Controlled Radical Polymerisation in Aqueous Media: New Approaches

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“The man who taught me how to diagram a segment of a molecule of plastic was Professor Walter H. Stockmayer of Dartmouth College. He is a distinguished physical chemist, and an amusing and useful friend of mine. I did not make him up. I would like to be Professor Walter H. Stockmayer. He is a brilliant pianist. He skis like a dream.

And when he sketched a plausible molecule, he indicated points where it would go on and on just as I have indicated them - ... with an abbreviation that means sameness without end.

The proper ending for a story about people it seems to me, since life is now a polymer in which the Earth is wrapped so tightly, should be that same abbreviation ... it is in order to acknowledge the continuity of that polymer that I begin so many sentences with 'And' and 'So,' and end so many paragraphs with '...and so on.'

And so on. 'It's all like an ocean!' cried Dostoevsky. I say it's all like cellophane.”

Kurt Vonnegut – *Breakfast of Champions*

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Abbreviations

AA	Acrylic Acid
AGET	Activators Generated by Electron Transfer
Am	Acrylamide
AOWP	Agent on Weight of Pigment
APC	Acryloyl Phosphatidyl Chloride
ARGET	Activators Regenerated by Electron Transfer
ASEC	Aqueous Size Exclusion Chromatography
ATRP	Atom Transfer Radical Polymerization
BA	Butyl Acrylate
BHT	Butylated Hydroxytoluene
BMA	Butyl Methacrylate
BPN	2-Bromoproprionitrile
BSA	Bovine Serum Albumin
BnA	Benzyl Acrylate
BnMA	Benzyl Methacrylate
CBL	Bovine Liver Catalase
CRP	Controlled Radical Polymerization
CTA	Chain Transfer Agent
DLS	Dynamic Light Scattering
DMAEA	Dimethylaminoethyl Acrylate
DMAEMA	Dimethylaminoethyl Methacrylate
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DP	Degree of Polymerization
DRI	Differential Refractive Index
eATRP	Electrochemical ATRP
EBiB	Ethyl Bromoisobutyrate
EBP	Ethyl Bromopropionate
EGMA	Ethylene Glycol methyl ether Methacrylate
EMA	Ethyl Methacrylate
FDA	Food and Drug Administration
FT-NIR	Fourier Transform Near Infrared
GMA	Glycidyl Methacrylate

GPC	Gel Permeation Chromatography
GRAS	Generally Regarded As Safe
Hb	Haemoglobin
HEA	Hydroxyethyl Acrylate
HEAm	Hydroxyethyl Acrylate
HEMA	Hydroxyethyl Methacrylate
HRP	Horseradish peroxidase
ICAR	Initiators for Continuous Activator Regeneration
IPA	Isopropyl Alcohol
ISET	Inner sphere Single Electron Transfer
KSPA	Potassium Sulfopropyl Acrylate
LCST	Lower Critical Solution Temperature
MA	Methyl Acrylate
MAA	Methacrylic Acid
MALDI-ToF MS	Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry
MBPA	Methyl Bromophenylacetate
MCP	Methyl Chloropropionate
Me_6Tren	Tris[2-(dimethylamino)ethyl]amine
MMA	Methyl Methacrylate
MPC	Methacryloxyethyl Phosphocholine
MWD	Molecular Weight Distribution
NaAMPS	2-Acrylamido-2-Methylpropane Sulfonic Acid sSodium Salt
Nam	*N*-acryloylmorpholine
NaMA	Sodium Methacrylate
NiPAM	*N*-isopropyl Acrylamide
NMP	Nitroxide Mediated Polymerization
NMR	Nuclear Magnetic Resonance
NVP	*N*-Vinyl Pyrrolidone
OSET	Outer Sphere Single Electron Transfer
PBS	Phosphate Buffer Solution
PEGA	Poly(ethylene glycol) Methyl Ether Acrylate
PEGMA	Poly(ethylene glycol) Methyl Ether Methacrylate
PMDETA	N,N,N′,N″,N″-Pentamethyldiethylenetriamine
ppm	Parts Per Million

PRE	Persistent Radical Effect
RAFT	Reversible Addition Fragmentation Chain Transfer
RDRP	Reversible Deactivation Radical Polymerization
SARA	Supplemental Activator and Reducing Agent
SEC	Size Exclusion Chromatography
SET-LRP	Single Electron Transfer Living Radical Polymerization
tBA	*Tert*-Butyl Acrylate
TDA	Tris (3,6-dioxa-heptyl) Amine
TEA	Triethylamine
THF	Tetrahydrofuran
TMEDA	N,N,N′,N′-Tetramethylethylenediamine
TMM-RDRP	Transition Metal Mediated RDRP
TPMA	Tris(2-pyridylmethyl)amine
VOC	Volatile Organic Compounds
VS	Viscometry
WSI	Water Soluble Initiator

Acknowledgements

First and foremost, I would like to thank Professor Dave Haddleton, for allowing me the opportunity to pursue a PhD in his group. I cannot thank him enough for all he has done for me. Dave is a great scientist, but what really makes the difference is how much he cares about his students. I remember feeling very dejected one morning working on some very difficult revisions for a paper, Dave came into the office and saw I wasn't very happy so started singing "For the good times" by Kris Kristofferson, not a karaoke classic like "teenage kicks", but it certainly put a smile on my face. What I admire most about Professor Haddleton is his pragmatism, which is something I will work to emulate in my future career. Whenever I think about experiments now I always hear a voice in my head saying "Just do it!"

Secondly, I would like to thank Dr Athina Anastasaki. Athina has been there for me from day 1 (even though she scared the living daylights out of me when I was a Masters student!). Her continued support has helped me at both the high and low points of PhD life, and I will forever be thankful to her. Athina's commitment to science is seconded only by her commitment to being a good person and a great friend. I look forward to attending her 3rd Nobel Prize acceptance speech.

I would also like to thanks the Lubrizol Corporation for funding my PhD research, particularly Dr Andrew Shooter, Dr Stewart Richards and Robert Jennings for all their help and advice.

Nikos (008) and I started our PhD's on the same day and sat opposite each other for 3 years. I'd like to thank him for all the hilarious adventures we've had together, especially the P2M conference in Lacanau, but sadly the acknowledgements section of a thesis is perhaps not the most appropriate place to mention that. I told him I'd make an Englishman of him, but I'm afraid he's turned me a bit Greek.

Richard has been a great friend all throughout our time as PhD students, even if he didn't wear the tee shirt I got him with a well-known UK political party logo. Richard's support during our second year is something I will always be thankful for. I'll never forget the great California adventure (driving with his eyes closed on the hills of San Francisco).

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Thanks also to my friends Ben, Emma, Gareth, James and Ed, and my housemates James and Dan, for putting up with (and maybe sometimes enjoying) my dark sense of humour.

Finally, I'd like to thank my parents for their unwavering support throughout my time at Warwick.

Declaration

Experimental work contained in this thesis is original research carried out by the author, unless otherwise stated, in the Department of Chemistry at the University of Warwick between October 2014 and June 2018. No material contained herein has been submitted for any other degree, or at any other institution.

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

Date:

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Glen R. Jones

Abstract

The aim of this work was to develop methods of controlling radical polymerization in aqueous and polar media using copper catalysts. Water as a solvent is important as it is cheap, abundant and environmentally benign. Control of radical polymerization in water is desirable as it allows for the synthesis of functional hydrophilic macromolecules with wide ranging applications.

As a starting point the aqueous Cu(0)-RDRP of acrylamide (Am) was optimized; yielding a process capable to controlling the polymerization of a monomer which has traditionally been seen as highly challenging. Reactions were found to proceed rapidly in aqueous media, with quantitative monomer conversion being attained in just a few minutes. High end group fidelity was proven *via in-situ* chain extensions to yield stimuli responsive block copolymers.

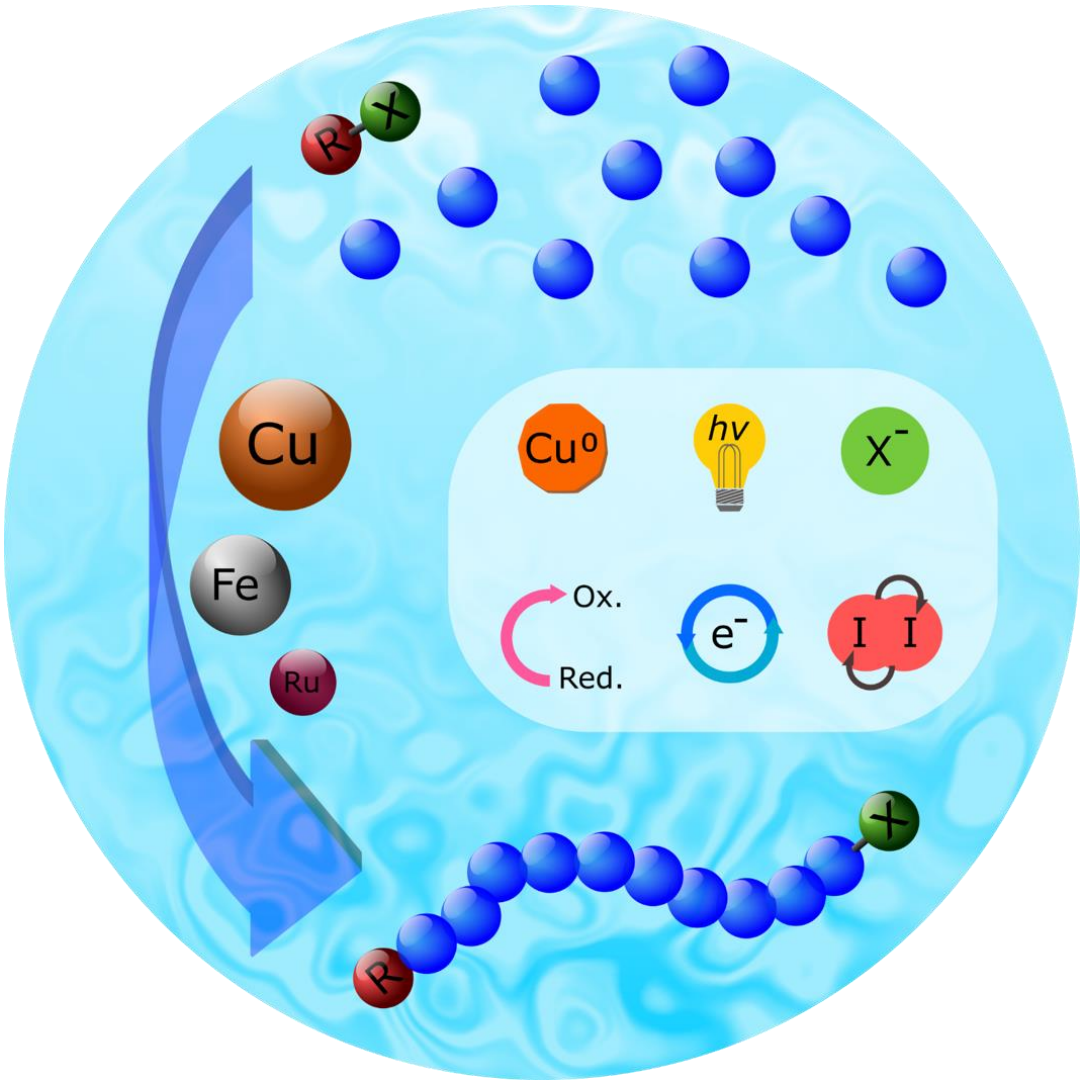
Photopolymerization mediated by excess tertiary amine ligand and a Cu(II) complex is well reported in organic media and has been successfully employed to synthesize a wide range of complex functional macromolecular architectures. However, attempts at conducting these polymerizations in aqueous media had proved challenging. The second part of this thesis optimizes and approach to aqueous photopolymerization by offsetting a deleterious side reaction through addition of a halide salt. Controlled polymerization was achieved at ppm copper concentrations with excellent temporal control.

Polymerization of methacrylates was then investigated in polar organic media. It was found that the stability of the initiating radical plays a significant role in the degree of control over the polymerization. This principle was also then applied in aqueous media, with limited success.

Finally, Cu(0) mediated RDRP was utilized to synthesize a number of novel pigment dispersants for use in waterborne coatings, including a series of polymers with varied molecular weight distributions. In collaboration with industry sponsors, Lubrizol, these polymers were milled with carbon black pigments in order to test their efficacy.

Chapter 1: Introduction

Transition Metal Mediated Reversible Deactivation Radical Polymerisation in Aqueous Media



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1.1 What are polymers?

The word ‘polymer’ is derived from the ancient Greek word *polus*, meaning ‘many’ and *meros* meaning ‘part’. The modern concept of polymers; molecules of high molecular weight comprised of multiple repeating units known as monomers, was first proposed by Staudinger in 1920 for which he won the Nobel prize in chemistry in 1953. Polymers are a large group of materials encompassing natural materials such as rubber, polysaccharides (e.g. cellulose), and polyamino acids (proteins) as well as a plethora of synthetic materials such as polyethylene and polystyrene.

1.2 Free Radical Polymerisation

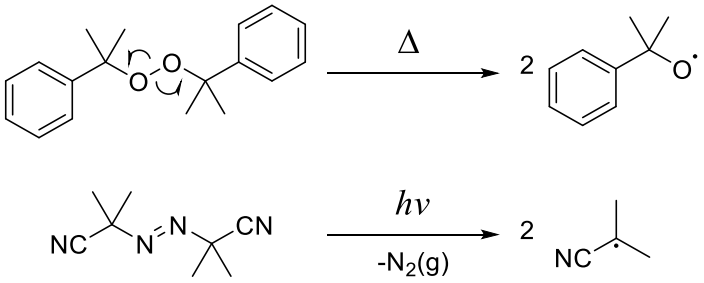
Free radical polymerisation is a method of chain growth polymerisation in which macromolecules are formed by successive addition of a radical to a monomer, usually containing a vinyl group. Advantages of radical polymerisations include relatively facile reaction conditions, high monomer compatibility as it is inert to most functional groups, good tolerance of trace impurities meaning that reagents and solvents do not have to be rigorously purified or dried and reactions can often be carried out in aqueous media.

During initiation a radical is formed from which a polymer chain starts growing. Examples of two common initiation methods, thermal decomposition and photolysis are depicted in scheme 1.1. Initiation consists of two steps: generation of radicals from initiator molecules (eq. 1.1, decomposition), and addition of the initiator radical species to a monomer unit (eq. 1.2, initiation).

$$I_2 \xrightarrow{k_d} 2I^{\bullet} \qquad \textbf{(1.1)}$$

$$I^{\bullet} + M \xrightarrow{k_i} P^{\bullet} \qquad \textbf{(1.2)}$$

The amount of initiating radicals that undergo the reaction in eq. 1.2 is described by the initiator efficiency, *f*, defined as the ratio between radicals that add to monomer versus those that undergo primary recombination or other deleterious side reactions. If all radicals undergo addition to monomer *f* takes a value of 1.



Scheme 1.1 *Top: thermal decomposition of dicumyl peroxide to give to initiating radicals. Bottom: photolysis of azoisobutylnitrile (AIBN) to give two initiating radicals with loss of nitrogen gas.*

Propagation is the chain growth process of a radical through successive radical addition to monomer, as shown in eq. 1.3. With each addition the chain grows by one monomer unit and, according to the long chain approximation, the reactivity of the resultant radical species remains constant. Propagation typically occurs very rapidly to give polymer chains with up to hundreds or thousands of monomer units, with the lifetime of a growing chain typically around 1 second.

$$P^{\bullet} + nM \xrightarrow{k_p} P_n^{\bullet} \qquad \textbf{(1.3)}$$

The propagating radical eventually undergoes termination, typically by either radical combination or radical disproportionation (eq. 1.4.) Combination involves two radicals coupling, giving a single 'dead' polymer chain with a chain length equal to the sum of the two terminated propagating radical chains. Disproportionation involves abstraction of a hydrogen to give one saturated and one unsaturated 'dead' polymer chains.

$$P_n^{\bullet} + P_m^{\bullet} \xrightarrow{k_t} P_n^{=} + P_m^{H} \; or \; P_{n+m} \qquad \textbf{(1.4)}$$

The rate of polymerisation can be defined as the rate of disappearance of monomer. Looking at equations 1.1-1.4, it can be seen that 1.2 and 1.3 involve the consumption of monomer, thus the rate of polymerisation is equal to the rate of initiation (R_i) added to the rate of propagation (R_p). Comparing the actual amounts of monomer consumed by these two reactions it becomes clear that propagation is a much more significant source of monomer depletion and hence the overall rate of polymerisation can be described by equation 1.5.

$$\frac{-d[\mathrm{M}]}{dt} = \mathrm{R_p} = k_p[\mathrm{P^\bullet}][\mathrm{M}] \qquad \textbf{(1.5)}$$

Equation 1.5 can be problematic to use as it is difficult to experimentally determine the concentration of radicals, [P•] in a reaction (typically on the order of 10^{-8} molar). Applying the steady state approximation to the concentration of radicals in a polymerisation gives a constant value and is used to simplify the equation. A result of this is that the rate of initiation and termination are effectively equal. The rate of termination is shown in equation 1.6. This expression can be rearranged to give equation 1.7, which can subsequently be substituted into equation 1.5 to give equation 1.8.

$$\mathrm{R_t} = 2k_t[\mathrm{P^\bullet}]^2 \qquad \textbf{(1.6)}$$

$$[\mathrm{P^\bullet}] = \left(\frac{\mathrm{R_i}}{2k_t}\right)^{\frac{1}{2}} \qquad \textbf{(1.7)}$$

$$\mathrm{R_p} = k_p[\mathrm{M}]\left(\frac{\mathrm{R_i}}{2k_t}\right)^{\frac{1}{2}} \qquad \textbf{(1.8)}$$

The initiation of a polymerisation is split into 2 steps, as shown in equations 1.1 and 1.2. Addition of an initiating radical to monomer is much faster than homolysis of the initiator, hence equation 1.1 is the rate determining step. Taking a rate expression for the initiation including the initiator efficiency, *f*, and substituting into equation 1.8 yields equation 1.9.

$$\mathrm{R_p} = k_p[\mathrm{M}]\left(\frac{fk_d[\mathrm{I}]}{k_t}\right)^{\frac{1}{2}} \qquad \textbf{(1.9)}$$

1.3 Living Polymerisation

Living polymerisation is a form of chain growth polymerisation in which the propagating polymer chains are unable to undergo chain transfer or termination reactions. In cases in which initiation is fast a linear dependence of molecular weight with conversion is observed, and as a result the degree of polymerisation (DP) is directly linked to the concentration of initiator at t_0 and the amount of monomer consumed. Living polymerisation was pioneered by Szwarc in the 1950's through work on the anionic polymerisation of styrene,[1] and later expanded to include a range of vinyl monomers with electron withdrawing substituents which can stabilize the negative charge through delocalization, including styrene derivatives and

(meth)acrylates.[2] The lack of chain transfer and termination allows for specific molecular weights to be targeted, as well as retention of activity after monomer conversion reaches 100%. This retention of the carbanion at the chain end means that polymerisation will continue if a second aliquot of monomer is added to the reaction vessel, giving access to block copolymers and other complex macromolecular architectures.

A key disadvantage of living anionic polymerisation is the stringent reaction conditions required to facilitate zero termination and chain transfer events; reactions are extremely moisture and carbon dioxide sensitive thus high vacuum techniques are required, and reactions cannot be carried out in protic media, with water and alcohols often used as common terminating agents. Certain monomer classes such as acrylamides are also not compatible with anionic polymerisation, as the anion can be more stable on a hetero atom such as nitrogen, leading to propagation from a non-carbanion species,[3] which will result in heteroatoms being introduced into the backbone of the polymer. A direct result of these disadvantages is that anionic polymerisation is not suited to the preparation of macromolecules in water.[4-6]

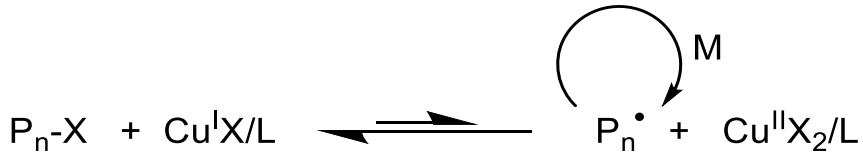
1.4 Reversible Deactivation Radical Polymerisation (RDRP)

Attaining a high degree of control over molecular weight, macromolecular architecture and chemical functionality using radical polymerisations had been a long standing goal in polymer chemistry. This was realized to certain extents in the 1980's with the advent of reversible deactivation radical polymerisation (RDRP) techniques. Broadly speaking, the chemistry of an RDRP is *via* a free radical propagating species which exists in an equilibrium with dormant species. Whilst only a small proportion of chains are actively propagating at any one instant in time, the interconversion between active and dormant states is relatively fast. This results in the same probability of growth for each chain yielding polymers with narrow molecular weight distributions (dispersity) and a number average molecular weight directly correlated with the ratio between monomer and initiator/RDRP agent.

Three main techniques have emerged as the most viable RDRP approaches: nitroxide mediated polymerisation (NMP),[7,8] reversible addition fragmentation chain transfer (RAFT) polymerisation,[9,10] and transition metal mediated approaches (e.g. atom transfer radical polymerisation, ATRP).[11-13]

1.5 Transition Metal Mediated RDRP in Aqueous Media

A particular advantage of RDRP is the ability to control polymerisation of vinyl monomers in aqueous media. The need for sustainable, high capacity and arguably environmentally friendly chemical processes has led to an increase in the use of water as a reaction medium.[14] If a solvent is to be used for a chemical reaction, water has advantages of being inexpensive, non-toxic and readily available. Water also has many unique properties which suit it to a wide range of chemistries and substrates: its high specific heat capacity is ideal for reactions which are exothermic, the solubility of salts allows for many additional effects such as salting-in or salting-out, pH can be simply varied, solutions can be buffered, and co-solvents can be utilized to further increase solubility and monomer scope. Crucially, the use of water as a reaction solvent is the ideal medium for biologically oriented applications – water is the preferred solvent for natural processes.



Scheme 1.2*: Simplified mechanism of atom transfer radical polymerisation (ATRP).*

Both RAFT and NMP have been successfully reported to proceed in aqueous media with relatively few restrictions, yielding well-defined polymers with narrow molecular weight distributions and high end group fidelity. On the contrary, ATRP (scheme 1.2) initially appeared to be much more sensitive under aqueous conditions and for a long time was considered too challenging to achieve. However, owing to the additional benefits offered through these strategies, including the possibility to run the polymerisations at very low temperatures and the facile functionalization of the halide end group, significant attention has been drawn.

Numerous reviews cover ATRP in heterogeneous aqueous media (i.e. dispersed systems),[4,5] and tend to predate the advances that have been made in copper mediated RDRP in aqueous *solution*. This introduction will focus on the developments of copper mediated RDRP in homogeneous aqueous media with emphasis given on how to produce well-defined polymeric materials. Challenges and associated solutions encountered upon conducting copper mediated polymerisation in aqueous media will be critically discussed and evaluated.

1.6 General Considerations for Copper Mediated Polymerisation in Aqueous Media

1.6.1 Desirable Qualities in Aqueous Polymerisation Systems

A number of desirable qualities describe an ideal polymerisation system in aqueous media. Broadly speaking: low copper catalyst concentration, high monomer conversions (ideally >90%), high end group fidelity and low temperatures have all been targets of recent developments in the field.

Low catalyst concentration is of importance for two main reasons; to reduce cost and to avoid metal contamination of the final material. Using less catalyst enables a more commercially exploitable technique, with recent work reducing catalyst concentrations to parts per million (ppm) levels in aqueous media.[15,16] Residual copper salts can discolour polymers green/brown (depending on the ligands present) thus additional purification techniques to remove metal contamination from polymeric products are required. High purity is also particularly required for electronic and biologically orientated applications and a reduction in catalyst concentration can aid in the facile preparation of these materials.[17] It is noted copper(II) salts are classified as GRAS (Generally Regarded As Safe) by the FDA and listed as an essential trace element for most plant and animal species.[18] However, despite the disadvantage of residual catalyst (including metal and coordinating ligands), the most toxic component of a radical polymerisation is the monomer (usually activated vinyl monomers such as (meth)acrylates or (meth)acrylamides). For this reason high monomer conversion is essential as it allows for fewer or less stringent purification procedures to be used which saves time, energy and reduces cost. Another benefit of being able to achieve near quantitative conversions with Cu-mediated polymerisation is the possibility of *in-situ* chain extensions to form complex macromolecular architectures. If polymerisation proceeds to high conversion with high end group fidelity (minimal loss of the ω-end group functionality), the synthesis of well-defined block copolymers in a one pot process can be achieved by iterative sequential monomer addition, eliminating the need for intermediate purification steps and thus significantly speeding up the process.

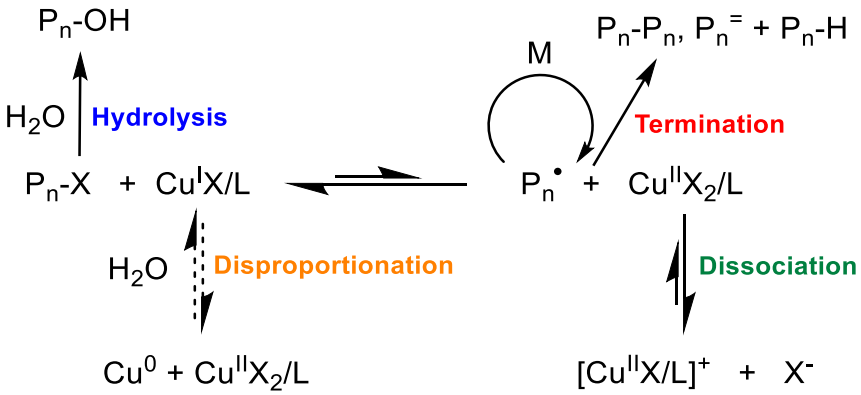
Low temperature polymerisation methods are of importance as they allow for the synthesis of polymers that exhibit thermoresponsive behaviour above certain

temperatures in aqueous media (*e.g.* PNiPAm) as well as allowing for polymerisation to occur in the presence of biological molecules which could potentially be denatured/damaged at elevated temperatures (*e.g.* enzymes and therapeutically relevant polypeptides.) Lower temperatures are also favourable in a number of cases to suppress side reactions.[19-21] The tertiary alkyl halide initiators/propagating chains in most Cu-mediated RDRP's can also undergo side reactions such as hydrolysis or elimination in aqueous media, resulting in loss of functionality, which is exacerbated at higher temperatures. Chain-end hydrolysis is discussed in further detail in section 1.6.2.

Another more recent consideration in RDRP has been the potential to introduce external stimuli to control the polymerisation. Specifically, light, mechanical, and electrochemical stimuli have been demonstrated to achieve impressive temporal control by switching the polymerisation "on" and "off" upon demand whilst maintaining narrow molecular weight distributions and high end group functionality, as discussed in subsequent sections.[22]

1.6.2 Challenges in Conducting Copper Mediated Polymerisation in Aqueous Media

ATRP has been reported to have many limitations when carried out in aqueous media. Reactions were generally found to be faster and exhibit a lower degree of control over chain length and molecular weight distributions which was ascribed to higher radical concentration leading to higher rates of radical-radical reaction and side reactions. This fast rate was thought to lead to an unacceptable rate of polymer termination and chain transfer via conventional radical events. A number of complex processes and equilibria which fundamentally control the catalytic process, thereby altering K_{ATRP} in water are shown in scheme 1.3: hydrolysis or elimination of the R-X or P-X bond, disproportionation of Cu(I) species to Cu(0) and Cu(II), dissociation of the deactivating Cu(II) species, and conventional radical-radical termination reactions.



***Scheme 1.3**: Mechanism of ATRP with potential side reactions and equilibria in aqueous media: blue: hydrolysis of alkyl halide chain end, red: radical-radical termination reactions, orange: disproportionation of Cu(I), green: dissociation of halide from Cu(II) complex.*

Perhaps the most significant side reaction associated with ATRP and copper mediated RDRP in aqueous media is the solvolytic displacement of halide ligands from deactivating Cu(II) complexes. For a controlled radical polymerisation to take place the concentration of radicals must remain low in order to reduce radical-radical termination reactions, obviously second order in [radical]. With ATRP the [radicals] is dictated by K_{ATRP} which can be expressed as k_{act} / k_{deact}. k_{deact} (governed by the concentration of halide containing 'deactivating' Cu(II) species) must be higher than k_{act} in order to keep radical concentration low. In aqueous media a problem arises because the highly polar nature of water aids the solvation of halide ions through the formation of hydrogen bonds. This can result in a very high proportion of Cu(II) species, depending on the ligands used, which cannot transfer a halide to a propagating polymer chain. Electrochemical investigation of activation and deactivation rates in aqueous media for common catalyst systems by Fantin *et al.* demonstrate that deactivation by dissociated complex is in fact highly efficient, but is hampered by the weak Cu-X bond.[23] It has been suggested that the free coordination site is then occupied by solvent[24] or by polar monomers.[23,25,26]

Hydrolysis of the alkyl halide at the ω chain end can be a significant problem in aqueous media which results in a loss of end group fidelity as the hydroxyl terminated polymer is unable to participate in further chain growth. This would result in dead chains and broadening of the molecular weight distribution. The rate of hydrolysis in Cu-RDRP's has been demonstrated to be effectively independent of copper concentration,[27] indicating that copper mediated hydrolysis is not significant, but is of

course dependent on the halide (R-Br is more readily hydrolyzed than R-Cl) and the nature of the monomer used (*i.e.* the nature of the alkyl halide polymer chain end). Hydrolysis can be particularly problematic in the polymerisation of acrylamides, in which it has been postulated that the nitrogen atom present in the penultimate monomer unit undergoes an intramolecular substitution reaction with the polymer chain end, giving a cyclized structure highly susceptible to hydrolysis.[28] Rapid disproportionation of Cu(I) to Cu(II) and Cu(0) in water is a further factor that complicates aqueous Cu-RDRP. Although disproportionation in many organic solvents *e.g.* toluene and acetonitrile is not appreciable, in highly polar aqueous media and in the presence of many common ligands it can be significant. Initially, disproportionation was presented as an *undesirable side reaction* which should be avoided, however, recent work has shown that it can in fact be beneficial under certain conditions (see section 1.9.2.).[19]

All of these processes can contribute to unbalancing the RDRP equilibrium, resulting in 'dead' chains from hydrolysis, altered activator and deactivator concentrations from disproportionation, and loss of deactivating species from dissociation. The net effect of this is often seen as a fast polymerisation rate and poor control over molecular weight and molecular weight distributions. Over the past 20 years different approaches to copper mediated RDRP have been developed which overcome these issues, as described in sections 1.7, 1.8 and 1.9.

1.7 Conventional ATRP in Aqueous Media

Conventional (or normal) ATRP is defined here as a process where Cu(I) is directly introduced (and NOT generated *in situ*) in the reaction mixture before the beginning of the polymerisation. On many occasions, an additional amount of Cu(II) is also added in the reaction mixture. Early work concerning conventional ATRP indicated that the process was not very tolerant to protic media. A series of reviews discussing controlled/'living' polymerisation from 2001 cite very few successfully controlled ATRP processes in water.[4,5] One of the first reported examples is the polymerisation of hydroxyethyl acrylate (HEA) in the presence of 2,2-bipyridine (bpy), by Matyjaszewski and coworkers in 1998.[29] Initial, experiments were carried out in bulk furnishing conversions of ~90% with dispersity values as low as 1.15 measured by size exclusion chromatography (SEC). When the same experiments were repeated in

aqueous solution (HEA:H_2O, 1:1 v/v), broader molecular weight distributions ($Đ$ > 1.30) were obtained.[29]

In 1999, utilizing a similar system of bpy with Cu(I)Cl and Cu(I)Br, Armes and coworkers reported the rapid polymerisation of poly(ethylene glycol) methyl ether methacrylate (PEGMA) in aqueous solution.[30] Reactions were conducted at 20 °C (the first examples of room temperature aqueous ATRP) and high conversions (>95%) were obtained in short time periods (~20 minutes) with dispersities as low as 1.12.[31] Selected reactions carried out in bulk were found to be significantly slower than analogous reactions in aqueous media. It was postulated that differences in the formed copper complexes in water are the reason for the observed rate acceleration. Similar conditions were also reported to control the polymerisation of sodium methacrylate (NaMA) and 2-(dimethylamino)ethyl methacrylate (DMAEMA), albeit with significantly lower conversion and higher dispersities, attributed to loss of catalyst activity through reactions with the functional monomer.[32]

Pyridyl methanimines, as developed by the Haddleton group, showed a number of advantages over bpy in organic media such as being particularly effective for the polymerisation of low k_p monomers such as methacrylates.[33,34] In a collaboration between Armes and Haddleton, ligands of this type were used that formed soluble complexes with copper in aqueous solution.[35] PEGMA was polymerised at 20 °C to high conversions (>90%) in a period of just 5 minutes, with dispersities between 1.10-1.40. Although pyridyl methanimines might not be expected to be stable to hydrolysis this proves not to be the case and can actually be prepared in the presence of large amounts of water. The high rate of polymerisation also means that hydrolysis is negligible within the timeframe of the reaction and no ligand hydrolysis was observed. This is further supported by reactions carried out at higher temperatures, which exhibited faster rates but broader molecular weight distributions.[35]

Poly(acrylamides) have proved to be much more difficult to synthesize by conventional ATRP in aqueous media.[28,36,37] In 2003 Jewrajka and Mandal reported the ATRP of acrylamide (Am) in aqueous and mixed aqueous/glycerol systems.[38] Both alkyl chloride and bromide initiators with bpy both resulted in poor control over polymerisation, with dispersities around 1.7 and low molecular weight tailing evident in SEC chromatograms. A later report using PMDETA as the ligand achieved a higher

degree of control over polymerisation (*Đ* as low as 1.24), albeit at severely limited conversions (9% in 48 h).[39] Similar trends were also noted by Jiang *et al.* using a tetramethylethylenediamine (TMEDA) ligand, with conversions below 20% in most cases and dispersities between 1.2-1.6.[40,41] More recently, Broekhuis and coworkers reported the polymerisation of Am and NiPAm using a Cu(I)X/tris[2-(dimethylamino)ethyl]amine (Me_6Tren) catalyst (figure 1.1).[42] The process exhibited a linear increase of molecular weight with conversion and reactions proceeded to relatively high conversions, however the degree of control (*Đ* > 1.4) is significantly poorer than that normally exhibited for ATRP of (meth)acrylates in organic media.

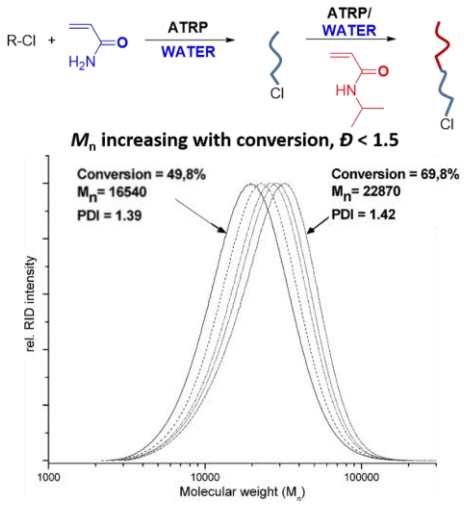
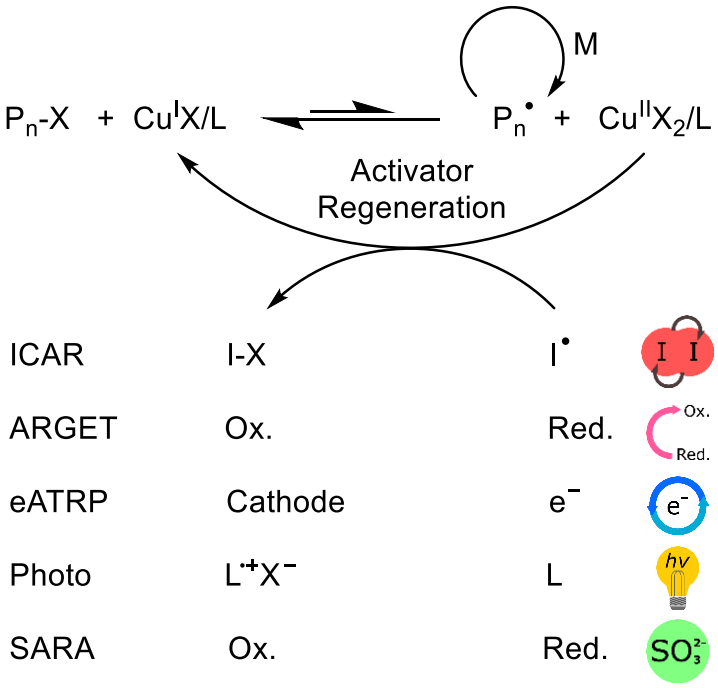


Figure 1.1: *ATRP of Am and NiPAm in aqueous media. Figure adapted from reference 42.*

Despite some success, particularly with water soluble methacrylates, conventional ATRP in aqueous environments has been shown to have significant drawbacks such as limited monomer scope (acrylamide polymerisation is not reported to be controlled) and limited demonstration of end group fidelity. Additionally, despite control over the chain length and dispersity of the products in certain cases, all of the examples of normal ATRP in aqueous media described above use at least stoichiometric amounts of copper(I) halide and ligand with respect to the number of polymer chains. As described in section 1.6.2, high copper concentrations (typically ~5000 ppm or higher) can be disadvantageous due to the added cost of purification, potential toxicity, and discolouration of products. Higher catalyst concentrations are necessary in conventional ATRP due to the high concentration of radicals present during the establishment of the ATRP equilibrium which leads to radical-radical termination events resulting in an associated increase in deactivator and decrease in activator,

known as the persistent radical effect (PRE).[43] Using stoichiometric amounts of catalyst ensures there is still sufficient activating species present at equilibrium. A further reason, particularly noteworthy for polymerisation in aqueous media, is that higher concentration of Cu(II) species in solution will lessen the observed effect of dissociation, whereby the concentration of halide containing deactivating Cu(II) species at the dissociation equilibrium is still sufficient to control polymerisation; as discussed in section 1.6.2. A number of different approaches have been subsequently developed which utilize external stimuli, either chemical or physical, to regenerate the active species lost during the initial stages of ATRP (scheme 1.4), hence allowing for much lower catalyst concentrations to be employed (section 1.8).

