1886.
7. T. Zhang, Y. Du, F. Muller, I. Amin and R. Jordan, *Polym. Chem.*, 2015, **6**, 2726-2733.
8. F. Zeng, Y. Shen, S. Zhu and R. Pelton, *J. Polym. Sci., Part A: Polym. Chem.*, 2000, **38**, 3821-3827.
9. V. Bütün, N. C. Billingham and S. P. Armes, *J. Am. Chem. Soc.*, 1998, **120**, 11818-11819.

10. J. V. M. Weaver, S. P. Armes and V. Butun, *Chem. Commun.*, 2002, 2122-2123.
11. S. Liu and S. P. Armes, *Langmuir*, 2003, **19**, 4432-4438.
12. K. Matyjaszewski, J.-L. Wang, T. Grimaud and D. A. Shipp, *Macromolecules*, 1998, **31**, 1527-1534.
13. K. Matyjaszewski, D. A. Shipp, J.-L. Wang, T. Grimaud and T. E. Patten, *Macromolecules*, 1998, **31**, 6836-6840.
14. W. Tang and K. Matyjaszewski, *Macromolecules*, 2007, **40**, 1858-1863.
15. D. M. Haddleton, A. M. Heming and D. Kukulj, *Chem. Commun.*, 1998, 1719-1720.
16. K. Matyjaszewski, D. A. Shipp, G. P. McMurtry, S. G. Gaynor and T. Pakula, *J. Polym. Sci., Part A: Polym. Chem.*, 2000, **38**, 2023-2031.
17. D. A. Shipp, J.-L. Wang and K. Matyjaszewski, *Macromolecules*, 1998, **31**, 8005-8008.
18. K. Matyjaszewski, H.-j. Paik, D. A. Shipp, Y. Isobe and Y. Okamoto, *Macromolecules*, 2001, **34**, 3127-3129.
19. M. A. J. Schellekens, F. de Wit and B. Klumperman, *Macromolecules*, 2001, **34**, 7961-7966.
20. C.-H. Peng, J. Kong, F. Seeliger and K. Matyjaszewski, *Macromolecules*, 2011, **44**, 7546-7557.
21. N. V. Tsarevsky and K. Matyjaszewski, *Chem. Rev.*, 2007, **107**, 2270-2299.
22. E. Kimura, T. Koike, M. Kodama and D. Meyerstein, *Inorg. Chem.*, 1989, **28**, 2998-3001.
23. N. Navon, G. Golub, H. Cohen, P. Paoletti, B. Valtancoli, A. Bencini and D. Meyerstein, *Inorg. Chem.*, 1999, **38**, 3484-3488.
24. G. Anderegg and V. Gramlich, *Helv. Chim. Acta*, 1994, **77**, 685-690.
25. A. M. Dittler-Klingemann, C. Orvig, F. E. Hahn, F. Thaler, C. D. Hubbard, R. van Eldik, S. Schindler and I. Fábián, *Inorg. Chem.*, 1996, **35**, 7798-7803.
26. G. Golub, A. Lashaz, H. Cohen, P. Paoletti, B. Andrea, B. Valtancoli and D. Meyerstein, *Inorg. Chim. Acta*, 1997, **255**, 111-115.
27. F. Thaler, C. D. Hubbard, F. W. Heinemann, R. van Eldik, S. Schindler, I. Fábián, A. M. Dittler-Klingemann, F. E. Hahn and C. Orvig, *Inorg. Chem.*, 1998, **37**, 4022-4029.
28. N. V. Tsarevsky, W. A. Braunecker, A. Vacca, P. Gans and K. Matyjaszewski, *Macromol. Symp.*, 2007, **248**, 60-70.
29. N. V. Tsarevsky, T. Pintauer and K. Matyjaszewski, *Macromolecules*, 2004, **37**, 9768-9778.
30. A. Simakova, S. E. Averick, D. Konkolewicz and K. Matyjaszewski, *Macromolecules*, 2012, **45**, 6371-6379.
31. D. Konkolewicz, P. Krys, J. R. Góis, P. V. Mendonça, M. Zhong, Y. Wang, A. Gennaro, A. A. Isse, M. Fantin and K. Matyjaszewski, *Macromolecules*, 2014, **47**, 560-570.
32. S. Smolne and M. Buback, *Macromol. Chem. Phys.*, 2015, **216**, 894-902.
33. A. B. Lowe and C. L. McCormick, *Chem. Rev.*, 2002, **102**, 4177-4190.
34. R. Barbey, L. Lavanant, D. Paripovic, N. Schüwer, C. Sugnaux, S. Tugulu and H.-A. Klok, *Chem. Rev.*, 2009, **109**, 5437-5527.
35. B. L. Andrew and L. M. Charles, in *Stimuli-Responsive Water Soluble and Amphiphilic Polymers*, American Chemical Society, 2000, vol. 780, pp. 1-13.
36. V. M. Monroy Soto and J. C. Galin, *Polymer*, 1984, **25**, 121-128.
37. D. N. Schulz, D. G. Peiffer, P. K. Agarwal, J. Larabee, J. J. Kaladas, L. Soni, B. Handwerker and R. T. Garner, *Polymer*, 1986, **27**, 1734-1742.
38. D.-J. Liaw, W.-F. Lee, Y.-C. Whung and M.-C. Lin, *J. Appl. Polym. Sci.*, 1987, **34**, 999-1011.
39. T. A. Wielema and J. B. F. N. Engberts, *Eur. Polym. J.*, 1987, **23**, 947-950.
40. A. B. Lowe, N. C. Billingham and S. P. Armes, *Chem. Commun.*, 1996, 1555-1556.

41. Z. Tuzar, H. Pospisil, J. Plestil, A. B. Lowe, F. L. Baines, N. C. Billingham and S. P. Armes, *Macromolecules*, 1997, **30**, 2509-2512.
42. M. S. Donovan, B. S. Sumerlin, A. B. Lowe and C. L. McCormick, *Macromolecules*, 2002, **35**, 8663-8666.
43. A. B. Lowe and C. L. McCormick, *Aust. J. Chem.*, 2002, **55**, 367-379.
44. M. Arotçaréna, B. Heise, S. Ishaya and A. Laschewsky, *J. Am. Chem. Soc.*, 2002, **124**, 3787-3793.
45. E. J. Lobb, I. Ma, N. C. Billingham, S. P. Armes and A. L. Lewis, *J. Am. Chem. Soc.*, 2001, **123**, 7913-7914.
46. A. M. Alswieleh, N. Cheng, I. Canton, B. Ustbas, X. Xue, V. Ladmiral, S. Xia, R. E. Ducker, O. El Zubir, M. L. Cartron, C. N. Hunter, G. J. Leggett and S. P. Armes, *J. Am. Chem. Soc.*, 2014, **136**, 9404-9413.
47. W. Ding, C. Lv, Y. Sun, X. Liu, T. Yu, G. Qu and H. Luan, *J. Polym. Sci., Part A: Polym. Chem.*, 2011, **49**, 432-440.
48. Q. Zhang, P. Wilson, Z. Li, R. McHale, J. Godfrey, A. Anastasaki, C. Waldron and D. M. Haddleton, *J. Am. Chem. Soc.*, 2013, **135**, 7355-7363.
49. K. Matyjaszewski and J. Xia, *Chem. Rev.*, 2001, **101**, 2921-2990.
50. M. Zhang, M. F. Cunningham and R. A. Hutchinson, *Polym. Chem.*, 2015.
51. P. Caliceti and F. M. Veronese, *Advanced Drug Delivery Reviews*, 2003, **55**, 1261-1277.
52. M. W. Jones, M. I. Gibson, G. Mantovani and D. M. Haddleton, *Polym. Chem.*, 2011, **2**, 572-574.
53. P. van de Wetering, N. J. Zuidam, M. J. van Steenbergen, O. A. G. J. van der Houwen, W. J. M. Underberg and W. E. Hennink, *Macromolecules*, 1998, **31**, 8063-8068.
54. R. N. Keller, H. D. Wycoff and L. E. Marchi, in *Inorg. Synth.*, John Wiley & Sons, Inc., 2007, pp. 1-4.

Conclusions

Conclusions

In this thesis, the development of "novel" strategies to yield functional telechelics by Cu(0)-mediated RDRP was presented. In the introduction chapter, a brief literature review was given, in order to give an historical background on the importance of telechelics in the development of polymer materials. Advances on the careful synthesis of telechelic polymers allowed the development of polymer matrixes which will later find their use in coatings, personal care, targeted delivery and many others. The developments in the synthetic tools, from CFRP to ionic polymerisation, followed by the recent advances in RDRP became of upmost importance to expand the scope of physical properties and functionalities achievable through the use of telechelic polymers.

Among the plethora of RDRP techniques available, the recent development on Cu(0)-mediate RDRP triggered the design of functional materials with excellent end-group fidelity and various reactive chain ends. Hence, in chapter 2, the versatility of the polymerisation tool was tested towards the design of α,ω-functional polyacrylates. Utilising Cu(0)-wire as the primary copper source in DMSO proved to be a versatile tool for the retention of halide chain ends at quantitative monomer conversion, whilst maintaining narrow MWD. This was exemplified by the controlled polymerisation of hydrophobic and hydrophilic monomer moieties, *i.e.* *n*-BA and $PEGA_{480}$, allowing the design of tailor-made (co)polymers. The reactive halide end groups could be further reacted post-polymerisation *via* nucleophilic substitution or atom transfer radical addition (ATRA). Indeed, 2-mercapto ethanol, dodecanethiol and allyl-alcohol were utilised to end-cap the halide chain ends and alter the end group functionality. Polyacrylate diols could be generated at high yield (> 90%), as

confirmed by a combination of NMR and MALDI-ToF MS. The reactivity of the *α,ω*-hydroxyl polymers was tested by reaction with isocyanates and with a more sophisticated ROP of ε-caprolactone, yielding an amphiphilic PCL-*b*-PBA-*b*-PCL triblock copolymer. Those investigations expanded the scope of functional structures attainable by Cu(0)-mediated polymerisation in organic medium, with Cu(0)-wire as the primary copper source. More importantly the hydroxyl chain ends will still retain good reactivity, as exemplified by further modifications.

In chapter 3, a pre-disproportionation approach, whereby [Cu^{I}(Me_6-TREN)Br] quantitatively yields Cu(0) particles and [Cu^{II}(Me_6-TREN)Br]Br in water prior to initiator and monomer addition, was selected as a robust tool to mediate the polymerisation of high k_p monomers (*e.g.* acrylamides, acrylates) in water. This process was tested to yield telechelic multiblock copolymers, whilst circumventing some issues arising from Cu-mediated processes in water. At first, telechelic polyacrylamides and polyacrylates were obtained in alcoholic media (IPA/H_2O 50 % *v/v*) with high conversions and narrow MWD (*Đ*< 1.2). However, more sophisticated structures, *i.e.* multiblock copolymers, could only be attained in water, with the use of a water-soluble bi-functional initiator. This allowed the design of heptablock copolymers with good tolerance over the monomer moieties (*e.g.* acrylates, acrylamides), with additional stimuli-responsive behaviour. Interestingly, the near quantitative hydrolysis of the halide chain ends resulted in rapid formation of *α,ω*-hydroxyl telechelic which could be further reacted post-polymerisation. The responsive behaviour of the copolymers was assessed by cloud point temperature (T_{cp}) measurement, wherein monomer composition, molecular weight and chain end hydrophilicity demonstrated to have a significant influence on T_{cp} values and aggregation properties of the material.

The investigations in chapter 2 and 3 gave two robust Cu(0)-mediated polymerisation methods to yield telechelic copolymers in both aqueous and organic media. Both Cu(0)-wire and *in situ* generated Cu(0)-particles have been utilised as the primary copper source to copolymerise high k_p monomers (*e.g.* acrylates, acrylamides) in DMSO and water

respectively. Nevertheless, neither of the two procedures has been tested for the copolymerisation of well-defined polymethacrylates. Hence, in chapter 4, a comprehensive study on the formation of polyether acrylates and methacrylates is provided in both DMSO and water. The effect of copper source, *i.e.* Cu(0)-wire and pre-disproportionated [Cu^{I}(L)Br], has been carefully assessed for the formation of well-defined homopolymers (through kinetic studies) and block copolymers *via in situ* chain extensions. Moreover, the combination of ligands (*e.g.* Me_6-TREN, PMDETA) and monomer (*e.g.* acrylates, methacrylates) with matching activity was investigated towards optimum retention of both MWD and chain end fidelity, which is not usually discussed in Cu(0)-mediated polymerisation. Indeed, the thorough examination of the effect of each component (*e.g.* copper source, solvent, ligand and monomer) revealed that a non-adapted combination would be deleterious for the *"living*" character of the polymerisation, the rate, the chain ends retention and MWD. In DMSO, the Cu(0)-wire mediated polymerisation of $PEGA_{480}$ and $PEGMA_{475}$ would result in good control over the MWD at high (> 78% by ^{1}H NMR) monomer conversion when using either Me_6-TREN or PMDETA as a ligand. However, the α,ω-Br chain ends could only be retained when the polyether acrylate was matched with Me_6-TREN ligand, whilst poor halide retention was observed for $PPEGMA_{475}$ with both ligands. Subsequently, the chain end fidelity and the rate of polymerisation were enhanced in aqueous medium, exploiting the pre-disproportionation of [Cu^{I}(L)Br] prior to initiator and monomer addition in situ. The careful selection of ligand and monomer with matching activities revealed to be of upmost importance to retain both "*livingness*", narrow distributions and good chain end fidelity. As such, polymethacrylates could be synthesised with near quantitative monomer conversion and narrow MWD ($Đ$< 1.38), thus enhancing the scope of materials accessible with Cu(0)-mediated polymerisation with halide chain ends retention.

Nevertheless, the exemplar polyether methacrylates could not be polymerised at higher molar mass with similar degree of control. Consequently, efforts have been conducted in

chapter 5 to further enhance the control over the (co)polymerisation of methacrylic moieties in aqueous media. At first, alteration of the carbon-bromide bond towards a stronger carbon-chloride bond was attempted through an halogen exchange between the initiating species and a $[Cu^{II}(PMDETA)Cl]Cl$ deactivating complex. However, the moderate stability of the Cu(II) species in water proved to be deleterious to carefully retain narrow distibutions. Hence, an external halide source, *i.e.* NaCl was introduced in the polymerisation mixture to enhance the stability of the deactivating species. This let to further reduction in the dispersity values for higher molar mass of $PPEGMA_{475}$ (M_n> 50000 g.mol^{-1}, $Đ$< 1.37) at quantitative monomer conversion. The presence of salt was found to be of upmost importance to yield block-copolymers with narrow distributions, for a wider range of monomer functionalities. As such, hydrophilic monomers such as MEMA and DMAEMA could be copolymerised with $PEGMA_{475}$ in aqueous media at high conversions and with good control over the MWD and halide chain ends. The scope of monomers moieties was further expanded to zwitterionic monomers, *i.e.* SBMA and MPC, which could be successfully (co)polymerised by Cu(0)-mediated polymerisation.

In conclusion, this work exploits the high chain end-fidelity attainable by a Cu(0)-mediated polymerisation process to yield telechelic polymers with various functionalities. Moreover, the initial investigations on Cu(0)-mediated RDRP of acrylates in organic solvents were further expanded in aqueous media, paving the way to a wide range of accessible monomer moieties, *i.e.* acrylamides and (meth)acrylates. This allowed the design of "smart" materials, with stimuli-responsive behaviour and high tolerance over the monomer moieties. The scope of telechelic materials was further expanded, through the incorporation of zwitterionic monomers in functional pentablock copolymers. Most importantly, in any part of this study, the nature of a telechelic polymer, "*reactive through its chain ends*", has been tested and pushed to its limits in various solvents, over different functionalities (halides, hydroxyl) and to various monomers. As such, the broad range of applications of telechelic polymers can be further expanded, having Cu(0)-mediated RDRP as "new" and versatile synthetic tool.

Perspectives

Perspectives

Exploiting the high end group fidelity attainable with Cu(0)-mediated RDRP proved to be a satisfactory route towards the design of functional α,ω-telechelics in polar media. Moreover, the expanded breath of polymerisable moieties accessible through this technique, *i.e.* (meth)acrylates, acrylamides, with various properties allows the preparation of sophisticated materials. However, the synthetic background of this thesis does not fully reflect the use of telechelics in an industrial context, which would be highly desirable. In addition, a mechanistic understanding of the synthetic tools employed in all chapters as well as further optimisation of (co)polymerisation conditions would be appreciated, in order to yield "tailor-made" telechelic polymers. In this section, several perspectives are suggested in order to improve, or exploit the investigations conducted herein.

From the synthesis of hydrophobic diols in chapter 2, utilising Cu(0)-wire as a primary copper source, several optimisations and future work come to mind. The high yield of diols (>95 %) could be improved, through further tuning of reaction conditions (*e.g.* temperature, ligand and copper ratios). This would have a significant impact on further use of such macrodiols to yield polyurethanes and/or polyesters. Moreover, changing the properties of the telechelic diols (*e.g.* glass transition temperature, response to various stimuli) could subsequently provide access to valuable polymer matrixes.

In chapter 3, the *in situ* synthesis of poly(acrylamide) diols could pave the way to a variety of acrylamide-containing materials, such as dispersants or thickeners. Indeed, the reactivity of the hydroxyl chain ends allows a facile tuning of the (co)polymers properties post-polymerisation.

In chapter 4 and 5, the synthesis of poly(methacrylates) *via* Cu(0)-mediated RDP was presented. Despite the design of various hydrophilic and zwitterionic copolymers, the broad MWD does not match the literature. The first optimisation of the synthetic tool should be towards initiation, through the use of more stable initiating radicals. This could provide enhanced control towards the design of α,ω-telechelics, with good chain end fidelity and narrow MWD

.

Appendix A

Appendix A

Initiator synthesis

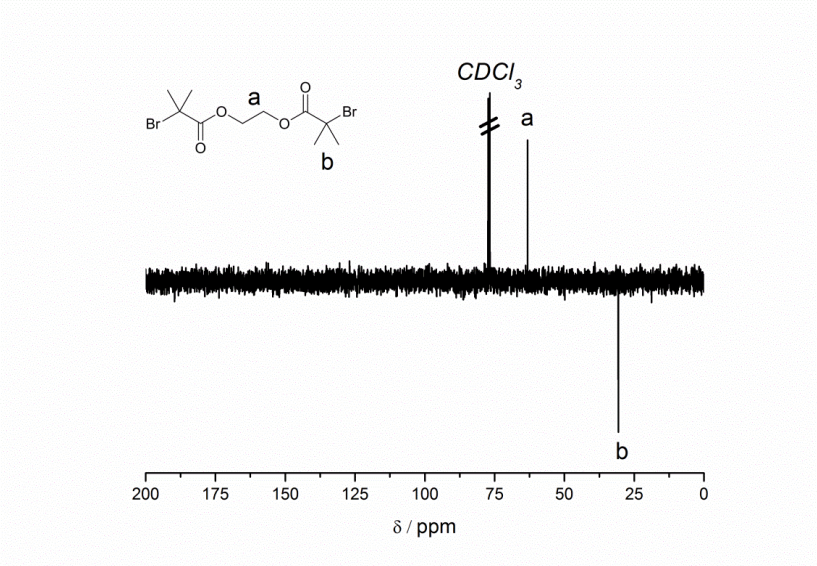


Figure A.1. ^{13}C NMR (100MHz, $CDCl_3$) spectrum of ethylene bis(2-bromoisobutyrate).

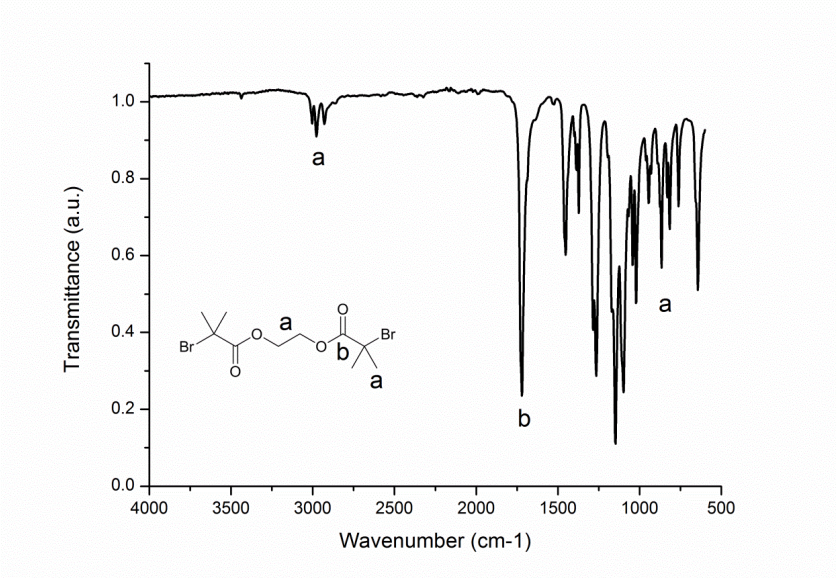


Figure A.2. FT-IR spectrum of ethylene bis(2-bromoisobutyrate).

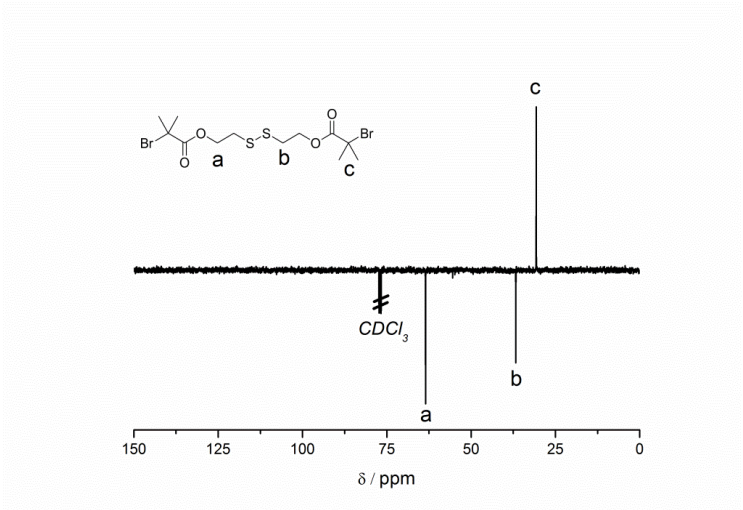


Figure A.3. ^{13}C NMR (100MHz, $CDCl_3$) spectrum of bis[2-(2-bromoisobutyryloxy)ethyl] disulphide.

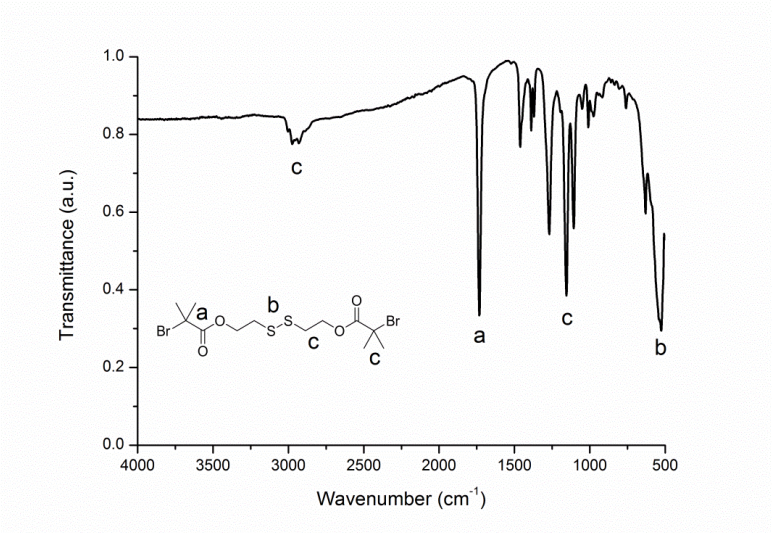


Figure A.4. FT-IR spectrum of bis[2-(2-bromoisobutyryloxy)ethyl] disulphide.

Polymer synthesis

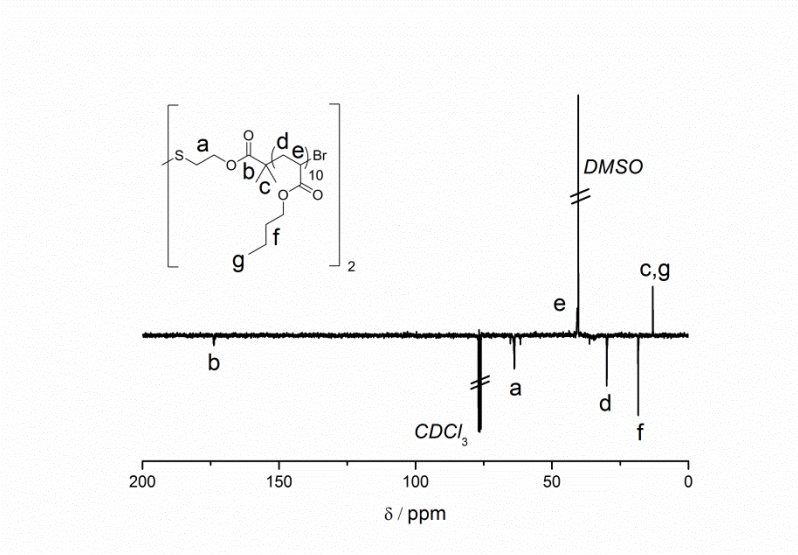


Figure A.5. ^{13}C NMR ($CDCl_3$, 75 MHz) of poly(*n*-butyl acrylate) (M_n= 3400 g.mol^{-1}, $Đ$= 1.10), initiated by bis[2-(2-bromoisobutyryloxy)ethyl] disulphide.

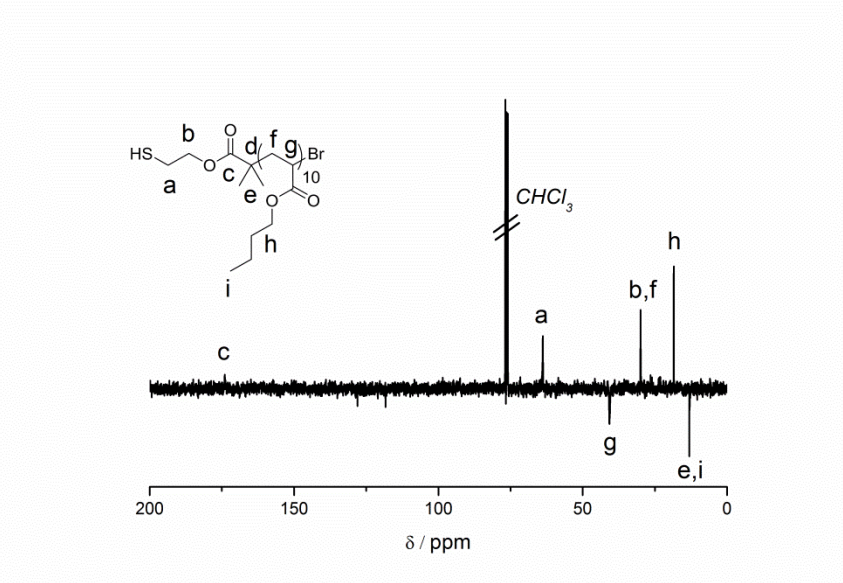


Figure A.6. ^{13}C NMR ($CDCl_3$, 75 MHz) of reduced poly(*n*-butyl acrylate) (M_n= 1400 g.mol^{-1}, $Đ$= 1.2), initiated by bis[2-(2-bromoisobutyryloxy)ethyl] disulphide.

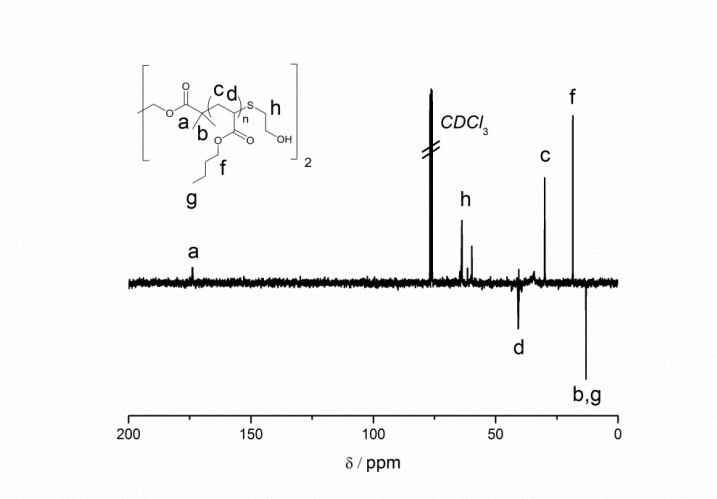


Figure A.7. ^{13}C NMR ($CDCl_3$, 75 MHz) of hydroxyl terminated poly(*n*-butyl acrylate) (M_n= 3600 g.mol^{-1}, $Đ$= 1.09).

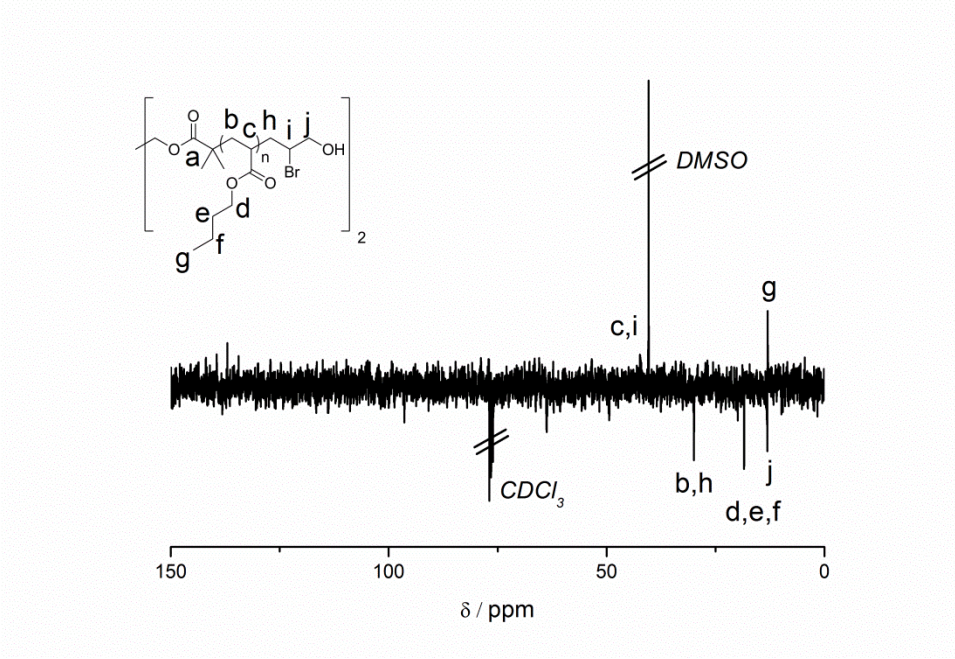


Figure A.8. ^{13}C NMR ($CDCl_3$, 75 MHz) of α,ω-hydroxyl terminated poly(*n*-butyl acrylate) utilizing allyl alcohol.