1.8 Activator Regeneration methods in Aqueous Media



Scheme 1.3: *Scheme depicting the numerous methods of activator regeneration used in ATRP.*

1.8.1 Initiators for Continuous Activator Regeneration (ICAR) ATRP

Initiators for continuous Activator Regeneration (ICAR) ATRP, first reported in the mid 2000's, uses a small amount of free radical initiator which can abstract the bromine atom from Cu(II) deactivating species to generate Cu(I) activating species. The continuous regeneration of activating species from deactivating species[44] facilitated by the radical initiator allows for much lower copper concentrations to be used compared to normal ATRP.[45] In 2012, Konkolewicz *et al.* successfully reported

the first example of ICAR ATRP in water (figure 1.2).[16] In the presence of low copper concentrations (<100 ppm well-defined poly(PEGMA) was obtained with dispersities between 1.09 and 1.56 (M_n = 37-70 kDa.) The key to controlling polymerisation was found to be addition of a bromide salt, tetraethylammonium bromide ($Et_4N^+Br^-$), which reduced the dispersity of the products from ~2 to as low as 1.09. This is attributed to the bromide ion promoting the formation of the Cu(II) deactivating complex, as supported by an associated decrease in rate with increasing salt concentration. The work also demonstrated the synthesis of a thermoresponsive block copolymer. Poly(PEGMA) (M_n = 16.5 kDa, $Đ$ = 1.41) was synthesized and then isolated to yield a macroinitiator used in the further ICAR ATRP of poly(ethylene oxide) methyl ether acrylate (PEGA) resulting in a block copolymer (M_n = 40 kDa, $Đ$ = 1.39). Although block copolymer synthesis was successful the dispersity of the obtained block was 1.39, which is relatively broader than other examples in aqueous media by other Cu-RDRP techniques, this is likely to be due to the homopolymerisation of PEGA initiated by the ICAR agent, as discussed in the original report of ICAR ATRP.[45] Thus, ICAR ATRP is a promising technique for controlled polymerisation in aqueous media, but drawbacks including the sacrifice of end group fidelity and dispersity due to the addition of the free radical initiator would seem to limit its applicability for the synthesis of high order macromolecular architectures.

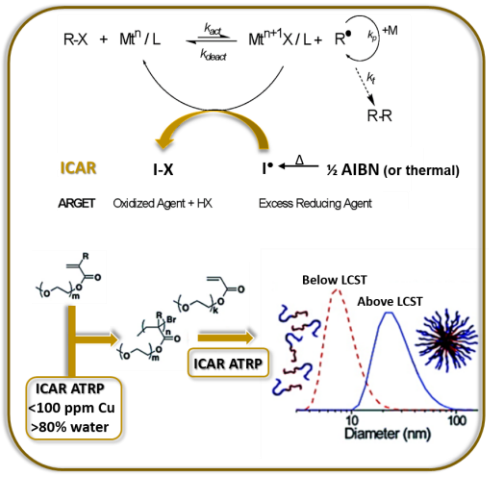


***Figure 1.2**: Representation of ICAR ATRP in water to synthesize thermoresponsive block copolymers. Figure adapted from reference 16.*

1.8.2 Activators (Re)Generated by Electron Transfer (AGET/ARGET) ATRP

Activators generated by electron transfer (AGET) ATRP is a process whereby activator (Cu(I) species) is generated from an oxidatively stable Cu(II) species through

utilization of a reducing agent. The process was first reported to effectively control polymerisation in water in 2006 by Matyjaszewski and coworkers.[46] Using the air stable Cu(II)/TPMA, ascorbic acid was used as a reductant to facilitate the *in-situ* generation of a Cu(I) complex yielding poly(PEGMA) with molecular weights of up to 87 kDa with dispersities lower than 1.3. In 2011 Averick *et al.* reported polymerisation of PEGMA from bovine serum albumin (BSA) modified to contain alkyl halide initiating motifs in biologically relevant aqueous media, later expanded upon by Maynard and coworkers.[47,48] Polymerisation was carried out at 30 °C in phosphate buffer solution (PBS), with Cu(II)/TPMA and ascorbic acid (figure 1.3). SEC analysis of polymers after cleavage from the protein yielded dispersities of 1.19, with an M_n of 83 kDa. Synthesis of protein-polymer hybrids (PPH's) by this 'grafting-from' approach is one of the key benefits of aqueous ATRP techniques, however copper concentrations in the reaction were very high, with 10 equivalents of Cu(II) per equivalent of initiator, meaning extensive purification of the final PPH was required.

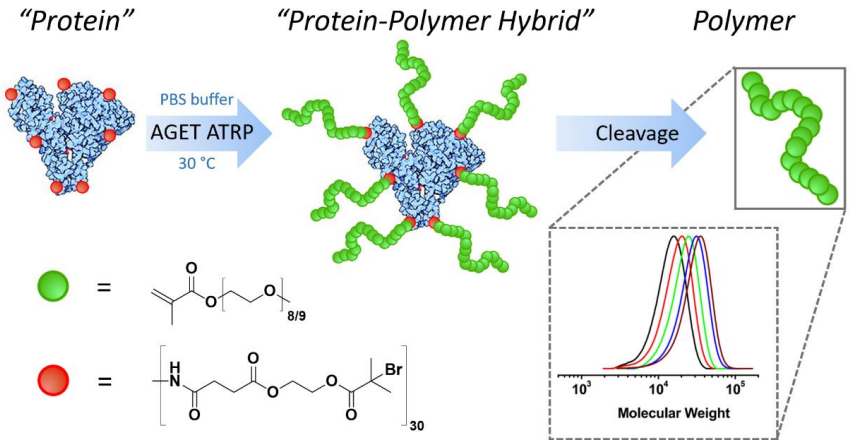


***Figure 1.3**: Synthesis of PPHs via (AGET) ATRP from [BSA]-O-iBBr30 and Selective Cleavage of Polymer. Figure adapted from reference 47.*

Activators regenerated by electron transfer (ARGET) ATRP follows a similar concept to AGET. In ARGET the reducing agent is slowly fed into the reaction, thus allowing for lower copper concentrations to be utilized, as (re)generation of Cu(I) from Cu(II) can occur throughout the reaction. Commonly employed reducing agents include FDA approved tin(II) 2-ethylhexanoate ($Sn(EH)_2$), ascorbic acid, and reducing sugars such as glucose.[49] In contrast to ICAR, ARGET is better suited to the preparation of block copolymers as the means of reducing deactivator cannot initiate homopolymerisation during the formation of the second block.

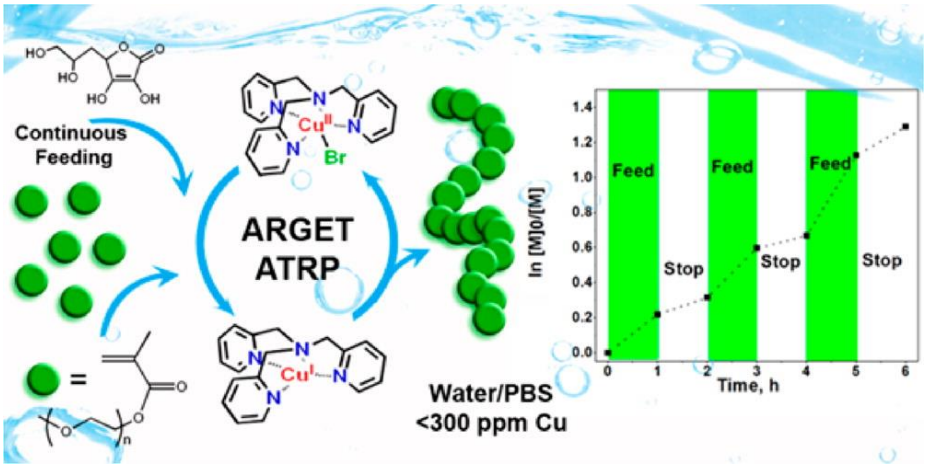


Figure 1.4: *Aqueous ARGET ATRP of PEGMA utilizing Cu/TPMA catalyst system, demonstrating temporal control. Figure adapted from reference 47.*

Aqueous ARGET ATRP was first reported in 2012 by Matyjaszewski and coworkers.[47] As opposed to ARGET ATRP carried out in organic media, aqueous ARGET ATRP is much more sensitive and relies on a number of factors including gradual feeding of the reducing agent and addition of a simple halide salt. A Cu/TPMA catalyst system was selected due to its stability at low concentrations and negligible disproportionation in aqueous media. It was demonstrated that feeding of the reducing agent (ascorbic acid) so that reduction occurred at a steady rate throughout the polymerisation gave better control, in line with previous studies.[47] Experiments in which feeding was not used resulted in poor control, attributed to significant termination events with the Cu/TPMA catalyst. In agreement with the previously discussed report on aqueous ICAR ATRP it was found that ARGET ATRP also required the presence of a halide salt in solution to provide halide ions which promote deactivator formation. Polymerisation of PEGMA proceeded to conversions of ~70% with dispersities of 1.3 and below at a reaction temperature of 30 °C. Temporal control of the reaction was demonstrated by stopping and starting the feed of reducing agent, with a decrease in rate associated with the ceased addition of ascorbic acid (figure 1.4), although the control was not as pronounced as other techniques which have since been developed.

1.8.3 Electrochemically Mediated (eATRP)

Electrochemical ATRP (*e*ATRP) reversibly generates Cu(I) species from air-stable Cu(II) by applying an electrochemical potential.[50] Varying the applied potential can effectively control the rate of polymerisation. Furthermore, cycling between time periods of applied potential and periods of no potential show that polymerisation is

slowed when electrochemical regulation was not employed, demonstrating a degree of temporal control over the reaction.

Following on from the initial report of copper based *e*ATRP in organic media, Matyjaszewski and coworkers expanded the technique to the polymerisation of PEGMA in aqueous media.[51] Reactions were conducted with a Cu/TPMA catalyst in water with various electrolytes including tetraethylammonium tetrafluoroborate ($Et_4N^+BF_4^-$), PBS buffer and $Et_4N^+Br^-$. As with the polymerisation of methyl acrylate (MA) reported in organic media, increasing the magnitude of the applied potential was found to increase the rate of the polymerisation, however in aqueous media it was found that a high rate had negative consequences on the degree of control over the polymerisation. E_{App} of -0.55 V (*vs.* standard calomel electrode) yielded poly(PEGMA) with a dispersity of 1.58, decreasing E_{App} to -0.31 V decreased the rate of polymerisation but had little effect on the degree of control ($Đ$ = 1.53). Further reduction of E_{App} to -0.21 V again showed a decrease in rate but with a marked increase in control ($Đ$ = 1.16) at 99% monomer conversion. Low levels of control at higher applied potential is attributed to increased bimolecular termination reactions at higher radical concentrations. One of the drawbacks of this protocol is the use of platinum electrodes, which is present an obstacle to larger scale synthesis due to cost. In 2016 Isse and coworkers demonstrated that *e*ATRP could also be conducted with non-noble metals such as NiCr and stainless steel by using a simplified reaction setup (an undivided cell and galvanostatic mode).[52]

Aqueous *e*ATRP has also been reported to control the polymerisation of acrylamides, significant due to the inability of many other ATRP techniques to effectively control the polymerisation of this class of monomer.[53,54] In one report Chmielarz *et al.* investigated polymerisation of AAm in mixed aqueous media (10 % v/v dimethyl formamide (DMF)). Of the catalysts employed, Cu/Me_6Tren catalyst system exhibited the best degree of control ($Đ$ as low as 1.09). *In-situ* chain extension with NiPAm demonstrated retention of the halide end group, however conversions of AAm were not reported to be quantitative, resulting in the second block being a statistical copolymer of Am and NiPAm. Chain extension by means of isolating a polyacrylamide macroinitiator was not reported, indicating that aqueous *e*ATRP is perhaps not an ideal approach for the synthesis of well-defined acrylamide block copolymer architectures.

1.8.4 Photoinduced ATRP

External regulation of RDRP's by photochemical mediation has attracted considerable attention in recent years due to wide availability, environmental benignity and the possibility of simple switching between active and dormant states.[22,55-57] Copper mediated photo-ATRP relies on free tertiary alkyl amine ligands in solution that is able to reduce Cu(II) species to Cu(I) when in a photoexcited state.

Photoinduced ATRP was first reported in aqueous media in 2015 by Matyjaszewski and coworkers, promoted by visible light and a Cu(II)X_2/TPMA catalyst.[15] PEGMA was able to be polymerised to high molecular weights (M_n > 100 kDa) with dispersities as low as 1.07. The key to controlling the reaction was found to be addition of an additional halide salt, which offsets the dissociation of Cu(II) species in aqueous media, as discussed in section 1.6.2. End group fidelity was demonstrated through chain extension of an isolated macroinitiator with a lower molecular weight PEGMA monomer to yield block copolymers with high molecular weight (M_n = 139 kDa, $Đ$ = 1.22). Temporal control was also demonstrated by cycling the reaction between periods of illumination and darkness (figure 1.5.)

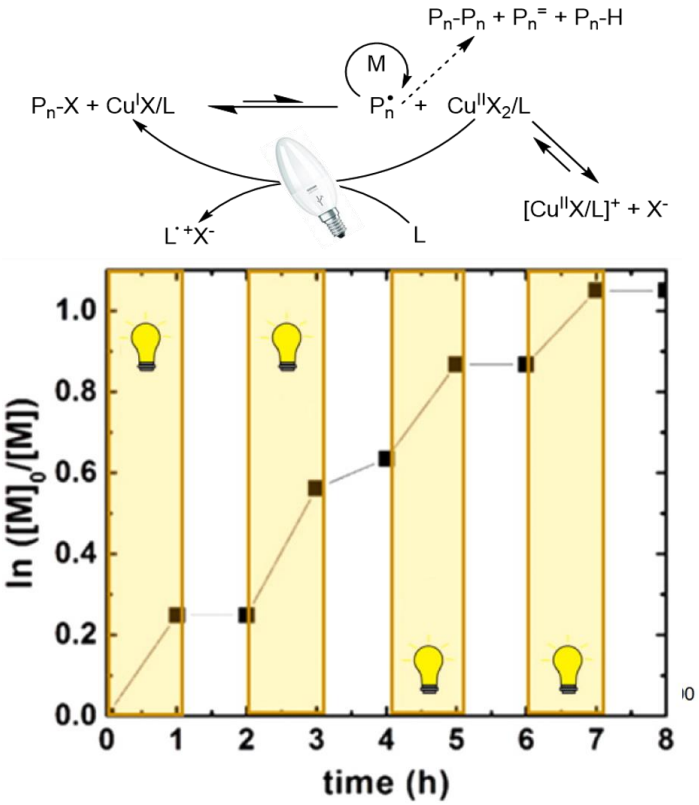


Figure 1.5*: Scheme demonstrating reduction of Cu(II) by photoexcitation of ligand in photo ATRP, and demonstration of temporal control. Figure adapted from reference 15.*

1.8.5 Supplemental Activator and Reducing Agent (SARA) ATRP

Supplemental activator and reducing agent (SARA) ATRP utilizes a species which can reduce deactivator to activator in a similar manner to ARGET (section 1.8.2), whilst also activating alkyl halides independent of other ATRP components. Most reports concerning SARA ATRP utilize Cu(0) as the SARA agent, however due to the large body of work associated with aqueous RDRP in the presence of Cu(0) and the mechanistic debate within the literature,[12] Cu(0)-RDRP is treated separately in section 1.9.

Matyjaszewski and coworkers introduced inorganic sodium sulfites (*a common additive in wine making*) as "SARA agents", which have been demonstrated to reduce Cu(II) to Cu(I) and activate alkyl halides.[58] Polymerisation of MA in organic media was demonstrated using various sulfites with a $CuBr_2$/Me_6Tren catalyst. More recently sodium sulfites have been utilized for SARA ATRP in aqueous media, as shown in figure 1.6.[59] Aqueous SARA ATRP was carried out using TMPA instead of Me_6Tren, in an effort to avoid disproportionation of Cu(I) formed from reduction of Cu(II). Both

PEGA and PEGMA were polymerised with dispersities of ~1.20 and the polymerisation rate could be slowed by stopping the feeding of sulfite.

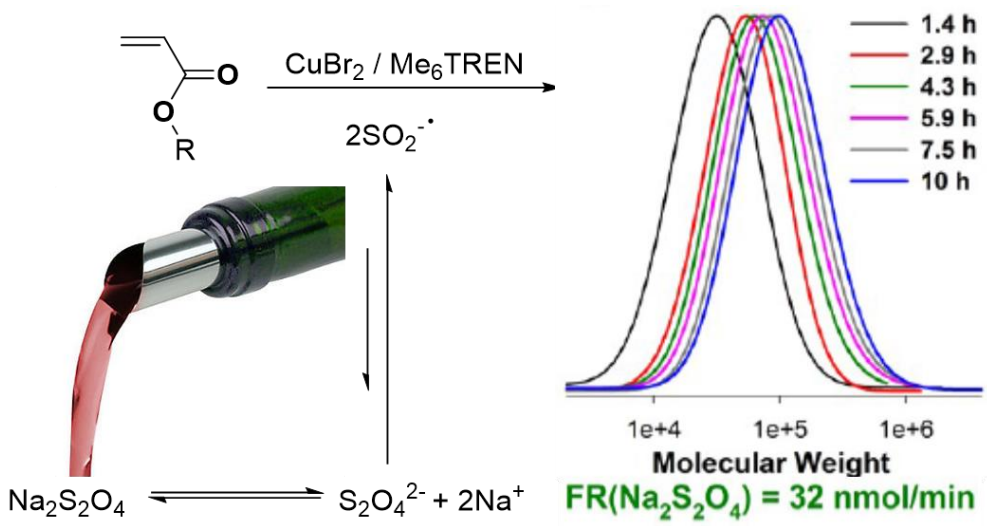


***Figure 1.6**: SARA ATRP utilizing sodium sulfite, a common additive in wine making, to reduce Cu(II) and form radicals from alkyl halides. Figure adapted from reference 59.*

1.9 Aqueous RDRP in the Presence of Metallic Copper (Cu(0)-RDRP)

RDRP in the presence of metallic copper was first reported Matyjaszewski in 1997 for bulk polymerisations,[60] with the apparent intention of utilizing Cu(0) as a reducing agent to reform Cu(I) from Cu(II) during polymerisation in a process similar to ARGET-ATRP. Matyjaszewski and coworkers noted enhanced rates and control over polymerisations in which Cu(0) was present. In 2006 Percec and coworkers reported an "ultrafast" polymerisation system using Cu(0) in dimethyl sulfoxide (DMSO).[61] Cu(0) mediated techniques in water can be broadly differentiated by the source of Cu(0) in the reaction, either externally added sources such as copper wire or powder, or *in-situ* generated particles through disproportionation or reduction reactions of higher oxidation state copper species.

1.9.1 Externally added Cu(0) (wire and powder)

The first reported method of conducting Cu(0)-RDRP in water was through use of an external source of Cu(0), commonly in the form of copper wire or copper powder. Early examples include the polymerisation of DMAm and NiPAm in a mixed solvent system of methanol (MeOH) and water.[62] Experiments with increasing water concentration dramatically increased the dispersity of the final product ($Đ$ = 1.12 in pure MeOH, $Đ$ = 1.68 in 30/70 MeOH/H_2O), indicating a clear loss of control in

aqueous environments. Uncontrolled polymerisation was also reported for Cu(0) wire mediated RDRP of HEA in water, in which it was noted that an insoluble gel formed around the wire at the beginning of the reaction.[63]

In contrast, Cu wire catalyzed polymerisation of PEGA in water has been reported to proceed to high conversions (>90%) with good control ($Đ$ ~ 1.25).[64] Utilization of halide salts has also enabled controlled polymerisation of PEGA at ppm copper concentrations.[65] 2-(Hydroxypropyl) methacrylamide, a monomer of considerable interest due to the biocompatibility and non-toxic nature of its polymers, has been reported to proceed in water in a copper wire catalyzed polymerisation, however dispersities were around 1.4.[66]

1.9.2 In-situ Generation of Cu(0) by Disproportionation of Cu(I)

In 2013 Haddleton, Zhang and coworkers introduced a new protocol for Cu(0) mediated RDRP in aqueous media, utilizing *in-situ* generation Cu(0), where Cu(0) is formed from the rapid disproportionation of Cu(I) *prior* to addition of monomer and initiator.[19] The disproportionation equilibrium of Cu(I) in water in the presence of certain aliphatic tertiary amine ligands is extremely high, with K_{disp} of the order of 10^6. This is altered when an excess of complexing ligand is present, dependent on the relative stabilization of Cu(I)X/L species to Cu(II)X_2/L species. By utilizing Me_6Tren, a ligand which greatly stabilizes Cu(II) in water, Cu(I)Br was shown to disproportionate fully in pure water on a timeframe of a few seconds (figure 1.7), generating metallic Cu(0) particles and Cu(II)Br_2/Me_6Tren. This disproportionated mixture was subsequently deoxygenated by ‘sparging’ with nitrogen for up to15 minutes. An aqueous deoxygenated solution of monomer and alkyl halide initiator was then injected into the predisproportionated catalyst mixture triggering polymerisation. Control over polymerisations was shown to be excellent, with dispersities below 1.10 even at quantitative monomer conversion.

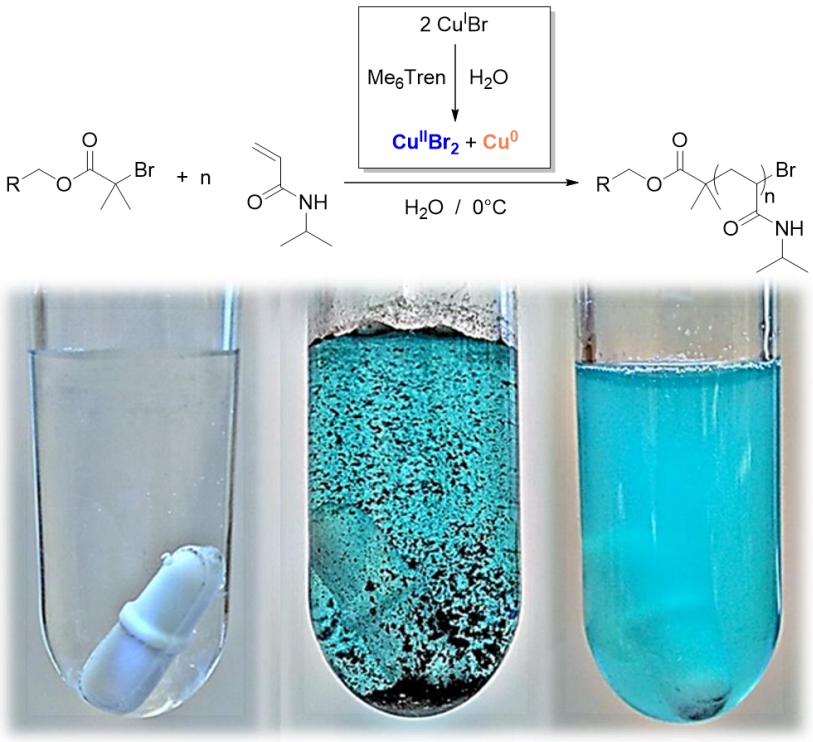


***Figure 1.7**: Polymerisation of an acrylamide via pre-disproportionation of Cu(I)Br. (a) aqueous solution of Me_6Tren. (b) Cu(0) particles and Cu(II) complex after addition of Cu(I)Br. (c) solution after addition of monomer and initiator.*

Numerous monomers have been successfully polymerised using this technique, including various acrylamides,[19,67,68] acrylates, methacrylates,[69] methacrylic zwitterionic monomers,[70] polyoxazoline macromonomers,[71] and glycomonomers[72] at room temperature or below. A significant advantage of the pre-disproportionation protocol is the ability to control the synthesis of poly(acrylamides), a class of monomer shown to be problematic for many by traditional ATRP techniques in both aqueous and organic media. The reaction has been demonstrated to be tolerant to multiple functional groups, with examples of controlled polymerisation in biologically relevant aqueous environments such as PBS and blood serum.[73] In addition to this the Haddleton group also reported controlled Cu(0)-RDRP in alcoholic beverages (mixed ethanol-water binary solvents between 3 and 50 vol% ethanol),[74] in which it was noted that carbonated solvents (including carbonated drinking water) allowed for both controlled polymerisation and *in-situ* depolymerisation, a very unusual phenomenon which has since been studied in further detail.[75]

Retention of chain-end functionality at conversions close to 100% is not a common feature of Cu mediated RDRP techniques in aqueous media, due to hydrolysis of the alkyl halide ω chain end (see section 1.6.2). In order to reduce the rate of hydrolysis

and increase the end group functionality the polymerisations were performed in an ice bath rather than room temperature. This allowed the synthesis of one-pot block copolymers using a wide range of monomers.[19,67,68] The ability of the technique to provide access to high-order block copolymer architectures was best exemplified by Alsubaie *et al.* yielding decablock copolymers prepared in one pot in very short time periods (Figure 1.8).[76] Timing of sequential additions of monomer was found to be crucial to controlling polymerisation, as leaving the reaction under conditions where [M]~0 leaves the bromide chain end susceptible to hydrolysis and side reactions.[77] Synthesis of other complex macromolecular architectures have also been reported, including multiblock star copolymers by Becer and coworkers[78] and well-defined polymer-protein bioconjugates by Wilson, Davis and Haddleton.[79,80]

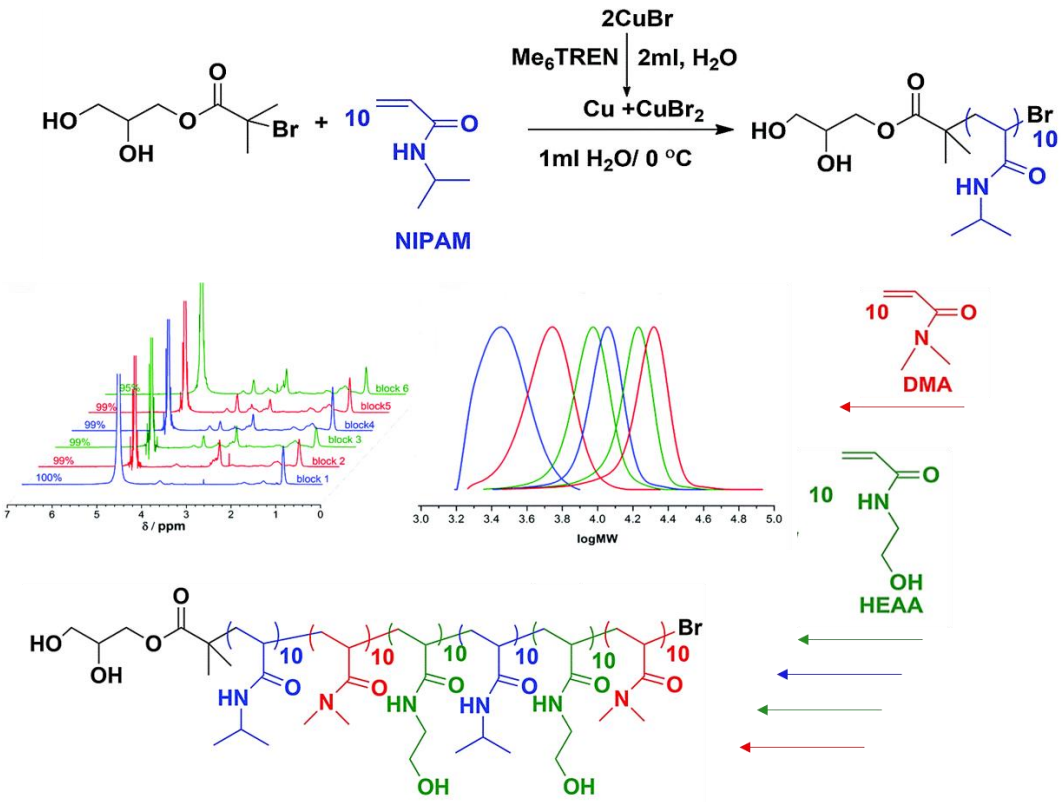


***Figure 1.8**: Synthesis of multi-block copolymers composed of NiPAm, DMA and HEAm by iterative Cu(0)-RDRP in H_2O, showing 1H NMR spectra and evolution of molecular weight by DMF SEC. Figure adapted from reference 76.*

Aqueous Cu(0)-RDRP by pre-disproportionation has the distinct benefit of being applicable to a wide range of monomers (particularly acrylamides) and being ideal for *in-situ* block copolymerisations despite the susceptibility of the bromide ω chain end to hydrolysis.[28,36] In terms of copper concentration, aqueous Cu(0)-RDRP typically use around 0.4 equivalents of Cu(I)Br relative to initiator, this is an improvement over

traditional ATRP techniques which are usually stoichiometric with respect to copper. However it is still significantly higher than activator regeneration ATRP methods which are typically conducted at ppm copper concentrations (~0.02 eq. relative to initiator.)

1.9.3 In-situ Generation of Cu(0) by Reduction of Cu(II)

In 2016 Monteiro and coworkers reported a novel method of aqueous Cu(0)-RDRP of NiPAm utilizing *in-situ* generated Cu(0) particles obtained *via* reduction of Cu(II)Br_2 with $NaBH_4$.[81] The reduction of Cu(II) to Cu(0) was shown to be quantitative and as a result of this the ratio between Cu(0) and Cu(II) in polymerisations could be tuned by simply changing the stoichiometry between $NaBH_4$ and Cu(II). Polymerisation of NiPAm was demonstrated to proceed to conversion close to 100% in just a few minutes with good agreement between theoretical and experimental molecular weights. Furthermore, the end group fidelity was also shown to be high (~95% at conversions approaching 100%) through matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-ToF MS) of samples 'end-capped' by a thio-bromo substitution reaction to eliminate hydrolysis.[27] This technique is one of the few Cu-mediated protocols shown to be effective for polymerizing an acrylamide monomer, however the scope currently only encompasses PNiPAm at relatively low molecular weights (M_n < 5 kDa) with no demonstration of chain extension, despite the high end group fidelity reported.

1.9.4 Mechanistic Studies of Cu(0)-RDRP in Water

The mechanism of RDRP in the presence of zero valent copper is a highly contentious topic in the literature, with many papers both in favour of and disagreeing with the proposed mechanism known as SET-LRP, in which it is stated that activation of alkyl halides by inner sphere electron transfer (ISET) with Cu(I) species does not occur due to the fast disproportionation of Cu(I) to Cu(0) and Cu(II). Activation is said to solely occur through outer sphere electron transfer (OSET) with Cu(0).[61] In SARA ATRP, the mechanistic alternative proposed by Matyjaszewski, activation of alkyl halides occurs through ISET with Cu(I), and Cu(0) serves to reduce Cu(II) to Cu(I) (comproportionation) in a process similar to ARGET ATRP whilst also activating alkyl halides but at a much reduced rate.[82] Although many publications exist discussing the mechanism, this section will focus on summarizing investigations into the mechanism of Cu(0)-mediated RDRP in aqueous media and identifying points

requiring further study. A broader summation of mechanistic investigations in organic media can be found in 2016 review on Cu(0)-mediated polymerisation by Anastasaki *et al*.[12]

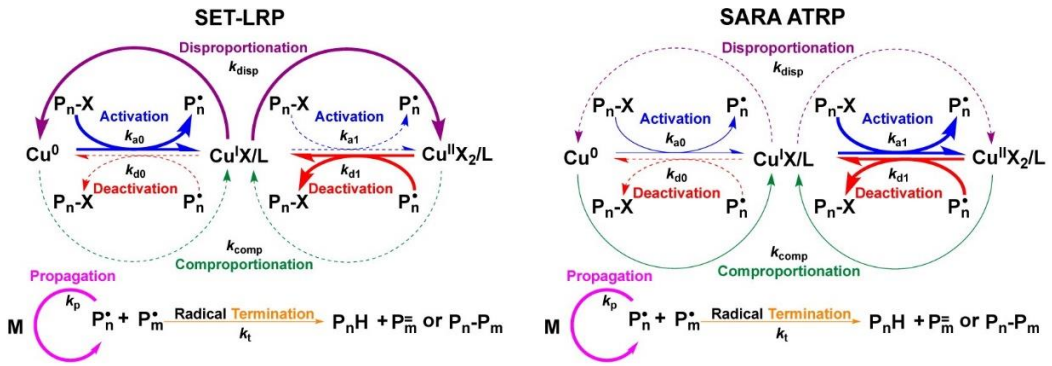


***Figure 1.9**: Two proposed mechanism of Cu(0)-RDRP: SET-LRP (left) and SARA ATRP (right). Arrow thickness denotes relative rates of reaction. Figure adapted from reference 65.*

Both the SET-LRP and SARA ATRP mechanisms contain the same reactions but are said to differ with their relative rates, as shown in figure 1.9. As pointed out by the Matyjaszewski group in their 2014 study into the mechanism of Cu(0)-RDRP of PEGA in water, the key points that differentiate the mechanisms are whether Cu(0) or Cu(I) is the major activator of alkyl halides and whether Cu(I) activates or disproportionates.[65] These questions are particularly pertinent for reactions conducted in aqueous media, as it is well established that disproportionation of Cu(I) to Cu(0) and Cu(II) is a favourable process, and utilization of this reaction prior to addition of monomer and initiator forms the crux of one of the most effective TMM-RDRP's reported to date (section 1.9.2.).

Through model kinetic reactions and simulations Konkolewicz *et al.* argue that whilst disproportionation of Cu(I)/Me_6Tren is thermodynamically favoured over comproportionation (as seen by the disproportionation protocol described in detail in section 5.2), the presence of an alkyl halide causes disproportionation to be kinetically minimized. It is further concluded that activation by Cu(I) is incredibly fast in aqueous media, thus [Cu(I)] is drastically lowered. Since disproportionation is proportional to $[Cu(I)]^2$, the lowering of [Cu(I)] from fast activation means that comproportionation is favoured under polymerisation conditions, consistent with the SARA ATRP mechanism. Kinetic simulations suggested that alkyl halide activation by Cu(0) is less than 1% of the total activation.[65] However, it is noted that many of these model

reactions, although designed to imitate typical polymerisation conditions, use a 20 fold excess of ligand with respect to copper which is highly atypical of experimental aqueous Cu(0)-RDRP.

In 2015 Haddleton and coworkers published an investigation into the mechanism of Cu(0)-RDRP in aqueous media focussing on disproportionation and comproportionation studies in the presence of both *in-situ* generated Cu(0) particles and Cu(0) wire.[83] Disproportionation of Cu(I)Br in water with Me_6Tren was found to proceed to >99% regardless of the concentration of Me_6Tren added (0.5-6 equivalents relative to Cu(I)) as measured by UV/Vis spectroscopy. This is unexpected as disproportionation should be maximum for 0.5 equivalents of Me_6Tren, and excess concentrations of ligand should drive the equilibrium back to Cu(I). Addition of monomer to disproportionated mixtures was found to decrease disproportionation, dependent on the type of monomer used (~86% for acrylamides, ~ 95% for acrylates). The result for PEGA (96%) is significantly higher than that reported by Matyjaszewski,[65] however the ligand concentration was significantly higher in that particular case (20 equivalents relative to copper) which doesn't accurately replicate typical polymerisation conditions. Interestingly carrying out the same experiments but with addition of monomer prior to addition of ligand resulted in even lower values of disproportionation, highlighting the significant effect that order of addition of reagents can have on the relative amounts of different copper species. This difference is reflected in the polymers produced; addition of monomer to a predisproportionated mixture results in a controlled polymerisation for acrylamides and acrylates, whereas addition of monomer prior to disproportionation results in uncontrolled polymerisation or no observable reaction. Comproportionation was found to be low in the presence of monomer and was not observed in the absence of monomer.

Experiments that utilize the Cu(I) stabilizing (and thus non-disproportionating) ligand, TPMA, demonstrate that both Cu(0) and ATRP protocols are effective for the polymerisation of acrylates, whereas Cu(0) was demonstrated to be crucial for the controlled polymerisation of acrylamides.[83] The reason that aqueous Cu(0)-RDRP is so effective for the polymerisation of acrylamides is a mechanistic question that still requires some attention.

1.10 Other Transition Metals in Aqueous Media

1.10.1 Iron Mediated ATRP

ATRP mediated by iron complexes was first reported in 1997,[84,85] and has attracted considerable attention due to the natural abundance of iron, its biocompatibility and apparent low toxicity, however, this claim is seldom backed up with evidence.

Much of the work reported on iron based ATRP catalysts in aqueous media has focused on using iron containing metalloenzymes and bioinspired catalysts.[86,87] In 2011 di Lena and coworkers demonstrated that catalase from bovine liver (CBL) and horseradish peroxidase (HRP), both iron containing proteins, could polymerise PEGA in aqueous solution 2-bromoproprionitrile (BPN) as initiator at 60 °C.[88] Ascorbic acid was used as a reducing agent to yield a process similar to an ARGET ATRP. Most reactions with CBL were limited to monomer conversions ~60%, with 80% being reported for a reaction in which ascorbic acid was premixed with CBL for one hour prior to polymerisation. However, control over polymerisations was shown to be reasonably poor, with dispersities increasing throughout polymerisation, typically being around 1.6 at cessation of polymerisation. Also in 2011, and independent of di Lena's work, Bruns and coworkers reported HRP as a catalyst for the aqueous polymerisation of NiPAm.[89] Dispersity was reported to be as low as 1.44 with M_n ranging from 50-220 kDa. In 2013, using haemoglobin (Hb) and ascorbic acid, Bruns also reported polymerisation of PEGA, PEGMA and NiPAm in an ARGET ATRP process (figure 1.10).[90] NiPAM was polymerised in an uncontrolled process, as demonstrated by kinetic analysis, with a final dispersity >2.5. Molecular weight for polymerisation of PEGA was demonstrated to increase with conversion, however control over the polymerisation was limited, with dispersity increasing throughout polymerisation to values around 1.4. Polymerisation of PEGMA proceeded with an increase of molecular weight with conversion and a final dispersity of <1.20 (M_n = 6 kDa). PEGMA has also been polymerised in aqueous media with iron ATRP using an AGET process starting from $Fe(III)Cl_3/6H_2O$ and a Tris (3,6-dioxa-heptyl) amine (TDA) ligand.[91]

More successfully controlled polymerisation has been achieved in aqueous media by using bioinspired enzyme mimetic catalysts. Simakova *et al.* used hemin, a ferric form of heme with a chloride ligand in place of the hydroxyl ligand found in hematin (structurally similar to the prosthetic groups found in CBL, HRP and Hb), to

polymerise PEGMA.[92] Polymerisation was found to be poorly controlled, which was attributed to copolymerisation of hemin (due to the vinyl groups present) and the poor water solubility of the catalyst. Subsequent modification of hemin by hydrogenation of the vinyl groups followed by PEGylation yielded water soluble Mesohemin-$(MPEG_{550})_2$. This new catalyst, in conjunction with halide salts to aid deactivation, was able to furnish poly(PEGMA) with molecular weights as high as 100 kDa ($Đ$ = 1.30).