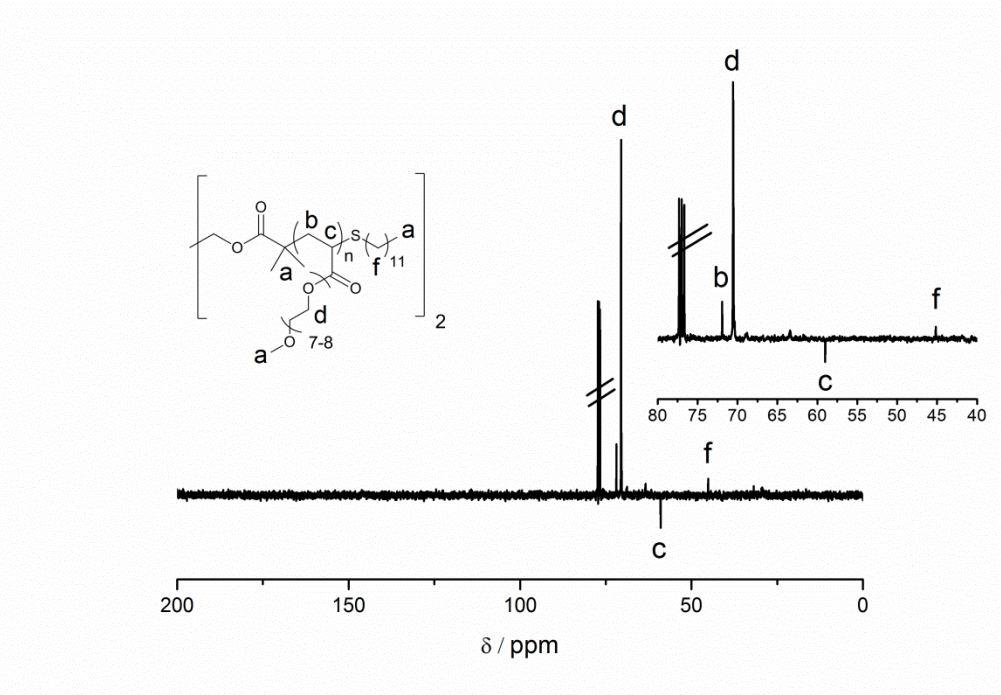


Figure A.9. ^{13}C NMR ($CDCl_3$, 100 MHz) of dodecanethiol modified poly[poly(ethylene glycol) methyl ether acrylate].

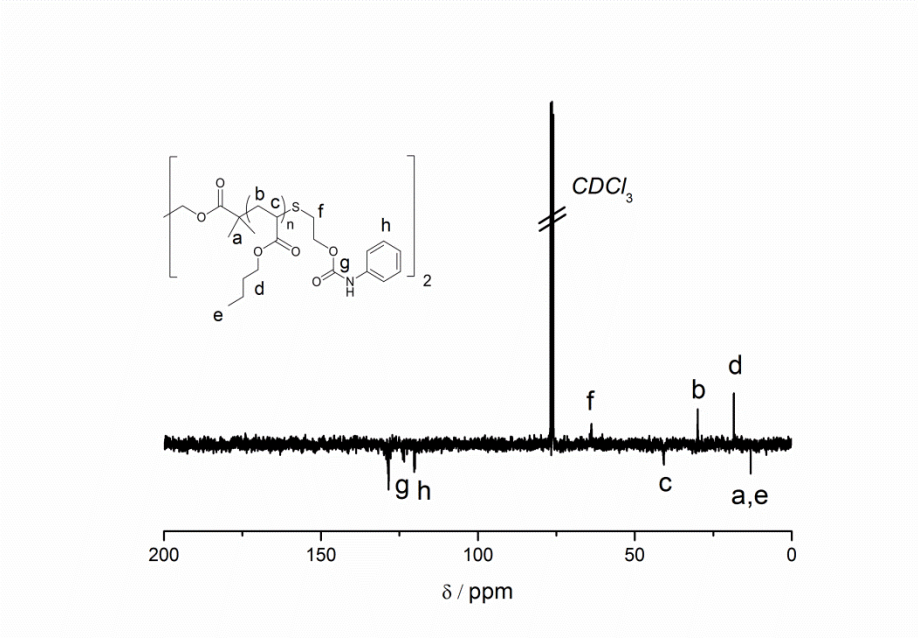


Figure A.10. ^{13}C NMR ($CDCl_3$, 75 MHz) of 'end-capped' α,ω-hydroxyl terminated poly(n-butyl acrylate) (M_n=3600 g.mol^{-1}, $Đ$= 1.09) with phenyl isocyanate.

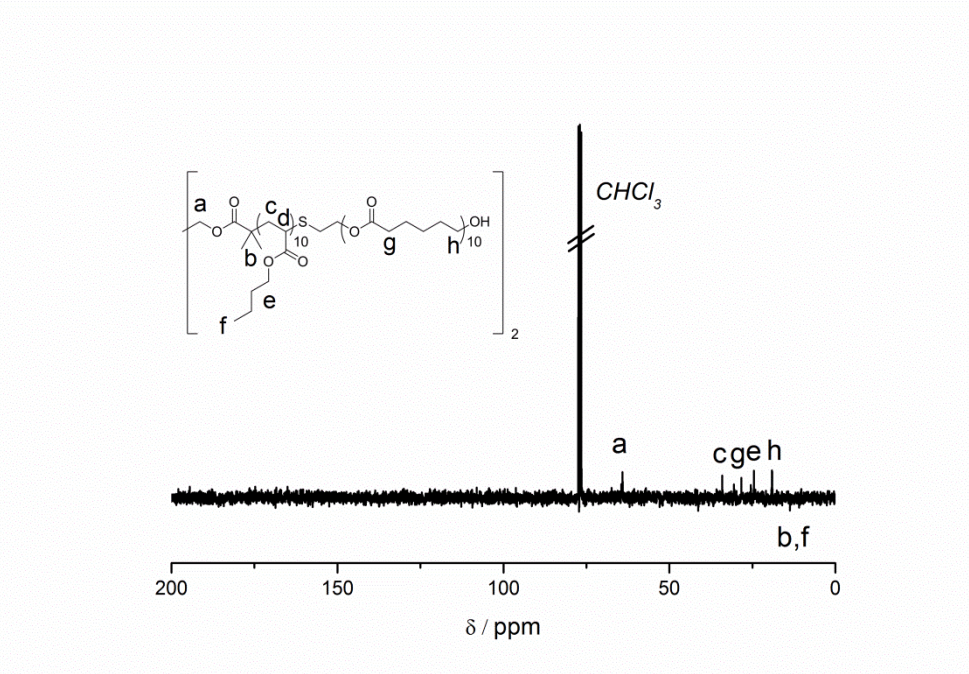


Figure A.11. ^{13}C NMR ($CDCl_3$, 75 MHz) of poly(ε-caprolactone)-block-poly(*n*-butyl acrylate)-block-poly(ε-caprolactone) (M_n= 5800 g.mol^{-1}, $Đ$= 1.4).

Appendix B

Appendix B

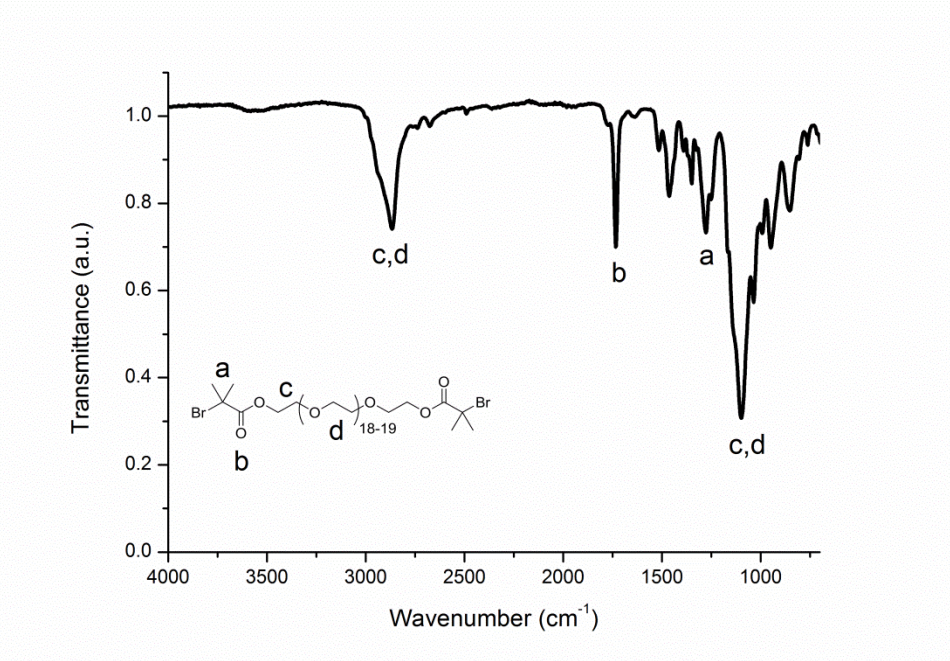


Figure B.1. FT-IR spectrum of poly(ethylene glycol) bis(2-bromoisobutyrate).

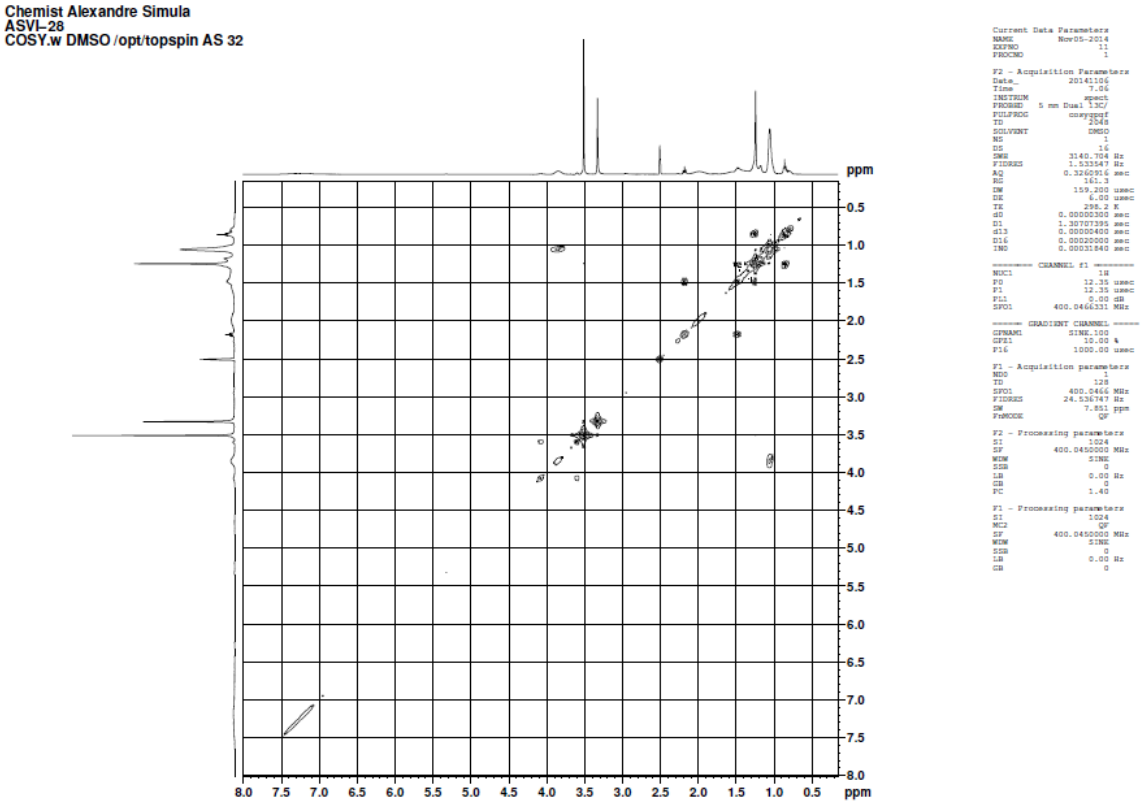


Figure B.2. COSY (d_6-DMSO, 400 MHz) of butyl isocyanate modified poly(*N*-isopropylacrylamide)$_{10}$-*b*-poly(ethylene glycol)-*b*-poly(*N*-isopropylacrylamide)$_{10}$.

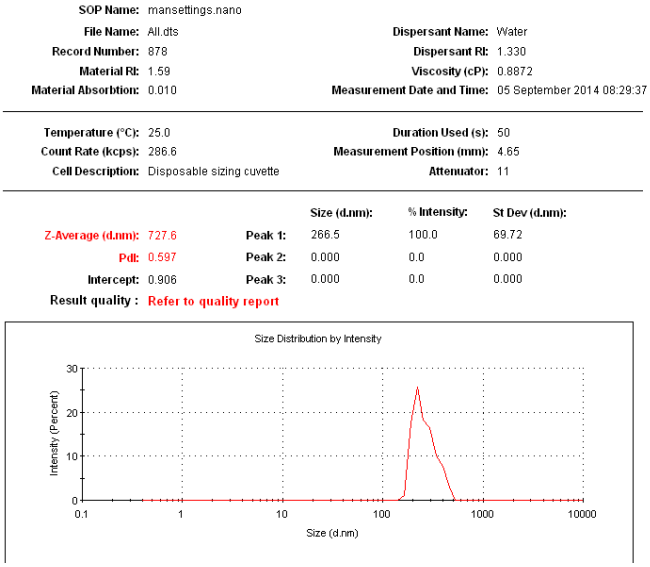


Figure B.3. DLS measurement of 1 mg/mL solution of hydrophobically modified poly(*N*-isopropylacrylamide)$_{10}$-*b*-poly(ethylene glycol)-*b*-poly(*N*-isopropylacrylamide)$_{10}$ in water, by intensity.

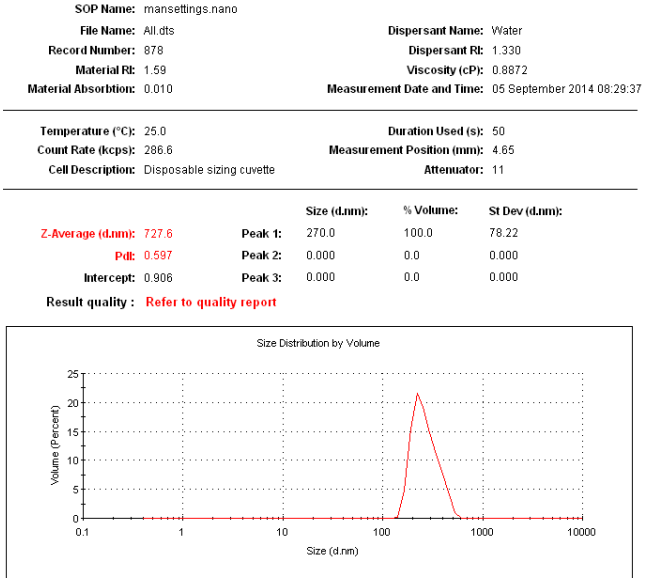


Figure B.4. DLS measurement of 1 mg/mL solution of hydrophobically modified poly(*N*-isopropylacrylamide)$_{10}$-*b*-poly(ethylene glycol)-*b*-poly(*N*-isopropylacrylamide)$_{10}$ in water, by intensity.

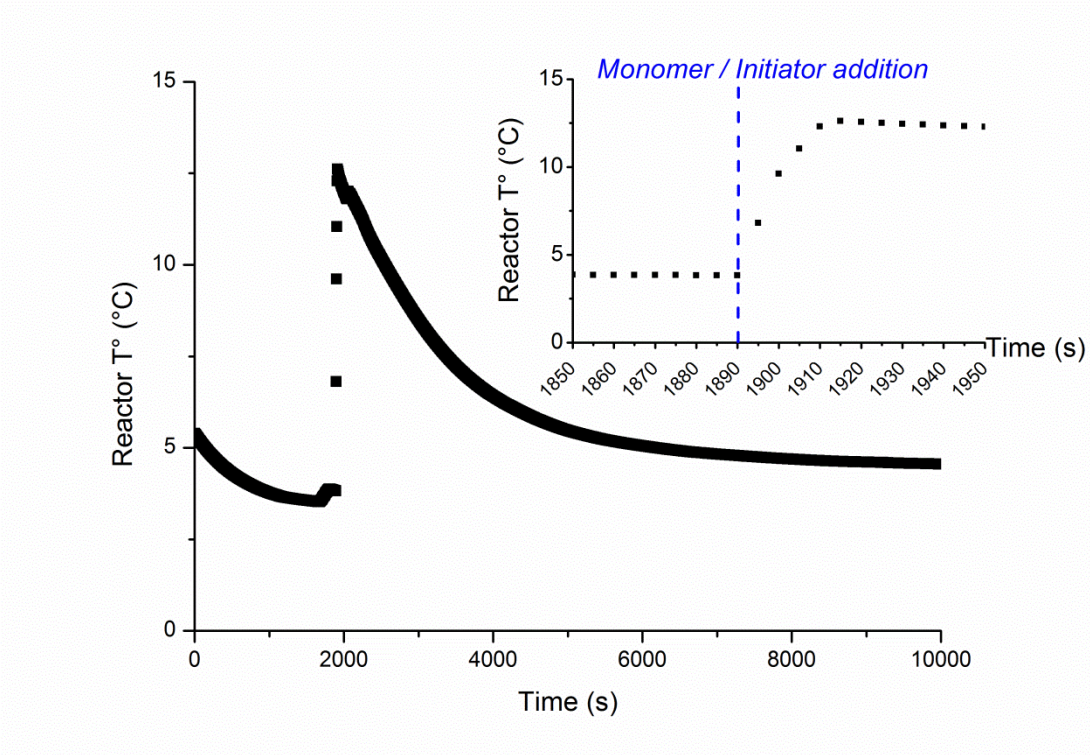


Figure B.5. *In situ* temperature monitoring of the polymerisation of NIPAAm ([I]:[M]:[Me_6-TREN]:[Cu(I)Br] 1: 20: 0.4: 0.8, 20% *w/w* monomer in water) at 5°C in a double jacketed reactor.

Appendix C

Appendix C

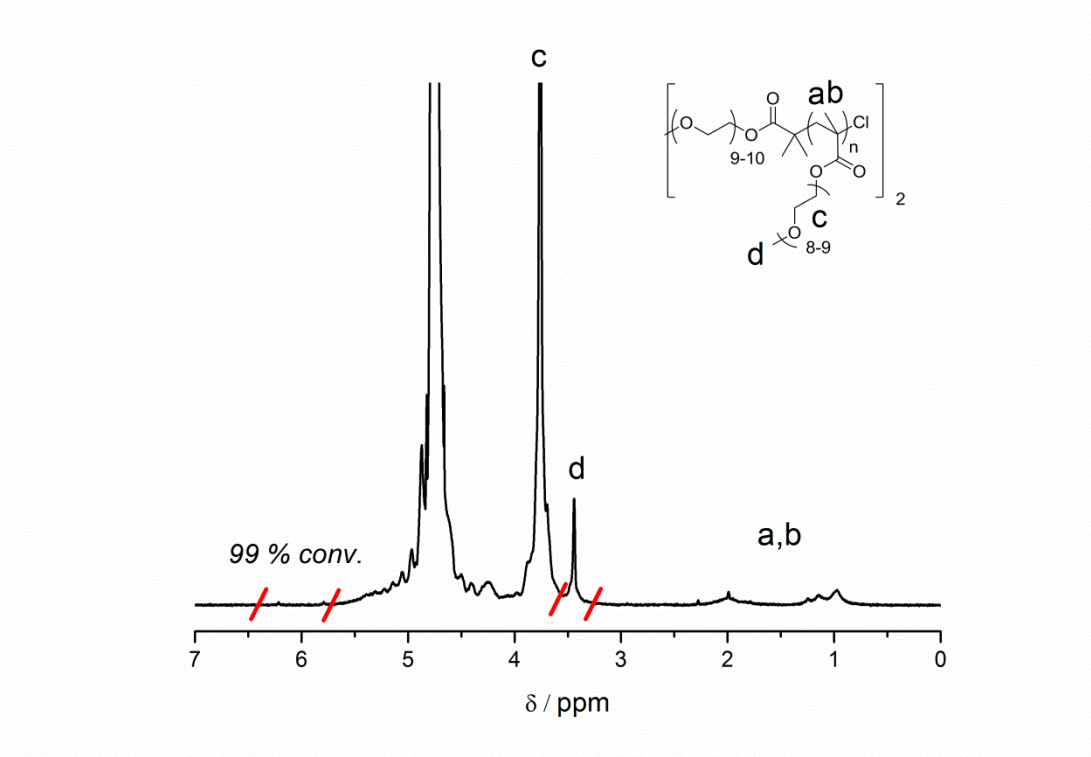


Figure C.1. Monitoring the polymerisation of $PEGMA_{475}$ in water ([I]:[M]:[PMDETA]:[CuCl]= 1:20:0.6:1.1, 20% *v/v* monomer in water) with NaBr (1M) at 0°C by ^{1}H NMR (D_2O, 250 MHz).

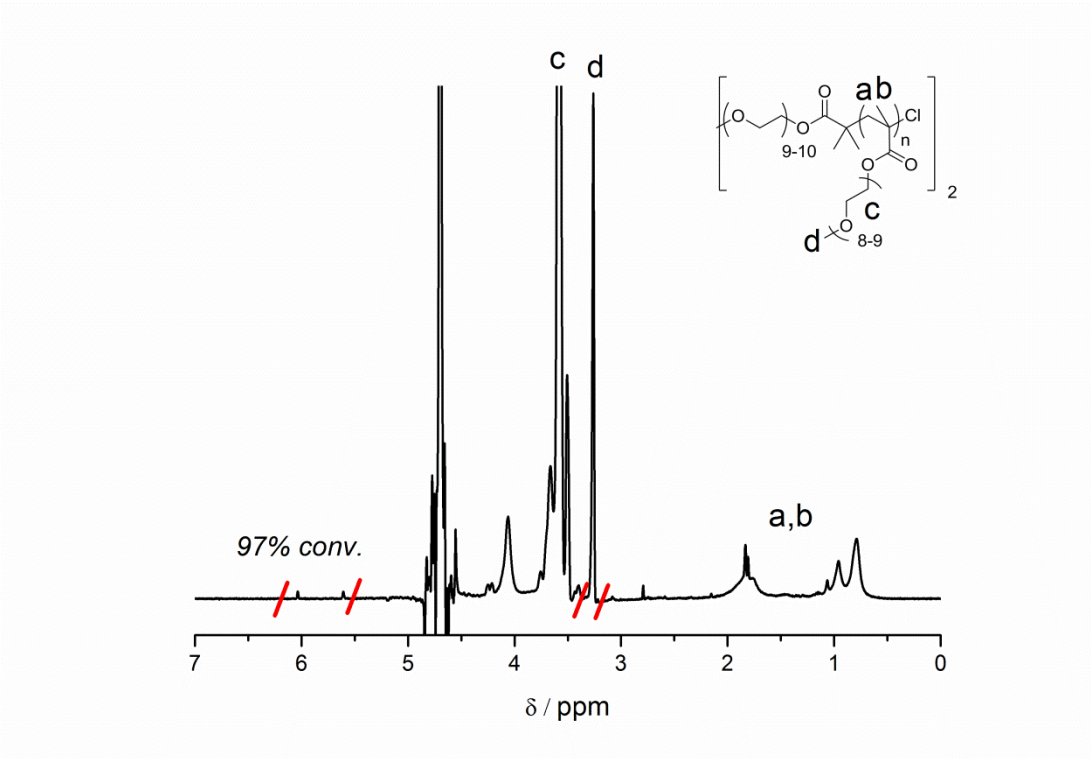


Figure C.2. Monitoring the polymerisation of $PEGMA_{475}$ in water ([I]:[M]:[PMDETA]:[CuBr]= 1:20:0.6:1.1, 20% *v/v* monomer in water) with NaCl (1M) at 0°C by ^{1}H NMR (D_2O, 250 MHz).

Appendix D: Towards functional materials; building telechelic polymers in an industrially relevant context

Specific design of α,ω-telechelic polymer is presented, in line with Lubrizol requirements over the course of the PhD thesis.

D.1 Introduction

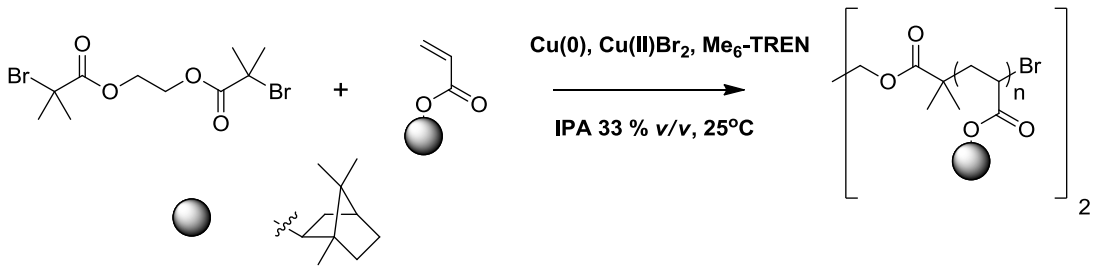
In previous chapters, the synthesis of α,ω-telechelics was presented, utilising Cu(0)-mediated RDRP as a synthetic tool. The versatility of the technique was investigated in various solvents (*e.g.* DMSO, IPA, water) wherein the nature of the copper source could be adapted, from Cu(0)-wire to a pre-disproportionated [Cu^{I}(L)X], yielding Cu(0)-particles and [Cu^{II}(L)X]X prior to initiator and monomer addition (X an halogen). The successful combination of ligand and copper source proved to be of upmost importance for the synthesis of well-defined block copolymers, with good tolerance over the monomer moieties, *i.e.* (meth)acrylates, acrylamides with various physical properties (*e.g.* hydrophilic, hydrophobic, stimuli-responsive and zwitterionic). However, the commercial applications of such materials have not been clearly assessed, despite the wide range of macromolecules available. Indeed, the industrial relevance of telechelic materials in Lubrizol ® products gives an extensive background to develop novel materials with tailor-made properties.

In this appendix, the focus is on specific design of two different types of telechelic materials. In a first section the development of high glass transition temperature (T_g) oil-soluble diols will be presented, for applications in resistance coatings, by Cu(0)-mediated RDRP and RAFT polymerisation. Subsequently, the design of water-soluble polyacrylamides diols will be presented in a second section to yield potential novel associative thickeners.

D.2 Results and discussions

D.2.1 Synthesis of high T_g poly(acrylate) diols

The high end group fidelity attainable with Cu(0)-mediated RDRP of acrylates utilising Cu(0)-wire as a copper source presented in chapter 2 is adapted to monomers which would enhance both the T_g and the oil solubility of the copolymer. Firstly, the increase of the T_g is assessed through the polymerisation of isobornyl acrylate (IA, T_g^{th}~ 94°C). IPA was selected as the solvent because of the poor solubility of IA in DMSO. The reaction conditions had to be adapted from the one presented in chapter 2 (see section 2.2.2) to [I]:[M]:[Me_6-TREN]:[Cu(0)-wire]:[$Cu^{II}Br_2$]= 1: DP_n: 0.18: 5 cm: 0.05, 66% *v/v* monomer in IPA at 25°C (scheme D.1). Utilising lower monomer concentration would result in undesired phase separation of the polymer associated with a cessation of the polymerisation and poor control (gel).



Scheme D.1. Homopolymerisation of IA by Cu(0)-mediated RDRP in IPA.

Pleasingly, good control of the polymerisation was attained, as evidenced by high monomer conversions (>74% by ^{1}H NMR) and narrow MWD ($Đ$< 1.11, figure D.1). Nevertheless,

long reaction time (15 hours) was necessary to yield high monomer conversion whilst only low molecular weight (M_n < 5000 g.mol^{-1}) could be attained.