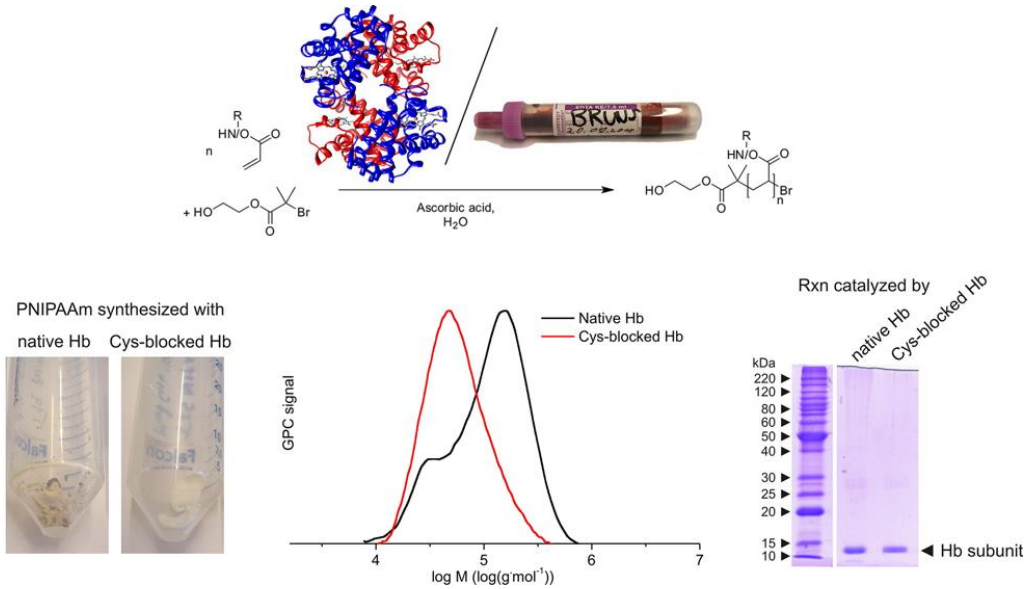


***Figure 1.10**: Iron ATRP mediated by Haemoglobin. Figure adapted from reference 90.*

1.10.2 Ruthenium Mediated ATRP

Ruthenium mediated ATRP was the first reported example of a controlled radical polymerisation with a transition metal, published by Sawamoto in 1995 and submitted to Macromolecules in 1994.

The first example of ruthenium mediated polymerisation in aqueous media was reported by Sawamoto and workers in 2012,[93] following on from previous work in which it was found that pentamethylcyclopentadienyl (Cp*)ruthenium complexes ($Cp^*Ru(Cl)L_2$: L= phosphine) could catalyze an ATRP reaction in polar media (ethanol). The catalytic cycle was enhanced by the addition of small amounts of water to the ethanol, with ^{31}P NMR analysis indicating that water was undergoing dynamic complexation with the Ru metal center.[94] This system was then expanded to the polymerisation of functional water soluble methacrylate in monomers in pure water. Ligation of the phenolic phosphine ligand PPh_2(*p*PhOH) to a $[Cp^*Ru(\mu_3\text{-}Cl)]_4$

precursor generated a highly active ATRP catalyst capable of controlled radical polymerisation of PEGMA in aqueous media with high rates, *in-situ* chain extension and block copolymerisations with HEMA, and high molecular weight polymers being reported at low catalyst loading at 40 °C.[93] Polymerisations were found to be dependent on pH, with reactions carried out in buffer solutions at pH 8 and 9.6 proceeding to high conversions but with a markedly increased dispersity (*Đ~1.6).* Loss of control was attributed to the poor solubility of the complex due to the phenolic ligand and the phosphine's coordination at higher pH.

Subsequent work on ligand design to improve water solubility and pH tolerance of the catalyst resulted in introduction of triethylene glycol (TEG) groups at the para position of the phosphine ligand.[95] Polymerisation of PEGMA to conversions >90% could be achieved in as little as 20 minutes with narrow molecular weight distributions (*Đ* < 1.16). The high activity of the ruthenium catalyst was exploited to demonstrate controlled polymerisation at low temperature (0 °C) and low catalyst loading ([I] : [Ru] = 1 : 0.01) of HEMA. Block copolymerisation of PEGMA with both HEMA and DMAEMA was also achieved (figure 1.11).

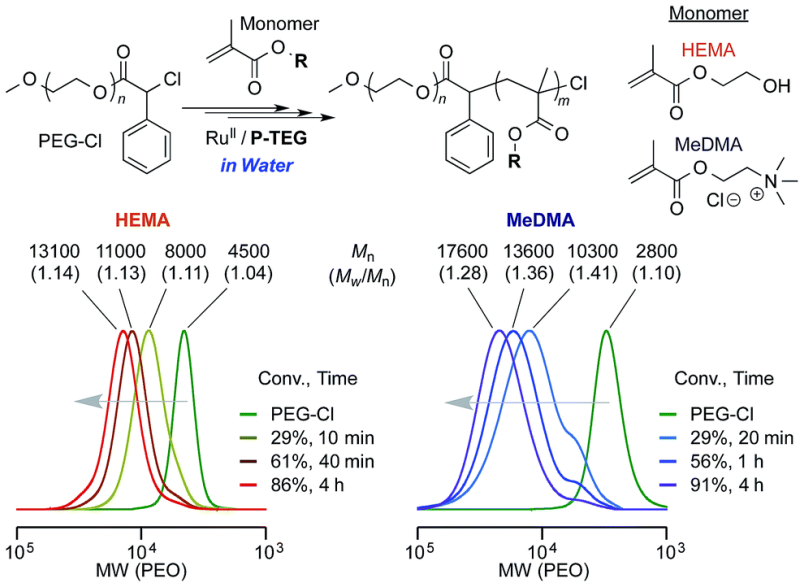


Figure 1.11*: Aqueous block copolymerisation of PEGMA with HEMA and DMAEMA by ruthenium mediated ATRP. Figure adapted from reference 95.*

1.11 Monomer Scope of Aqueous Cu-Mediated RDRP

1.11.1 Acrylates, Methacrylates and Acrylamides

The main focus of this literature review has examined in detail the polymerisation of methacrylate, acrylate and acrylamide monomers in aqueous solution; all of which can

yield water soluble materials with wide ranging uses. Controlled polymerisation of (meth)acrylates has been successful with many of the techniques described, whereas acrylamide polymerisation is more problematic, with far fewer reports. However, the development of Cu(0)-RDRP *via in-situ* disproportionation has overcome this limitation, giving controlled polymerisation with almost quantitative conversion and end group fidelity; also yielding similar results for the polymerisation of (meth)acrylates.

Successful aqueous Cu-mediated RDRP also enables the polymerisation of charged and acidic monomers, which often have poor solubility in organic solvents. The following sections will discuss and examine some of the Cu-mediated RDRP techniques which have enabled advances in the polymerisation of challenging monomers, for example monomers containing cationic amine moieties, acidic groups, and zwitterionic characteristics.

1.11.2 Charged Monomers

Due to the limited solubility of charged and zwitterionic monomers in organic solvents, the polymerisation of this monomer family is typically limited to aqueous solution, with many examples carried out in solvent mixtures commonly of water with DMF, MeOH or isopropanol. The polymerisation of these monomers and aqueous media in general is incompatible with anionic polymerisation and is also challenging with controlled radical polymerisation conditions vary significantly between those used for positive, negative and zwitterionically charged monomers. These monomers can often be hygroscopic, difficult to handle, and contain acidic functionalities (see subsequent section), for example sulfonates and phosphonates which can provide further challenges and compete with the ligand for complexation to the copper catalyst.

The first example of the polymerisation of a charged monomer in a purely aqueous solution was in 2000 by Armes,[96] who reported the polymerisation of methacryloxyethyl phosphocholine (MPC). The issues surrounding the spontaneous uncontrolled polymerisation of this monomer were overcome by the rapid rate of ATRP polymerisation, yielding 90% conversion in 5 minutes at ambient temperature. These reactions utilized a Cu(I)Br, bpy catalytic system and in all cases illustrated a conversion greater than 96%, but only low molecular weights were targeted (less than 10 kDa) and some degree of control was lost at the higher end of this range with

dispersity of 1.4 for those greater than 7 kDa. The work was later expanded to higher molecular weights, by fine tuning the ratio of initiator to copper to ligand, yielding higher molecular weights *(M_n* = 22 kDa , dispersity 1.26).[97] The group subsequently showed the presence of end group fidelity by chain extension of PMPC (DP_{20}, 99% conversion, M_n = 6 kDa, Đ = 1.12) with OEGMA generating a well-defined block copolymer (M_n = 16 kDa, $Đ$ = 1.27),[98] and also illustrated the first example of a block copolymer of two zwitterionic polymers, by incorporating [2-(methacryloyloxy)ethyl]dimethyl(3-sulfopropyl)ammonium hydroxide (SBMA) as the second block. Note however that higher molecular weights, and a broader scope of block copolymers could only be achieved by utilizing methanol or methanol water mixtures.[97,99] The copolymerisation of SBMA (also known as *N*,*N*-dimethyl-*N*-methacryloyloxyethyl-*N*-sulfobutyl ammonium (DMBS)) and acrylamide has also been reported utilizing Cu(0)-RDRP in aqueous media, utilising Cu(0) powder and $CuCl_2$/Me_6Tren as the catalyst.[100] Both PMPC and PSBMA were homopolymerised by Simula *et al*,[70] utilizing the predisproportionation of Cu(I)Cl in the presence of Cu(II)Cl and PMDETA.

Other reports of charged methacrylates include the synthesis of well-defined poly(2-[(methacryloyloxy)ethyl]trimethylammoniumdimethylaminoethyl methacrylate chloride)(MeDMA) (the quaternized form of PDMAEMA) in aqueous solution utilizing aqueous ATRP, with a Cu(I)Br catalyst and bpy as the ligand at room temperature.[101] All reactions proceeded to high conversions (>90%) and were reasonably well controlled with dispersities of 1.20-1.30. However, similarly to previous reports, to prepare well-defined block copolymers solvent mixtures of water with methanol or isopropanol was required. Later, the synthesis of star polymers of MeDMA were reported with similar polymerisation conditions.[102,103]

The most successful report to date is the polymerisation of acryloyl phosphatidyl chloride (APC), a zwitterionic acrylate monomer containing ammonium and phosphate functionalities *via* aqueous Cu(0)-mediated LRP, generating PAPC up to DP_{50} with dispersities in the range of 1.07-1.22.[68] This is the only example of a zwitterionic polymer synthesized with Cu-mediated RDRP that has a dispersity of less than 1.10, but as in previous cases increasing the molecular weight further resulted in a reduction in conversion and a loss of control. However, charged or zwitterionic acrylamides and methacrylamides are even less explored than methacrylates and

acrylates, with the only example up to date being the use of carboxybetaine functionalized acrylamide and methacrylamides by Edlund et al, utilizing Cu(0) wire, a hemicellulose macroinitiator and Me_6Tren as the ligand.[104] Pseudo first order kinetics were observed for both monomers, with conversions of greater than 90% achieved suggesting a good degree of control over the process, however no SEC data was reported. Further examples are limited to solvent mixtures, with poly(3-acrylamidopropyl)-trimethylammonium chloride synthesised and chain extended in water ethanol mixtures *via* Cu(0)-RDRP, illustrated high end group fidelity at 90% conversion yielding block copolymers with a dispersity of around 1.30.[105]

There are many remaining challenges in the synthesis of charged polymers in pure water *via* Cu-mediated RDRP, with limited successful reports to date. The synthesis of block copolymers and molecular weights higher than 15 kDa for homopolymers is challenging with broad dispersities common, showing there are many remaining avenues of improvement to optimize this important group of monomers.

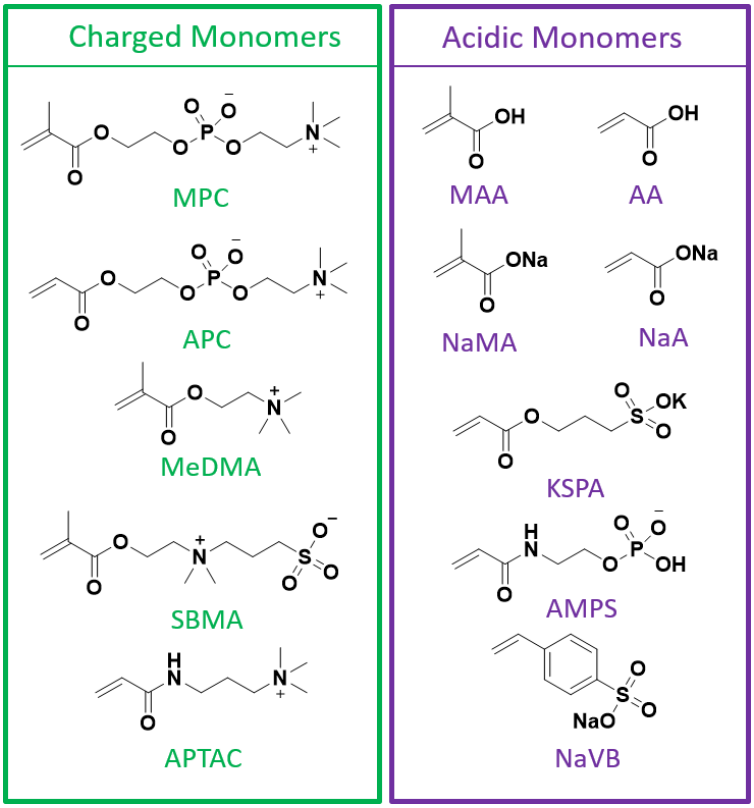


***Figure 1.12**: Examples of charged and acidic monomers successfully polymerised by aqueous Cu-mediated RDRP*

1.11.3 Acidic Monomers

Polymerisation of acidic monomers by Cu-RDRP is challenging in both organic and aqueous media. Most reports of controlled polymerisations are of monomer salts, in which the acidic moiety is not protonated (figure 9).

The first example of ATRP of an acidic monomer was by Armes and coworkers in 1999.[32] NaMA, the sodium salt of methacrylic acid (MAA), was polymerised in aqueous media using Cu(I)Br and bpy. Molecular weights of up to 7.3 kDa were successfully prepared with good conversions (50-80%) with a high degree of control ($Đ$ = 1.20-1.30) However, targeting higher molecular weights resulted in a loss of control with $Đ$ > 2. pH was found to be a critical parameter for successful polymerisation as no polymerisation was observed below pH 6, at which point bpy becomes protonated. This is a dramatic change from free radical polymerisation, in which it is favourable to polymerise MAA at low pH, to avoid a build-up of anionic charge on the polymer backbone. The same group also reported the polymerisation of sodium 4-vinylbenzoate in aqueous solution (pH 11), using Cu(I)Br as the catalyst, a PEG functionalized isobutyrate or sodium 4-(bromomethyl)benzoate as an initiator at

ambient temperature, illustrating linear kinetics and an M_n close to theory, even at very high conversions (>95%, Đ =1.30).[106]

Cu(0)-RDRP utilizing predisproportionation of Cu(I)Br has been reported to be efficient for the polymerisation of the sodium salt of 2-acrylamido-2-methylpropane sulfonic acid (NaAMPS), an important monomer in a variety of biological and industrial applications.[107-109] Nikolaou *et al.* demonstrated the polymerisation of NaAMPS with molecular weights up to 30 kDa with dispersities below 1.30.[68] A monomer with similar functionality, sulfopropyl acrylate potassium salt (KSPA), was reported to polymerise with a similar degree of control utilizing the predisproportionation of Cu(I)Br in the presence of Me_6Tren with a dispersity of 1.20 for DP_{40}. As target DP was increased beyond 80, control was also lost with dispersities greater than 1.50 illustrated in all cases.

Direct polymerisation of acidic monomers in their protonated form, such as MAA or acrylic acid (AA), was commonly considered to be impossible for most copper mediated RDRP systems, due to protonation of the ligand at the low pH required. Even in organic media only a small amount of MAA can be copolymerised whilst retaining control.[110,111] Direct polymerisation is attractive as k_p can be higher for the protonated monomer (10 times higher in the case of MAA *vs.* NaMA),[112] polymerisation is not inhibited by build-up of anionic charge on the polymer backbone, complexation to copper will be significantly lessened, and no titration of the final product is required. In 2015 Fantin *et al.* conducted an electrochemical investigation into three commonly used catalyst systems in aqueous ATRP: CuX/Me_6Tren, CuX/PMDETA, and CuX/TPMA, and found that polymerisations of PEGMA with TPMA could proceed effectively at low pH (1.5).[113] This apparent stability at low pH was subsequently used to demonstrate the polymerisation of MAA in acidic aqueous solution using *e*ATRP and Cu(0)-RDRP (figure 10).[114] Conducted at low pH (~1), poly(MAA) was prepared with molecular weights up to 87 kDa, with varying degrees of control ($Đ$ = 1.33->2.0). However, initiator efficiencies varied significantly, in some cases being greater than 100%. Despite the high conversions attained in some cases, no chain extensions are reported either *in-situ* or from an isolated PMAA macroinitiator.

1.11.4 Current Limitations of Aqueous Cu-mediated RDRP

Despite the impressive advancements made in controlled polymerisation in aqueous media using copper catalysts, there are still a number of challenges to be overcome, most of which relate to monomer scope; some classes of monomer have yet to be polymerised with high degrees of control.

Polymerisation of *N*-vinyl monomers such as *N*-vinyl pyrrolidone (NVP) is challenging by Cu-mediated RDRP; this is due to lack of resonance stabilization of the generated radicals and strongly electron donating pendant groups, which makes them highly reactive and means that end group fidelity is compromised by radical-radical termination, chain transfer reactions and hydrolysis.[115] Few reports also exist of the successful polymerisation of methacrylamides, either in aqueous or organic media, with results in aqueous media showing linear kinetics but a lack of control over molecular weight distributions ($Đ$ = 1.47->2.0).[66] These two monomer classes could be particularly useful as their polymers exhibit good water solubility and can exhibit interesting biological behaviour.[66,116] The controlled polymerisation of charged monomers to high molecular weights with degrees of control similar to uncharged water soluble monomers is another key area that needs development in the field of aqueous Cu-mediated RDRP.

1.11.5 Summary and Outlook

Aqueous Cu-RDRP has seen very encouraging advances since the first report of ATRP in aqueous media. Many techniques have been developed which yield high levels of control over chain length, molecular weight distribution, and macromolecular architecture. Activator regeneration methods in ATRP allow catalyst concentrations on a ppm level to be utilized to give better control than ever before, and the advent of aqueous Cu(0)-RDRP has made great advancements in the synthesis of block copolymers thanks to retention of halide end groups at quantitative monomer conversions. However, a number of challenges still remain. Important classes of monomers such as NVP and methacrylamide that yield biologically relevant polymers are still relatively poorly reported in Cu-RDRP and have not been optimized to the same extent that other monomer classes have, with work to date reporting mostly uncontrolled polymerisations. There are also limited successful reports of the polymerisation of acidic and charged monomers in solution and no examples of block copolymer synthesis with protonated acidic monomers. Further challenges

surrounding the uncontrolled spontaneous polymerisation of zwitterionic monomers in water has also not been surmounted. Techniques which have demonstrated excellent qualities such as ultra-low catalyst loadings and high conversions have often only been optimized for one or two monomer classes. An ideal aqueous transition metal mediated system able to control the polymerisation of a wide range of (meth)acrylates, (meth)acrylamides, charged, acidic and *N*-vinyl monomers to quantitative conversions with high end group fidelity at ppm catalyst concentrations still remains elusive.

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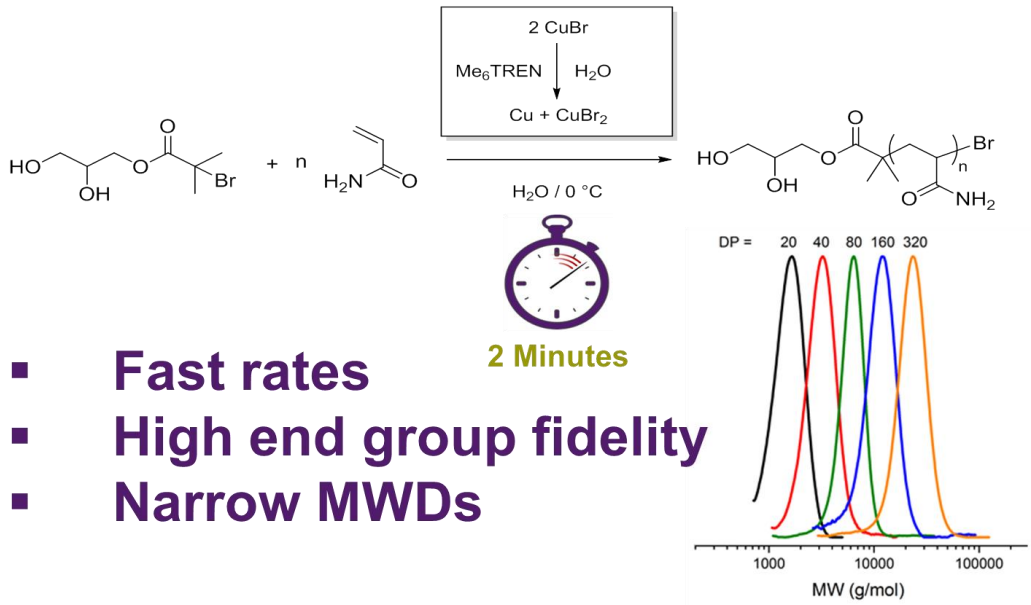
Chapter 2: Rapid Synthesis of Well Defined Polyacrylamide by Aqueous Cu(0)-Mediated Reversible Deactivation Radical Polymerisation



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2.1 Introduction

Polyacrylamide belongs to a highly versatile group of polymers that can find use in a wide range of applications including wastewater treatment,[1] oil recovery,[2,3] soil conditioning, agriculture,[4] biochemistry and biomedical applications[5,6] and even as a subdermal filler for aesthetic surgical procedures.[7] The toxicity of these polymers has also attracted considerable attention as some of the aforementioned applications include direct contact with either humans or animal livestock. The concentration of the residual monomer in particular, has to be in ppm levels (~500 ppm) and hence polymerisation reactions that can afford quantitative monomer conversion are highly desired.[8,9]

Free radical polymerisation has been utilized for the synthesis of AM homopolymers and statistical block copolymers. However, the need for enhanced control over the MWD's and sophisticated architectures facilitated the employment of controlled radical polymerisation methods (CRP). Reversible-deactivation radical polymerisation of acrylamide and derivatives has been until recently an area dominated by reversible addition-fragmentation transfer (RAFT) methodology with well-defined polyacrylamide and derivatives as well as excellent sequence control being demonstrated.[10-15] Although RAFT has been reported to give good control over the MWD's, the reaction generally requires 24 h to reach conversions greater than 90% at ambient temperature while in situ chain extensions and block copolymers from a polyacrylamide macroinitiator were not reported under the conditions employed.[10,12]

The other most promising methodology of reversible-deactivation radical polymerisation, transition metal mediated reversible-deactivation polymerisation (TMM-RDRP),[16-19] (usually utilising copper) has proved challenging for acrylamide, cited as being due to in sufficient deactivation and numerous side reactions involving radical abstraction and combination.[19,20] Atom transfer radical polymerisation (ATRP) of acrylamide and its derivatives has been attempted in various organic solvents[21,22] as well as mixed aqueous media[23-27] with varying degrees of success, however, research into transition metal mediated polymerisation of acrylamide in particular has been limited and has proved relatively unsuccessful compared to more established protocols for the polymerisation of acrylates and methacrylates.[16,28-31]

Specifically, in 2003 Jewrajka and Mandal reported on the ATRP of acrylamide in both water and a glycerol-water medium.[24] Using both chlorine and bromine containing initiators and a copper bipyridine complex as catalyst Jewrajka et al. found that addition of $Cu(II)X_2$ reduced the dispersity of the resultant polyacrylamide. However, even under optimized conditions the dispersity was relatively high (~1.7), with size exclusion chromatography (SEC) traces revealing low molecular weight tailing, thus indicating extensive termination events, it is noted that this ligand will stabilise copper(I) due to the presence of low lying π* orbitals accepting electron density from the metal. These results were further optimized in a later report by utilising aqueous glycerol media with a Cu(I)X /pentamethyldiethylenetriamine (PMDETA) based catalyst.[25] Although lower dispersity was reported ($Đ$ = 1.24) for a bromine based initiating system, monomer conversion and molecular weight was severely limited (9%, M_n = 1200, in 48 hours).

In a further report, Jiang *et al.* investigated the preparation of polyacrylamide by ATRP using a chloride initiator and tetramethylethylenediamine (TMEDA) as ligand.[26,27] Low dispersity polyacrylamides (*$Đ$=1.19-1.57)* were obtained in aqueous and mixed aqueous media, however, similar to Jewrajka and Mandal's work, monomer conversion was found to be low, less than 20% in most cases, even after long reaction times (>48 hours). In addition to this, the experimental molecular weights were significantly deviating from the theoretical values, indicating severe termination. ATRP in aqueous media using a Cu(I)X/ tris[2-(dimethylamino)ethyl]-amine (Me_6Tren) catalyst system was also performed by Broekhuis and coworkers in 2012.[32] The molecular weight was demonstrated to evolve linearly with conversion, and monomer conversion was found to be significantly higher than previously reported. However, the dispersities of the resultant polyacrylamides (>1.4) were higher than those typically reported for the ATRP of acrylates and methacrylates.

The most recent example of polyacrylamide synthesis by ATRP was published in 2015 by Matyjaszewski and co-workers.[23] Using electrochemistry (eATRP) to tune redox parameters, acrylamide was polymerised from a poly(ethylene glycol) macroinitiator showing good agreement between theoretical and experimentally determined molecular weights and dispersity as low as 1.09 for lower targeted molecular weight species. However, a water/DMF mixture was used (not pure water) and the integrity

of the reported diblock copolymer was compromised when the macroinitiator reached a conversion of only 84% prior to the subsequent monomer addition.

Cu(0)-RDRP, commonly referred to as single electron transfer living radical polymerisation (SET-LRP)[33-45] of acrylamides has also been attempted. However, the introduction of high contents of water in the solvent composition resulted in significant broadening of the MWDs suggesting inefficient deactivation under the conditions used.[43,46-48] In 2013 the Haddleton group introduced a novel protocol for the polymerisation of acrylamide monomers in aqueous solution in the presence of Cu(0).[49] The key to the success of the polymerisations was to utilise the fast and complete disproportionation of Cu(I)Br to Cu(0) and Cu(II) species in an aqueous solution of Me_6Tren *prior* to the addition of either monomer and initiator. The Haddleton group demonstrated that this technique is an extremely powerful tool for the synthesis of both polyacrylamides and other water soluble monomers such as PEG based acrylates over very short time scales. Poly(*N*-isopropylacrylamide) (PNiPAM), poly(*N*,*N*-dimethylacrylamide), poly(poly(ethylene glycol) acrylate), poly(2-hydroxyethyl acrylate) (PHEA), poly(*N*-acryloyl morpholine) (PNAM)[50] and polymers from an acrylamido glycomonomer[51] were all synthesized with narrow MWDs ($Đ < 1.10$ in many cases). The robust nature of the system was further demonstrated by successful polymerisations of NiPAM in complex mixed solvent systems (beverages) as well as polymerisations in biologically relevant media (blood serum).[52-56]

Herein, a thorough investigation of the polymerisation of AM via aqueous Cu(0)-RDRP is presented. Careful tuning of the ratio of [Cu(I)Br]:[Me_6Tren] allows for the rapid, quantitative and controlled polymerisation of Am to a range of chain lengths (DP_n = 20-640). Under well optimized conditions polyacrylamides could be obtained within 15 min, in a quantitative manner (>99% conversion) with narrow molecular weight distributions ($Đ \sim 1.10$ in most cases). Kinetic experiments were also performed to assess the living character and the polymerisation rate, in which it was found that >90% conversion is achieved in just 2 minutes. The control retained during polymerisation has been subsequently exemplified by in situ chain extensions and block copolymerisations furnishing higher molecular weight polymers within 30 min (>99% conversion) while maintaining low dispersity.

2.2 Results and Discussion

2.2.1 Initiator Synthesis

The most common initiator utilized for aqueous Cu(0) mediated polymerisation is a water soluble glycerol derivative first reported by Perrier *et al.* for aqueous ATRP.[57] NMR characterization in this original publication was conducted in deuterated DMSO, however during the course of the present investigation it was found that an impurity is present in the proton NMR in D_2O which is not observable in DMSO-d_6. The nature of the impurity was determined using a combination of proton, COSY, ^{13}C, HMQC, and HMBC and was found to be a structural isomer of the desired product, as show in figure 2.1, figure 2.12 (experimental section) and scheme 2.1.

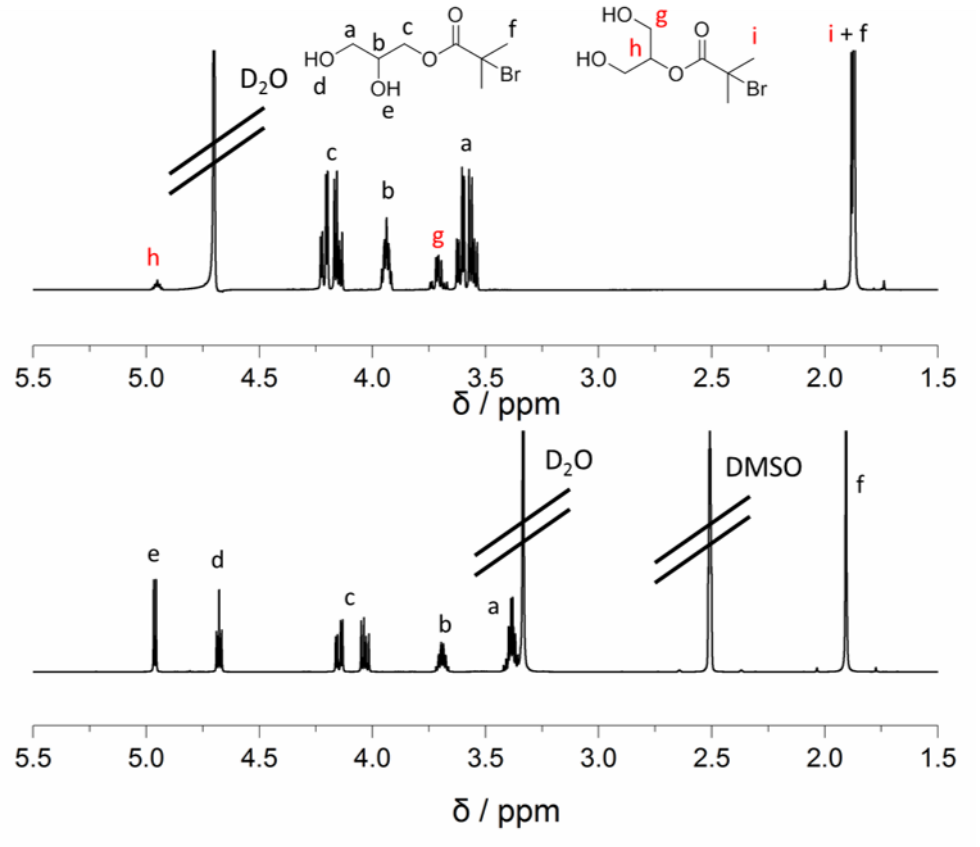
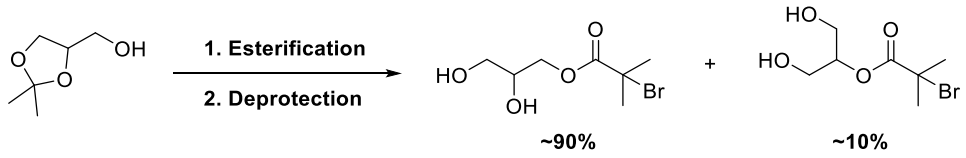


***Figure 2.1**: Proton NMR's of the water soluble initiator used in this study. Top: spectra collected using D_2O solvent, with full assignment of major product and structural isomer impurity. Bottom: spectra collected in deuterated DMSO showing absence of impurity.*

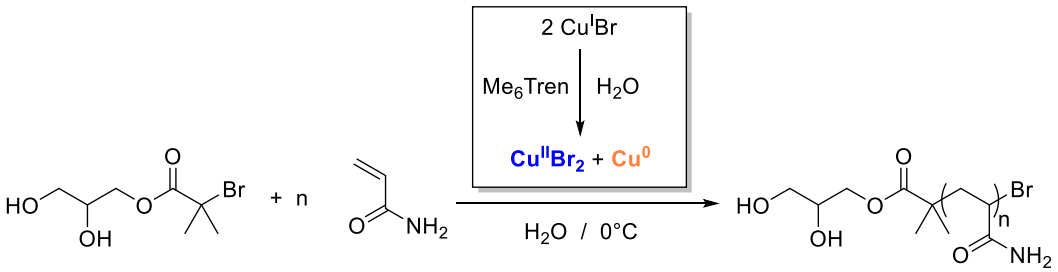
The initiator is prepared from the protected glycerol, solketal, through esterification subsequent deprotection of the acetonide. It is suggested that isomerization occurs through intramolecular transesterification in aqueous media. However, it is noted that

this is also a dihydroxyl water soluble initiator which will lead to a very similar product and is expected to have essentially identical rates of initiation. As separation of the two isomers proved difficult and due to the similarity of the reactivity of the final products it was decided to continue with the mixed initiator.



***Scheme 2.1**: Synthesis of water soluble initiator showing the main product and isomer.*

2.2.2 Optimization of Homopolymerisation of Acrylamide



***Scheme 2.2**: Homopolymerisation of acrylamide by aqueous Cu(0)-RDRP via predisproportionation of Cu(I)Br with Me$_6$Tren.*

Homopolymerisations of acrylamide (Scheme 2.2) were initially carried out using a ratio of [Am]:[I]:[Cu(I)Br]:[Me$_6$Tren] of [20]:[1]:[**0.4**]:[**0.4**]. Cu(I)Br was added to a Schlenk tube containing a deoxygenated aqueous solution of Me$_6$Tren (figure 2.2 (a)), the solution rapidly turned blue (indicating the formation of Cu(II)Br$_2$/Me$_6$Tren) and a dark metallic Cu(0) precipitate was formed (figure 2.2 (b)). In a separate vial an aqueous solution of monomer and initiator was deoxygenated for 15 minutes in an ice bath. This solution was then transferred to the Schlenk tube *via* deoxygenated syringe and the reaction was left to proceed in an ice bath. NMR analysis demonstrated full monomer conversion was attained within 15 minutes, as determined by the absence of vinyl protons (~ 5.75 - 6.5 ppm). Aqueous SEC analysis revealed an excellent agreement between the theoretical and the experimental molecular weights and a symmetrical molecular weight distribution ($Đ$ ~ 1.10, entry 1, table 2.1; figure 2.5). Similar conditions ([40]:[1]:[0.4]:[0.4]) were subsequently applied targeting a degree of polymerisation of 40. ^{1}H NMR revealed again near quantitative conversion (> 99%) in 15 min and SEC showed a low dispersity polymer ($Đ$ ~ 1.12, figure 2.5).

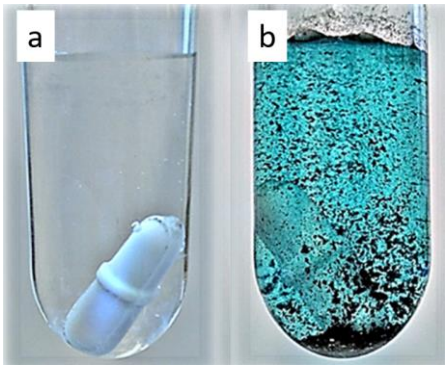


***Figure 2.2**:(a) Colourless aqueous solution of Me_6Tren. (b) Solution after addition of Cu(I)Br showing Cu(II) complex and Cu(0) precipitate.*

***Table 2.1**: Aqueous Cu(0)-RDRP of Acrylamide with varied degree of polymerisation.*

Entry	[M]:[I]:[Cu(I)Br]:[Me_6Tren]	Conv. (%)	$M_{n\ (Theo)}$ (Da)	$M_{n\ (SEC)}$ (Da)	*Đ*
1	**20 : 1 : 0.4 : 0.4**	**>99**	**1700**	**1500**	**1.10**
2	**40 : 1 : 0.4 : 0.4**	**>99**	**3100**	**2900**	**1.12**

Similar results were obtained for a targeted degree of polymerisation of 80, however, a slight broadening of the molecular weight distribution was also observed (entry 1, table 2.2; blue trace, figure 2.3). Attributing this broadening to insufficient deactivation of propagating polymer chains the concentration of the copper was doubled to [I]:[Cu(I)Br]:[Me_6Tren] = [1]:[0.8]:[0.4] effectively giving a higher concentration of the deactivating species: [Cu(II)(Me_6Tren)Br_2]; it is again noted that this ratio of 2:1 Cu/ligand is very different to "typical polymerisation conditions" used in previous work where this ratio is between 1:6 and 1:20.[34,58] Entry 2, table 2.2 shows that the dispersity of the resultant polymer improved slightly (*Đ* = 1.11 compared to *Đ* = 1.17; green trace, figure 2.3), although conversion was somewhat limited (~93% vs >99% for previous polymerisations). This was attributed to the excess of deactivator that not only gives better control over the MWDs but is also compromising the rate of polymerisation. It should be also noted that for aqueous systems, propagation needs to be fast as exposure of the bromine end group to the aqueous media for prolonged periods can result in hydrolysis and other side reactions such as elimination.[53] It has also been shown that the concentration of the ligand relative to the copper is an essential parameter that needs to be carefully considered to afford a well-defined polymer at an acceptable polymerisation rate.[59,60] Thus, in an attempt to obtain an acceptable balance between control over polymerisation and a rate at which

higher conversions can be effectively reached the relative concentration of ligand was increased to [0.8 : 0.6]. Entry 3, table 2.2 shows that the improved ratios yielded polyacrylamide of lower dispersity ($Đ$ = 1.09, Figure 1) and higher conversion (>99%; red trace, figure 2.3) with excellent agreement between experimental and theoretical molecular weight.

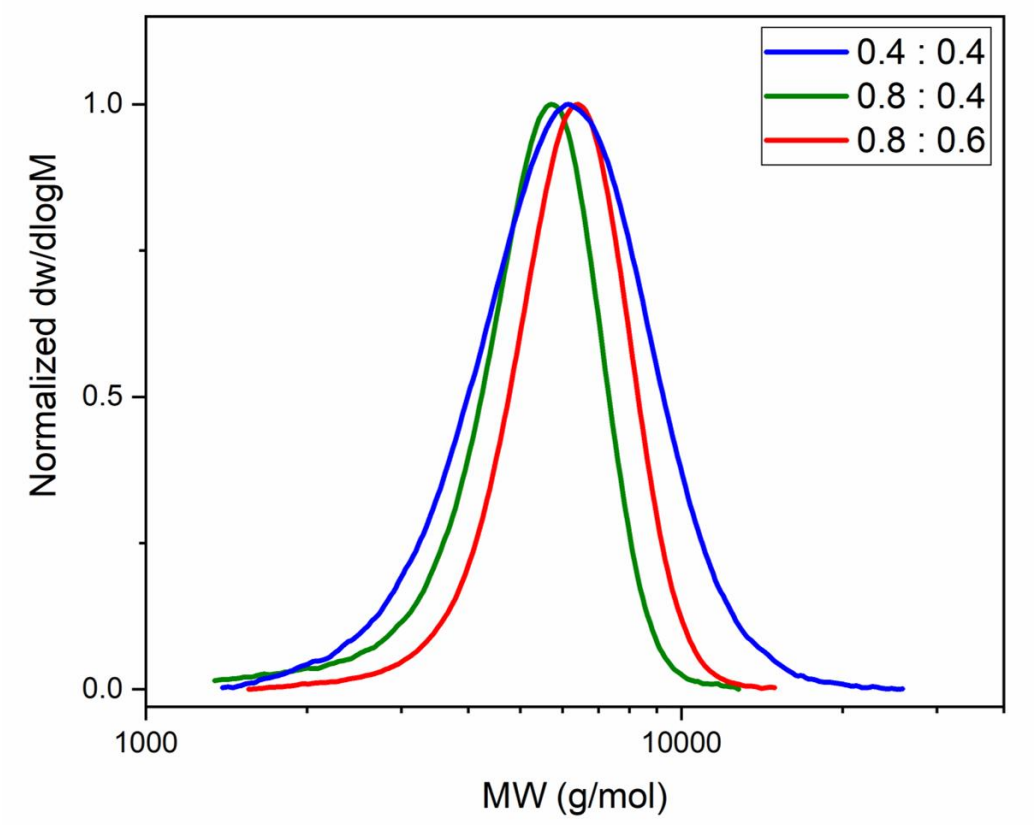


***Figure 2.3**: SEC traces from optimization of poly(acrylamide) synthesis with targeted DP of 80, data corresponds to entries 3-5 in table 2.2.*

***Table 2.2:** Aqueous Cu(0)-RDRP of Acrylamide (DP = 80) with varied Cu(I)Br and Me_6Tren concentration.*

Entry	[M]:[I]:[Cu(I)Br]:[Me_6Tren]	Conv. (%)	$M_{n\ (Theo)}$ (Da)	$M_{n\ (SEC)}$ (Da)	$Đ$
1	80 : 1 : 0.4 : 0.4	>99	5900	5500	1.17
2	80 : 1 : 0.8 : 0.4	93	5500	4900	1.11
3	**80 : 1 : 0.8 : 0.6**	**>99**	**5900**	**5800**	**1.09**

The necessity to tune the ratio between ligand and copper content was further highlighted when targeting an even higher degree of polymerisation (DP_n = 160). The initial conditions ([Cu(I)Br]:[Me_6Tren]=[0.4]:[0.4]) yielded a relatively uncontrolled polymer with a broad molecular weight distribution (entry 1, table 2.3; blue trace, figure 2.4) while when higher copper content relative to ligand was employed (generating more deactivating Cu(II)Br_2) lower conversions were evident and quantitative conversion could not be achieved, even when the reaction was left to proceed overnight (entry 2, table 2.3; green trace, figure 2.4). However, when both the copper and ligand concentration was optimized full conversion could be reached within 15 min with aqueous SEC revealing symmetrical, mono-modal polymer peak distributions (entry 3, table 2.3; green trace, figure 2.4) and good agreement between the theoretical and experimental molecular weights.

Table 2.3: *Aqueous Cu(0)-RDRP of Acrylamide (DP = 160, 320) with varied Cu(I)Br and Me_6Tren concentration.*

Entry	**[M]:[I]:[Cu(I)Br]:[Me_6Tren]**	**Conv. (%)**	**$M_{n\ (Theo)}$ (Da)**	**$M_{n\ (SEC)}$ (Da)**	***Đ***
1	160 : 1 : 0.4 : 0.4	>99	11600	12900	1.46
2	160 : 1 : 0.8 : 0.4	96	11100	9700	1.07
3	**160 : 1 : 0.8 : 0.6**	**>99**	**11600**	**11000**	**1.09**
4	320 : 1 : 0.4 : 0.4	99	22700	18800	6.20
5	320 : 1 : 0.8 : 0.4	95	21800	18400	1.10
6	**320 : 1 : 0.8 : 0.6**	**>99**	**22700**	**23100**	**1.12**

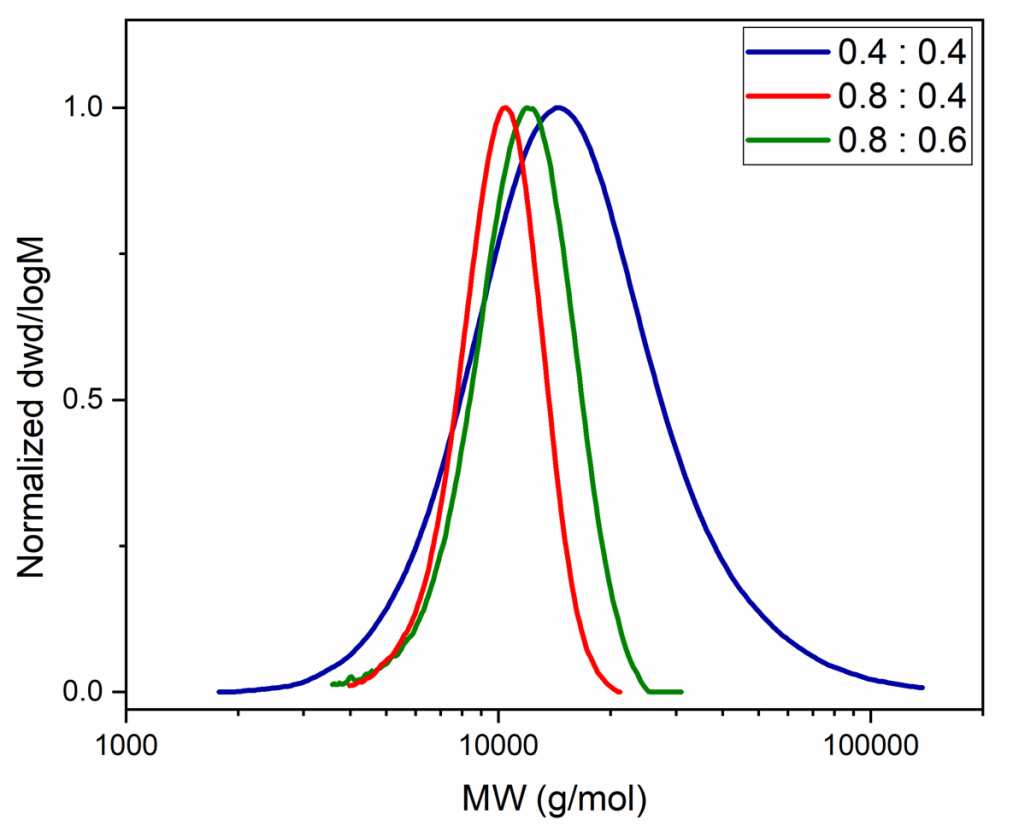


***Figure 2.4**: SEC traces from optimization of poly(acrylamide) synthesis with targeted DP of 160, data corresponds to entries 3-5 in table 2.3. blue – entry 1, red – entry 2, green – entry 3.*

The synthesis of polyacrylamide with targeted DP of 320 was optimized in a similar fashion. A polymerisation utilizing 0.4 : 0.4 equivalents of Cu(I)Br and Me_6Tren resulted in an uncontrolled polymerisation with a very high dispersity ($Đ$ = 6.2; entry 4, table 2.3). Again, this suggests that the amount of deactivation occurring is not sufficient, resulting in high molecular weight species as well as low molecular weight species from termination. Increasing the amount of Cu(I)Br by a factor of 2 has a dramatic effect on the dispersity of the resultant polymer ($Đ$ = 1.10; entry 4, table 2.3). Adjusting the ligand concentration to 0.6 then gives a polymerisation with good control of molecular weight and quantitative conversion.

Figure 2.5 shows SEC traces for the optimized polymerisations of polyacrylamide with targeted DP's of 20-320. Controlled synthesis of polyacrylamide at these low molecular weights is of particular interest because low molecular weight polyacrylamide is difficult to achieve with free radical polymerisation due to the high propagation rate constant.

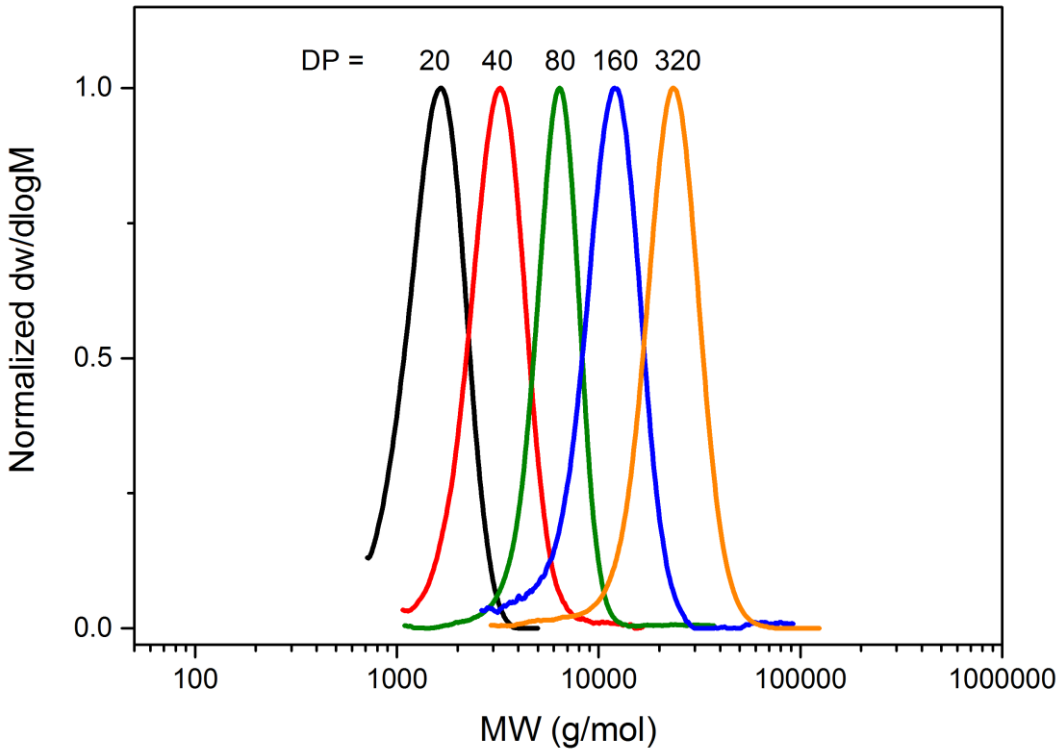


***Figure 2.5**: Molecular weight distributions of polyacrylamide (DP_n = 20, 40, 80, 160, 320) synthesized under optimized conditions (bold entries, tables 2.1-3) as measured by aqueous SEC.*

2.2.3 Targeting Higher Molecular Weight

In order to probe the potential of the technique to obtain higher molecular weight polyacrylamide, a reaction targeting DP_n = 640 was conducted. Due to the loss of control observed when lower copper and ligand concentrations were utilized, initial work into the synthesis of polyacrylamide of DP_n = 640 employed the previously optimized ratios of [1]:[0.8]:[0.6] ([I]:[Cu(I)Br]:[Me_6Tren]). These initial conditions successfully polymerised acrylamide to high conversion (>99%) once again with good agreement between theoretical and experimental molecular weights (table 2, entry 1). However, the ASEC analysis (blue trace, figure 2.6) showed a much broader polymer peak distribution than those of lower molecular weights synthesized when identical conditions were employed (entry 1, Table 2). Increasing the copper ratio to the point of being in excess of initiator concentration results in a narrower molecular weight distribution ($Đ$ = 1.27 compared to $Đ$ = 1.41; red trace, figure 2.6) whilst retaining high conversion and expected molecular weight, whereas increasing copper and ligand concentration results in a broadening of the MWD. The broader dispersity of $Đ$ = 1.27 as compared to much lower values for lower molecular weights is either due to the use

of a mixed type column as opposed to an Aquagel column designed for differentiation between smaller differences in molecular weight, or possibly due to more side reactions at prolonged reaction times (more monomer units being added per propagating chain). Attempts to further optimize the control over the MWDs were unsuccessful (green trace, figure 2.6), suggesting that the limits of the system had been reached (entry 3, table 2.4).

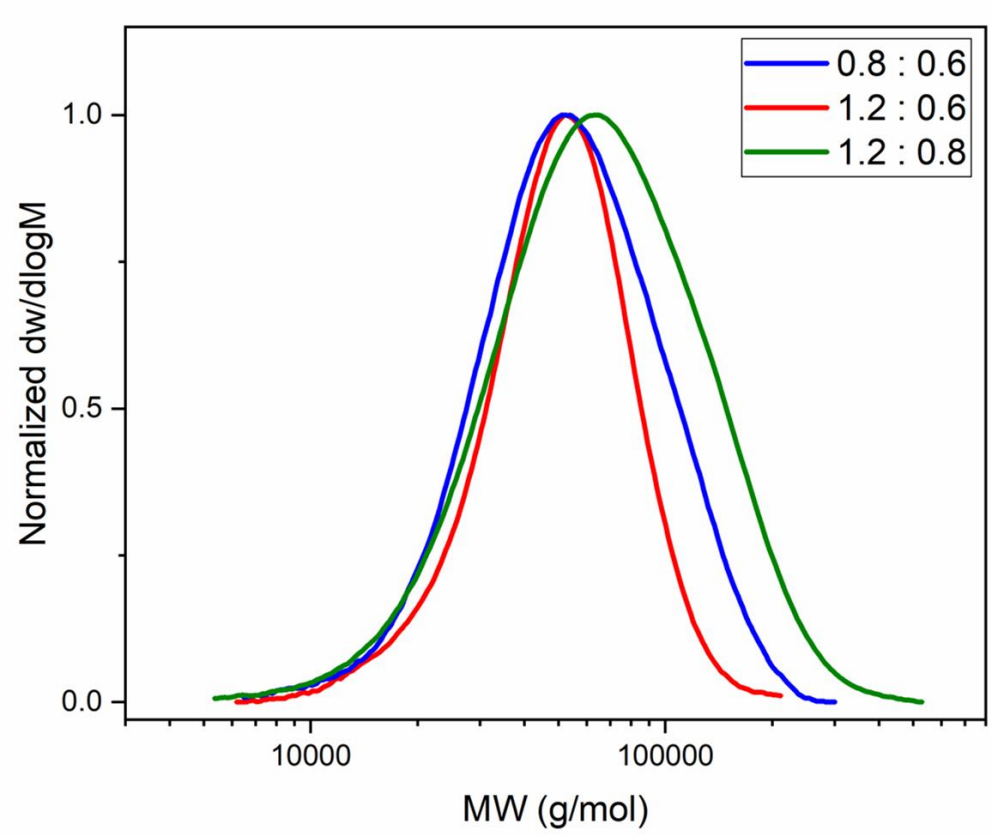


***Figure 2.6**: Molecular weight distributions of polyacrylamide (DP_n = 640) synthesized under optimized conditions (table 2.4) as measured by aqueous SEC.*

***Table 2.4**: Optimization of homopolymerisation of acrylamide by aqueous Cu(0)-RDRP (DP_n = 640).*

Entry	[M]:[I]:[Cu(I)Br]:[Me_6Tren]	Conv. (%)	$M_{n\ (Theo)}$ (Da)	$M_{n\ (SEC)}$ (Da)	*Đ*
1	640 : 1 : 0.8 : 0.6	>99	44500	45700	1.41
2	**640 : 1 : 1.2 : 0.6**	**>99**	**44500**	**42900**	**1.27**
3	640 : 1 : 1.2 : 0.8	>99	44500	49400	1.60

2.2.4 Polymerisation of Acrylamide on a Larger Scale

Thus far all polymerisations carried out to optimize the procedure for controlled synthesis of polyacrylamide had been performed in a 25 mL Schlenk tube on a gram scale. In order to test the procedure's applicability to higher scales a reaction was attempted using a jacketed 500 mL Radleys Reactor on a 50 g scale.

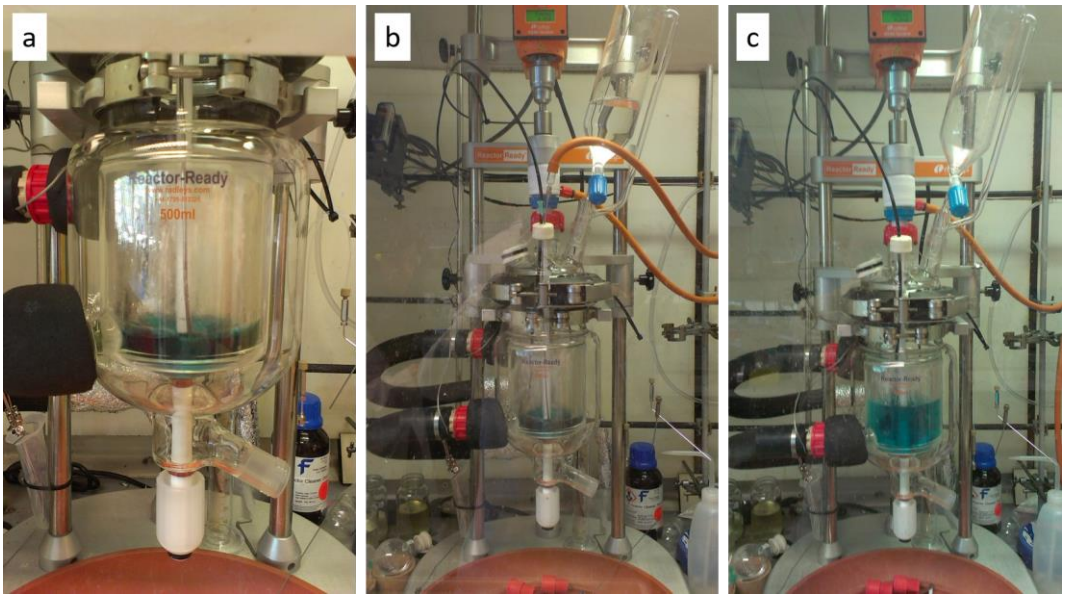


***Figure 2.7**: (a) Large scale disproportionation in a 500 mL reactor. (b) Reactor with dropping funnel containing monomer and initiator solution. (c) Reaction after addition of monomer and initiator.*

The reaction was carried out in a similar fashion to the small scale optimizations; Cu(I)Br was disproportionated in an aqueous solution of Me_6Tren and deoxygenated by nitrogen sparging (figure 2.7 (a)). The monomer and initiator solution was charged to a pressure equalized dropping funnel with ice cold water and deoxygenated in a similar fashion (figure 2.7 (b)). After deoxygenating both solutions for 15 minutes via nitrogen sparging, the monomer and initiator solution was added into the reactor with rapid stirring (figure 2.7 (c)). The reaction was sampled after 1 hour and analysed by aqueous SEC and NMR. Conversion was found to be >99% with a M_n of 3000 Da, and a dispersity of 1.55. The dispersity for this larger scale reaction is markedly higher than small scale analogues. A major difference between the two protocols is that addition of the monomer/initiator solution is almost instantaneous for the small scale reaction, whereas for the larger scale it took around 1 minute for the dropping funnel to fully transfer the solution to the reaction. This in effect means than the first molecules of monomer/initiator to reach the catalyst has 1 minute longer to react than

the last added. It is thought that this would have the effect of broadening the molecular weight distribution.

2.2.5 Investigation into the Rate of Acrylamide Polymerisation

In 2015 Alsubaie *et al*. reported on aqueous Cu(0)-RDRP as a tool for the synthesis of sequence controlled multiblock copolymers in which it was demonstrated that chain extension is much more efficient if sequential monomer addition is performed at, or as close to full conversion as possible, so as to minimise exposure to conditions at which monomer concentration is low.[53] To this end a kinetic investigation revealed that quantitative monomer conversion is obtained in just 11 minutes for the polymerisation of NiPAM.

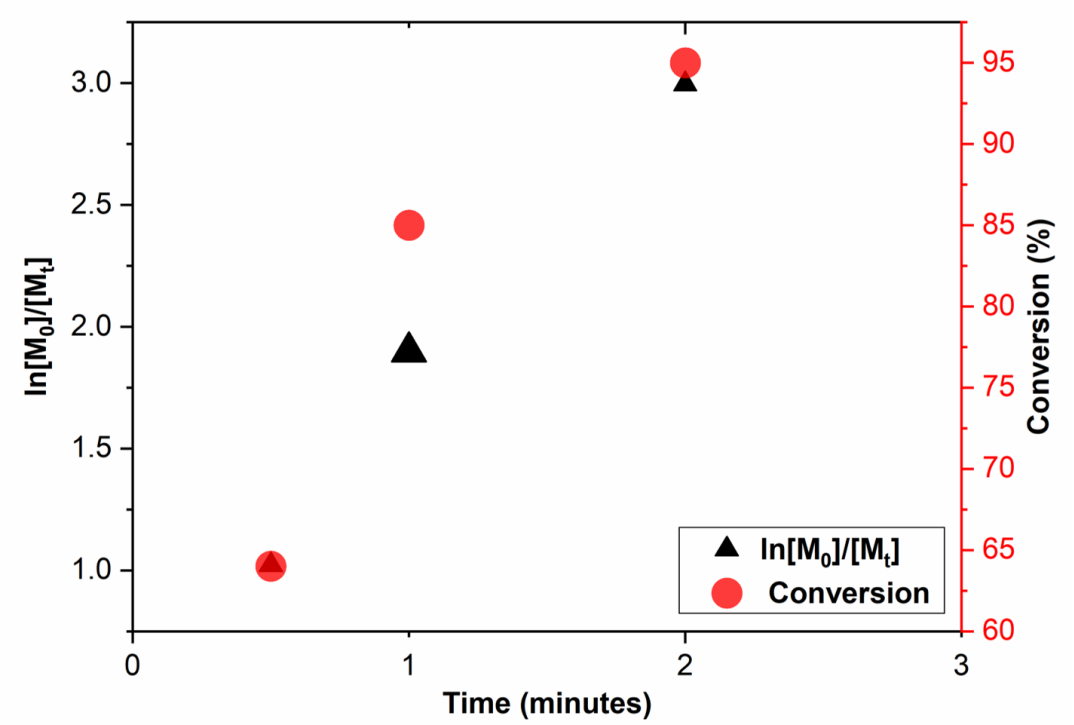


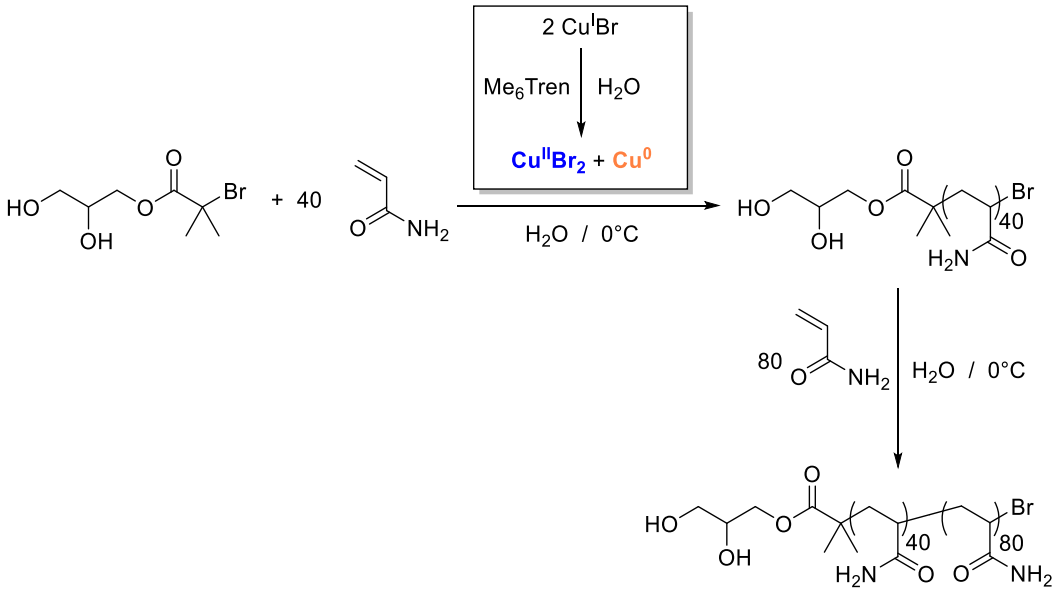
***Figure 2.8**: Kinetic plot of acrylamide polymerisation (target DP = 80).*

By placing a digital probe thermometer into the Schlenk tube during polymerisation in an ice bath under optimized conditions it could be seen that in the case of the polymerisation of acrylamide (DP_n = 80) the reaction exotherms to reach ~6 °C. Attempts at a full kinetic analysis of this system proved challenging due to the extremely fast reaction, with regular sampling compromising the reaction yielding incomplete conversion. This can be attributed to the heterogeneous nature of the system as multiple samples could disrupt the polymerisation equilibrium (e.g. by removing random amounts of Cu(0) per sample the concentration of active species is

inconsistent), or by introduction of small amounts of oxygen. Scaling up the reaction in order to overcome this was also found to be unconducive to kinetic analysis as the speed of the reaction coupled with the need to add a large volume of monomer and initiator solution effectively yields monomer feeding conditions and propagation is already occurring whilst the solution is still being added, as also noted in the 50 g scale reaction in the previous section. Taking single samples from multiple smaller scale reaction revealed 95% conversion in just 2 minutes.

2.2.5 Chain Extensions and Block Copolymerisations of Polyacrylamide

Although obtaining such low dispersity polymers in a matter of minutes is impressive and indicates excellent control over the molecular weight, it offers no insight on the end group fidelity of the resultant polymers. In order to assess the living nature of the polymerisation, chain extension experiments were performed by a sequential monomer addition. Acrylamide (DP_n = 40) was polymerised as previously described, sampled after 5 minutes (a timeframe long enough for quantitative conversion to be reached) and a second aliquot of degassed acrylamide solution was immediately transferred into the reaction vessel via degassed syringe (Scheme 2.3).



***Scheme 2.3**: Chain extension of poly(acrylamide)40 with 80 eq. of acrylamide.*

The reaction mixture was sampled again after 30 minutes and analysed by ^{1}H NMR and ASEC. Conversion of both the first and second block was found to be >99%. Aqueous SEC traces (figure 2.9) shows the first block to have a narrow, symmetrical, monomodal peak ($Đ$ = 1.14). The chain extended polyacrylamide is also found to have

a narrow, monomodal molecular weight distribution (*Đ* = 1.12). The clear shift to higher molecular weight shows only a very small amount of tailing, thus indicating that the vast majority of polymer chains were able to further react with additional monomer, demonstrating the high end-group fidelity of the polymerisation at even quantitative conversion.

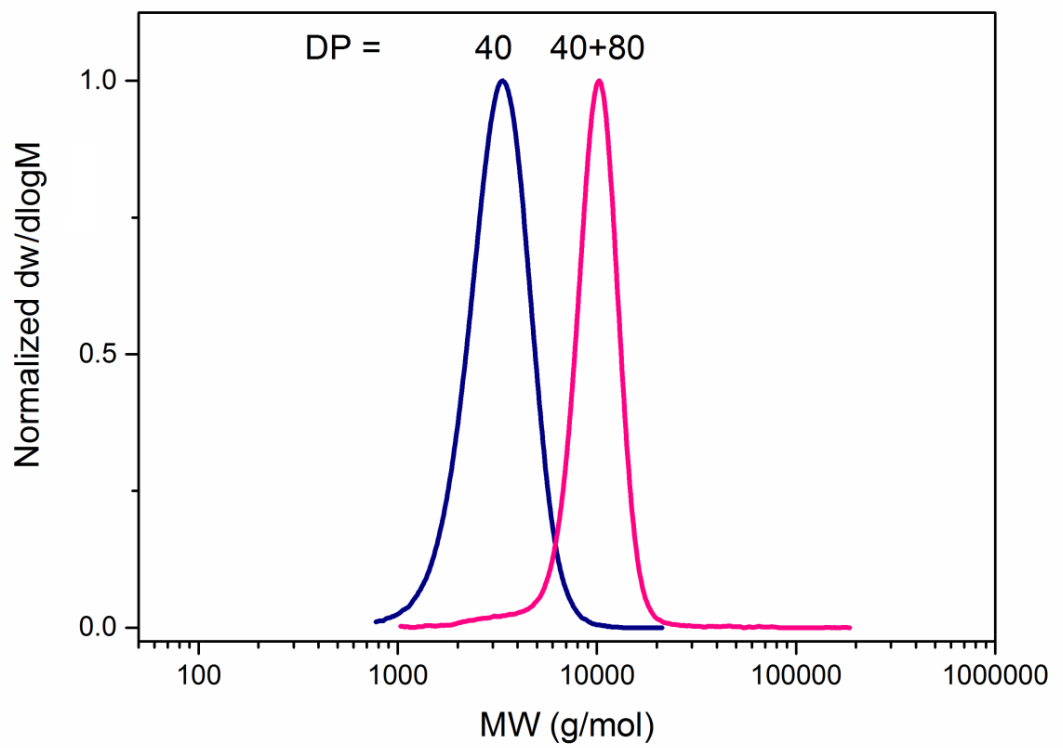


***Figure 2.9**: Molecular weight distribution of poly(acrylamide) (DP_n = 40) (Đ = 1.14) and poly(acrylamide)$_{40}$-b- poly(acrylamide)$_{80}$ as measured by aqueous SEC (Đ = 1.12).*

Similarly, efficient one-pot block copolymerisation by sequential addition of hydroxyethyl acrylamide (poly(acrylamide)$_{40}$-b-poly(hydroxyethyl acrylamide)$_{80}$) could also be achieved. ASEC traces, shown in figure 2.10 show a shift in molecular weight, retaining a narrow monomodal distribution with little evidence of unreacted polyacrylamide homopolymer, with conversion >99% for both blocks (figure 2.13, experimental section). The reverse one pot block copolymerisation utilizing poly(*N*-hydroxyethyl acrylamide) this time as the macroinitiator was also investigated. The final diblock copolymer was attained within 30 min presenting narrow MWDs, even at quantitative conversions, demonstrating the versatility of the approach.

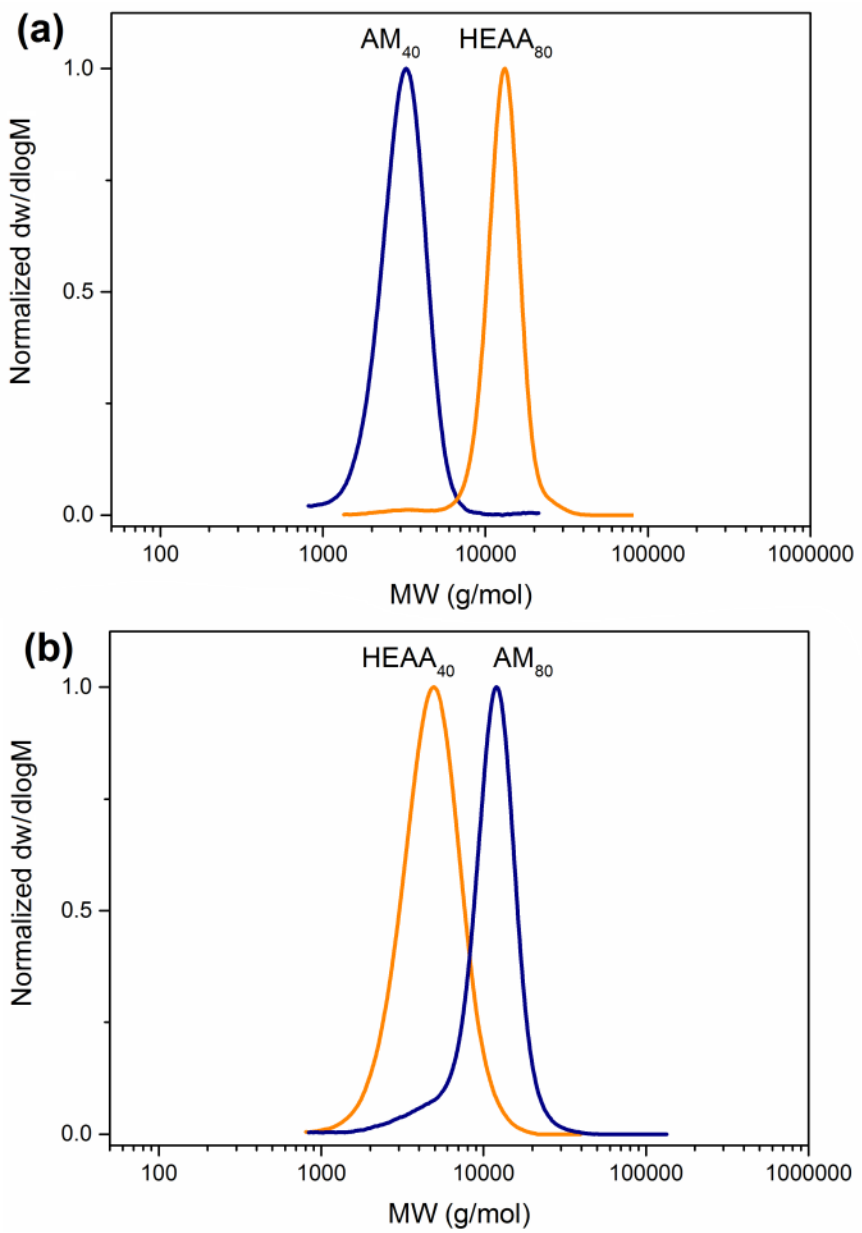
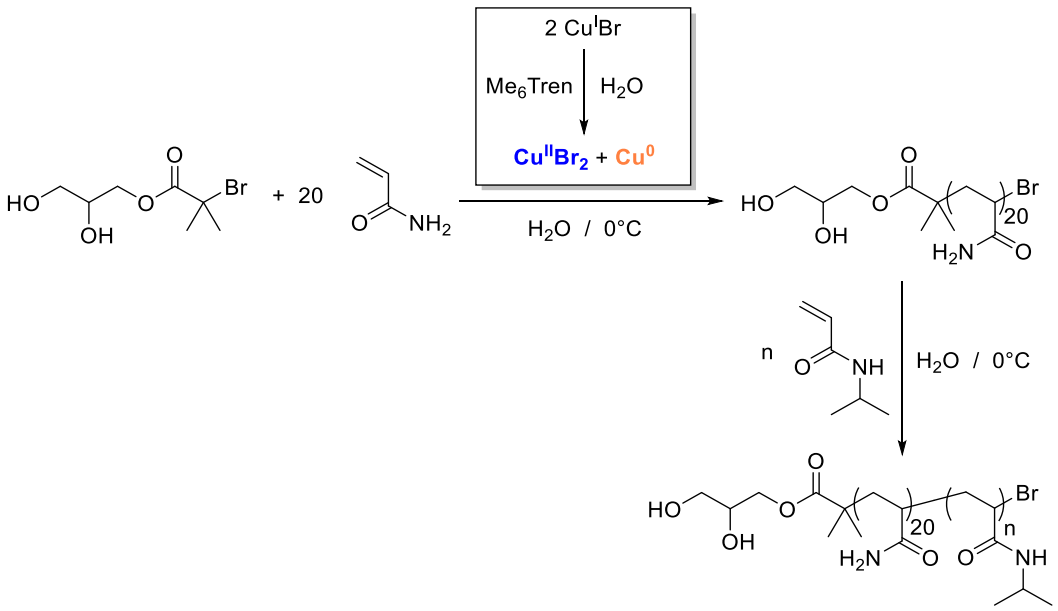


***Figure 2.10**: (a) Molecular weight distribution of poly(acrylamide) (DP_n = 40) (Đ = 1.13) and poly(acrylamide)$_{40}$-b-poly(hydroxyethyl acrylamide)$_{80}$ (Đ=1.09) as measured by aqueous SEC. (b) Molecular weight distribution of poly(hydroxyethyl acrylamide) (DP_n = 40) (Đ=1.19) and poly(hydroxyethyl acrylamide)$_{40}$-b-poly(acrylamide)$_{80}$ (Đ=1.19)as measured by aqueous SEC.*

2.2.6 Thermoresponsive Block Copolymers

In order to probe the potential of the technique for the synthesis of thermoresponsive materials, NiPAM was subsequently selected as a second block. Utilizing the previously optimized conditions, polyacrylamide of DP = 20 was initially targeted, followed by the in situ addition of NiPAM when quantitative conversion was reached.