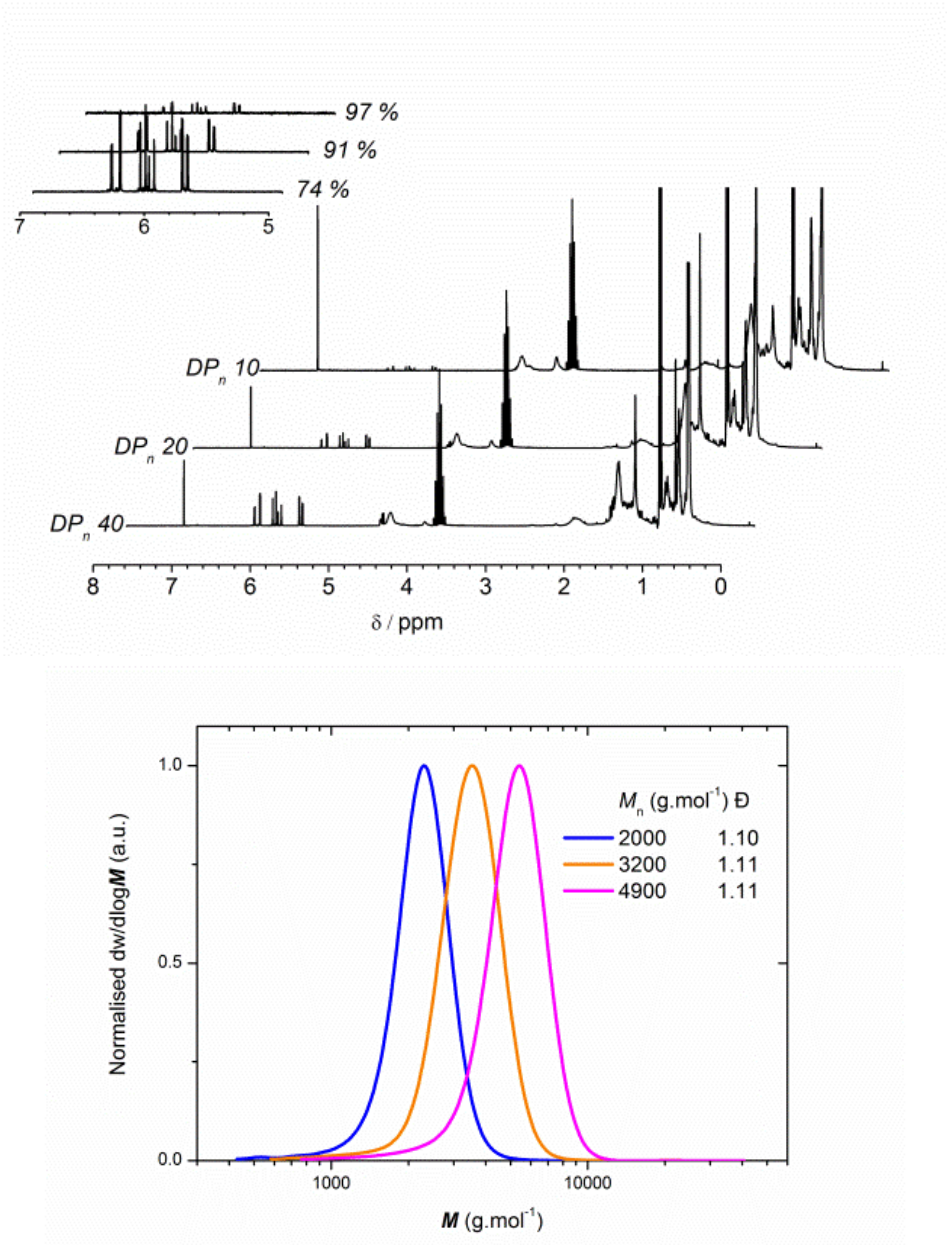


Figure D.1. Monitoring the polymerisation of various DP_n of IA in IPA at 25°C.

Subsequently, IA was copolymerised with oil soluble acrylates, *i.e.* lauryl acrylate (LA) and ethylhexyl acrylate (EHA), under similar conditions. A molecular weight of 3.5 kDa was targeted, as requested by the Lubrizol corporation.

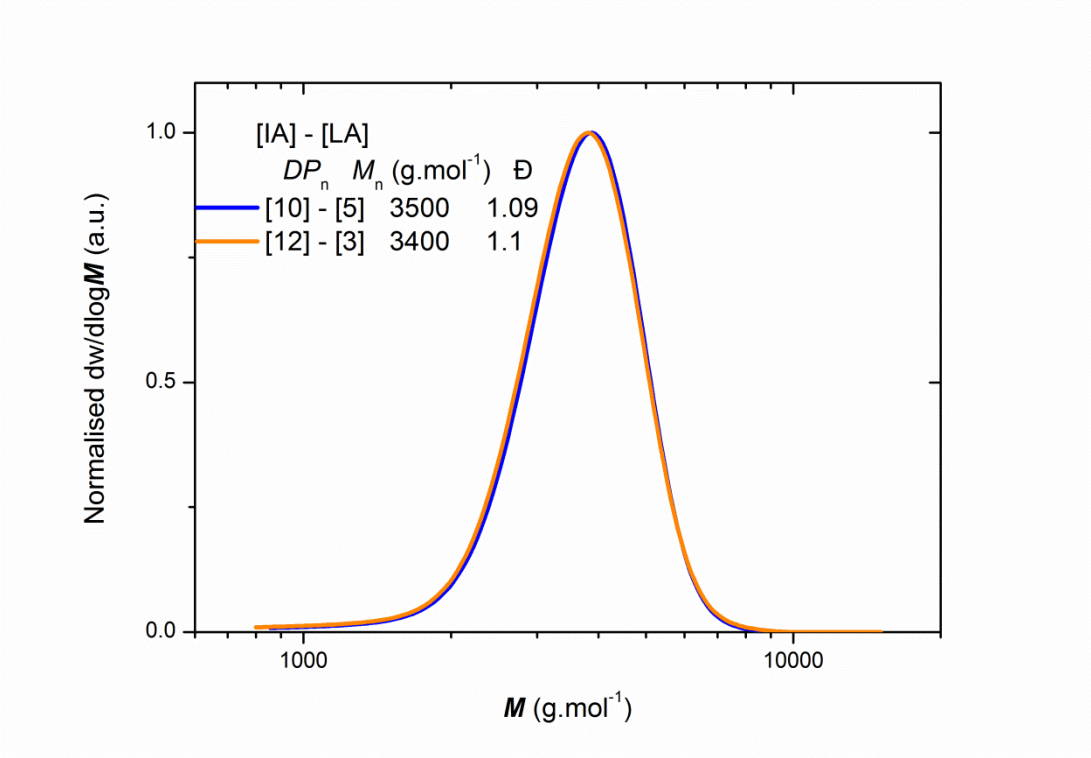


Figure D.2. Monitoring the copolymerisation of IA with LA in IPA at 25°C.

Pleasingly, copolymerisation of LA and IA does not affect the control over the polymerisation, as seen by quantitative monomer conversion and narrow MWD (figure D.2), with a similar level of control observed as for EHA (figure D.3).

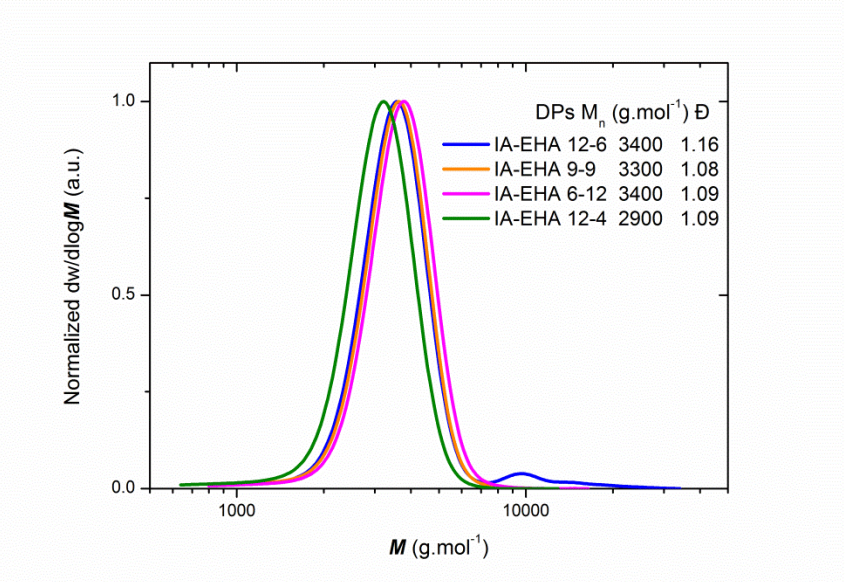


Figure D.3. Monitoring the copolymerisation of IA with EHA in IPA at 25°C.

Upon complete polymerisation, the polymers were purified by precipitation in cold methanol to yield a highly viscous liquid or a powder. Adapting the nature and ratios between co-monomers resulted in the expected change in the T_g of the resulting homo-telechelic polymer, as presented in table D.1. The DSC of the copolymers was conducted in triplicate and copolymers containing EHA did not give reproducible analysis. Consequently, the resulting T_g are not reported.

Table D.1. T_g of α,ω-telechelic poly(acrylates).

Entry	Copolymer	M_n (g.mol^{-1})[a]	T_g (°C)[b]
1	PIA_{10}	2000	78
2	PIA_{20}	3200	102
3	PIA_{40}	4000	116
4	PIA_{10}-***r***-PLA_5	3500	39
5	PIA_{12}-***r***-PLA_3	3600	71

[a] *obtained by SEC ($CHCl_3$ eluent) over PMMA standards.* [b] *obtained by DSC (see experimental for details).*

Although good control over both the polymerisation and the change in T_g observed, the halide chain end functionality was not suitable for a use in polyurethane synthesis. Hence, α,ω-OH end groups were introduced similarly as in chapter 2 (*e.g. via* nucleophilic substitution with 2-mercaptoethanol or addition of allyl alcohol). Unfortunately, no MALDI-ToF MS analysis could be provided, due to the poor ionisation of the sample (see section 2.4 for details). Nevertheless, a copolymer of α,ω-hydroxy telechelic PIA_{10}-***r***-PLA_5 was sent to Lubrizol for further tests.

D.2.2 Synthesis of high T_g poly(methacrylate) diols

Cu(0)-mediated RDRP proved to be a robust tool to mediate the polymerisation of acrylates at ambient temperatures, with good chain end fidelity. This tool has been applied for a variety of functional monomers and was exploited to introduce reactive chain ends, *i.e.* hydroxyl groups. However, such good control over the polymerisation could not be retained for hydrophobic methacrylates. Indeed, only a few reports deal with the synthesis of

functional methacrylates. Nevertheless, the polymerisation of *n*-butyl methacrylate (BMA) was attempted, utilising PMDETA as a ligand under previously reported conditions ([I]:[M]:[PMDETA]:[Cu(0)-wire]:[$Cu^{II}Br_2$]= 1: DP_n: 0.18: 5 cm: 0.05, 20% *v/v* monomer in DMSO at 25°C). Noteworthy, a phase separation of the polymer from the catalyst phase was observed, similarly as PBA (section 2.2).

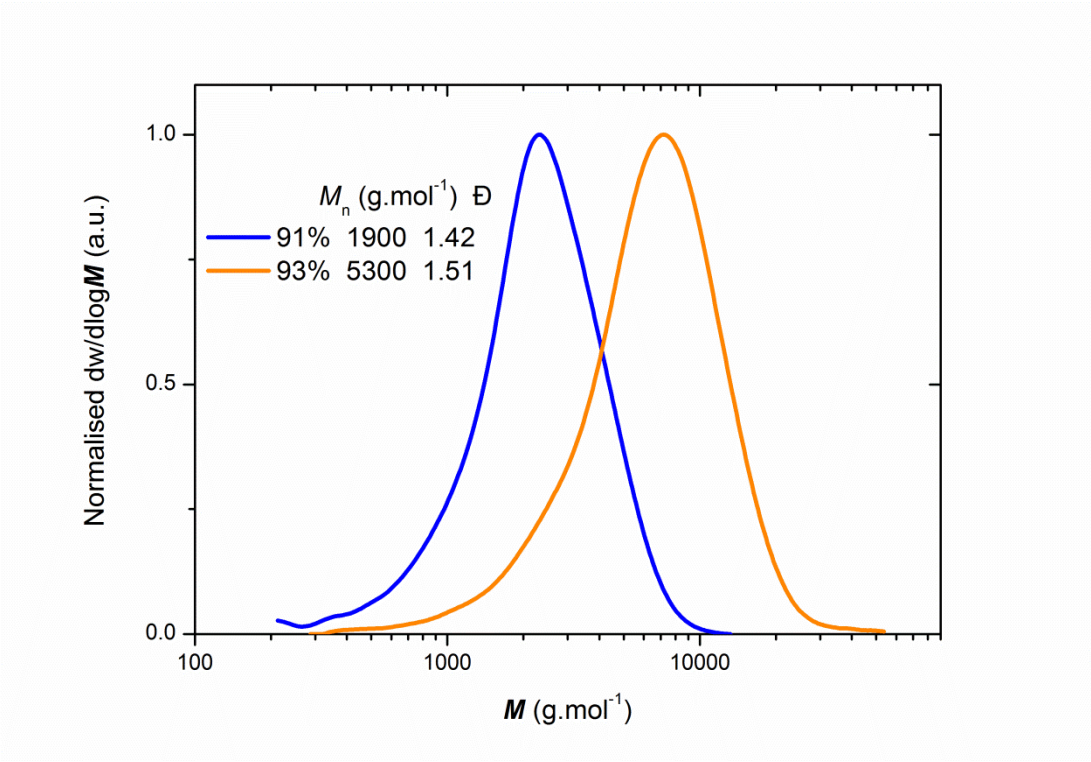


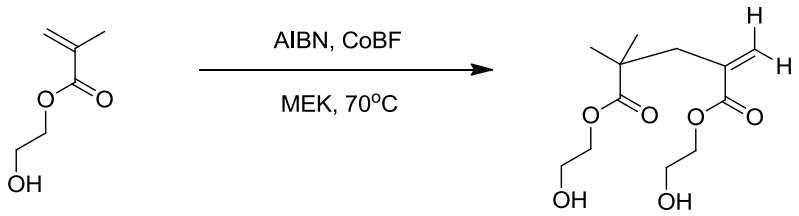
Figure D.4. Monitoring the chain extension of PBMA in DMSO at 25°C by SEC ($CHCl_3$ eluent).

Although high monomer conversion could be attained in 2 hours (> 91 % by ^{1}H NMR), broader MWD were observed in SEC (*Đ*~ 1.4-1.5, figure D.4.) as compared to the polyacrylate analogue (see section 2.2), which could be due to a poorer control and/or low initiator efficiency. The halide end group fidelity was indirectly tested by *in situ* addition of a deoxygenated aliquot of BMA. Pleasingly, a shift towards higher MWD is observed in SEC, suggesting the presence of the *α,ω*-Br ends. However, a slight increase in dispersity

values, in addition to the presence of residual tailing at low MW suggests a loss of reactive chain ends, which would be detrimental for further uses. Unfortunately, the presence of halide chain ends could not be confirmed by MALDI-ToF MS due to the poor ionisation of the polymer. It appears that Cu(0)-mediated RDRP is not suitable for the polymerisation of hydrophobic methacrylates under those conditions, as the end group fidelity is dramatically affected.

Consequently, it was decided to utilise a synthetic route more suitable for the polymerisation of methacrylates, whilst retaining good *α,ω*-chain ends functionality. The use of CCTP (see section 1.2.2.) has proved to be of importance to yield oligo(methacrylates) with an *ω*-unsaturated double bond. Such macromonomers can be employed as (macro)CTAs for the polymerisation of methacrylates by RAFT polymerisation (section 1.3.3.4). Herein, HEMA-dimer is synthesised by CCTP in bulk, in order to yield *α,ω*-hydroxyl telechelic poly(methacrylates).

HEMA was polymerised under with high concentration of the CTA, cobalt(II) cobaloxime (CoBF) to preferentially yield dimer and trimer (scheme D.2).



Scheme D.2. Synthesis of HEMA-dimer by CCTP.

Subsequently, the mixture was distilled under reduced pressure (150°C, 0.1 mbar) to yield a pure HEMA-dimer, as evidenced by NMR (figure D.5.).