***Scheme 2.4**: Synthesis of thermoresponsive block copolymers via chain extension of poly(acrylamide)$_{20}$ with N-isopropylacrylamide.*

***Table 2.5**: Synthesis of poly(acrylamide)-poly(N-isopropylacrylamide) block copolymers.*

Entry	Block no.	Monomer	Conv. (%)	$M_{n\ (Theo)}$ (Da)	$M_{n\ (SEC)}$ (Da)	*Đ*
1	1	Am (20 eq.)	>99	1700	1300	1.07
2	2	NiPAm (80 eq.)	>99	10700	19000	1.05
3	1	Am (20 eq.)	>99	1700	1300	1.07
4	2	NiPAm (160 eq.)	>99	19800	38200	1.10

The resultant polymer (Poly(acrylamide)$_{20}$-b-Poly(*N*-isopropyl acrylamide)$_{80}$) presented narrow MWDs (*Đ* = 1.07 for block 1, *Đ* = 1.05 for block 2) and cloud point of 44.9 °C (figure 2.11). A lower cloud point (39.2 °C) could also been obtained when higher contents of NiPAM were employed ((poly(acrylamide)$_{20}$-b-poly(*N*-isopropyl acrylamide)$_{160}$ (*Đ* = 1.07 for block 1, *Đ* = 1.10 for block 2), which is anticipated due to the incorporation of lower ratio of the hydrophilic poly(acrylamide) block. Thus, we demonstrated the robustness of the protocol to provide access to the facile and rapid synthesis of tuneable thermoresponsive materials.

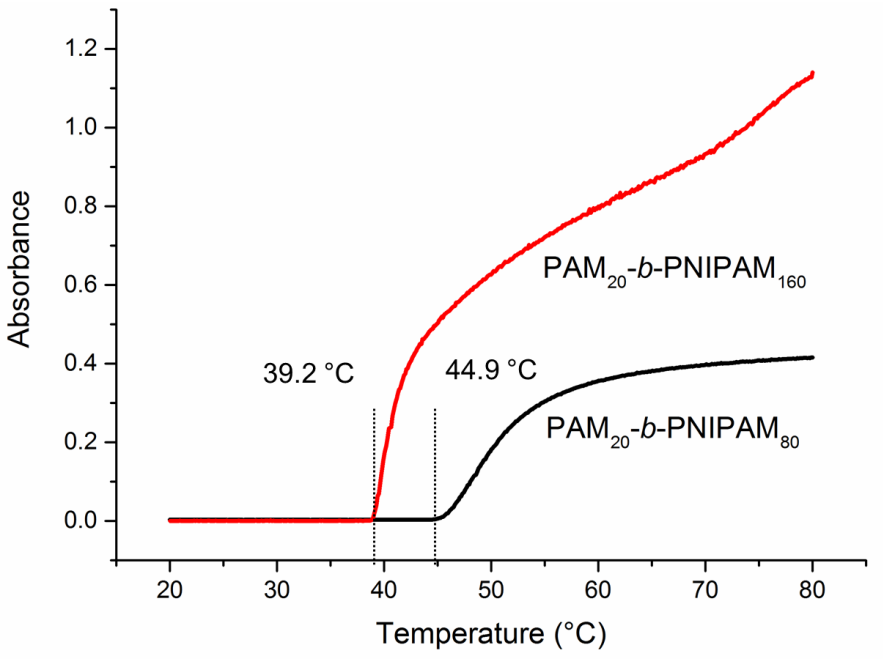


***Figure 2.11**: Cloud point measurements of Poly(acrylamide)20-b-Poly(N-isopropyl acrylamide)80 and Poly(acrylamide)$_{20}$-b-Poly(N-isopropyl acrylamide)$_{160}$.*

2.3 Conclusions

In summary, the synthesis of well-defined poly(acrylamide) has been demonstrated utilizing aqueous Cu(0)-mediated RDRP. A range of molecular weights has been targeted (DP_n = 20-640) demonstrating narrow MWDs ($Đ$ ~ 1.10 in most cases) and rapid polymerisation rates (full conversion within 15 min). An investigation into the rate of polymerisation of acrylamide of targeted DP = 80 revealed that >95% conversion could be attained in 2 min, further highlighting the speed of the reaction without compromising the control over the molecular weight distributions. Careful optimization of the copper to ligand ratio proved critical to afford polymers with high end group fidelity as exemplified by in situ chain extensions and block copolymerisations providing access to the facile synthesis of hydrophilic and thermoresponsive materials.

2.4 Experimental

2.4.1 Materials

Acrylamide (≥99% for electrophoresis), *N*-hydroxyethyl acrylamide (97%) were obtained from Sigma-Aldrich and used as received. *N*-isopropyl acrylamide (97%) were obtained from Sigma-Aldrich and purified by recrystallization from hexanes.

Tris[2-(dimethylamino)ethyl]-amine (Me_6Tren) was synthesized according the procedure in section 2.4.3 and stored under nitrogen and refrigerated prior to use.

Water soluble initiator, 3-dihydroxypropyl 2-bromo-2-methylpropanoate was synthesized according to the procedure in section 2.4.3.

Copper(I) bromide (Cu(I)Br, 98%) was purchased from Sigma-Aldrich and purified by sequentially washing with acetic acid and ethanol and dried *in vacuo* to remove Cu(II)Br_2 impurities. Purified Copper(I) bromide was stored in a foil wrapped vial in a desiccator to prevent oxidation.

2.4.2 Instrumentation

NMR spectra were recorded on Bruker AV-250 MHz and DPX-400 MHz spectrometers using deuterated solvents purchased from Sigma-Aldrich and Cambridge Isotope Laboratories Inc. Monomer conversion was calculated by comparison of vinyl protons (5.5-7.0 ppm) with polymer backbone protons (1.3-2.5 ppm.) NMR spectra for the water soluble initiator were conducted on a Bruker AV III-500 HD spectrometer using a cryoprobe.

Aqueous SEC was conducted on an Agilent Technologies Infinity 1260 MDS instrument equipped with a differential refractive index (DRI), light scattering (LS) and viscometry (VS) and UV detectors. The column set used was 2 Agilent PL Aquagel OH 30 and a 5 μm Aquagel guard column. The mobile phase used was 0.1 M $NaNO_3$. Column oven and detector temperatures were regulated to 35 °C, flow rate 1 mL/min. Poly(ethylene oxide) standards (Agilent EasyVials) were used for calibration (100-30,000 g/mol.) Analyte samples were filtered through a hydrophilic membrane with 0.22 μm pore size before injection. Experimental molar mass ($M_{n\,SEC}$) and dispersity ($Đ$) values of synthesized polymers were determined by conventional calibration using Agilent GPC/SEC software.

Cloud point measurements were conducted on an Agilent Cary 60 UV-Vis at a fixed wavelength of 500 nm, at polymer concentrations of 1 mg/mL. Temperature was increased by 1 °C per minute for 3 cycles.

2.4.3 Experimental Procedures

2,2-Dimethyl-1,3-dioxolan-4-yl-α-bromoisobutyrate

The protected initiator was prepared by esterification of 2,2-dimethyl-1,3-dioxolane-4-methanol (*solketal*) with α-bromoisobutyryl bromide. Solketal (80 mmol, 10.6 g), triethylamine (160 mmol, 16.2 g) and anhydrous tetrahydrofuran (THF) were charged to a 250 mL 3 necked round-bottom flask. A pressure equalizer dropping funnel was fitted to the round-bottom flask and charged with α-bromoisobutyryl bromide (88 mmol, 10.9 mL) and 25 mL THF. Both the round bottom flask and the dropping funnel were deoxygenated *via* sparging with nitrogen gas for 15 minutes. After this time the round-bottom flask was placed in an ice bath and the α-bromoisobutyryl bromide solution was added dropwise over the course of an hour. The reaction mixture was poured into an excess of cold water and extracted with diethyl ether (3 x 50 mL). The organic layer was then washed with a saturated solution of Na_2CO_3, 0.5N HCl and a second aliquot of Na_2CO_3. The organic layer was then dried over Na_2SO_4 and the solvent removed *in vacuo.* 2,2-Dimethyl-1,3-dioxolan-4-yl-α-bromoisobutyrate was isolated as a yellow oil (93%).

^{1}H NMR [DMSO-d_6] δ: 1.28 and 1.35 [s, 3H, $OC(CH_3)_2O$], 1.90 [s, 6H, $C(CH_3)_2Br$], 3.72 [dd, 1H, $OC\underline{H_a}H_b$, J_{ab} = 7.9 Hz , J_z = 6.4 Hz], 4.03 [dd, 1H, $OCH_a\underline{H_b}$, J_{ab} = 7.9 Hz, J_z = 6.8 Hz], 4.15 [dd, 1H, $C\underline{H_a}H_b$, J_{ab} = 11.5 Hz, J_z = 4.8 Hz], 4.21 [dd, 1H, $CH_a\underline{H_b}$, J_{ab} = 11.5 Hz, Jz = 4.0 Hz], 4.30 [m, 1H, CH].

^{13}C NMR (DMSO-d_6) δ: 25.5 and 26.7 [1C, $O\underline{C}(CH_3)_2O$], 30.4 [2C, $C(\underline{C}H_3)_2Br$], 57.2 [1C, $\underline{C}(CH_3)_2Br$], 65.3 [1C, CH_aH_b], 65.6 [1C, CH_aH_b], 73.11 [1C, CH], 109.0 [1C, $O\underline{C}(CH_3)_2O$], 170.9 [1C, C=O].

2,3-Dihydroxypropyl α-bromoisobutyrate

A mixture of 10.0 g of 1, 30 mL of glacial acetic acid, 80 mL of water, and a few drops of anisole were charged to a 250 mL round-bottom flask and stirred vigorously for 30 min at 80 °C, after which the mixture had homogenized. The solution was cooled to room temperature in an ice bath prior to the addition of 100 mL of diethylether. The

aqueous layer was collected and slowly saturated with solid sodium–hydrogen carbonate by portionwise addition resulting in CO_2 formation. The aqueous layer was then washed with 3 x 50 mL of diethyl ether. The organic layers were combined and the solvent removed *in* vacuo. The crude product was obtained as a yellow oil which crystallized when left overnight at ambient temperature. The crude product was then recrystallized from a small amount of hot toluene to yield pearlescent crystals of 2,3-dihydroxypropyl α-bromoisobutyrate (77%).

^{1}H NMR [DMSO-d_6] δ: 1.91 [s, 6H, $C(CH_3)_2Br$], 3.39 [m, 2H, CH_2OH], 3.69 [m, 1H, CHOH], 4.03 [dd, 1H, $C\underline{H}_aH_bOC{=}O$, J_{ab} = 11.1 Hz, Jz = 6.0 Hz], 4.15 [dd, 1H, $CH_a\underline{H}_bOC{=}O$, J_{ab} = 11.1 Hz, J_z = 4.3 Hz], 4.68 [t, 1H, $CH_2O\underline{H}$, J_z = 5.2 Hz], 4.96 [d, 1H, $CHO\underline{H}$].

^{13}C NMR (DMSO-d_6) δ: 30.31 [2C, $C(\underline{C}H_3)_2Br$], 57.40 [1C, $\underline{C}(CH_3)_2Br$], 62.44 [1C, CH_2OH], 67.06 [1C, $\underline{C}H_2C{=}O$], 69.09 [1C, CHOH], 170.81[1C, $CH_2\underline{C}{=}O$].

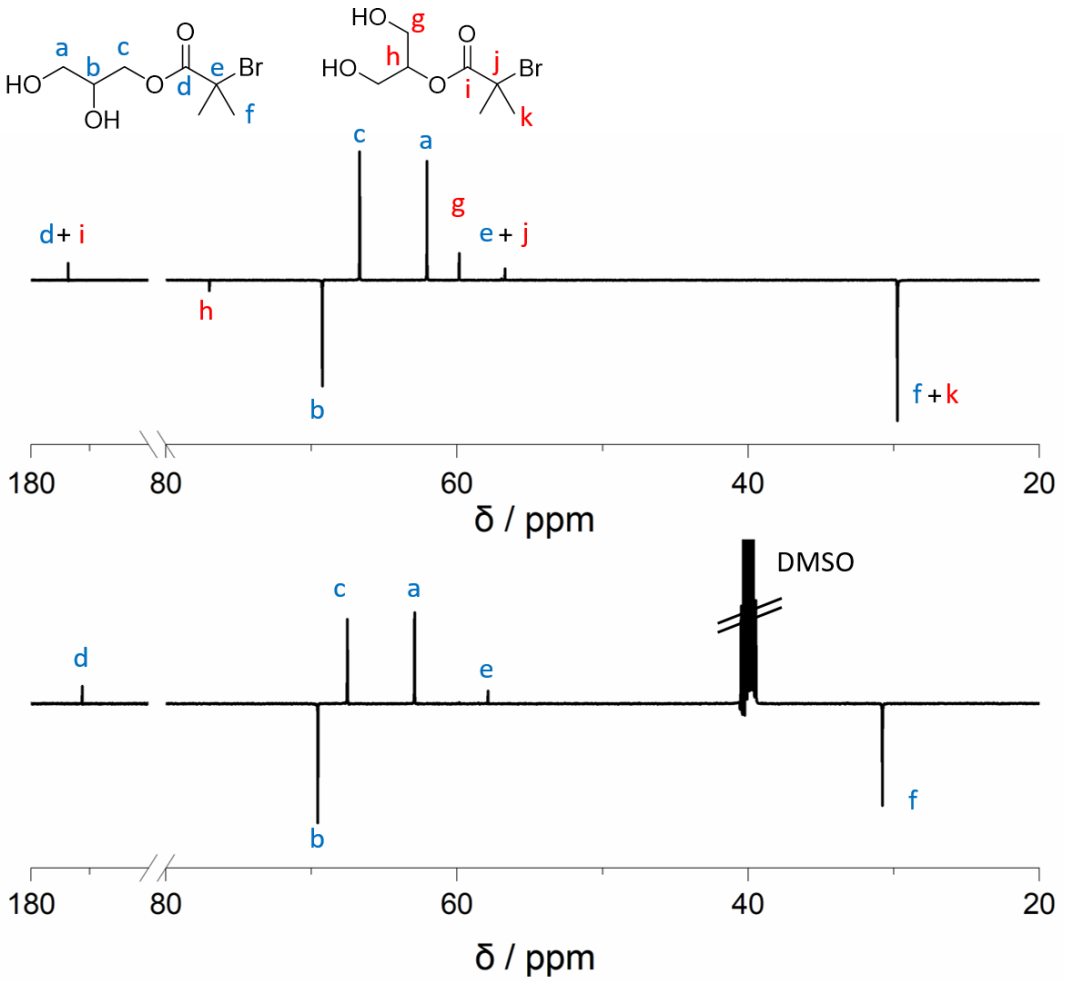


***Figure 2.12**: ^{13}C NMR's of water soluble initiator in D_2O (top) and DMSO-d_6 (bottom) showing presence of structural isomer in D_2O spectra only.*

Synthesis of tris(2-(dimethylamino)ethyl)amine) (Me_6Tren)

Tris(2-(dimethylamino)ethyl)amine) (Me_6Tren) was synthesized by methylation of tris(2-aminoethyl)amine (Tren) in an Eschweiler-Clarke reaction. A 1 L round-bottom flask was charged with formic acid (320 mL, 8.15 mol), formaldehyde 37% v/v (271 mL, 3.65 mol), and a stirrer bar. The flask was placed in an ice bath and Tren (50 mL, 0.33 mol) was added dropwise over one hour. The reaction was then refluxed at 125 °C overnight, at which point the evolution of CO_2(g) had ceased. The reaction mixture was cooled and volatiles were removed *in vacuo*. The resultant orange solution was placed in an ice bath and the pH was slowly adjusted to 10 by addition of a saturated NaOH solution. The product separated from solution as an oil upon pH adjustment. This oil was then extracted with 3 X 150 mL chloroform and the combined organic layers dried with $MgSO_4$. The crude product was obtained as a yellow-orange oil after

removing the chloroform *in vacuo*. The crude product was distilled under reduced pressure to yield a colourless oil (57 %).

^{1}H NMR [$CDCl_3$] δ: 2.12 (s, 18H, $N(CH_3)_2$), 2.27 and 2.50 (t, 6H, NCH_2CH_2N J_z = 7.1 Hz)

^{13}C NMR [$CDCl_3$] δ: 45.69 (6C), 52.85 (3C), 57.7 (3C)

Example aqueous polymerisation of acrylamide (targeted degree of polymerisation = 80)

H_2O (1 mL) and Me_6Tren (14 µL, 52.7 µmol, 0.6 eq.) were charged to a 25 mL Schlenk tube with a magnetic stirrer bar and a rubber septum. The solution was deoxygenated by bubbling with nitrogen for 2 minutes. Cu(I)Br (10.1 mg, 70.3 µmol, 0.8 eq.) was added with rapid stirring, disproportionation was seen to occur after a few seconds. The disproportionated solution was placed in an ice bath and deoxygenated for a further 15 minutes. Simultaneously, a vial was charged with 3-dihydroxypropyl 2-bromo-2-methylpropanoate (21.2 mg, 87.9 µmol, 1 eq.), acrylamide (0.5g, 7.03 mmol, 80 eq.) and 3.5 mL of H_2O. The vial was fitted with a septum, stirred and degassed with nitrogen in an ice bath for 15 minutes. Subsequently the degassed monomer/initiator solution was transferred into the Schlenk tube containing the disproportionated solution via degassed syringe. The polymerisation mixture was allowed to react for 15 minutes, after which a sample (~0.1 mL) was taken for analysis. The sample for SEC was filtered through a plug of neutral alumina to remove catalyst residues prior to analysis. The sample for ^{1}H NMR analysis was diluted with D_2O. Monomer conversion was calculated by comparison of vinyl protons with polymer backbone protons. Conversion >99%, $M_{n\,(SEC)}$ 5800 Da, $Đ$ = 1.09.

Large scale polymerisation of acrylamide (targeted degree of polymerisation = 40)

H_2O (100 mL) and Me_6Tren (1.88 mL, 7 mmol, 0.4 eq.) were charged to a 500 mL Radleys jacketed reactor vessel. The solution was deoxygenated by sparging with nitrogen for 5 minutes. Cu(I)Br (1.01 g, 7 mmol, 0.4 eq.) was added with rapid stirring, disproportionation was seen to occur after a few seconds. The disproportionated solution was cooled to 4 °C and deoxygenated for a further 15 minutes. Simultaneously, a 500 mL pressure-equalized dropping funnel was charged with 3-dihydroxypropyl 2-bromo-2-methylpropanoate (4.24 g, 17.6 mmol, 1 eq.), acrylamide

(50 g, 0.7 mol, 40 eq.) and 350 mL of ice cold H_2O. The dropping funnel was sealed with a rubber septum, fitted to the reactor and degassed with nitrogen for 15 minutes. Subsequently the degassed monomer/initiator solution was transferred into the reactor containing the disproportionated solution. The polymerisation mixture was allowed to react for 1 hour, after which a sample (~0.1 mL) was taken for analysis. The sample for SEC was filtered through a plug of neutral alumina to remove catalyst residues prior to analysis. The sample for ^{1}H NMR analysis was diluted with D_2O. Monomer conversion was calculated by comparison of vinyl protons with polymer backbone protons. Conversion >99%, $M_{n\,(SEC)}$ 3000 Da, $Đ$ = 1.55.

Chain extension of polyacrylamide: poly(acrylamide)$_{40}$-b-poly(acrylamide)$_{80}$

H_2O (1 mL) and Me_6Tren (18.8 µL, 70.4 µmol, 0.4 eq.) were charged to a 25 mL Schlenk tube with a magnetic stirrer bar and a rubber septum. The solution was deoxygenated by bubbling with nitrogen for 2 minutes. CuBr (10.1 mg, 70.4 µmol, 0.4 eq.) was added with rapid stirring, disproportionation was seen to occur after a few seconds. The disproportionated solution was placed in an ice bath and deoxygenated for a further 15 minutes. Simultaneously, a vial was charged with 3-dihydroxypropyl 2-bromo-2-methylpropanoate (42.4 mg, 176 µmol), acrylamide (0.5 g, 7.03 mmol, 40 eq.) and 3.5 mL of H_2O. The vial was fitted with a septum, stirred and deoxygenated with nitrogen in an ice bath for 15 minutes. Subsequently the degassed monomer/initiator solution was transferred into the Schlenk tube containing the disproportionated solution via degassed syringe. The reaction mixture was sampled after 15 minutes and analysed by SEC and NMR. Immediately after this a degassed solution of acrylamide (1 g, 14.06 mmol, 80 eq. in 2 mL H_2O) was transferred into the reaction vessel by degassed syringe, and the reaction mixture sampled once again after 15 minutes. Block one: >99% conversion, M_n = 3000, $Đ$ = 1.14. Block two: >99%, M_n = 9200 Da, $Đ$ = 1.12.

Synthesis of acrylamide - N-hydroxyethyl acrylamide block copolymer

Poly(acrylamide)$_{40}$ was synthesized in a procedure identical to the chain extension experiment. The reaction mixture was sampled after 15 minutes and analysed by SEC and NMR. Immediately after this a degassed solution of *N*-hydroxyethyl acrylamide (1.46 mL, 14.06 mmol, 80 eq. in 1.5 mL H_2O) was transferred into the reaction vessel by degassed syringe, and the reaction mixture sampled once again after 15 minutes.

Block one: >99% conversion, M_n = 2900, $Đ$ = 1.13. Block two: >99%, M_n = 12600 Da, $Đ$ = 1.06.

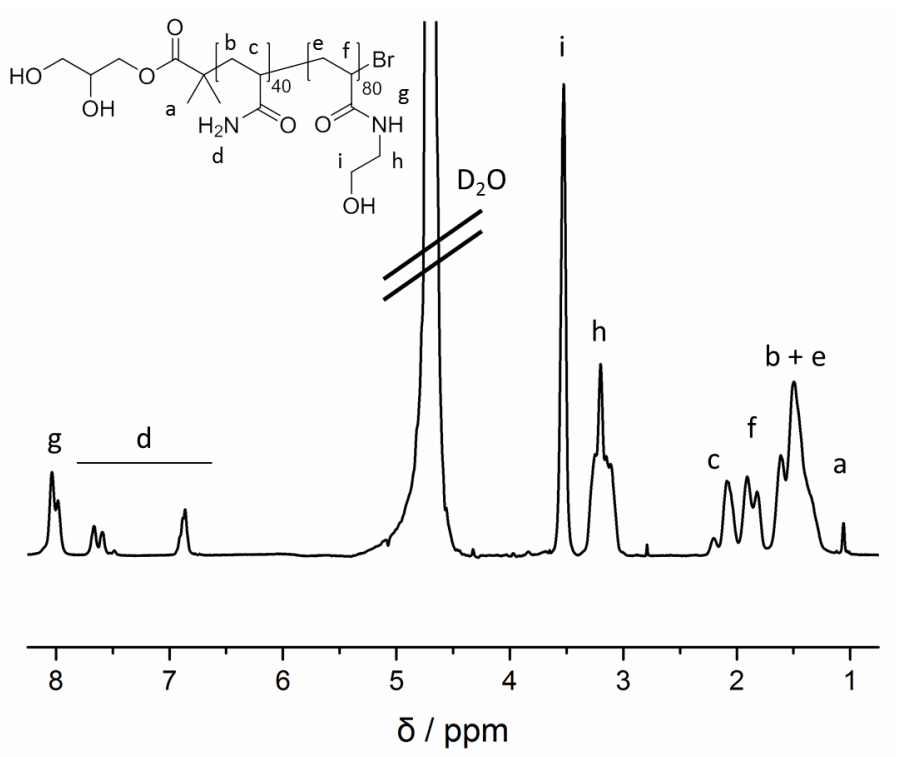


***Figure 2.13**: Proton NMR of poly(acrylamide$_{40}$-b-poly(N-hydroxyethyl acrylamide)$_{80}$.*

Synthesis of N-hydroxyethyl acrylamide - acrylamide block copolymer

H_2O (1 mL) and Me_6Tren (18.8 µL, 70.4 µmol, 0.4 eq.) were charged to a 25 mL Schlenk tube with a magnetic stirrer bar and a rubber septum. The solution was deoxygenated by bubbling with nitrogen for 2 minutes. CuBr (6.9 mg, 48.3 µmol, 0.4 eq.) was added with rapid stirring, disproportionation was seen to occur after a few seconds. The disproportionated solution was placed in an ice bath and deoxygenated for a further 15 minutes. Simultaneously, a vial was charged with 3-dihydroxypropyl 2-bromo-2-methylpropanoate (29.1 mg, 121 µmol), *N*-hydroxyethyl acrylamide (0.5 mL, 4.82 mmol, 40 eq.) and 3.5 mL of H_2O. The vial was fitted with a septum, stirred and deoxygenated with nitrogen in an ice bath for 15 minutes. Subsequently the degassed monomer/initiator solution was transferred into the Schlenk tube containing the disproportionated solution via degassed syringe. The reaction mixture was sampled after 15 minutes and analysed by SEC and NMR. Immediately after this a degassed solution of acrylamide (0.686g, 9.65 mmol, 80 eq. in 0.7 mL H_2O) was transferred into the reaction vessel by degassed syringe, and the reaction mixture

sampled once again after 15 minutes. Block one: >99% conversion, M_n = 4300, $Đ$ = 1.19. Block two: >99%, M_n = 9800 Da, $Đ$ = 1.19.

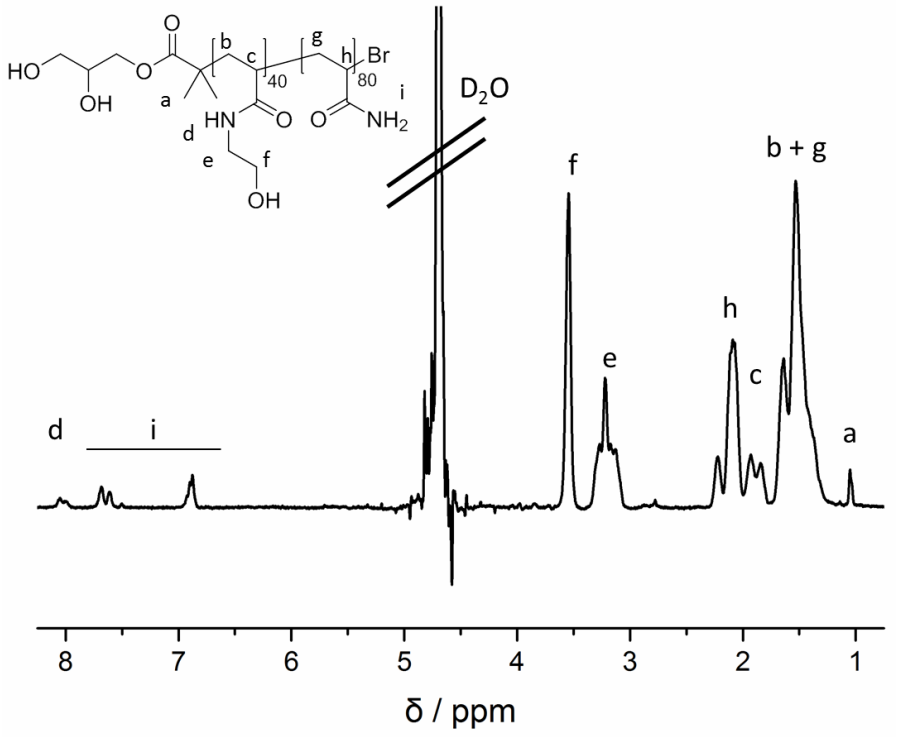


***Figure 2.14**: Proton NMR of poly(N-hydroxyethyl acrylamide$_{40}$-b-poly(N-hydroxyethyl acrylamide)$_{80}$.*

Example synthesis of thermoresponsive block copolymer (poly(acrylamide$_{20}$-b-poly(N-isopropyl acrylamide)$_{80}$)

H_2O (1 mL) and Me_6Tren (18.8 µL, 70.4 µmol, 0.4 eq.) were charged to a 25 mL Schlenk tube with a magnetic stirrer bar and a rubber septum. The solution was deoxygenated by bubbling with nitrogen for 2 minutes. CuBr (10.1 mg, 70.4 µmol, 0.4 eq.) was added with rapid stirring, disproportionation was seen to occur after a few seconds. The disproportionated solution was placed in an ice bath and deoxygenated for a further 15 minutes. Simultaneously, a vial was charged with 3-dihydroxypropyl 2-bromo-2-methylpropanoate (42.4 mg, 176 µmol), acrylamide (0.5g, 7.03 mmol, 40 eq.) and 3.5 mL of H_2O. The vial was fitted with a septum, stirred and deoxygenated with nitrogen in an ice bath for 15 minutes. Subsequently the degassed monomer/initiator solution was transferred into the Schlenk tube containing the disproportionated solution via degassed syringe. The reaction mixture was sampled after 15 minutes and analysed by SEC and NMR. Immediately after this a degassed solution of *N*-isopropyl acrylamide (1.59 g, 14.06 mmol, 80 eq. in 2 mL H_2O) was

transferred into the reaction vessel by degassed syringe, and the reaction mixture sampled once again after 15 minutes. The reaction was then dialyzed against water overnight to remove the catalyst and any residual monomer. The resulting aqueous solution was then freeze-dried to yield pure block copolymer. Block one: >99% conversion, M_n =1300, $Đ$ = 1.07. Block two: >99%, M_n = 19000 Da, $Đ$ = 1.05.

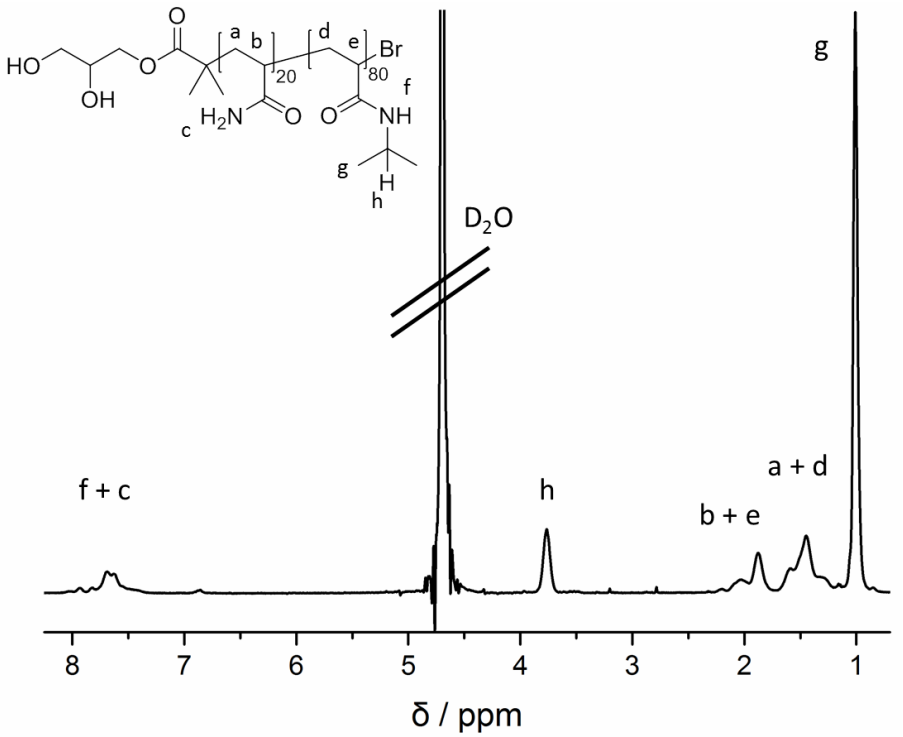


***Figure 2.15**: Proton NMR of poly(acrylamide$_{20}$-b-poly(N-isopropyl acrylamide)$_{80}$.*

2.5 References

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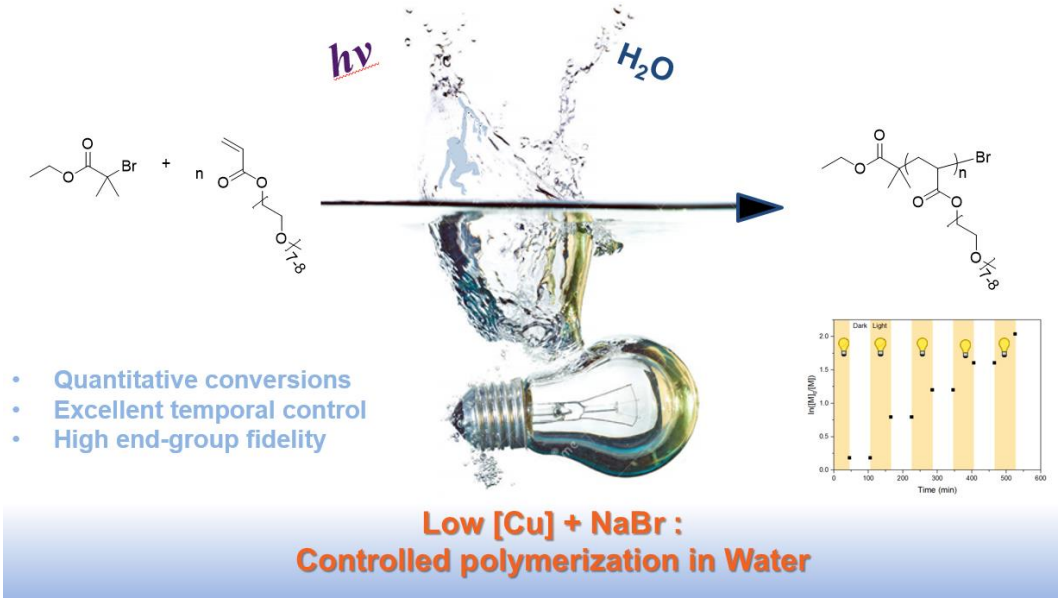
Chapter 3: Aqueous Copper(II) Photoinduced Polymerisation of Acrylates



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3.1 Introduction

The development of reversible-deactivation radical polymerisation (RDRP) techniques such as atom transfer living radical polymerisation (ATRP)[1-5], Cu(0) mediated reversible deactivation radical polymerisation (Cu(0)-RDRP)[6-9](often called single electron transfer living radical polymerisation, SET LRP), nitroxide-mediated radical polymerisation (NMP)[10-12] and reversible addition-fragmentation chain transfer (RAFT)[13-16] has allowed for the synthesis of polymers of targeted molecular weight, macromolecular architecture, end group functionality and narrow molecular weight distributions. These techniques work by establishing an equilibrium between dormant and active species in which the dormant state is predominant; as a result of this the concentration of *free* radicals is very low which suppresses bimolecular termination reactions. ATRP in polar media, such as water, has proved challenging typically exhibiting a lower degree of control. This has been attributed to higher values of K_{ATRP}, the equilibrium constant that defines the balance between active and dormant species, resulting in higher radical concentrations and consequently higher probability of termination reactions. A range of new processes have been developed such as initiators for continuous activator regeneration (ICAR) ATRP[17], activators regenerated by electron transfer (ARGET) ATRP[18] and aqueous Cu(0)-RDRP[7,9,19,20] in an attempt to attain a higher degree of control over polymerisation in aqueous media. Although some progress has been made by these approaches, significant drawbacks such as low conversions or high catalyst concentrations still remain a challenge and possibly limit the scope of such techniques.

Within recent years considerable focus has been placed on developing RDRP and other polymerisation systems in which the equilibrium between dormant and active species is mediated by various external stimuli such as allosteric[21,22], electrochemical[23], mechanochemical[24] and photochemical control.[23,25-29] Such external stimuli allow for dynamic control over polymerisations thus introducing new opportunities for advanced materials synthesis. Photochemical mediation is of increasing interest due to its wide availability and being environmentally benign. Photochemistry also allows for lower activation energy pathway processes such as initiation and repeat reactivation of dormant chains, faster rates of polymerisation, and simple implementation of temporal control by turning off the light source.

Among the various RDRP techniques, ATRP has become a popular photopolymerisation route. The emergence of photoinduced RAFT polymerisation is also noted with Boyer and co-workers reporting some excellent examples of Photoinduced Electron Transfer RAFT polymerisation (PET-RAFT).[30-37] Cu-mediated photoinduced ATRP systems both in the presence and absence of photosensitizers and photoinitiators have been developed by Yagci and co-workers.[38,39] In a bulk polymerisation of MMA using *N,N,N′,N′,N″*-pentamethyldiethylenetriamine (PMDETA) and Cu(II)Br_2 it was proposed that a Cu(II)X_2/L complex can be directly reduced to Cu(I)X/L which can rapidly generate carbon-centred radicals from alkyl bromide initiators. Addition of a small amount of methanol to the system was reported to enhance control over molecular weights and yield narrower MWD's, this is attributed to better solubility of Cu(II) species and the *in situ* generation of hydroxymethyl radicals that act as reducing agents.[40] Konkolewicz *et al.* has reported a Cu based photoinduced ATRP system using Cu(II)Br_2 with Tris(2-pyridylmethyl)amine (TPMA) based ligands. The polymerisation of both MMA and methyl acrylate (MA) were shown to proceed with a high degree of control (*Đ* as low as 1.05) at parts per million (ppm) catalyst loadings.[41] A series of control experiments lead to the conclusion that photoreduction of Cu(II) occurs via ligand to metal charge transfer in an excited state, with a later mechanistic study concluding that the main route of radical (re)generation occurs via reduction of Cu(II) complexes by free amines (uncomplexed ligand).[42] Recently Matyjaszewski and coworkers expanded the scope of this technique to aqueous media for the polymerisation of PEG methacrylates, whilst control was demonstrated over the polymerisation conversions were limited, hence chain extension required purification of a macroinitiator as opposed to an in-situ approach.[43]

Hawker and co-workers have demonstrated the controlled radical polymerisation of methacrylates and acrylates using an iridium photoredox catalyst.[44,45] The catalyst is proposed to proceed by absorption of visible light by *fac*-[Ir(III)$(ppy)_3$] to give an excited state which can abstract bromide from a conventional alkyl bromide initiator. Polymerisation of methyl methacrylate (MMA) was demonstrated to proceed with a high degree of control over MWD's (*Đ*~1.2) at low catalyst loadings (0.005 mol%). The technique was also demonstrated to work efficiently using photo-masking on

surface grafted initiators to give three-dimensional polymer brush nanostructures[46] and in a flow system.[47]

In 2014 Hawker, Fors and co-workers reported the first metal-free ATRP system utilising phenothiazine as a photoredox catalyst.[48] Control over the molecular weight with products of low dispersities were reported for methacrylates along with excellent spatiotemporal control, demonstrated by kinetic analysis with repeated cyclization of light and dark conditions. Furthermore the synthesis of a variety of well controlled block copolymers was demonstrated by both concurrent metal-free ATRPs and a combination of metal-free, copper and iridium based systems. This metal-free approach was later expanded upon by Matyjaszewski to include the synthesis of poly(acrylonitrile) with predictable molecular weights, low dispersities and high preservation of chain-end functionality.[49] The use of *exotic* catalysts potentially limits the applicability of these techniques, as well as relatively low conversions, necessitating purification for the synthesis of block copolymers. More recently Luo and coworkers expanded the metal free ATRP technique to polymerisation in aqueous media.[50] Using a combination of pentramethyldiethyltriamine (PMDETA) and eosin Y the polymerisation of $PEGA_{480}$ was achieved upon irradiation with visible light. Dispersities obtained were as low as 1.26, however the conversions reported were between 40-70%. A major drawback of this technique is that the reaction requires stoichiometric amounts of eosin Y to initiator as well as a large excess of PMDETA (10 eq. with respect to initiator). This is in stark contrast to transition metal mediated techniques in which ppm concentrations of catalyst can be effective.

In 2014 the Haddleton group reported on the photoinduced polymerisation of acrylates mediated by low concentrations of $Cu(II)Br_2$ and the aliphatic tertiary amine ligand tris[2-(dimethylamino)ethyl]amine (Me_6Tren) in UV and visible light.[51] A range of acrylate and methacrylate monomers were successfully polymerised with excellent control over MWD's, quantitative conversions and near perfect end-group fidelity. This approach has been subsequently applied to the synthesis of a range of sequence-controlled materials including high order multiblock copolymers, telechelic, and methacrylate-acrylate block copolymers, and utilised in flow based systems.[52-54] Junkers and coworkers have reported the synthesis of sequence controlled materials as well as acrylate-methacrylate blocks via ligand switching.[55-58] The use of Cu(II) formate complexes has also be shown to polymerise (meth)acrylates in a controlled

manner, with the distinct benefit of using stable, discrete catalyst complexes as opposed to those generated *in situ,* and enhanced spatiotemporal control.[59,60] Efficient control over polymerisation has been reported in DMSO, DMF, IPA, toluene/methanol mixtures, and a range of ionic liquids.[51,54,61] However, attempts at utilizing aqueous media has until now proved challenging, furnishing polymers with broad MWD's.

This chapter reports the controlled polymerisation of PEGA in aqueous medium utilizing a photo-induced polymerisation approach. The addition of sodium bromide results in a significant enhancement of the control over the molecular weight distributions in the presence of ppm concentration of copper. Quantitative conversions can be achieved without compromising the high end group fidelity which is assessed through successful in situ chain extensions. The ability of the approach to exhibit spatiotemporal control is also evaluated via intermediate "on" and "off" cycles and the synthesis of higher MW polymers is also attempted.

3.2 Results and Discussion

3.2.1 Initial Work

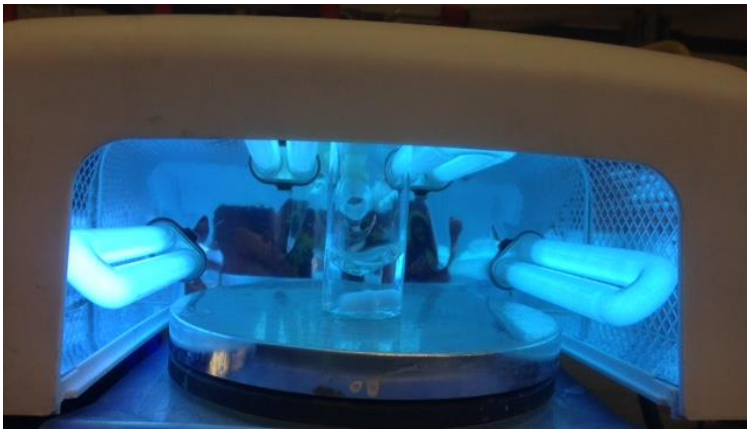
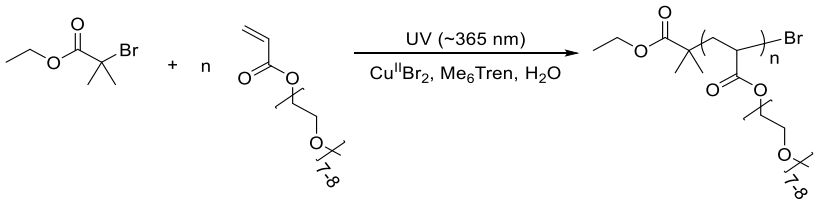


Figure 3.1: *Broad spectrum (centred at λ = 365 nm) UV curing lamp used for polymerisations.*



Scheme 3.1*: Aqueous polymerisation of PEGA$_{480}$ under UV irradiation with Cu(II)Br$_2$/Me$_6$Tren.*

Initially, the homopolymerisation of PEGA$_{480}$ (targeted DP$_n$ = 20) (scheme 3.1) was attempted in water (50% v/v) with 0.02 equivalents of Cu(II)Br$_2$ and 0.12 equivalents of Me$_6$Tren using an inexpensive UV lamp (figure 3.1) with a broad low intensity emission centred at approximately λ = 365 nm (entry 1, table 3.1) as described previously.[51] Sampling after 8 hours showed full monomer conversion by ^{1}H NMR, however, SEC analysis revealed an uncontrolled polymerisation process with the polymer showing a dispersity of 3.75. This is not surprising for aqueous systems with low copper concentrations as the lack of control could be attributed to insufficient deactivation due to dissociation of the Cu(II) complex.

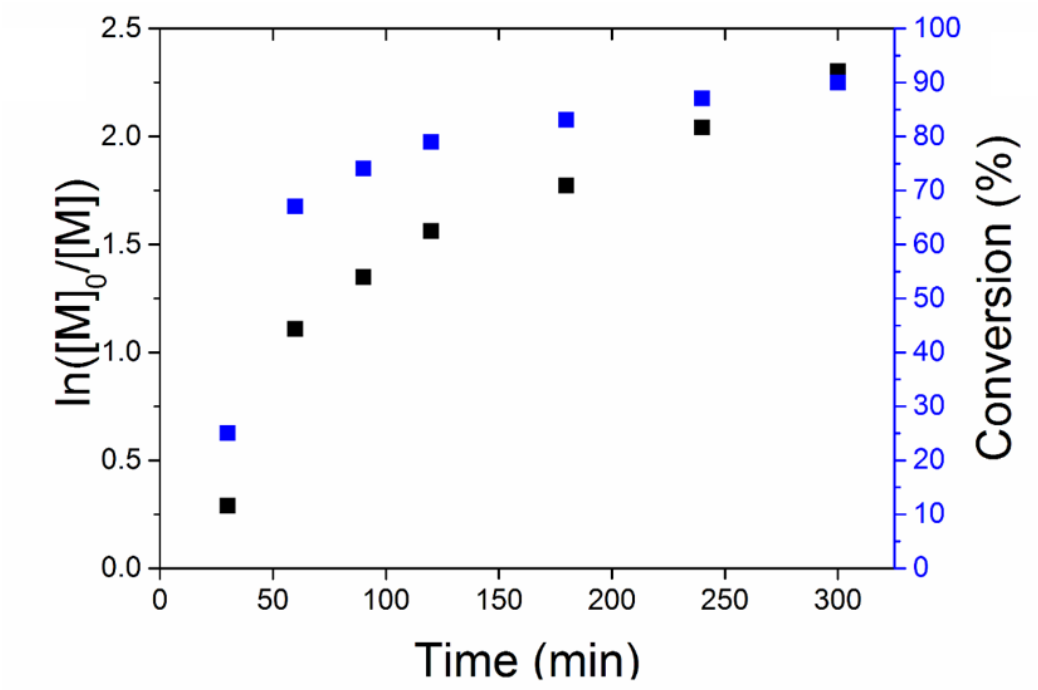


***Figure 3.2**: Kinetic plot for the polymerisation of $PEGA_{480}$ (0.02 eq. $Cu(II)Br_2$, 0.12 eq. Me_6Tren), entry 1, table 3.1. Blue squares – conversion, black squares – kinetic plot.*

In order to gain further in site into this uncontrolled reaction kinetic analysis was performed by repeating the reaction and sampling every 30 minutes (figure 3.2). As expected from the final broad molecular weight distribution, the kinetic analysis revealed a non-linear first order kinetics throughout the polymerisation. The initial polymeric species formed were higher molecular species, as seen in the SEC trace corresponding to 30 minutes (figure 3.3). However, as the polymerisation proceeds the molecular weight decreases; probably due to the gradual accumulation of $Cu(II)Br_2$ as a result of pronounced termination events, although the accumulated $Cu(II)Br_2$ is still not efficient enough to facilitate a controlled polymerisation yielding broad bimodal distributions throughout the reaction.

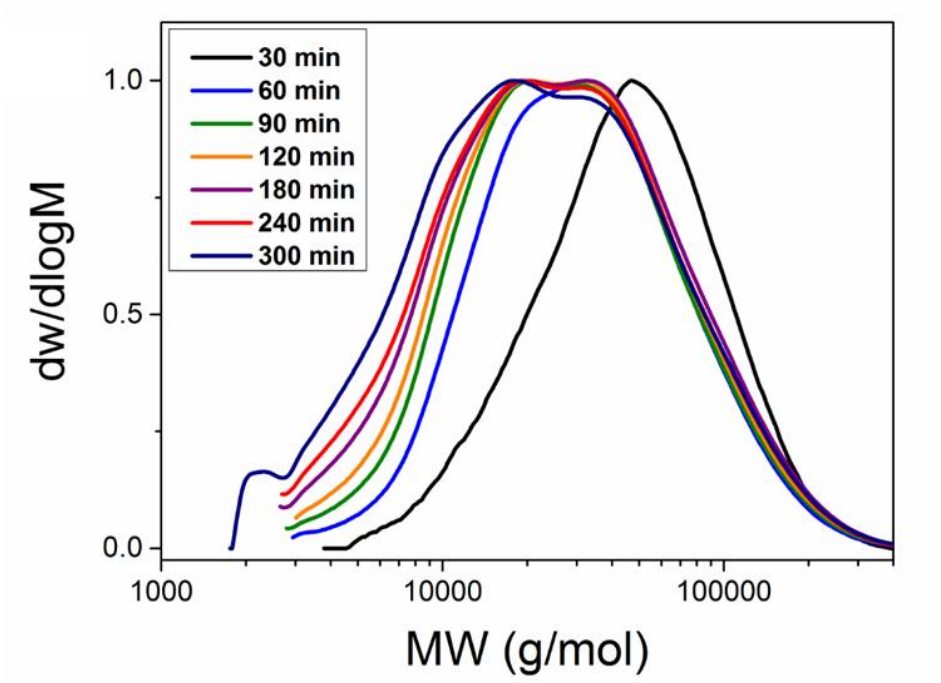


***Figure 3.3**: SEC plots showing molecular weight evolution of kinetic data from figure 3.2.*

3.2.2 Altering Ligand and Copper Concentrations

In order to test the hypothesis that photopolymerisation is uncontrolled in water due to insufficient deactivation the copper content was increased to 0.04 equivalents (a twofold increase, entry 2, table 3.1) resulting in slightly lower dispersities, although the process was still lacking control. A further increase of the copper content up to five fold (0.10 equivalents, entry 3, table 3.1) gave rise to a significant lowering of the dispersity ($Đ$ = 1.28), confirming that a higher copper(II) concentration is essential in order to maintain good control over the molecular weight distributions. Following the typical small induction period observed in this system, the inclusion of more copper resulted in near linear first order kinetics (figure 3.4) and significantly less pronounced termination during the initial stage of the polymerisation (figure 3.5). The good correlation between the theoretical and the experimental molecular weights further attests to the controlled/living character of the system, confirming that the presence of higher concentrations of deactivator is essential in order to establish the desired equilibrium.

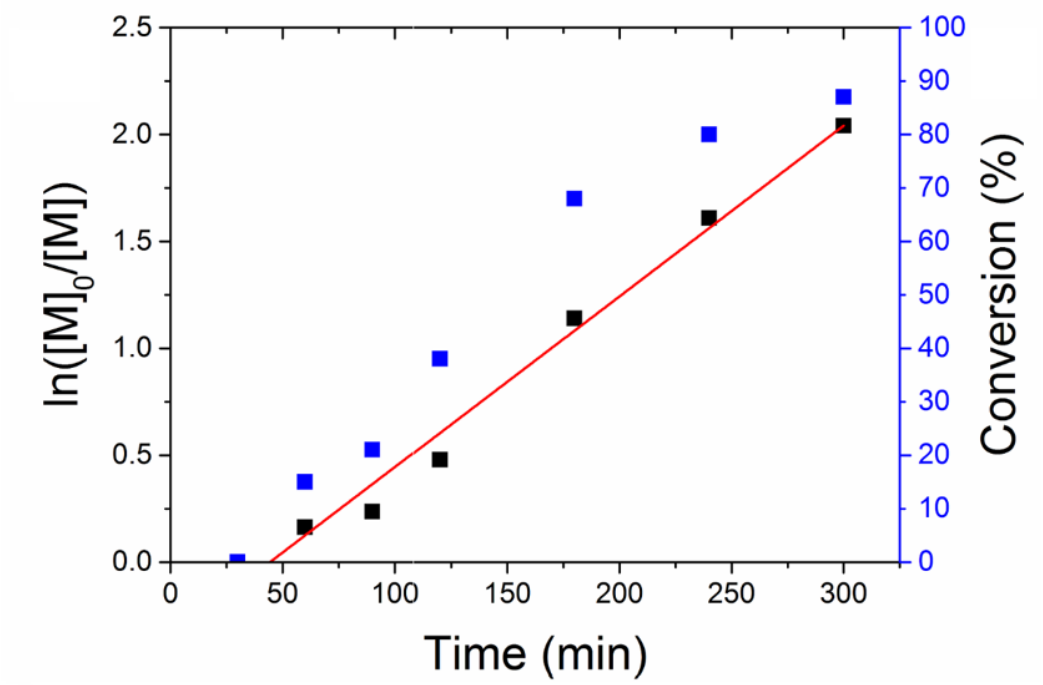


***Figure 3.4**: Kinetic plot for the polymerisation of PEGA$_{480}$ (0.01 eq. Cu(II)Br$_2$, 0.12 eq. Me$_6$Tren), entry 2, table 3.1. Blue squares – conversion.*

***Table 3.1**: Photopolymerisation of PEGA$_{480}$ with varying Cu(II)Br$_2$ and Me$_6$Tren concentrations.*

Entry	**[M]:[I]:[Cu(II)Br] :[Me$_6$Tren]**	**Time (hours)**	**Conv. (%)**	**M$_{n\ (Theo)}$ (Da)**	**M$_{n\ (SEC)}$ (Da)**	***Đ***
1	20 : 1 : 0.02 : 0.12	8	>99	9800	17500	3.75
2	20 : 1 : 0.04 : 0.12	8	>99	9800	12500	2.14
3	20 : 1 : 0.10 : 0.12	8	>99	9800	12600	1.28
4	20 : 1 : 0.02 : 0.02	24	-	-	-	-
5	20 : 1 : 0.12 : 0.12	24	-	-	-	-
6	20 : 1 : 0.10 : 0.60	8	>99	9800	10800	1.60
7	20 : 1 : 0.20 : 0.25	8	>99	9800	12500	1.11

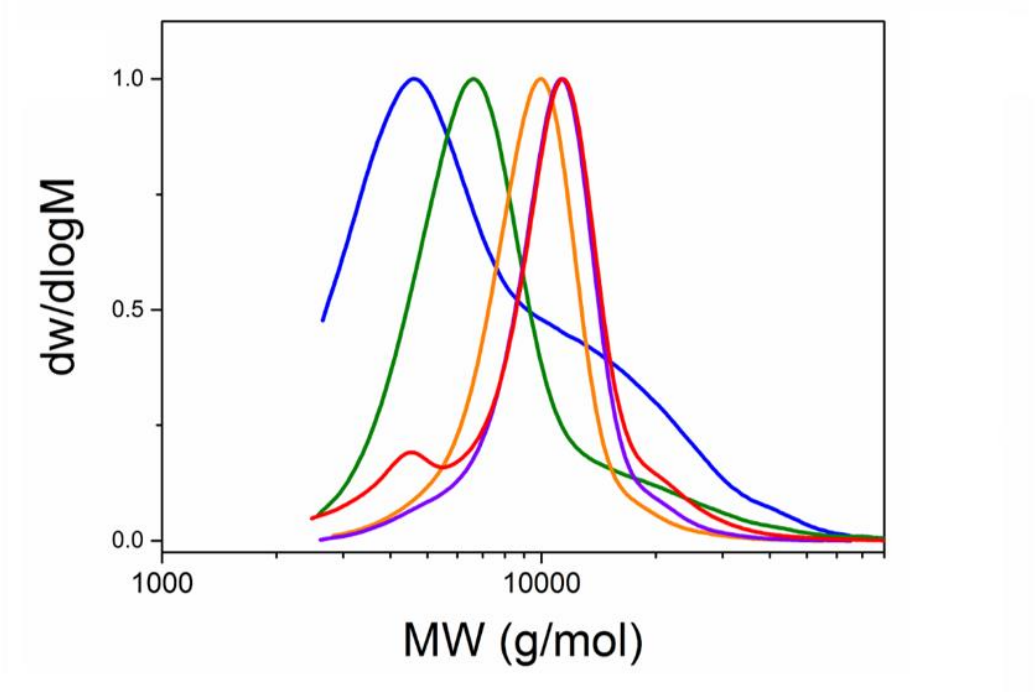


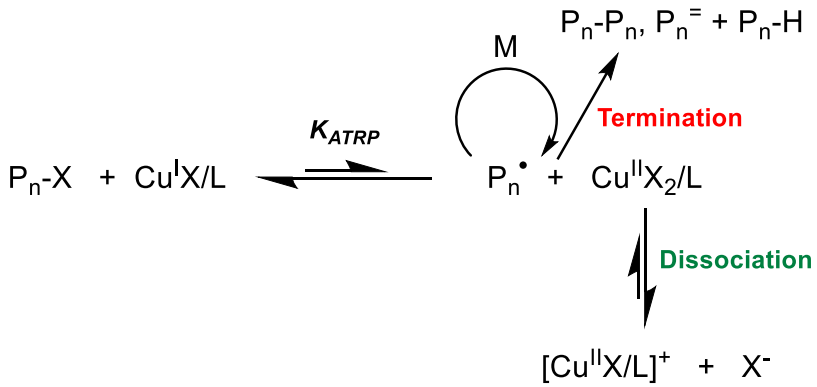
***Figure 3.5**: SEC plots showing molecular weight evolution of kinetic data from figure 3.4, showing an increase in molecular weight with time.*

It should be noted that a potential increase of the [Cu(II)] solely would be impossible without also adjusting the [ligand] as when [copper]:[ligand] is equal or < 1, there is no excess of ligand to facilitate the photo reduction of Cu(II) into the active species and hence the polymerisation does not occur. This was demonstrated in an organic solvent (dimethyl sulfoxide, DMSO) by Anastasaki *et al.*[51] As expected, no polymerisation occurred at this ratio even when the reaction was left to proceed for 24 h highlighting the necessity of an excess of Me_6Tren in the polymerisation mixture (entry 4, table 3.1), which is in agreement with the mechanistic studies of Frick *et al.*[62] Identical results were obtained when higher amounts of copper and ligand were utilized (Cu(II)]:[L]=[0.12]:[0.12]), concluding that regardless of the chosen amount of copper and ligand, equimolar amounts result in cessation of the polymerisation (entry 5, table 3.1). Thus, in order to reach higher levels of copper, the [ligand] should also be adjusted.

However, increasing the concentration of both Me_6Tren and Cu(II)Br_2 by 5 fold showed an increase in dispersity ($Đ$ = 1.60), (entry 6, table 3.1), this is attributed to extended termination events due to the excess of the ligand, in line with previous investigations.[63] In order to use a higher copper content but also maintain the ligand

concentration at moderate levels, the ratio of [Cu]:[L]=[0.20]:[0.25] was subsequently utilized which resulted in a further decrease in the dispersity value from 1.28 to 1.11 (entry 7, table 3.1). Hence, it was concluded that controlled polymerisation of an acrylate in aqueous media can be facilitated in the presence of high concentrations of copper and ligand resulting in narrow MWDs at quantitative conversions.

3.2.3 Addition of Sodium Bromide



***Scheme 3.2**: Simplified mechanism of ATRP showing dissociation of the Cu(II) complex.*

Although the previous section demonstrates that increasing [Cu(II)] and [ligand] can effectively control the polymerisation of PEGA in aqueous media, high amounts of these compounds should be reduced, if not eliminated, as they can potentially induce undesired properties to the final material as well as increasing cost. Me_6Tren is a relatively expensive compound and thus its usage should be reduced to the minimum. The addition of halide salts has previously been reported to increase the control of ATRP processes by effectively increasing the concentration of deactivating species without disrupting the equilibrium between [Cu(I)] and [Cu(II)].[43,64,65] In aqueous media the Cu(II)Br_2/Me_6Tren complex readily dissociates, as shown in scheme 3.2, meaning it cannot efficiently transfer bromine back to a propagating radical. An excess of halide ions drives the equilibrium back to the non-dissociated form. This approach is also beneficial as it allows for a much lower concentration of copper species to be utilized. In order to assess whether the presence of halide salts would be compatible with this photoinduced polymerisation method, we conducted the polymerisation of PEGA in the presence of various concentrations of sodium bromide (NaBr).

The addition of 0.5 equivalents of NaBr with respect to the initiator (entry 1, table 3.2) gave rise to an improved dispersity (1.25) when compared to entry 1, table 3.1, where the absence of the salt resulted in a complete lack of control. Thus, the presence of an excess of halide ions resulted in better control over the MWDs. A further increase of NaBr to 1, 2 and 3 equivalents led to a gradual reduction of the dispersity with the best result achieving 1.12 as well as reaching quantitative monomer conversion (entries 2-4, table 3.2.)

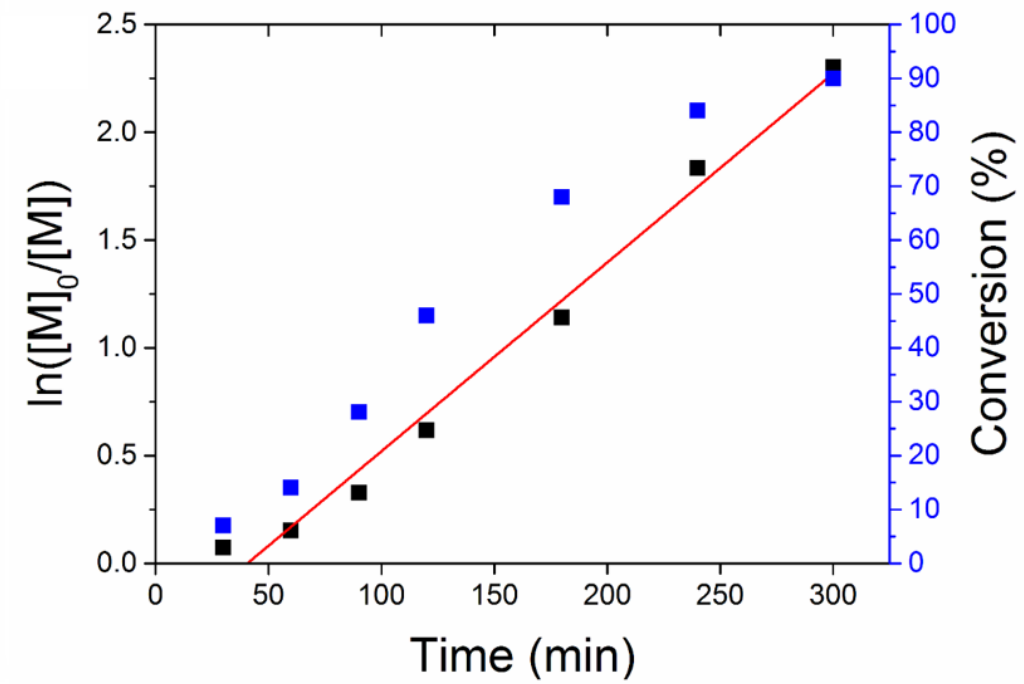


***Figure 3.6**: Kinetic plot for the polymerisation of $PEGA_{480}$ (0.01 eq. $Cu(II)Br_2$, 0.12 eq. Me_6Tren, 3 eq. NaBr), entry 4, table 3.2.*

***Table 3.2**: Polymerisations of $PEGA_{480}$ in the presence of NaBr. Reaction time = 8 hours for all experiments.*

Entry	**[M]:[I]:[Cu(II)Br] :[Me_6Tren]**	**[NaBr]**	**Conv. (%)**	**$M_{n\ (Theo)}$ (Da)**	**$M_{n\ (SEC)}$ (Da)**	***Đ***
1	20 : 1 : 0.02 : 0.12	0.5	>99	9800	12700	1.25
2	20 : 1 : 0.02 : 0.12	1	>99	9800	12300	1.16
3	20 : 1 : 0.02 : 0.12	2	>99	9800	12000	1.13
4	20 : 1 : 0.02 : 0.2	3	>99	9800	12200	1.12

The inclusion of NaBr, as opposed to higher copper content, gave rise to similar kinetic data, with ln[M]/[M_0] increasing linearly with time consistent with a constant concentration of radicals (figure 3.6), the molecular weight is increasing linearly with conversion and the dispersity values decreasing throughout the polymerisation. Hence, under our optimized conditions all the criteria of a living polymerisation have been maintained.

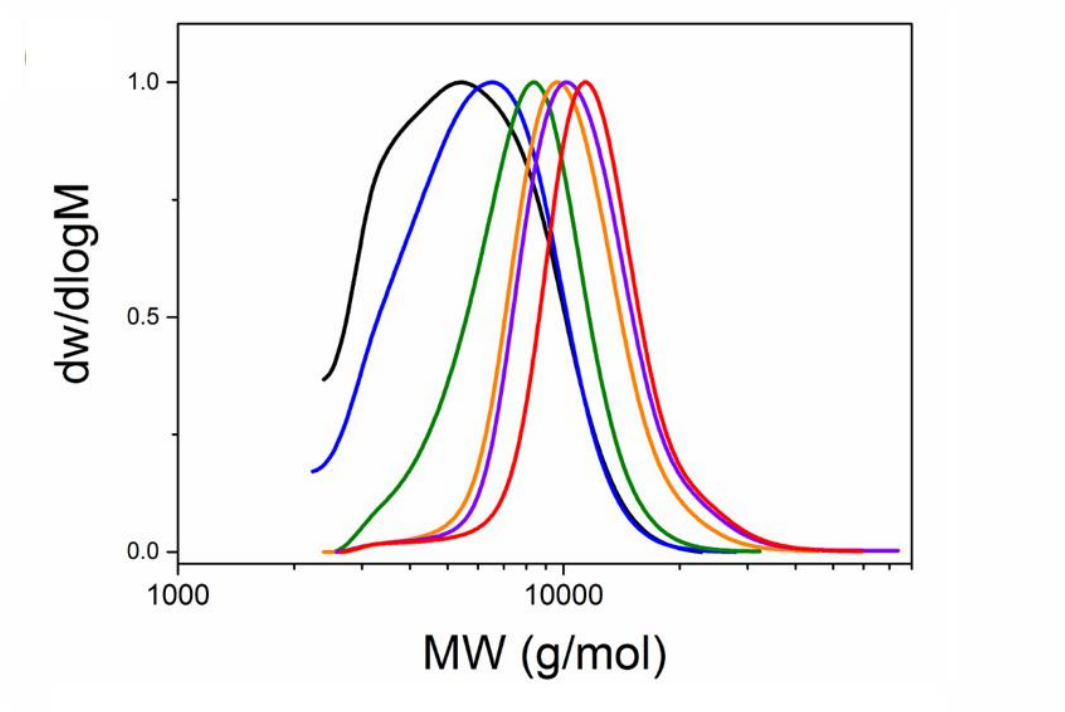


***Figure 3.7**: SEC plots showing molecular weight evolution of kinetic data from figure 3.6, showing an increase in molecular weight with time.*

3.2.4 Reduction of Catalyst Loading

Catalyst loading is an important parameter in ATRP reactions, particularly in their applicability to industrial scale syntheses, where low catalyst concentration is valued for its lower cost. It is important to note that the *toxicity* of copper salts is often cited as a key drawback in ATRP, and reduction of catalyst loadings or even moving towards metal-free ATRP are promoted as ways to overcome this. However, many copper(II) salts are generally regarded as safe (GRAS) by the US FDA.[66] Other compounds present in a typical polymerisation, e.g. ligands or residual monomer, are potentially toxic, thus the toxicological advantages of a reduction in catalyst concentration are potentially negated if it is at the expense of conversion.

By maintaining a relative high salt content, the copper content can be reduced to 67 ppm, although slightly broader MWD's resulted (entry 1, table 3.3). Dispersity was shown to increase as [copper] was further reduced to 26 ppm and 13 ppm (entries 2 and 3, table 3.3). In the presence of just 26 ppm of copper the dispersity value is still as low as 1.26 and thus demonstrates good control over the MWDs despite such a low concentration of catalytic species. Nevertheless, in order to maintain a good balance between copper concentration and control, 250 ppm of copper (0.02 eq.) was chosen for the remaining polymerisations (subsequent sections).

Table 3.3*: Polymerisation of $PEGA_{480}$ at reduced copper catalyst loadings.*

Entry	**[M]:[I]:[Cu(II)Br] :[Me_6Tren]**	**[NaBr]**	**Conv. (%)**	**$M_{n\ (Theo)}$ (Da)**	**$M_{n\ (SEC)}$ (Da)**	***Đ***
1	20 : 1 : 0.01 : 0.12	3	>99	9800	14300	1.17
2	20 : 1 : 0.005 : 0.12	3	>99	9800	14500	1.26
3	20 : 1 : 0.001 : 0.12	3	>99	9800	15000	1.57

An interesting result of the reduction of catalyst concentrations is that the polymerisation appears almost colourless. Figure 3.8(a) shows a typical polymerisation, whereas figure 3.8(b) shows a typical aqueous metal-free ATRP (as reported by Bian *et al.*) using eosin Y and PMDETA. Reaction "a", a copper mediated photopolymerisation of PEGA achieves >99% conversion in a controlled manner, whereas the metal free ATRP, "b", achieves a much lower conversion with a similar final dispersity. Interestingly the concentration of tertiary amine compounds (Me_6Tren in a, PMDETA in b) is ~100 times lower in reaction a.

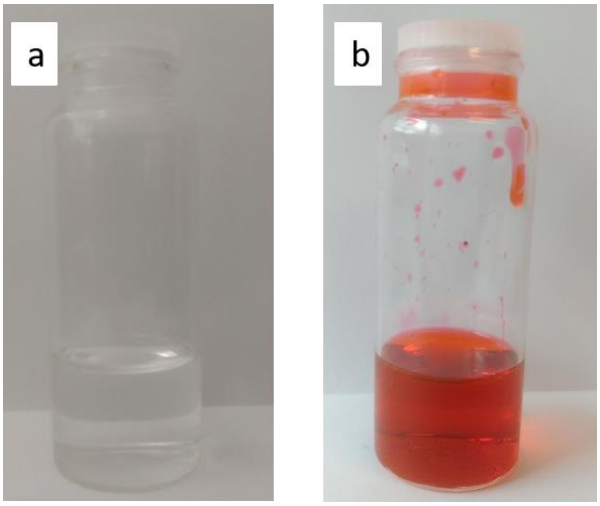


***Figure 3.8**: (a) Photo of the reaction described in entry 2, table 3.3. (b) Photo of a metal-free ATRP of PEGA using Eosin Y and PMDETA.*

3.2.5 Temporal Control

In order to demonstrate "on/off" temporal control a polymerisation was carried out with intermittent exposure to both light and dark periods. PEGA (DP_n = 20) (conditions from entry 4, table 3.2) was polymerised in a UV light box for an initial 45 minutes, followed by 1 hour periods cycled between a dark room and the light box, with samples taken for NMR and SEC analysis at every change of light/dark conditions. The total time the reaction was exposed to light was 285 minutes (final conversion = 85%, M_n = 10,000 Da, $Đ$ = 1.12), Figure 3.9. It can be seen that there was no conversion observed during dark periods. This demonstrates the necessity of UV irradition for both initiation and propagation allowing for the possibility of temporal control.

In order to investigate this further, an experiment was carried out in which a longer dark period was employed in order to demonstrate reactivation of alkyl halides after a prolonged inactive period. A reaction was exposed to UV light for 45 minutes, followed by an hour dark period and a second hour in light. The reaction was then placed in a dark room for six hours, after which it was sampled and placed back into UV light for a final time. No conversion is observed during dark periods, including a prolonged exposure to dark conditions, furthermore reinitiation was found to occur and the polymerisation proceeds in a controlled manner ($Đ$ = 1.12), figure 3.10. It is noted that temporal control in aqueous media appears to be significantly enhanced

when compared to similar reactions in DMSO, in which a slight increase in conversion is observed.[51]

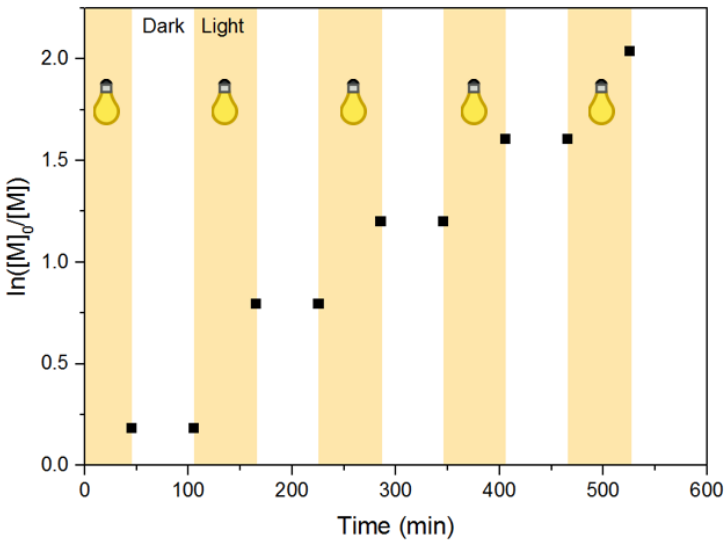


***Figure 3.9**: Kinetic plot demonstrating temporal control over the polymerisation of $PEGA_{480}$ (conditions from entry 4, table 3.2), dark periods (white), irradiated periods (yellow).*

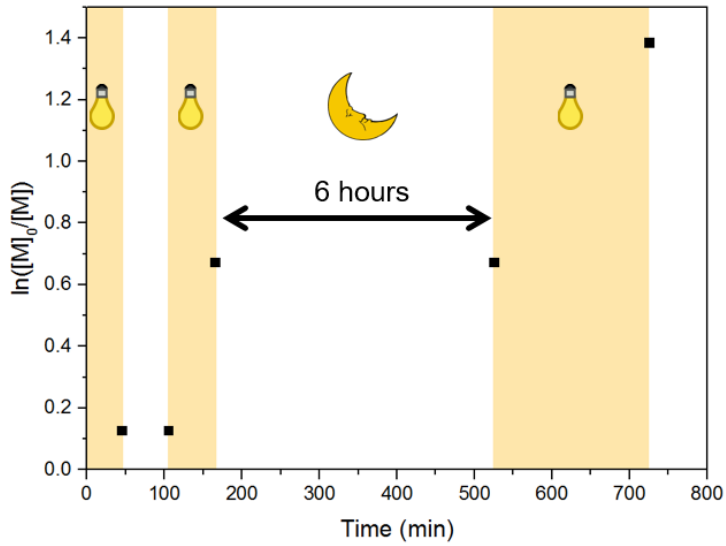


***Figure 3.10**: Kinetic plot demonstrating temporal control over the polymerisation of $PEGA_{480}$ (conditions from entry 11, table 1) during a prolonged dark period (white), irradiated periods (yellow).*

The observation that this aqueous polymerisation system (low copper concentration with NaBr) demonstrates enhanced temporal control compared to similar polymerisations in organic media was further studied in a collaboration with the

Hawker group at the University of California Santa Barabara. In Feburary 2017 the Hawker group reported a method of directly illuminiting an NMR sample to enable *in-situ* monitoring of photochemical processes (figure 3.11 (a), (b).)[67] The method utilizes a modular LED controller and optical fibre to conduct reactions within an NMR tube.