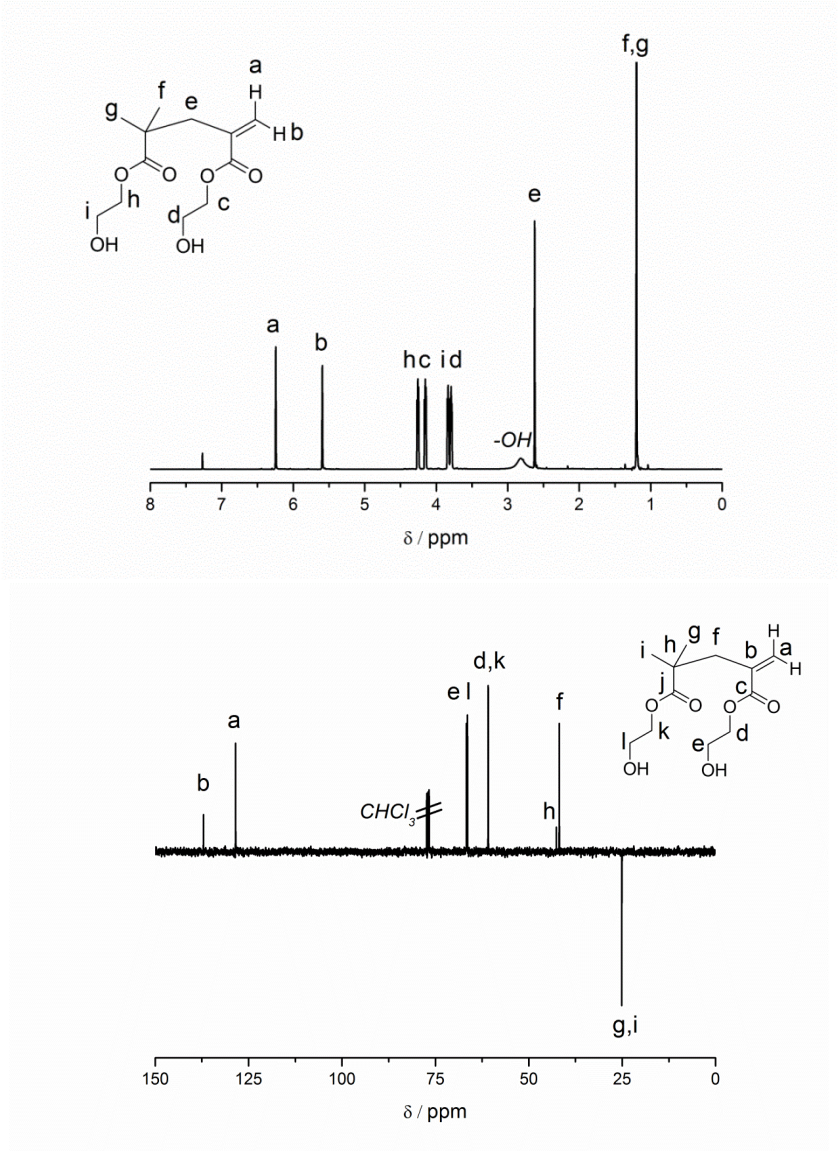
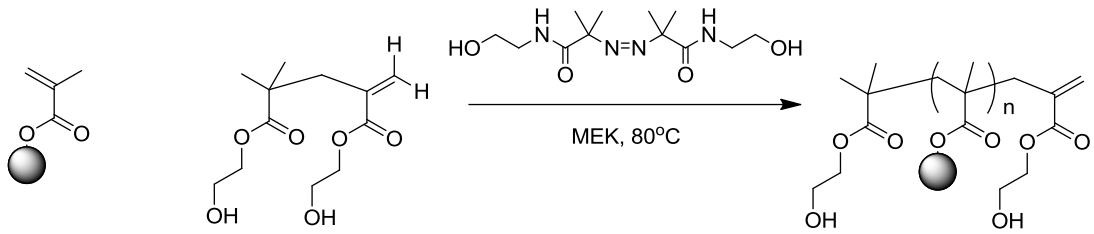


Figure D.5. ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of purified HEMA-Dimer.

Subsequently, HEMA-dimer was utilised as a CTA to mediate the polymerisation of MMA in MEK, utilising VA-086 as the radical source (scheme D.3). A hydroxyl containing initiator is preferred in order to maximise the yield of diols.



Scheme D.3. Polymerisation of methacrylates with HEMA-dimer as chain transfer agent.

The polymerisation of MMA was first attempted as a model monomer. The conditions employed followed previous reports, with [I]:[M]:[HEMA-Dimer]= 0.02: 1: 3, 50 % *w/w* in MEK at 80°C for 92 hours, thus targeting a polymer of M_n~ 5000 kDa. The resulting polymer was then precipitated in cold methanol to yield a white powder, which was further analysed by NMR and SEC (figure D.6).

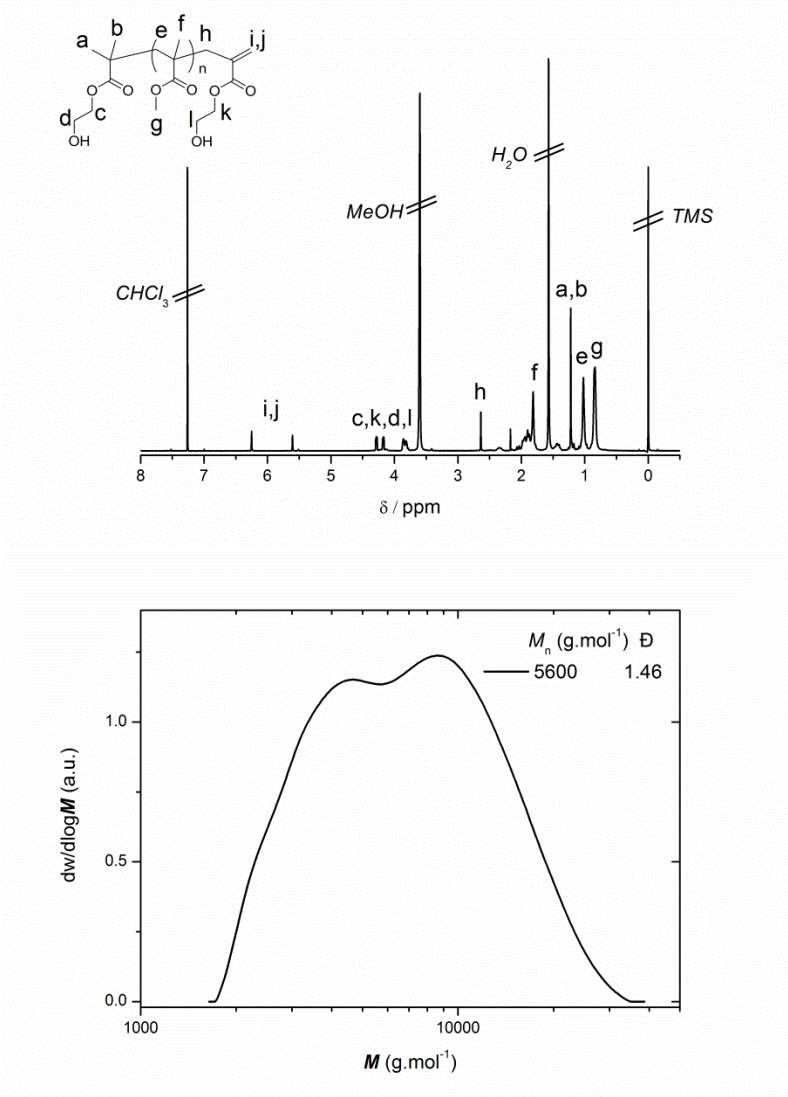


Figure D.6. Monitoring the polymerisation of MMA utilising HEMA-dimer as a CTA, by ^{1}H NMR (400 MHz, $CDCl_3$) and SEC (DMF eluent).

NMR analysis of the resulting polymer reveals the presence of hydroxyl groups on both ends of the polymer chain. Consequently, similar conditions were employed to polymerise IMA, yielding a polymer with slightly higher molecular weight.

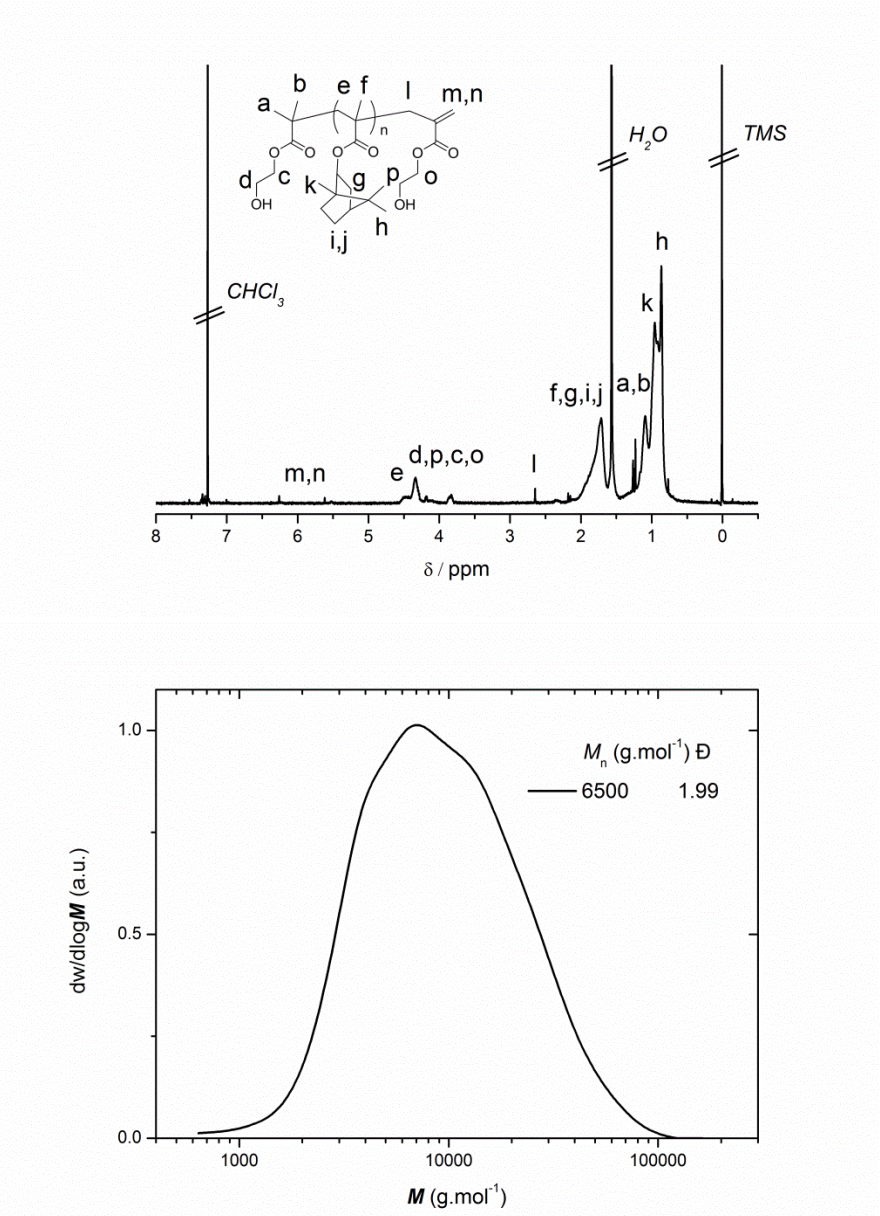
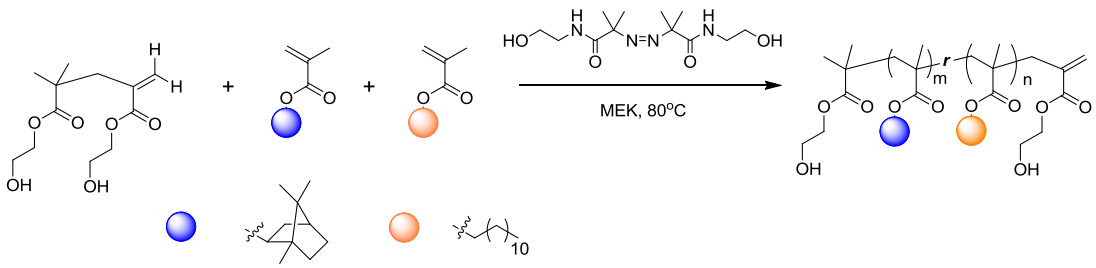


Figure D.7. Monitoring the polymerisation of IMA utilising HEMA-dimer as a CTA, by ^{1}H NMR (400 MHz, $CDCl_3$) and SEC (DMF eluent).

Unfortunately, the control over the polymerisation could not be retained as opposed to MMA. Although the presence of hydroxyl ends is evidenced by NMR, the yield of diols is not clear (figure D.7). Nevertheless, the versatility of the synthetic tool was tested towards a hydrophobic, oil soluble, high T_g polymer, PIMA-***r***-PLMA (scheme D.4).



Scheme D.4. Synthesis of PIMA-*r*-PLMA utilising HEMA-dimer as a CTA.

Unfortunately, low monomer conversion (50 %) gave rise to a lower MW copolymer containing IMA and LMA (figure D.8), wherein identical conditions were followed, [I]:[IMA]:[LMA]:[HEMA-dimer]= 0.02: 1: 1: 3, 50% *w/w* in MEK at 80°C.

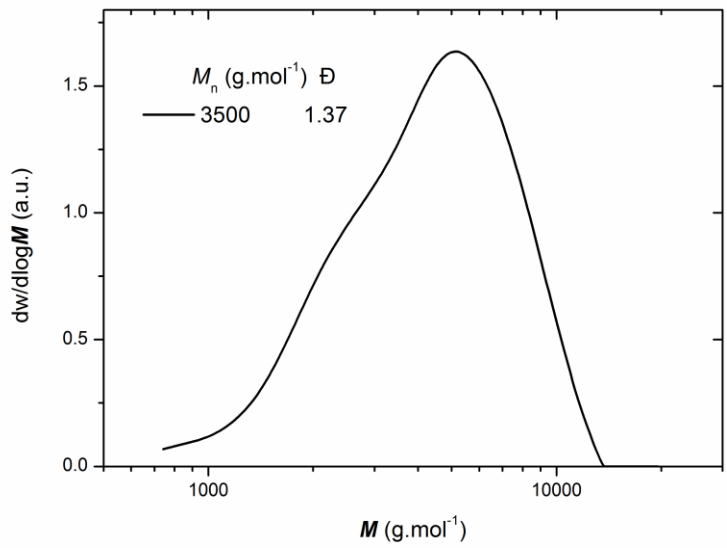


Figure D.8. Monitoring the copolymerisation of IMA and LMA utilising HEMA-dimer as a CTA, by SEC (DMF eluent).

In this section, we assessed the synthesis of high T_g diols by RDRP techniques. The synthesis of IA-containing diols proved to be accessible *via* a Cu(0)-mediated route, with good retention of the halide chain ends. However, the synthesis of higher T_g polymers, utilising methacrylate monomers did not show similar success. Consequently, RAFT

polymerisation was conducted, utilising a HEMA-dimer CTA, thus yielding to macro-diols with the targeted properties. Nevertheless, in order to demonstrate that PIMA could be utilised in a polyurethane formulation, a similar MW was targeted for a ω-hydroxyl polymer. Indeed, IMA was polymerised by CCTP in MEK, which was subsequently reacted with 2-mercapto ethanol to yield the targeted polymer. The reaction was monitored by NMR and SEC (figure D.9).