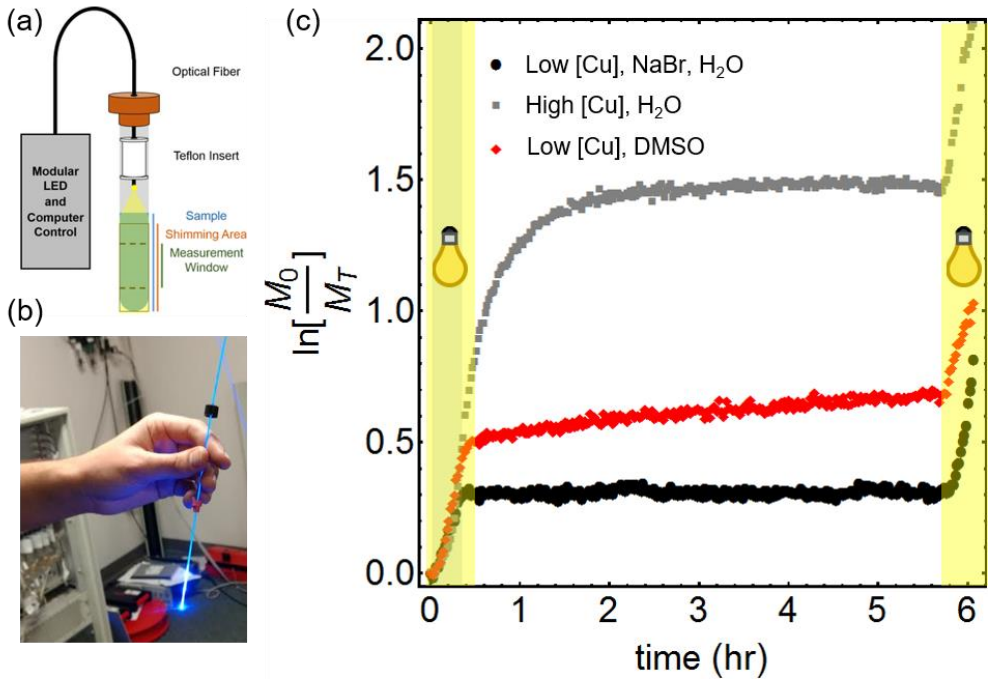


***Figure 3.11**: **(a)** Scheme depicting experimental set-up of in-situ monitoring of photopolymerisations, reproduced from reference 67. **(b)** Photo of fibre optic cable with attached NMR tube lid. **(c)** Kinetic plots of photopolymerisations of $PEGA_{480}$ with extended period of darkness.*

Applying this *in-situ* technique to the polymerisation of $PEGA_{480}$ in water with optimized conditions (3 eq. NaBr) similar to entry 4 table 3.2, yielded the kinetic plot shown in black in figure 3.11 (c). It can be seen that polymerisation ceases when the light source is turned off, and restarts once illumination is resumed, consistent with the sampled experiment detailed in figure 3.10. Temporal control for a similar reaction in DMSO (red trace in figure 3.11 (c)) was shown to be significantly worse: the polymerisation slows but does not completely cease. The grey trace however, shows a reaction with a high copper concentration, similar to entry 3, table 3.1. It can be seen that the reaction still proceeds in darkness, but conversion tails off until the polymerisation finally ceases. The reaction then reinitiates when the light source is reintroduced.

3.2.6 Higher Molecular Weights

***Table 3.4**: Polymerisation of $PEGA_{480}$ of different targeted molecular weight with varying sodium bromide concentrations. Reaction time = 8 hours in all cases.*

Entry	[M]:[I]:[Cu(II)Br] :[Me_6Tren]	[NaBr]	Conv. (%)	$M_{n\ (Theo)}$ (Da)	$M_{n\ (SEC)}$ (Da)	*Đ*
1	10 : 1 : 0.02 : 0.12	3	>99	5000	6700	1.13
2	40 : 1 : 0.02 : 0.12	3	>99	19400	21600	1.18
3	40 : 1 : 0.02 : 0.12	6	>99	19400	19900	1.14
4	80 : 1 : 0.02 : 0.12	3	>99	38600	34000	1.24
5	80 : 1 : 0.02 : 0.12	12	>99	38600	35500	1.58
6	160 : 1 : 0.02 : 0.12	3	>99	77000	*gel*	-
7	160 : 1 : 0.02 : 0.12	24	>99	77000	*gel*	-

Homopolymerisation of PEGA of various targeted molecular weights were attempted using the optimized conditions found during the investigation into copper, ligand and halide salt concentrations. The conditions for DP_{20} (1 : 0.02 : 0.12 : 3, I : Cu(II) : L : NaBr) were applied to targeted degrees of polymerisation of 10, 40, 80, and 160 (table 3.4). For DP_{10} the polymerisation reaches quantitative conversion (entry 1, table 3.4), and SEC analysis revealed a narrow MWD (*Đ* = 1.13, Figure 3.12). DP_{40} (>99% conversion, M_n = 21600 Da, *Đ* = 1.18) and DP_{80} (>99% conversion, M_n = 34000 Da, *Đ* = 1.24) were also successfully targeted (entries 2 and 4, table 3.4; figure 3.12).

Keeping the vol% of monomer constant (50 vol%) results in lower molar concentrations of Cu, L and NaBr (as low as 62 ppm levels of $Cu(II)Br_2$). In order to ascertain whether this reduction in NaBr concentration has an effect on the dispersity of the resultant polymer, reactions targeting DP_{40} and DP_{80} were carried out under the same conditions but with double and quadruple the amount of NaBr, giving the same effective concentration of salt in solution as the optimized DP_{20} conditions (entries 3 and 5, table 3.4). It can be seen that a higher concentration of NaBr gives a similar result to entry 2, table 3.4 (DP_{40}), however when targeting a higher molecular weight (DP_{80}) the higher salt concentration results in a broader dispersity product. Attempts to polymerise PEGA to higher molecular weight (entries 6 and 7, table 3.4) resulted in the formation of a "covalent hydrogel"; this is postulated to be due to the presence of

diacrylate impurity in the monomer, further supported by the appearance of the high molecular weight shoulders, figure 3.12, which become more prevalent at higher degrees of polymerisation.

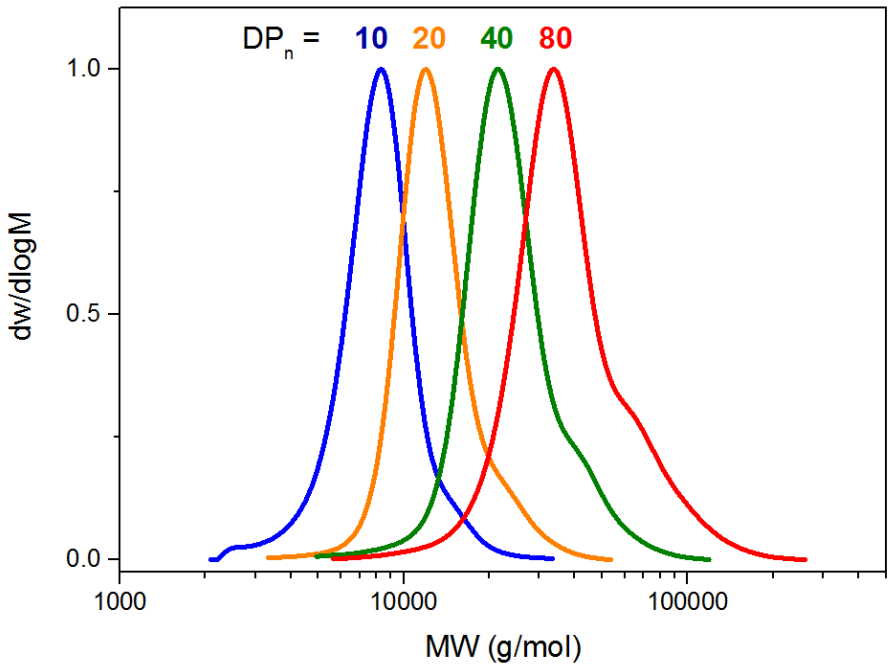


***Figure 3.12**: Molecular weight distributions of poly(PEGA) (DP$_n$ = 10, 20, 40, 80) synthesized under optimized conditions (entries 1, 2, 4, table 3.4; entry 4, table 3.2) as measured by DMF SEC.*

3.2.7 Monomer Scope

In addition to PEGA, other water soluble functional acrylates can be successfully polymerised in the presence of UV light and halide salts. The homopolymerisation of hydroxyethyl acrylate (HEA) DP$_n$ = 40-160 was targeted using 1 : 0.02 : 0.12 : 3, I : Cu(II) : L : NaBr in an identical manner to polymerisations of PEGA (table 3.5). In the case of DP$_{40}$ the reaction reached 96% conversion in 8 hours; and SEC analysis showed a monomodal peak (M_n = 10900 Da, $Đ$ = 1.20, figure 5). DP$_{80}$ (95% conversion, M_n = 18700 Da, $Đ$ = 1.16) and DP$_{160}$ (82% conversion, M_n = 26000 Da, $Đ$ = 1.13) were also successfully targeted using the same conditions showing good control over the MWDs (figure 3.13).

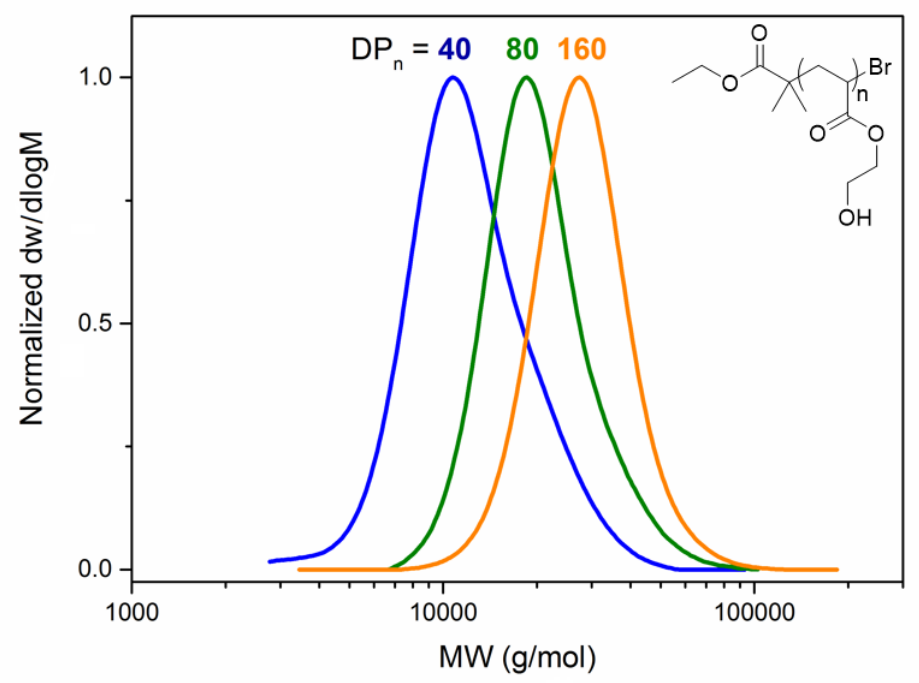


***Figure 3.13**: Molecular weight distributions of poly(HEA) (DP_n = 40, 80, 160) synthesized under optimized conditions (table 3.5) as measured by DMF SEC.*

***Table 3.5**: Polymerisation of HEA of different targeted molecular weight in the presence of sodium bromide. Reaction time = 8 hours in all cases.*

Entry		**[M]:[I]:[Cu(II)Br]:[L]**	**[NaBr]**	**Conv. (%)**	**$M_{n\ (SEC)}$ (Da)**	***Đ***
1	HEA	40 : 1: 0.02 : 0.12	3	96	10900	1.20
2	HEA	80 : 1: 0.02 : 0.12	3	95	18700	1.16
3	HEA	160 : 1: 0.02 : 0.12	3	82	26000	1.13
4	SPA K^+	20 : 1: 0.02 : 0.12	3	>99	9500	1.24
5	PEGMA*	20 : 1: 0.02 : 0.12	3	>99	16600	1.27

The polymerisation of a charged monomer, 3-sulfopropyl acrylate potassium salt was also attempted. It was found that the initiator used in previous polymerisations, EBiB, was insoluble in aqueous mixtures of the sulfonate monomer so instead the water soluble initiator 2,3-dihydroxypropyl 2-bromo-2-methyl propanoate was utilized. Targeting a DP of 20 using 1 : 0.02 : 0.12 : 3, I : Cu(II) : L : NaBr yielded conversion of 83% after 8 hours (M_n = 9500 Da, $Đ$ = 1.24 by aqueous GPC, figure 3.14).

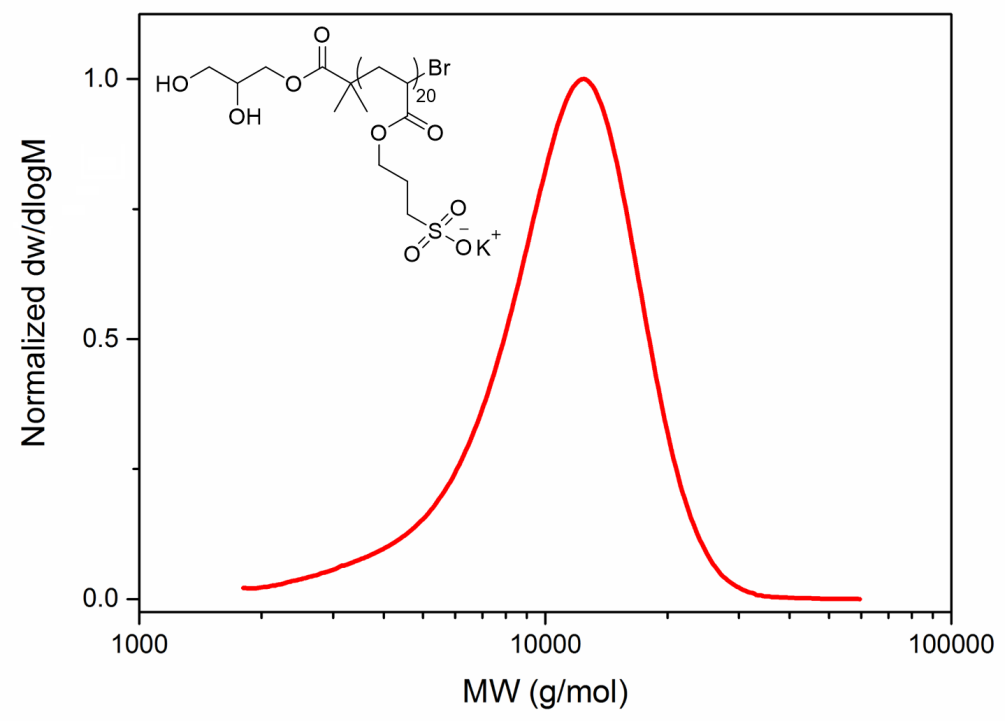


***Figure 3.14**: Molecular weight distribution of poly(SPA$^-$K$^+$) (DP$_n$ = 20) synthesized under optimized conditions (low [Cu], 3 eq. NaBr) as measured by DMF SEC.*

Successful controlled polymerisation of PEG_{500} methacrylate proved more challenging, with reactions reaching quantitative conversions but exhibiting broad dispersities ($Đ$ > 3.0) under the optimized conditions for PEGA. By using tris(2-pyridylmethyl)amine (TPMA) as the ligand instead of Me_6Tren in ambient light the reaction proceeded to quantitative conversion (>99%, M_n = 9500 Da, $Đ$ = 1.27, figure 3.15).

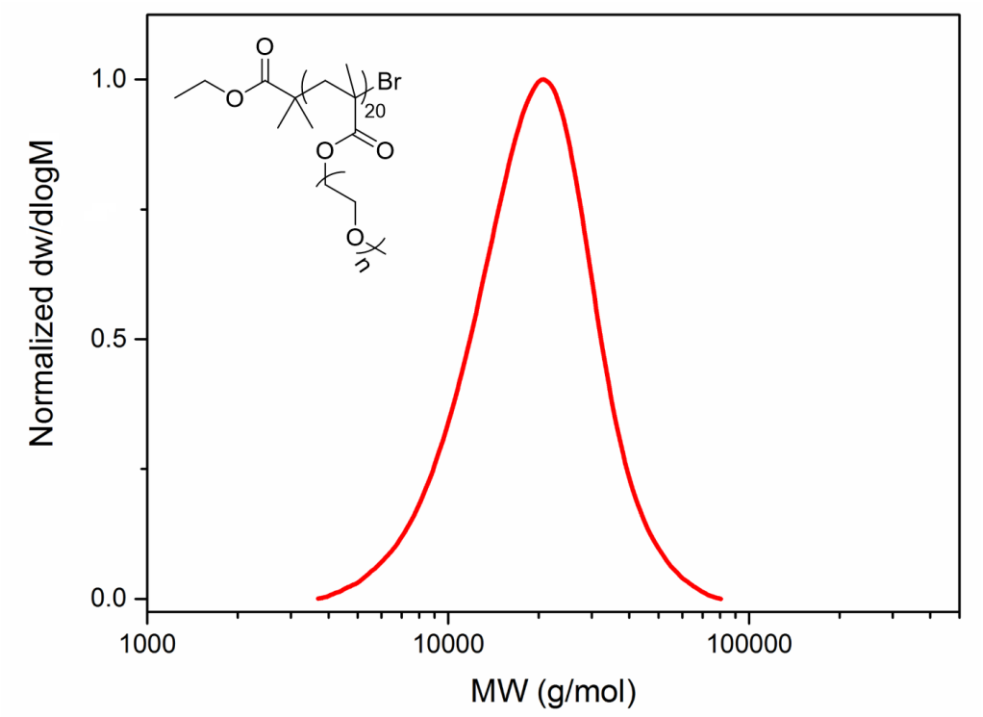
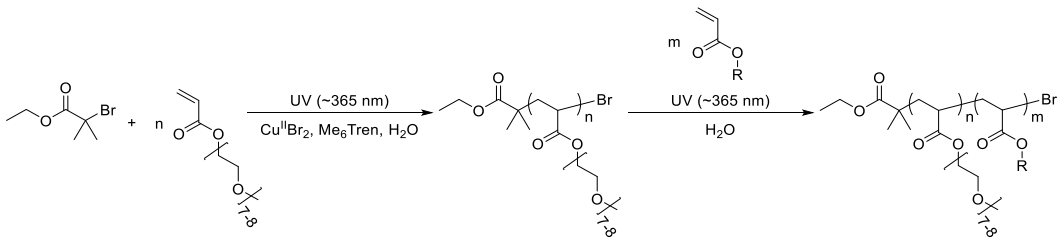


***Figure 3.15**: Molecular weight distribution of poly(PEGMA$_{500}$ (DP$_n$ = 20) synthesized under optimized conditions (low [Cu], 3 eq. NaBr) with TPA as ligand; measured by DMF SEC.*

3.2.8 Chain Extension

In an attempt to demonstrate the end group fidelity of this aqueous polymerisation technique an in-situ chain extension of poly(PEGA) was attempted. Poly(PEGA)$_{10}$ was targeted using 3 eq. of NaBr and when the reaction reached full monomer conversion (>99% conversion , M$_n$ = 7600 Da, *Đ* = 1.12, figure 6) a second aliquot of PEGA was subsequently added (scheme 3.3). The reaction was then allowed to proceed overnight, yielding a chain extended polymer (>99% conversion, M$_n$ = 11000 Da, *Đ* = 1.11, figure 3.17, experimental).



***Scheme 3.3**: General scheme showing the preparation of block copolymers via in-situ chain extension: polymerisation of PEGA via copper mediated photo ATRP following by addition of second monomer when first block reaches quantitative conversion.*

The synthesis of double hydrophilic block copolymers was also demonstrated by in-situ chain extension of Poly(PEGA)$_{10}$ (>99% conversion , M_n = 6400 Da, $Đ$ = 1.12, figure 3.16) with HEA (targeted DP = 20), added as an aqueous solution with 0.02 eq. of Cu(II)Br$_2$ and 0.12 eq. of ligand with respect to the PPEGA macroinitiator. (66% conversion, M_n = 14700 Da, Đ = 1.20, figure 3.16).

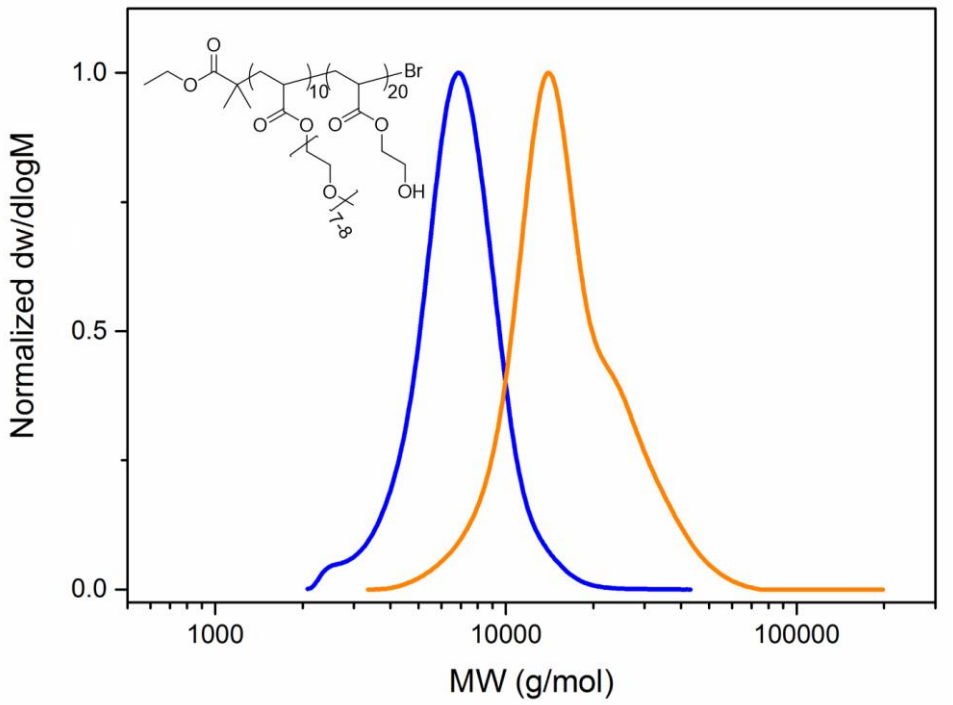
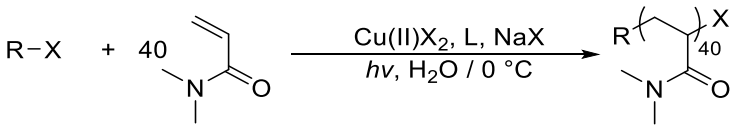


***Figure 3.16**: Molecular weight distributions of poly(PEGA)$_{10}$-b-poly(HEA)$_{20}$; measured by DMF SEC. Blue trace: first block, poly(PEGA)$_{10}$. Orange trace: block copolymer.*

3.2.9 Photopolymerisation of Acrylamide Monomers

Photomediated RDRP of acrylamide monomers has been reported by Boyer and coworkers[35] and Sumerlin and coworkers[68] using trithiocarbonates to achieve RAFT polymerisation under light of various wavelengths.



***Scheme 3.4**: Photopolymerisation of dimethylacrylamide.*

Controlled copper mediated photopolymerisation has been demonstrated for acrylates and methacrylates, using Me$_6$Tren and TPMA respectively. Cu(0)-RDRP utilizing Me$_6$Tren has been reported to control the polymerisation of acrylamide monomers

(previous chapter). A photomediated polymerisation of acrylamide would have certain benefits over Cu(0)-RDRP, such as spatiotemporal control and much lower catalyst loadings, for this reason the polymerisation of an acrylamide monomer, dimethyl acrylamide (DMAm), was attempted using optimized conditions: a water soluble initiator, 0.02 equivalents of $Cu(II)Br_2$, 0.12 equivalents of Me_6Tren and 3 equivalents of NaBr (entry 1, table 3.6) for a targeted DP of 40. The reactions were placed in a UV lamp and was found to have gelled after 3 hours. Repeating the experiment with no NaBr resulting in gelling after only 30 minutes (entry 2, table 3.6). These uncontrolled polymerisation could be the result of insufficient deactivation, consistent with the fact that addition of NaBr delays the time taken to reach the gel point. To test this, a reaction was performed using the same molar ratios, but substituting components for chloride analogues: $Cu(II)Cl_2$, methyl 2-chloropropionate (MCP). Using chloride instead of bromide should move the ATRP equilibrium towards the deactivated side, as chloride is more difficult to abstract from the chain end than bromide. Under these conditions the polymerisation of DMAm proceeded to 42% in one hour. However, the polymerisation was completely uncontrolled, with SEC analysis yielding a dispersity > 4.

***Table 3.6**: Polymerisations of dimethyl acrylamide with various catalytic systems.*

Entry	**Conditions**	**Time (hours)**	**Conv. (%)**	**$M_{n\ (SEC)}$ (Da)**	***Đ***
1	$Cu(II)Br_2$, Me_6Tren, WSI, NaBr	1	-	-	*gel*
2	$Cu(II)Br_2$, Me_6Tren, WSI	3	-	-	*gel*
3	$Cu(II)Cl_2$, Me_6Tren, MCP NaCl	1	42%	23800	4.56

3.3 Conclusions

In summary, this works presents a new methodology to effectively expand the scope of photoinduced copper mediated RDRP to include the controlled polymerisation of water soluble acrylates in aqueous media at relatively low copper concentrations. Addition of NaBr was demonstrated to give effective control over the polymerisation ($Đ$ as low as 1.11) with high conversions (>99% by NMR). These optimized conditions have also been demonstrated to control the polymerisation of HEA and sulfopropyl acrylate potassium salt. Furthermore, the reaction was shown to have a high degree of temporal control, exemplified by 'on-off' experiments in which the reaction was exposed to intermittent periods of light and dark conditions. The technique was demonstrated to apply to a range of monomers, targeted molecular weights and exhibit high end group fidelity, exemplified by in-situ chain extensions.

3.4 Experimental

3.4.1 Materials

All materials were purchased from Sigma Aldrich and used as received unless otherwise stated.

Tris[2-(dimethylamino)ethyl]-amine (Me_6Tren) was synthesized according to the procedure in chapter 2 and stored under nitrogen and refrigerated prior to use.

The water soluble initiator 2,3-dihydroxypropyl α-bromoisobutyrate was synthesized according to the procedure in chapter 2.

Sodium bromide (NaBr) 99+% (dry wt.) was purchased from Alfa Aesar and used as received.

HPLC grade water (H_2O, VWR international, LLC) was used as the solvent for all polymerisations.

Hydroxyethyl acrylate was dissolved in excess water. Diacrylate impurities were removed by extracting with hexane (10 times.) the aqueous phase was then saturated with sodium chloride and the monomer extracted with diethyl ether to separate trace amounts of acrylic acid. A small amount of hydroquinone was added to the ether and trace amounts of water were removed by addition of sodium sulfate. The ether was removed *in vacuo* to yield pure hydroxyethyl acrylate which was stored in a fridge prior to use.

Sodium bromide (NaBr) 99+% (dry wt.) was purchased from Alfa Aesar and used as received.

3.4.2 Instrumentation

NMR spectra were recorded on Bruker AV-300 MHz and DPX-400 MHz spectrometers using deuterated solvent (D_2O) purchased from Sigma-Aldrich. Monomer conversion was calculated by comparison of vinyl protons (5.8-6.5 ppm) with methyl ether protons (3.36 ppm.) *In-situ* NMR was conducted on a Varian 600 MHz spectrometer with temperature regulated to 25 °C. A 365 nm UV LED was coupled to a fibre optic which could be fed through a drilled NMR tube cap.

Size exclusion chromatography was conducted on a Varian 390-LC system using DMF as the Mobile phase with 5 mM NH_4BF_4 additive (50 ^oC). The system was

equipped with differential refractive index, viscometer and UV detectors, 2 PLgel 5 mm mixed-D columns (300 x 7.5 mm), 1 PLgel 5 mm guard column (50 x 7.5 mm) and an autosampler. The system was calibrated using Agilent Polymethyl Methacrylate EasiVials between 550 and 1.5 million g mol^{-1}) and polystyrene standards (Agilent Polystyrene Medium EasiVials between 162 and 364,000 g mol^{-1}) and fitted with second order polynomials. Samples were filtered through a plug of neutral alumina followed by filtration through 0.45 μm PTFE filter prior to analysis. All data is reported using PMMA Mark Houwink constants.

Aqueous SEC was conducted on an Agilent Technologies Infinity 1260 MDS instrument equipped with differential refractive index (DRI) and UV detectors. The column set used were Agilent PL Aquagel OH30 * 2 and a 5 μm Aquagel guard column. 0.1 M $NaNO_3$ was used as the mobile phase and column oven and detector temperatures were regulated to 35°C, at a flow rate 1 mL/min. Poly(ethylene oxide) standards (Agilent EasyVials) were used for calibration (100-30,000 g mol^{-1}) and fitted with a second order polynomial. Samples were filtered through a hydrophilic membrane with 0.22 μm pore size before injection.

The UV source used for all polymerisations was a UV nail gel curing lamp (λ_{max} ~ 365 nm) with four 9 Watt bulbs (figure 3.1).

3.4.3 Experimental Procedures

Example photoinduced polymerisation in the presence of sodium bromide (targeted DP_n = 20)

A 20 ml vial containing 140 mg of NaBr was charged with a 4 ml aliquot of stock solution of Cu(II)Br_2 in HPLC grade water (0.51 mg/mL) and a stirrer bar. 14.6 μL of Me_6Tren was added via microliter syringe prior to the addition of 4 mL of poly(ethylene glycol methyl ether) acrylate and 66.7 μL of ethyl α-bromoisobutyrate (EBiB). The vial was fitted with a rubber septum and deoxygenated by bubbling with nitrogen for 15 minutes. After this time the vial was placed in a UV nail lamp with a stirrer (see figure S1). After 8 hours the reaction was sampled and analysed by proton NMR and SEC.

Example kinetic analysis (polymerisation in the presence of sodium bromide (targeted DP_n = 20)

A 20 ml vial containing 140 mg of NaBr was charged with a 4 ml aliquot of stock solution of Cu(II)Br_2 in HPLC grade water (0.51 mg/mL) and a stirrer bar. 14.6 µL of Me_6Tren was added via microliter syringe prior to the addition of 4 mL of poly(ethylene glycol methyl ether) acrylate and 66.7 µL of ethyl α-bromoisobutyrate (EBiB). The vial was fitted with a rubber septum and deoxygenated by bubbling with nitrogen for 15 minutes. After this time the vial was placed in a UV nail lamp with a stirrer (see figure S1). Sampling was performed under a positive pressure of nitrogen at regular intervals (30, 60, 90, 120, 180, 240 and 300 minutes). All samples were diluted in cold D_2O and stored in foil wrapped vials immediately after sampling in order to stop polymerisation.

Example temporal control experiment

A reaction was set up as described above, and degassed in a darkroom. The reaction mixture was placed in a UV nail lamp with stirring. After 45 minutes the reaction was removed from the UV lamp, sampled under a positive pressure of nitrogen and placed on a stirrer in a darkroom. After one hour the solution was sampled and again placed in the UV lamp. This process was repeated for a total of 285 minutes of exposure to light. All samples were diluted in cold D_2O and stored in foil wrapped vials immediately after sampling in order to stop polymerisation.

In-situ monitoring of temporal control

Temporal control experiments with online NMR monitoring were performed at the University of California, Santa Barbara. All experiments were conducted at 33vol% monomer. Reactants were added together in the dark and deoxygenated with argon. The polymerisation solution was transferred to a foil wrapped NMR tube and fitted with an argon filled balloon whilst transferring to the NMR spectrometer.

Polymerisation of sulfopropyl acrylate potassium salt (targeted DP_n = 20)

A vial containing 133 mg of NaBr was charged with 2 mL aliquot of stock solution of Cu(II)Br_2 in HPLC grade water (0.96 mg/mL) and a stirrer bar. 13.8 µL of Me_6Tren was added via microliter syringe prior to the addition of 2 g of sulfopropyl acrylate potassium salt and 63.1 mg of water soluble initiator, 2,3-dihydroxypropyl 2-bromo-2-methyl propanoate. The vial was fitted with a rubber septum and deoxygenated by

bubbling with nitrogen for 15 minutes. After this time the vial was placed in a UV nail lamp with a stirrer (see figure S1).

Polymerisation of $PEGMA_{500}$ (targeted $DP_n = 20$)

A 20 ml vial containing 133 mg of NaBr was charged with a 4 ml aliquot of stock solution of $Cu(II)Br_2$ in HPLC grade water (0.48 mg/mL) and a stirrer bar. 17.5 mg of TPMA was added prior to the addition of 4 mL of poly(ethylene glycol methyl ether) methacrylate and 63.4 µL of ethyl α-bromoisobutyrate (EBiB). The vial was fitted with a rubber septum and deoxygenated by bubbling with nitrogen for 15 minutes. After this time the vial was placed in a UV nail lamp with a stirrer (see figure S1). After 8 hours the reaction was sampled and analysed by proton NMR and SEC.

Chain extension

A 20 ml vial containing 280 mg of NaBr was charged with a 4ml aliquot of stock solution of $Cu(II)Br_2$ in HPLC grade water (1.02 mg/mL) and a stirrer bar. 29.1 µL of Me_6Tren was added via microliter syringe prior to the addition of 4 mL of poly(ethylene glycol methyl ether) acrylate and 133.3 µL of ethyl α-bromoisobutyrate (EBiB). The vial was fitted with a rubber septum and deoxygenated by bubbling with nitrogen for 15 minutes. After this time the vial was placed in a UV nail lamp with a stirrer (see figure S1). After 6 hours the reaction was sampled and analysed by proton NMR and SEC. A degassed aliquot of 4 mL of PEGA in 4 mL of water was then transferred into the reaction vessel which was subsequently placed into the UV lamp overnight.

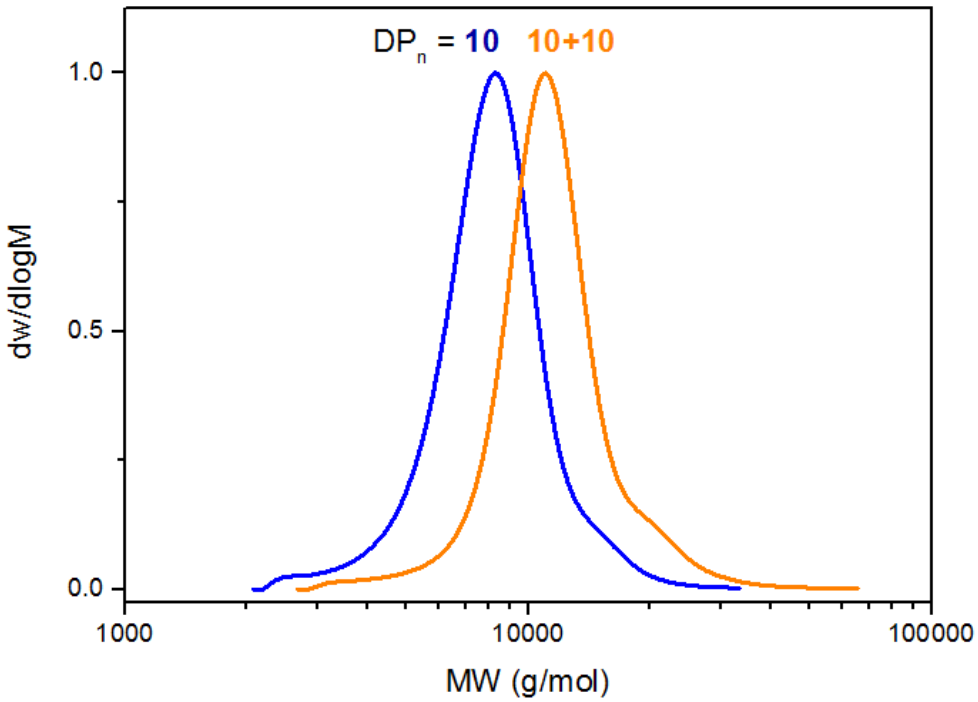


***Figure 3.17**: Molecular weight distributions of poly(PEGA)$_{10}$-b-poly(PEGA)$_{10}$; measured by DMF SEC. Blue trace: first block, poly(PEGA)$_{10}$. Orange trace: block copolymer.*

Chain extension of PPEGA with HEA

A 20 ml vial containing 280 mg of NaBr was charged with a 4ml aliquot of stock solution of Cu(II)Br$_2$ in HPLC grade water (1.02 mg/mL) and a stirrer bar. 29.1 µL of Me$_6$Tren was added via microliter syringe prior to the addition of 4 mL of poly(ethylene glycol methyl ether) acrylate and 133.3 µL of ethyl α-bromoisobutyrate (EBiB). The vial was fitted with a rubber septum and deoxygenated by bubbling with nitrogen for 15 minutes. After this time the vial was placed in a UV nail lamp with a stirrer (see figure S1). After 6 hours the reaction was sampled and analysed by proton NMR and SEC. 4.16 mL of a degassed 50% (v/v) aqueous solution of HEA (20 eq. rel. to PPEGA) with 4.08 mg of Cu(II)Br$_2$ and 14.6 µL of Me$_6$Tren was then added to the reaction mixture via degassed syringe and placed into the UV lamp and left to react overnight (66%, figure 3.18, M_n = 14700 Da, $Đ$ = 1.20).