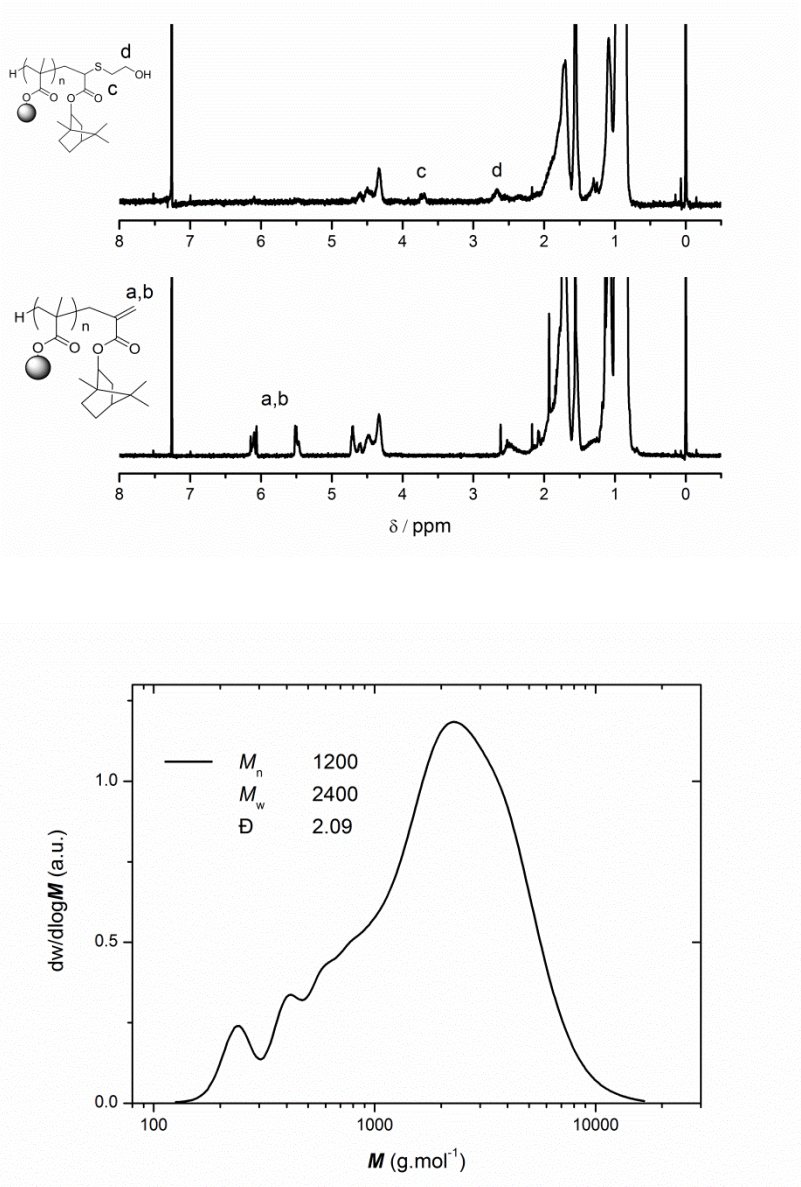


Figure D.9. Monitoring the synthesis and functionalisation of PIMA by CCTP, by ^{1}H NMR (400 MHz, $CDCl_3$, top) and SEC (DMF eluent, bottom).

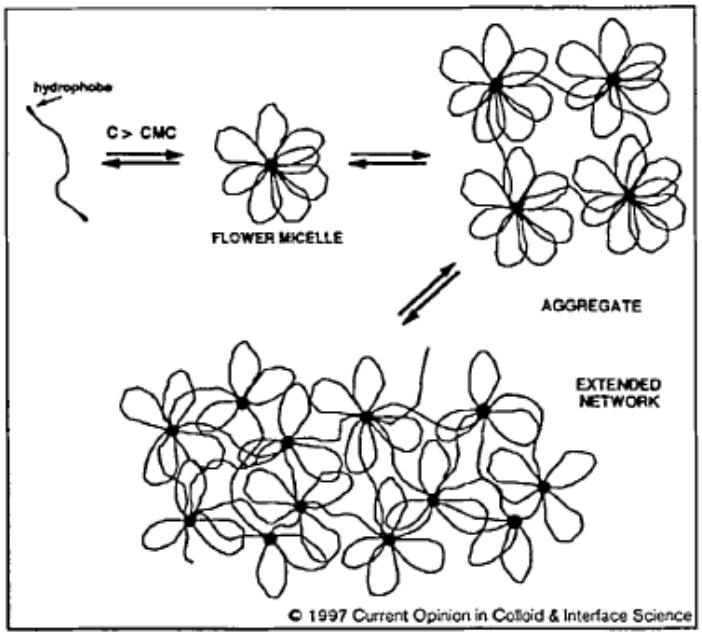
Pleasingly, the presence of hydroxyl groups on the ω-end of the PIMA is evidenced by NMR, with appearance of –C$\boldsymbol{H}_2$ peaks at 2.5-4 ppm. Such polymer was further sent to Lubrizol for testing as a "high T_g end-capping polymer" for a polyurethane formulation.

D.2.2.1 Perspectives

The polymerisation of high T_g acrylates and methacrylates has been carried out by Cu(0)-mediated RDRP, as well as sulphur-free RAFT polymerisation utilising an HEMA-dimer. However the yield of α,ω-hydroxyl telechelics is not always clear, and the synthesis could be improved. In this section, the main objective is to provide perspectives and guidelines towards an improved synthesis of such materials. For the use of Cu(0)-mediated RDRP, the focus should be in improving the reaction conditions (ligand and $Cu^{II}Br_2$ concentration, temperature) in order to improve the solubility of the resulting polymer, whilst retaining high chain end fidelity. Subsequently, strategies presented in section 2.2 could be applied. In the polymerisation of methacrylates by addition-fragmentation polymerisation in the presence of a HEMA-dimer, several points should be addressed. Firstly, the use of a low C_T CTA would involve an extensive improvement of the synthesis and future work would include the determination of the actual C_T of such dimer in those conditions, in order to tune the [I]/[M] and [CTA]/[M] ratios for an optimised RAFT process.[1, 2] Secondly, efforts could be made to improve the yield of CTA upon polymerisation and purification *via* distillation. Finally, the design of functional polyurethanes should be tested, employing the discussed α,ω-hydroxyl telechelics.

D.2.3 Towards acrylamide-based associative thickeners

The use of PEG-based hydrophobically modified ethoxylated urethanes (HEUR) associative thickeners, wherein a α,ω-hydroxyl PEG, a diisocyanate linker and a hydrophobic alcohol are reacted in order to self-assemble, proved to be of importance for the rheological behaviour of waterbone coatings and personal care formulations.[3-7]



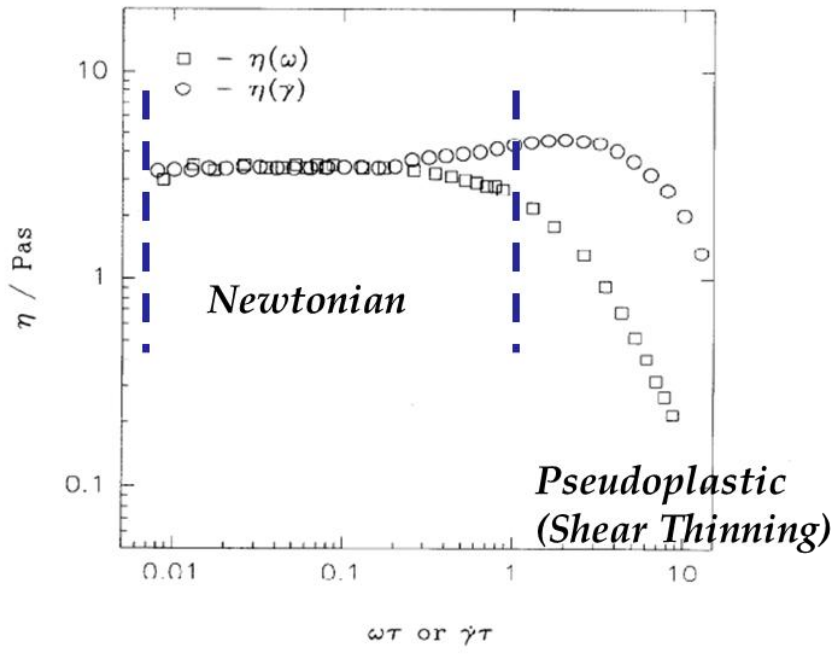
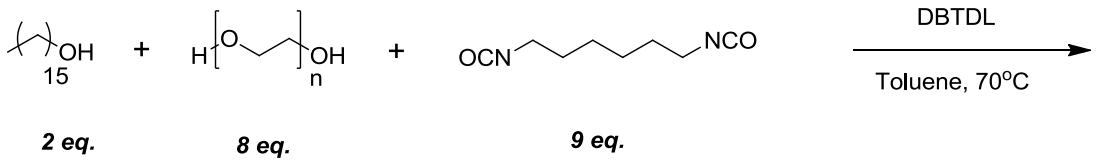


FIG. 3. Comparison of steady shear and dynamic viscosities as a function of reduced shear rate or frequency for C16/35 K at 1.5%w/v. T = 298 K.

Figure D.10. Self-assembly pathway of HEUR associative thickeners (top) and typical rheological behaviour (bottom), adapted from Glass.[8]

In this section, the focus is on the conducted attempts to (partially) replace the dihydroxyl PEG, with a poly(acrylamide) based diol synthesised in chapter 3. Firstly, the synthesis of such HEUR was assessed utilising two different sizes of PEG, M_n~ 3000 Da and M_n~ 4400 Da, with hexadecanol as an end-capping alcohol and hexamethylene diisocyanate (HDI) as the linker, with ratios provided by Lubrizol.



Scheme D.5. Synthesis of PEG-based HEURs.

The mixture of alcohol and PEG was azeotropically distilled in toluene, in order to remove residual water, before addition of HDI and tin catalyst. Upon complete disappearance of the hydroxyl ends (typically 3 hours), the polymer was precipitated in cold petroleum ether to yield a dry powder for SEC analysis (figure D.11).

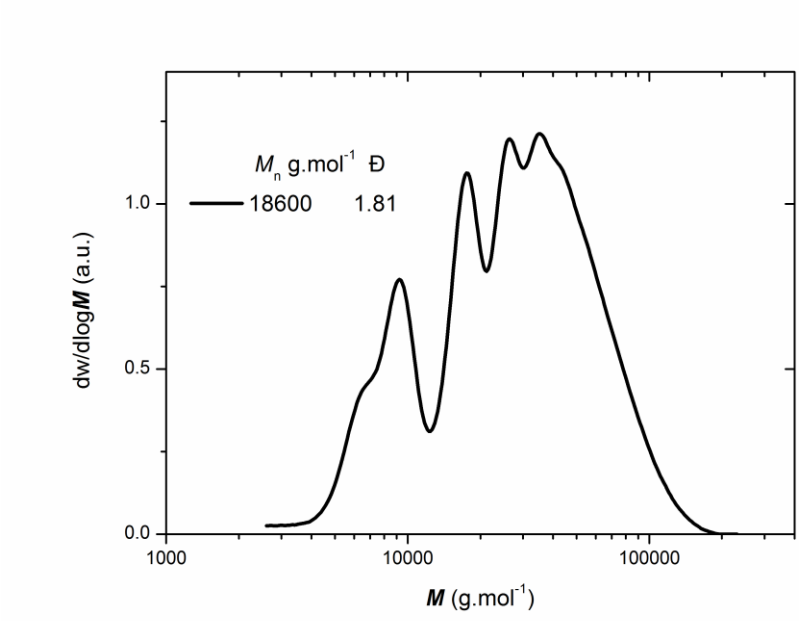


Figure D.11. Monitoring the synthesis of PEG based (av M_n=3000 g.mol^{-1}) HEUR by SEC (DMF eluent).

Similar MWD was observed for the PEG with av. M_n=4400 g.mol^{-1}. Subsequently, the polymers we solubilised at 2 *wt.* % in deionised water for rheology. The selected geometry was a cone/plate (2 rad/ 6 cm diameter), at 0.03 mm distance and at a shear rate ranging from 0.1 to 1000 s^{-1} (figure D.12).

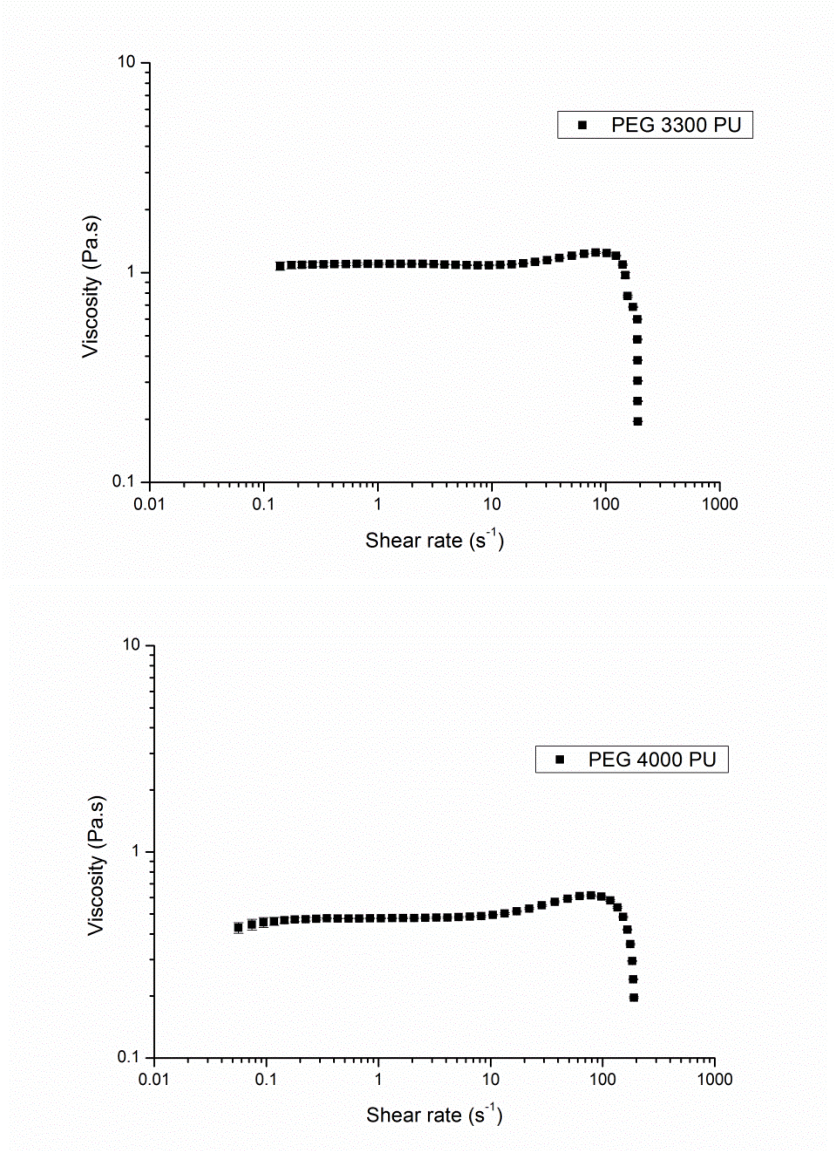
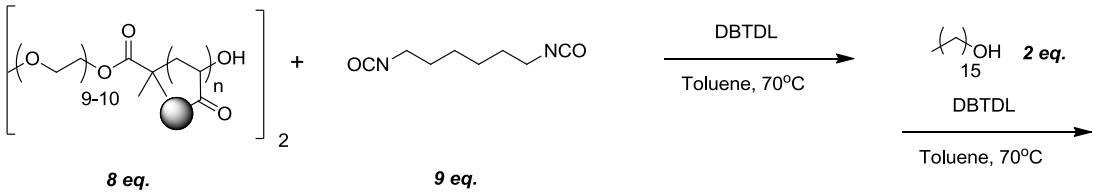


Figure D.12. Rheological behaviour of PEG-based HEUR; cone/plate (2 rad/ 6 cm diameter), at 0.03 mm distance and at a shear rate ranging from 0.1 to 1000 s^{-1}.

Although the measured viscosity in the Newtonian regime is lower than expected (probably due to the low molecular weight of the polyurethane), the shear-thinning regime at high shear rates is evident in the rheological response (figure D.12), suggesting a successful formation of HEUR thickeners.

The synthesis of poly(acrylamide) based HEUR was then attempted, following a similar synthetic route. However, the difference in reactivity between a secondary hydroxyl group (at the α,ω-end of the polymer) and the primary hydroxyls (at the α-end of the hexadecanol) towards isocyanates implies a modification in the order of addition before polycondensation (scheme D.6).



Scheme D.6. Synthesis of poly(acrylamide) based HEUR.

The solution of PNIPAAm diol (M_n=3500 g.mol^{-1}) in toluene was azeotropically distilled before addition of HDI and tin catalyst. After 2 hours of reaction, a pre-distilled solution of hexadecanol in toluene was added and the mixture reacted for an extra 5 hours. Unfortunately the polymer product had a lower MW than expected, as evidenced by SEC (figure D.13).

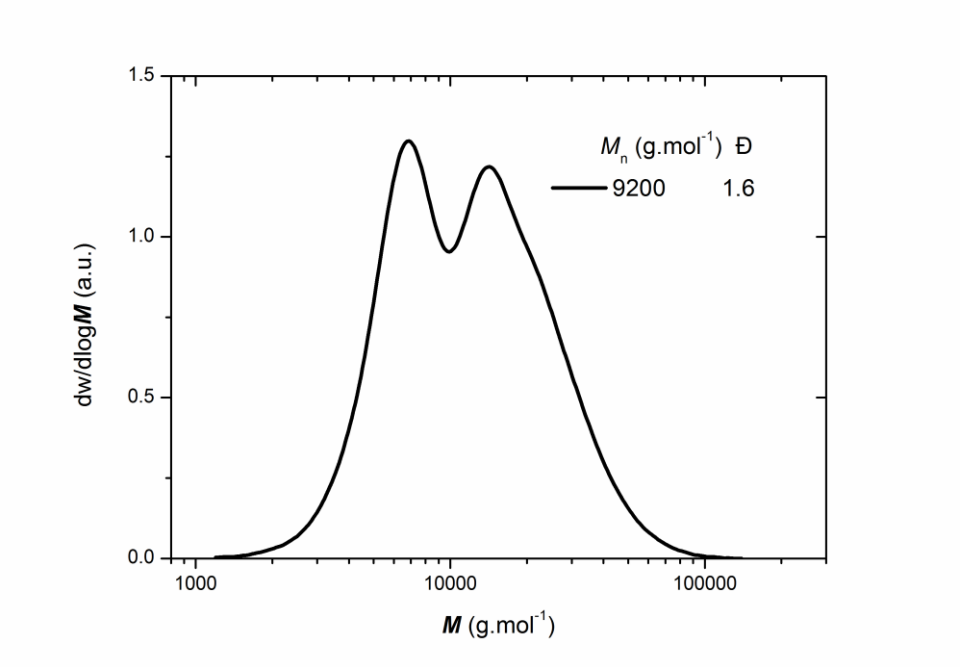


Figure D.13. Monitoring the synthesis of PNIPAAm based (av M_n=3000 g.mol^{-1}) HEUR by SEC (DMF eluent).

This poor control over the polycondensation step could be due to a water contamination of the dried PNIPAAm diol, a poorer reactivity of the secondary α,ω-hydroxyl ends and/or an underestimated hydroxyl chain end fidelity. The low MW of the final polymer was detrimental for the expected rheological behaviour of a 2 *wt.* % in DI water. Indeed, a Newtonian behaviour was observed within the range of tested shear rates.

Consequently, numerous effort were conducted in order to improve the synthesis of a poly(acrylamide) containing polyurethane, first by extensive drying of the solution, then by changing the ratios of [diol]:[diisocyanate] from 8:9 to 8:10 without any significant change in the resulting MW. Subsequently, a PDMA diol of similar MW (M_n~ 3500 g.mol^{-1}) was employed as the building telechelic, though no significant change in MW upon polycondensation.

D.2.3.1 Perspectives

The design of poly(acrylamide) based associative thickeners is extremely interesting for the development of novel shear thinning polyurethanes. Hence, the current investigations merit further investigations towards this end. Future work could include the optimisation of the ratios between dissocyanate and diol in order to yield a high MW polymer. Moreover, the use of a more hydrophobic end-capping alcohol could improve the self-assembly of low MW polyurethanes. Finally, changing the properties (*e.g.* stimuli-responsive behaviour) of the macrodiol could yield to highly sophisticated polyurethanes.

D.3 Experimental

D.3.1 Materials

Previously used compounds can be found in previous sections. All monomers employed were purchased from Sigma-Aldrich at the highest available grade, passed through basic alumina column and kept refrigerated. Hexamethylene diisocyanate (97%, Fisher Scientific) and 1-hexadecanol (98%, Sigma-Aldrich) were used as received without further purification. Cobalt(II) cobaloxime (CoBF) was synthesised according to a reported procedure.[9] 2,2'-Azobis(2-methyproprionitrile) (AIBN, 98%) was purchased from Sigma-Aldrich and 2,2'-azobis[2-methyl-*N*-(2-hydroxyethyl)propionamide] (VA-086) was purchased from Wako and used without further purification.

D.3.2 Characterisation

^{1}H, ^{13}C NMR spectra were recorded on Bruker ACF-250, DPX-300, DPX-400 and DPX-500 spectrometers using deuterated solvents obtained from Sigma-Aldrich.

DMF SEC traces were obtained on a Varian 390-LC system using a DMF (+ 5 mM NH_4BH_4) eluent at 50°C, equipped with refractive index and UV detectors, 2 × PLgel 5 mm mixed D columns (300 × 7.5 mm), 1 × PLgel 5 mm guard column (50 × 7.5 mm) and autosampler. Narrow linear poly(methyl methacrylate) standards in range of 200 to 1.0×10^6 $g \cdot mol^{-1}$ were used to calibrate the system. All samples were passed through 0.45 µm PTFE filter before analysis.

Differential scanning calorimetry (DSC) was conducted on a Mettler Toledo DSC1-400 whereby three cycles using a temperature grade from -50°C to 150°C at 10°C/min were applied.

Rheology was conducted on a TA Instruments AR G2 Rheometer at 25°C, using a cone/plate (2 rad/ 6 cm diameter) geometry, at 0.03 mm distance and at a shear rate ranging from 0.1 to 1000 s^{-1}, in triplicate.

D.3.3 Synthesis of high T_g poly(acrylates)

Refer to section 2.4 and 4.4 for details.

D.3.4 Synthesis of HEMA-dimer

In a 500 mL RB flask was added HEMA (150 mL) and MEK (150 mL). The solution was deoxygenated with nitrogen for at least 30 minutes before adding CoBF (100 mg) and AIBN

(500 mg) under a nitrogen blanket. The solution was deoxygenated for an extra 30 minutes before heating at 60°C for 48 hours. Subsequently BHT (~50-100 mg) was added to the solution and MEK was removed by rotary evaporation. HEMA-dimer was then collected by vacuum distillation (150°C, 0.1 mbar), as the 3rd fraction (1st, residual MEK; 2nd HEMA, 35-140°C, 0.1 mbar) as a viscous colourless liquid and kept under nitrogen at -10°C.

D.3.5 Synthesis of high T_g poly(methacrylates) by RAFT

This generic procedure for MMA can be applied for other monomers.

HEMA-Dimer (2.2 g, 3 eq.) was added to a Schlenk tube, along with MMA (0.53 mL, 4.9 mmol, 1 eq.), VA-086 (28.8 mg, [I]/[M]= 2%) and MEK (3 mL, 50 % *w/w*). The solution was deoxygenated for 15 minutes with nitrogen and placed in an oil bath at 80°C for over 48 hours. Subsequently, the polymer was precipitated in cold methanol to yield a white powder.

D.3.6 Synthesis of HEUR associative thickeners

This procedure can be adapted to any HEUR synthesis presented.

In a 250 RB flask was added PEG (av. M_n= 3300 g.mol^{-1}, 5.27 g, 8 eq.), 1-hexadecanol (0.1 g, 2 eq.) and toluene (200 mL). The mixture was stirred and azeotropically distilled to remove residual water (~ 75 mL). Subsequently, hexamethylene diisocyanate (HDI, 297 µL, 9 eq.) and dibutyltin dilaureate (3 drops) were added under nitrogen, and the reaction stirred at 70°C for 5 hours. The resulting polymer was precipitated in cold petroleum ether to yield a white powder.

D.4 References

1. G. Gody, T. Maschmeyer, P. B. Zetterlund and S. Perrier, *Macromolecules*, 2014, **47**, 639-649.
2. G. Gody, T. Maschmeyer, P. B. Zetterlund and S. Perrier, *Macromolecules*, 2014, **47**, 3451-3460.
3. J. E. Glass, *Polymers in aqueous media: performance through association*, American Chemical Society, 1989.
4. J. P. Kaczmarski and J. E. Glass, *Macromolecules*, 1993, **26**, 5149-5156.
5. A. P. Mast, R. K. Prud'homme and J. E. Glass, *Langmuir*, 1993, **9**, 708-715.
6. T. Annable, R. Buscall and R. Ettelaie, *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 1996, **112**, 97-116.
7. J. E. Glass, *Associative Polymers in Aqueous Solutions*, American Chemical Society, 2000.
8. J. E. Glass, *Journal of Coatings Technology*, 2001, **73**, 79-98.
9. A. Bakac and J. H. Espenson, *J. Am. Chem. Soc.*, 1984, **106**, 5197-5202.

Appendix E

Appendix E: List of peer-reviewed publications

(12) Methacrylic zwitterionic, thermoresponsive and hydrophilic (co)polymers via Cu(0)-polymerization; the importance of halide salt additives; **Alexandre Simula**, Athina Anastasaki and David M. Haddleton, *Macromolecular Rapid Communication*, 2015, accepted manuscript.

(11) Investigating the mechanism of copper(0)-mediated living radical polymerization in aqueous media; Fehaid Alsubaie, Athina Anastasaki, Vasiliki Nikolaou, **Alexandre Simula**, Gabit Nurumbetov, Paul Wilson, Kristian Kempe and David M. Haddleton, *Macromolecules*, 2015, **48**, 6421-6432.

(10) Investigating the mechanism of copper(0)-mediated living radical polymerization in organic media; Fehaid Alsubaie, Athina Anastasaki, Vasiliki Nikolaou, **Alexandre Simula**, Gabit Nurumbetov, Paul Wilson, Kristian Kempe and David M. Haddleton, *Macromolecules*, 2015, **48**, 5517-5525.

(9) The effect of ligand, solvent and Cu(0) source on the efficient polymerization of polyether acrylates and methacrylates in aqueous and organic media; **Alexandre Simula**, Vasiliki Nikolaou, Fehaid Alsubaie, Athina Anastasaki and David M. Haddleton, *Polymer Chemistry*, 2015, **6**, 5940-5950.

(8) Copper(II) gluconate (a non-toxic food supplement/dietary aid) as a precursor catalyst for effective photo-induced living radical polymerisation of acrylates; Vasiliki Nikolaou, Athina Anastasaki, Fehaid Alsubaie, **Alexandre Simula**, David Fox and David Haddleton, *Polymer Chemistry*, 2015, **6**, 3581-3585

(7) Photoinduced Synthesis of α,ω-Telechelic Sequence-Controlled Multiblock Copolymers; Athina Anastasaki , Vasiliki Nikolaou , Nicholas William McCaul , **Alexandre Simula**, Jamie Godfrey , Christopher Waldron, Paul Wilson, Kristian Kempe and David M. Haddleton, *Macromolecules*, 2015, **48**, 1404-1411.

(6) Synthesis of well-defined α,ω-telechelic multiblock copolymers in aqueous medium: *In situ* generation of α,ω-diols; **Alexandre Simula**, Vasiliki Nikolaou, Athina Anastasaki, Fehaid Alsubaie, Gabit Nurumbetov, Paul Wilson, Kristian Kempe and David M. Haddleton, *Polymer Chemistry*, 2015, **6**, 2226-2233.

(5) Polymerization-Induced Thermal Self-Assembly (PITSA); Charles Adrian Figg, **Alexandre Simula**, Kalkidan Asmelash Gebre, Bryan S Tucker, David Haddleton and Brent S Sumerlin, *Chemical Science*, 2014, **6**, 1230-1236.

(4) Synthesis and reactivity of α,ω-homotelechelic polymers by Cu(0)-mediated Living Radical Polymerization; **Alexandre Simula**, Gabit Nurumbetov, Athina Anastasaki, Paul Wilson and David M. Haddleton, *European Polymer Journal*, 2014, **62**, 294-303.

(3) Expanding the Scope of the Photoinduced Living Radical Polymerization of Acrylates in the Presence of $CuBr_2$ and Me_6-Tren; Athina Anastasaki, Vasiliki Nikolaou, **Alexandre Simula**, Jamie Godfrey, Muxiu Li, Gabit Nurumbetov, Paul Wilson, and David M. Haddleton, *Macromolecules*, 2014, **47** (12), 3852–3859.

(2) Aqueous Copper-Mediated Living Radical Polymerisation of *N*-Acryloylmorpholine, SET-LRP in Water; A. Anastasaki, A. J. Haddleton, Q. Zhang, **A. Simula**, M. Droesbeke, P. Wilson and D. M. Haddleton, *Macromolar Rapid Communication*, 2014, **35**(10), 965-970.

(1) Absolut "copper catalyzation perfected"; robust living polymerization of NIPAM: Guinness is good for SET-LRP; C. Waldron, Q. Zhang, Z. Li, V. Nikolaou, G. Nurumbetov, J. Godfrey, R. McHale, G. Yilmaz, R. K. Randev, M. Girault, K. McEwan, D. M. Haddleton, M. Droesbeke, A. J. Haddleton, P. Wilson, **A. Simula**, J. Collins, D. J. Lloyd, J. A. Burns, C. Summers, C. Houben, A. Anastasaki, M. Li, C. R. Becer, J. K. Kiviaho and N. Risangud, *Polymer Chemistry*, 2014, **5**, 57-61.