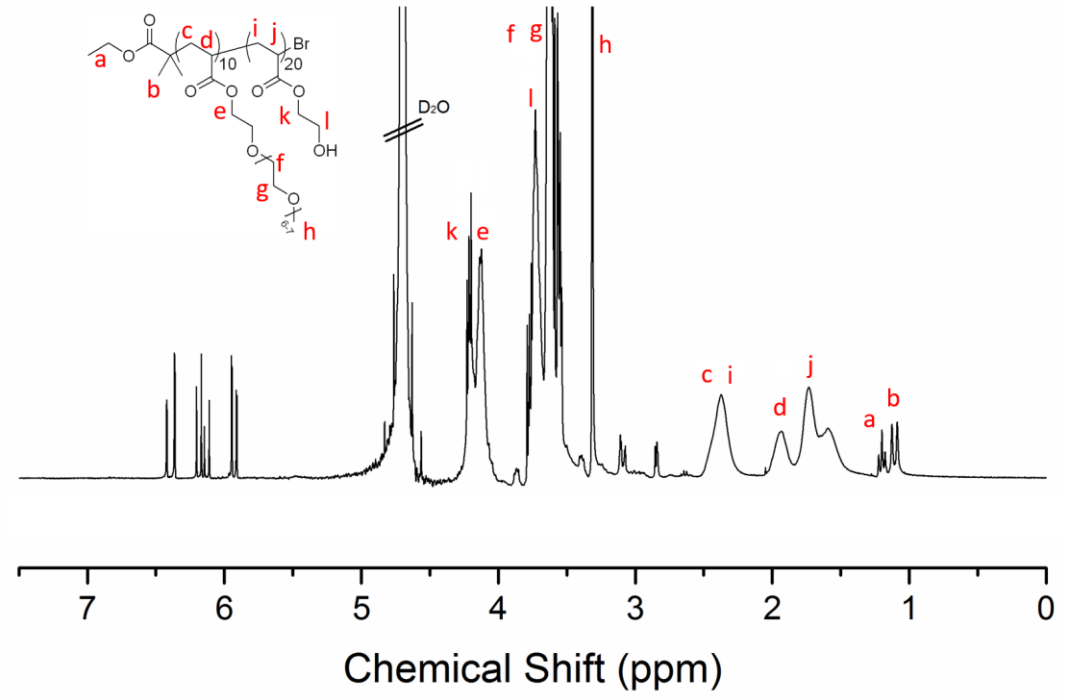


Figure 3.18:*Crude ^{1}H (400 MHz, D_2O) NMR of poly(PEGA)$_{10}$-b-poly(HEA)$_{20}$.*

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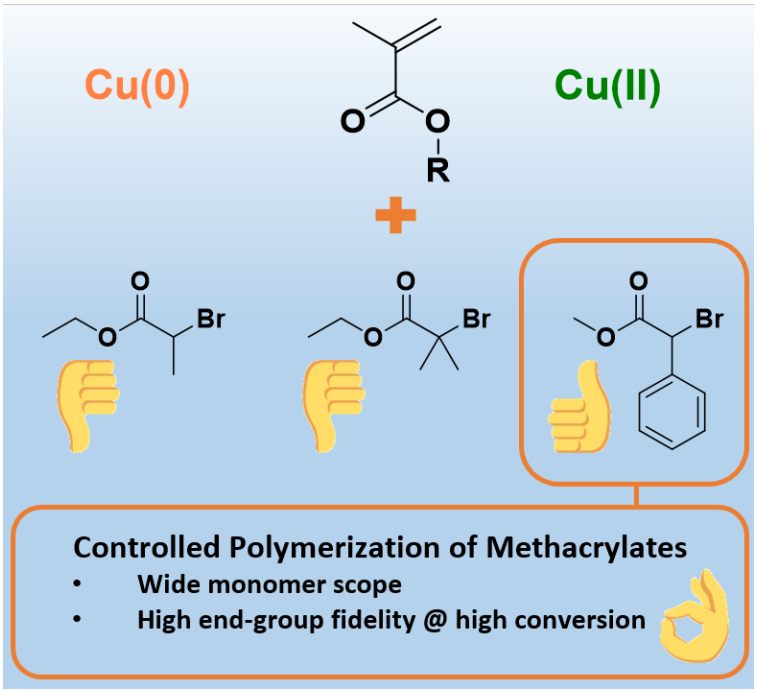
Chapter 4: Cu(0)-RDRP of Methacrylates in DMSO: Importance of the Initiator



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4.1 Introduction

Cu(0)-mediated reversible deactivation radical polymerisation (RDRP) has emerged as a useful and versatile tool for the synthesis of polymers in both aqueous and organic media, yielding very well-defined materials often with complex and designed macromolecular architectures.[1-9] When compared to other controlled/living radical polymerisations methods, Cu(0)-mediated RDRP exhibits a number of advantages including narrow molecular weight distributions even at near quantitative conversions, high end group functionality, very low concentrations of copper catalyst (ppm) with both a simple set up and deoxygenation procedures.[10,11] The majority of the polymerisations are performed at ambient temperature or below thus allowing additional access to well defined protein/polymer conjugates and monomers that exhibit lower critical solution temperature (LCST) behaviour upon polymerisation.[12-16]

Acrylates and acrylamides are the most studied monomer classes investigated by Cu(0)-mediated RDRP, with methyl acrylate (MA) and *N*-isopropylacrylamide (NIPAM) often used as model monomers for the optimization of reaction conditions. Cu(0)-wire and Cu(0) particles, either externally added or generated *in-situ via* disproportionation of CuBr/Me_6Tren (tris[2-(dimethylamino)ethyl]amine) systems have been extensively explored to afford the polymerisation of a wide range of hydrophobic, hydrophilic, semi-fluorinated and functional acrylates and acrylamides to yield polymers with narrow molecular weight distributions.[12,17-19] A number of complex architectures further demonstrates the excellent control and high end group fidelity accessible through these techniques as shown by the synthesis of sequence controlled multiblock copolymers,[17,20] stars[21-24] and dendritic hyperbranched structures.[25]

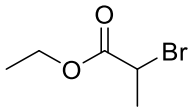
In contrast to acrylates and acrylamides, reports of the RDRP of methacrylates using Cu(0)-based synthetic protocols are far fewer in number. Both Percec and Perrier have reported the controlled polymerisation of methacrylates *via* Cu(0)-RDRP with initiators such as aryl sulfonyl halides and ethyl bromoisobutyrate (EBiB), although the resultant materials exhibit moderate control over the molecular weight distributions (*Đ* typically >1.20-1.30) when compared to the acrylic analogues (*Đ* typically ~ 1.10).[1,2,8,26-29] The synthesis of block copolymers *via* chain extension *in situ* was not reported in these studies. Conversions of 50-80% are typically reported

and the monomers exemplified are usually limited to MMA; monomers with higher degrees of functionality have yet to be exploited in this context. Furthermore, relatively high temperatures (>60°C) are often required for these polymerisations, thus potentially limiting the application of the resultant polymers.

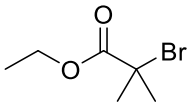
Aqueous Cu(0)-RDRP of methacrylates was reported by Simula *et al.* in 2015. The polymerisation of poly(ethylene glycol) methyl ether methacrylate (PEGMA) was attempted in aqueous media *via* a predisproportionation approach. The study found that polymerisation of PEGMA proceeded to ~89% under standard aqueous Cu(0)-RDRP conditions (CuBr, Me_6Tren, 2,3-dihydroxypropyl α-bromoisobutyrate). The molecular weight distribution was found to be broad ($Đ$ > 1.7) indicating an uncontrolled reaction. Upon switching the ligand to PMDETA polymerisations proceeded with a higher degree of control ($Đ$ ~ 1.3), however attempts at chain extension were relatively unsuccessful: addition of a second aliquot of PEMGMA only resulted in 20% conversion after 15 hours, suggesting a significant loss of end-group fidelity.

This study presents an optimization of the Cu(0)-RDRP of methacrylates in DMSO. The aforementioned challenges are circumvented by selecting a suitable initiator, temperature and ligand so as to identify optimal polymerisation conditions for methacrylates. Methyl α-bromophenylacetate (MBPA) is an active and commercially available initiator and is shown to facilitate the controlled polymerisation of MMA as well as a range of hydrophobic, hydrophilic and functional methacrylates at ambient temperature. The effect of temperature, ligand, and catalyst concentration are also explored. The utility of the optimized conditions are then exemplified through the preparation of polymers of low dispersity at high monomer conversion, (>90 %), high molar molecular weight polymers (>70 kDa), and successful synthesis of block copolymers *via in-situ* chain extension. The possibility of exploiting the bromophenylacetate motif for polymerisation of methacrylates in aqueous media is also explored.

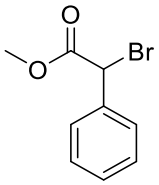
4.2 Results and Discussion



EBP



EBiB

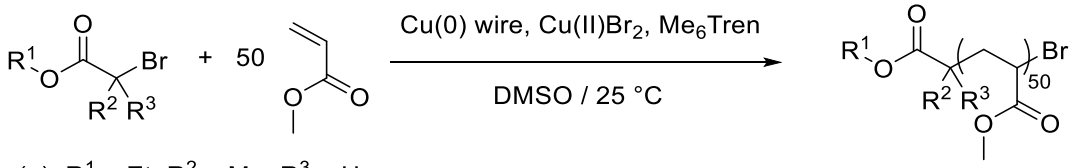


MBPA

Scheme 4.1: *Initiators used in this study; EBP: Ethyl 2-bromopropionate. EBiB: Ethyl α-bromoisobutyrate. MBPA: Methyl α-bromophenylacetate.*

4.2.1 Polymerisation of Methyl Acrylate with different Initiators

Cu(0)-wire mediated polymerisation of acrylates is often conducted at ambient temperature using Me_6Tren as the ligand, EBiB as a typical initiator, DMSO as the solvent with a small amount of $CuBr_2$ added to deactivate the polymer chains so to yield narrower molecular weight distributions. Under these conditions (scheme 4.2 (b)), low dispersity and high end group fidelity poly(methyl acrylate), capable of facilitating *in-situ* chain extensions, can be observed at high monomer conversion, consistent with previous reports (entry 2, table 4.1; figure 4.1 centre).[10,11,30] The use of DMSO, a disproportionating solvent which solubilizes Cu(II), has previously been shown to furnish polymers with high end group fidelity.[31-33]



(a) R^1 = Et R^2 = Me R^3 = H
(b) R^1 = Et R^2 = Me R^3 = Me
(c) R^1 = Me R^2 = Ph R^3 = H

Scheme 4.2: *Polymerisation of methyl acrylate (targeted DP = 50) by Cu(0)-RDRP in DMSO utilizing 3 different initiators: (a) EBP, (b) EBiB, (c) MBPA.*

On switching from the tertiary initiator (EBiB) to the secondary (EBP), MA exhibited comparable polymerisation rate, polymer dispersity and end group fidelity with good agreement between theoretical and experimental molecular weights (scheme 4.2 (a), entry 1, table 4.1). In stark contrast, the polymerisation of MA initiated with MBPA exhibited substantially lower monomer conversion even after a significantly longer reaction time (24 h) (entry 3, table 4.1). This difference is ascribed to an lower rate of initiation (k_i) from the highly-stabilized MBPA-derived radical towards MA to give a substantially less stabilized PMA propagating radical (i.e. $k_{act,MBPA} >> k_i$ and $k_{act,MBPA}$

>> $k_{act,\ PMA}$). Although low dispersity was observed in this case, the slow rate of polymerisation manifests in the inability to reach high conversion even after a prolonged reaction time. This led us to conclude that MBPA is not the optimal initiator to facilitate the controlled polymerisation of acrylates under these conditions employed.

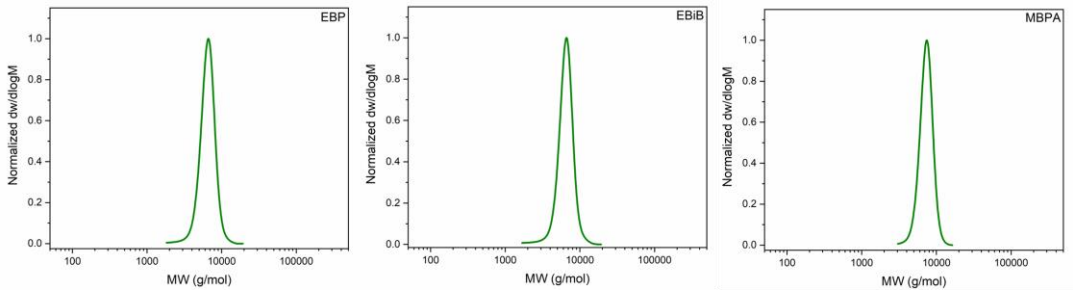
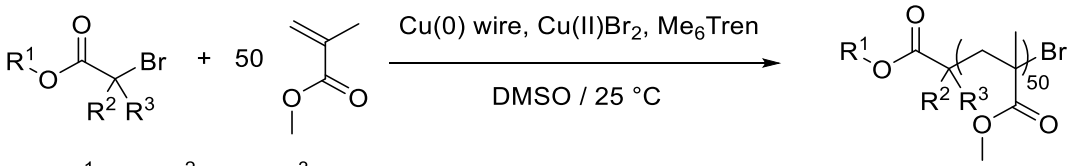


Figure 4.1: *SEC traces of polymerisation of methyl acrylate with EBP, EBiB and MBPA from table 4.1.*

Table 4.1: *Polymerisation of methyl acrylate in DMSO with three different initiators. [M]:[I]:[Cu(II)Br$_2$]:[Me$_6$Tren] = 50:1:0.05:0.18. 50 vol% monomer, 5 cm Cu(0) wire.*

Entry	Initiator	Time (hours)	Conv. (%)	$M_{n\ (Theo)}$ (Da)	$M_{n\ (SEC)}$ (Da)	*Đ*
1	EBP	3	98	4400	4200	1.06
2	EBiB	3	97	4300	4600	1.10
3	MBPA	24	55	3000	4900	1.09

4.2.2 Polymerisation of Methyl Methacrylate with different Initiators and Me$_6$Tren



(a) R^1 = Et R^2 = Me R^3 = H
(b) R^1 = Et R^2 = Me R^3 = Me
(c) R^1 = Me R^2 = Ph R^3 = H

Scheme 4.3: *Polymerisation of methyl methacrylate (targeted DP = 50) by Cu(0)-RDRP in DMSO utilizing 3 different initiators: (a) EBP, (b) EBiB, (c) MBPA.*

Under identical reaction conditions neither EBiB nor EBP were able to provide a high degree of control over the polymerisation of MMA (scheme 4.3 (a) & (b)), yielding polymers with relatively high dispersity (entries 1 & 2, table 4.2, figure 4.2) and in the

case of EBP, limited conversion (38%, entry 1, table 4.2). The size exclusion chromatography (SEC) chromatograms for these polymerisations (figure 4.2) also show low molecular weight tailing, suggesting that significant termination events are occurring.

Table 4.2: *Polymerisation of methyl methacrylate in DMSO with three different initiators. [M]:[I]:[$Cu^{II}Br_2$]:[Me_6Tren] = 50:1:0.05:0.18. 50 vol% monomer, 5 cm Cu(0) wire.*

Entry	**Initiator**	**Time (hours)**	**Conv. (%)**	**$M_{n\ (Theo)}$ (Da)**	**$M_{n\ (SEC)}$ (Da)**	***Đ***
1	EBP	24	38	200	6500	2.12
2	EBiB	24	80	4100	7200	1.49
3	MBPA	24	90	5000	8200	1.10

When the same conditions were employed using MBPA as the initiating species PMMA could be synthesized with a dispersity of 1.10 even at high conversion (90%, entry 3, table 4.2, figure 4.2). As expected in comparison to the MA examples, the polymerisation of MMA was much slower due to the lower propagation rate constant (k_p) for MMA polymerisation.[34] Discrepancies between theoretical and observed M_n for the polymerisation of MMA are attributed to reduced initiator efficiency (75%) as previously reported.[29,35,36]

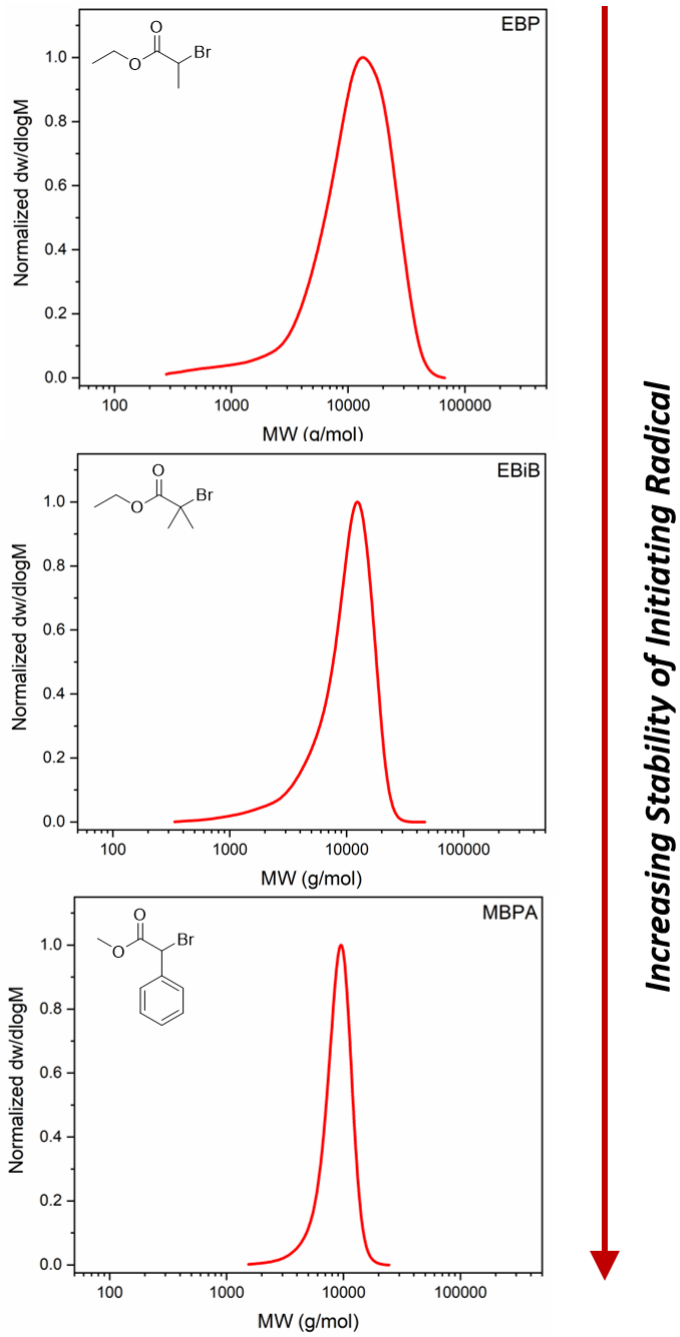


Figure 4.2: *SEC traces of polymerisation of methyl methacrylate with EBP, EBiB and MBPA from table 4.2, showing the increased stability of the initiating radical and the associated increase in control.*

4.2.3 Polymerisation of Methyl Methacrylate with different Initiators and PMDETA

Previous studies investigating the Cu(0) mediated polymerisation of methacrylate monomers have highlighted the choice of ligand as an important parameter for achieving a desired controlled process.[37,38] With this in mind polymerisations of MMA with the three initiators described previously were repeated using PMDETA as the ligand.

Table 4.3: *Polymerisation of methyl methacrylate in DMSO with three different initiators. [M]:[I]:[Cu(II)Br$_2$]:[PMDETA] = 50:1:0.05:0.18. 50 vol% monomer, 5 cm Cu(0) wire.*

Entry	**Initiator**	**Time (hours)**	**Conv. (%)**	**M$_{n\ (Theo)}$ (Da)**	**M$_{n\ (SEC)}$ (Da)**	***Đ***
1	EBP	24	86	4500	11300	2.04
2	EBiB	24	84	4400	7400	1.52
3	MBPA	24	90	4700	11500	1.40

As can be seen from table 4.3, EBP and EBiB in conjunction with PMDETA yielded higher conversions, but molecular weight distributions were similarly broad to reactions carried out utilizing Me$_6$Tren. For the phenyl acetate derived initiator, MBPA, conversion is similar to the reaction with Me$_6$Tren, however, there is interestingly a marked increase in dispersity observed (1.40 compared to 1.10), with noticeable low molecular weight tailing observed in the SEC chromatograms (figure 4.3), suggesting that appreciable termination events were occurring. This termination has previously been reported by Voit and coworkers who illustrated termination in the ATRP of MMA when PMDETA was utilised as the ligand.[39] This shows that ligand selection is important in combination with the highly active MBPA initiator, ([MBPA]:[Cu(II)Br$_2$]:[Me$_6$Tren]:[MMA] = [1]:[0.05]:[0.18]:[50]) to synthesize poly(methyl methacrylate) to high conversions whilst maintaining narrow molecular weight distributions.

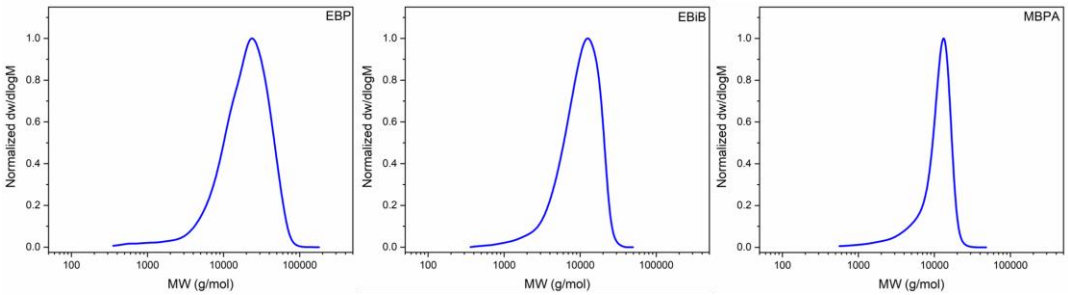


Figure 4.3: *SEC traces of polymerisation of methyl methacrylate (PMDETA) with EBP, EBiB and MBPA from table 4.3.*

4.2.4 Effect of Temperature on Cu(0)-RDRP of MMA

The polymerisation of MMA under the optimized conditions was repeated at three different temperatures, in order to ascertain whether increased temperature could yield

greater polymerisation rates and higher conversions whilst maintaining the good degree of control over molecular weight distribution (MWD). At 50 °C it was found that the reaction proceeds much faster, with conversion found to be 65% by ^{1}H NMR after three hours, compared to just 5% at 25 °C. However after 24 hours the reaction had only reached a marginally higher conversion (94% compared to 90% at 25 °C, table 4.4), and furthermore the dispersity was significantly higher (*Đ =1.30* at 50 °C, figure 4.4, compared to 1.10 at 25 °C). At 75 °C, this trend is further illustrated with conversion reaching almost 90% in 3 hours (entry 5, table 4.4), but an even higher dispersity (table 4.4). All subsequent reactions were performed at ambient temperature to minimize the termination events occurring at higher temperatures.

Table 4.4: *Polymerisation of methyl acrylate using MBPA initiator with varying temperature.*

Entry	**Temp. (°C)**	**Time (hours)**	**Conv. (%)**	**$M_{n\ (Theo)}$ (Da)**	**$M_{n\ (SEC)}$ (Da)**	***Đ***
1	25	3	5	-	-	-
2		24	90	4700	10800	1.10
3	50	3	65	3400	6100	1.18
4		24	94	4900	9900	1.30
5	70	3	86	4500	8900	1.60
6		24	91	4800	11200	1.50

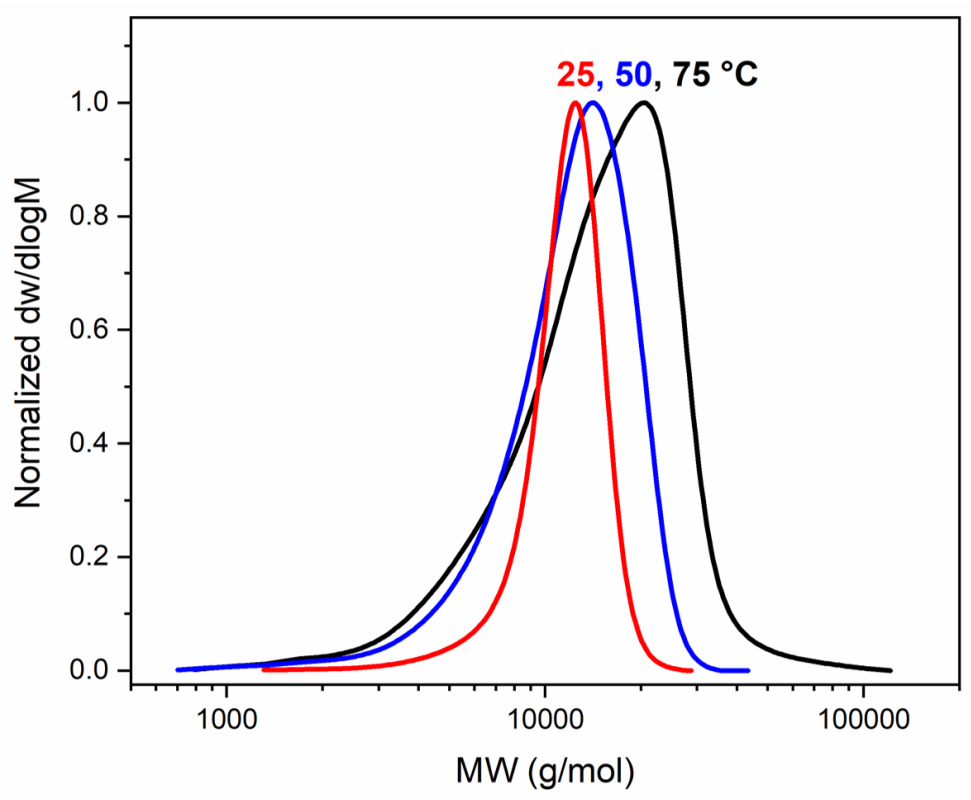


Figure 4.4: *SEC traces for polymerisation of methyl methacrylate with Me_6Tren and MBPA at different temperatures. Samples taken after 24 hours (entries 2, 4, and 6, table 4.4).*

4.2.3 Effect of Cu(II) concentration on Cu(0)-RDRP of MMA

The initiator efficiency for the polymerisation of MMA in DMSO with MBPA was found to be 75%. This is not ideal as it means that there is deviation between targeted and observed molecular weight for polymerisation. A possible reason for this low efficiency could be loss of initiating species at the beginning of the reaction. A series of reactions were carried out with increased Cu(II)Br_2 concentrations in order to determine whether more deactivation from the start of the polymerisation would improve the initiator efficiency. Table 4.5, entries 1-4 show that conversion reaches values above 95% regardless of Cu(II) concentration, however the number average molecular weight measured by SEC decreases with increasing [Cu(II)], indicating that the initiator efficiency is increasing. Upon increasing the ligand concentration control of the polymerisation was lost, consistent with previous literature reports of side reactions in the presence of excess ligand.[40] In addition to this it also reported that addition of 5% of Cu(II)Br_2 is beneficial as it has been reported to allow for more efficient synthesis of diblock copolymers *via in-situ* approaches.[41]

Table 4.5: *Polymerisation of methyl methacrylate with increasing Cu(II) concentrations.*

Entry	**[I] : [Cu(II)Br_2] : [Me_6Tren]**	**Time (hours)**	**Conv. (%)**	**$M_{n\ (Theo)}$ (Da)**	**$M_{n\ (SEC)}$ (Da)**	***Đ***
1	1 : 0 : 0.18	24	95	5000	9900	1.21
2	1 : 0.05: 0.18	24	96	5000	8900	1.17
3	1 : 0.10: 0.18	24	96	5000	7400	1.18
4	1 : 0.20: 0.18	24	98	5200	7100	1.16
5	1 : 0.20: 0.72	24	98	5200	11300	2.88

4.2.4 Kinetic analysis of MMA Polymerisation with online FT-NIR Monitoring

In order to gain a better understanding of these polymerisations, kinetic analysis using online FT-NIR monitoring was employed allowing for the measurement of monomer conversion as a function of time (figure 4.13, section 4.3). Online monitoring of polymerisation kinetics is beneficial as it allows kinetic data to be collected without disturbing the balance of the system (e.g. by introducing oxygen or changing monomer : catalyst ratios through repeated sampling). The FT-NIR spectrum of MMA reveals a prominent signal at 6170 cm^{-1} (from the first overtone of the 2 $\gamma(=CH_2)$ absorption) which upon integration allows for the relative monomer concentration to be calculated, as previously reported by Haddleton *et. al.*[42,43]

The first order kinetic plot ($\ln[M_0]/[M_t]$ vs time) for the polymerisation of MMA was obtained by measuring the relative decrease in the absorption at 6170 cm^{-1} (ascribed to the vinyl group of the monomer) as the monomer is converted to polymer. Figure 4.5 shows the kinetic plot for the polymerisation of MMA with EBP (an initiator which forms a secondary radical), it can be seen that there is no linear relationship, indicating a non-constant concentration of radicals which results in an uncontrolled reaction (final dispersity = 2.12).

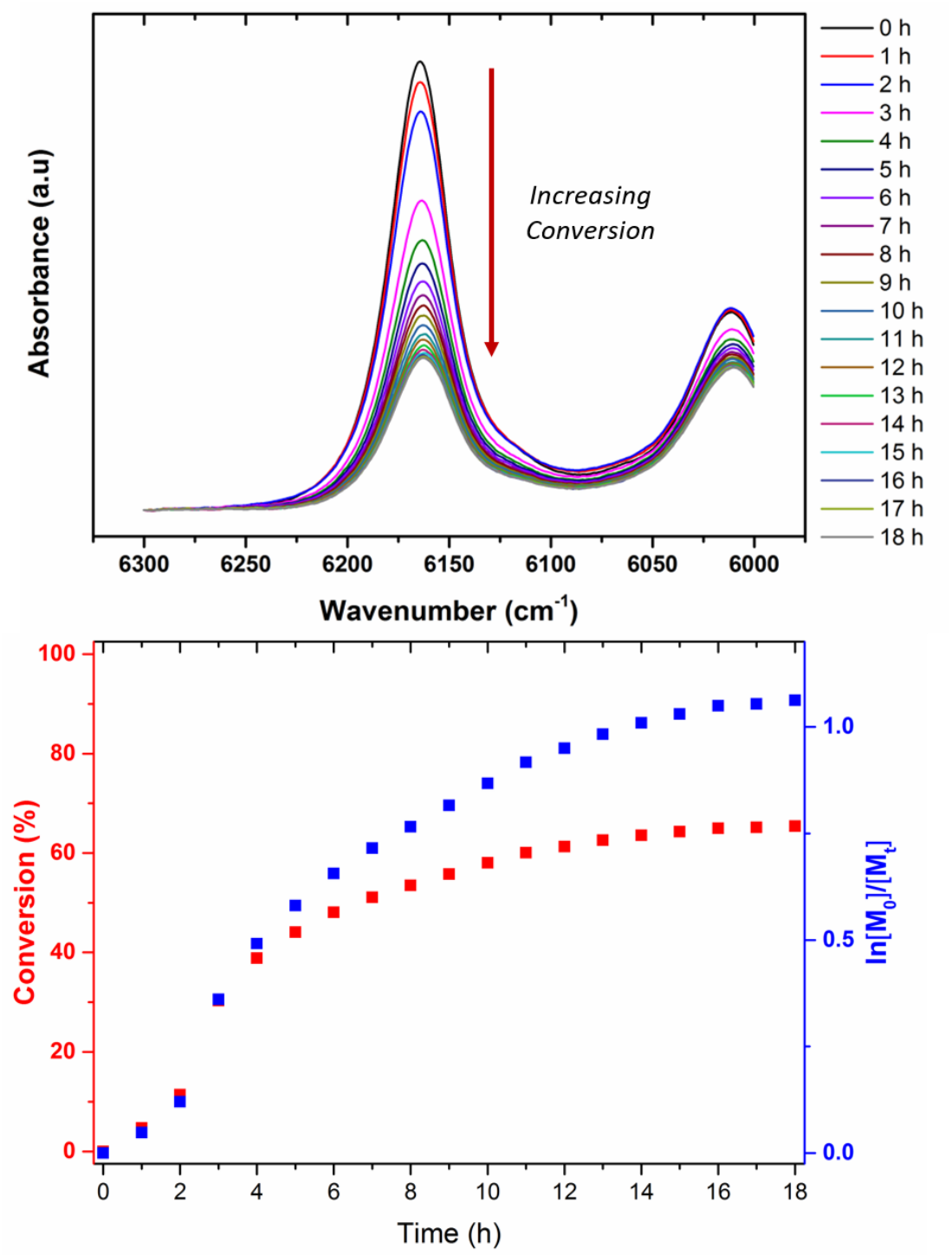


Figure 4.5: *Top: FT-NIR data showing a decrease in =CH2 absorption over time for the polymerisation of MMA with EBP. Bottom: kinetic plots from the FT-NIR data.*

When EBiB was employed (an initiator capable of generating a more stable tertiary radical) linear kinetics were only observed up to 4 h, before a subsequent loss of linearity and loss of control (figure 4.6). The lack of control of this polymerisation is highlighted by SEC analysis of the final sample which exhibited a dispersity of 1.60.

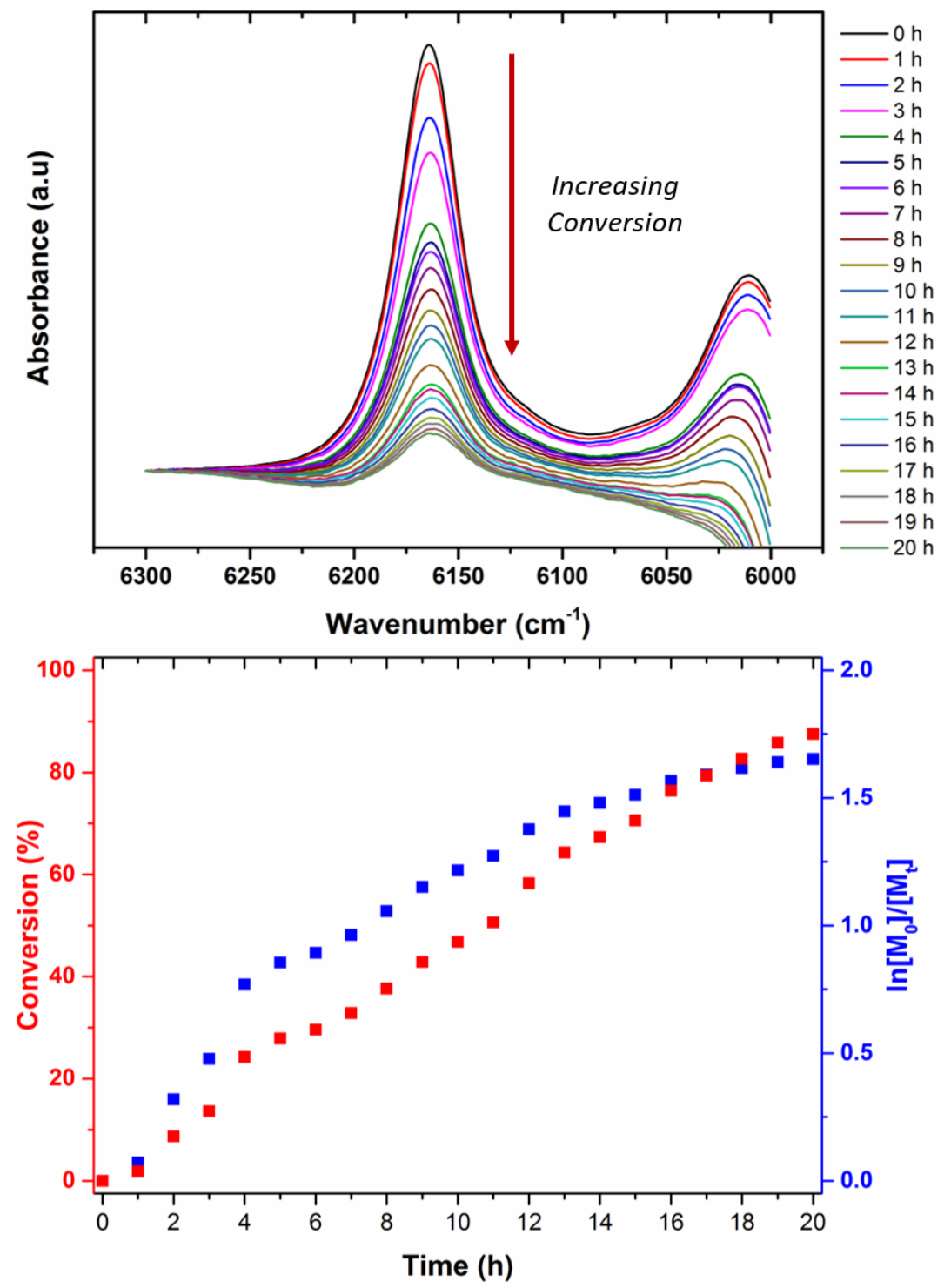


Figure 4.6: *Top: FT-NIR data showing a decrease in =CH2 absorption over time for the polymerisation of MMA with EBiB. Bottom: kinetic plots from the FT-NIR data.*

On the contrary kinetic analysis of the polymerisation using MBPA, an initiator where the initiating radical is further resonance stabilized by the adjacent phenyl group, a much more linear behaviour was observed following an initial induction period (attributed to selective initiation, where MPBA is transformed to the single monomer

unit adduct prior to polymerisation of MMA) that has also been previously observed (figure 4.7).[44,45] Importantly, the final sample exhibited a narrow molecular weight distribution ($Đ$ = 1.10 at 90% conversion), demonstrating an impressive degree of control over the polymerisation.

The "cross-propagation" of the more electron rich MBPA initiator derived radical to MMA is faster than the homopropagation of PMMA$^{\bullet}$ to MMA and the MPBA derived radical is more stable as it is doubly stabilized by two resonance stabilizing groups; PMMA$^{\bullet}$ is less stable as it has only one resonance stabilizing group. This results in initiation being a much faster process that propagation, so all polymer chains have an equal chance of propagating and are therefore similar in length (hence a narrow molecular weight distribution is obtained.) In the case of EBP and EBiB the PMMA$^{\bullet}$ is more stable due to the back strain effect, in which the release of steric strain from the dormant PMMA-Br species as it undergoes transformation from a sp^3 hybridized to sp^2 hybridized configuration through activation makes the formation of the radical more enthalpically valuable.[46,47] Taken altogether, this data concludes that in the case of acrylates, all three initiators result in narrow molecular weight distributions although clearly MBPA is less ideal due to much slower polymerisation rates. On the contrary, in the case of methacrylates only MBPA can facilitate a well-controlled polymerisation delivering polymers of low dispersity.

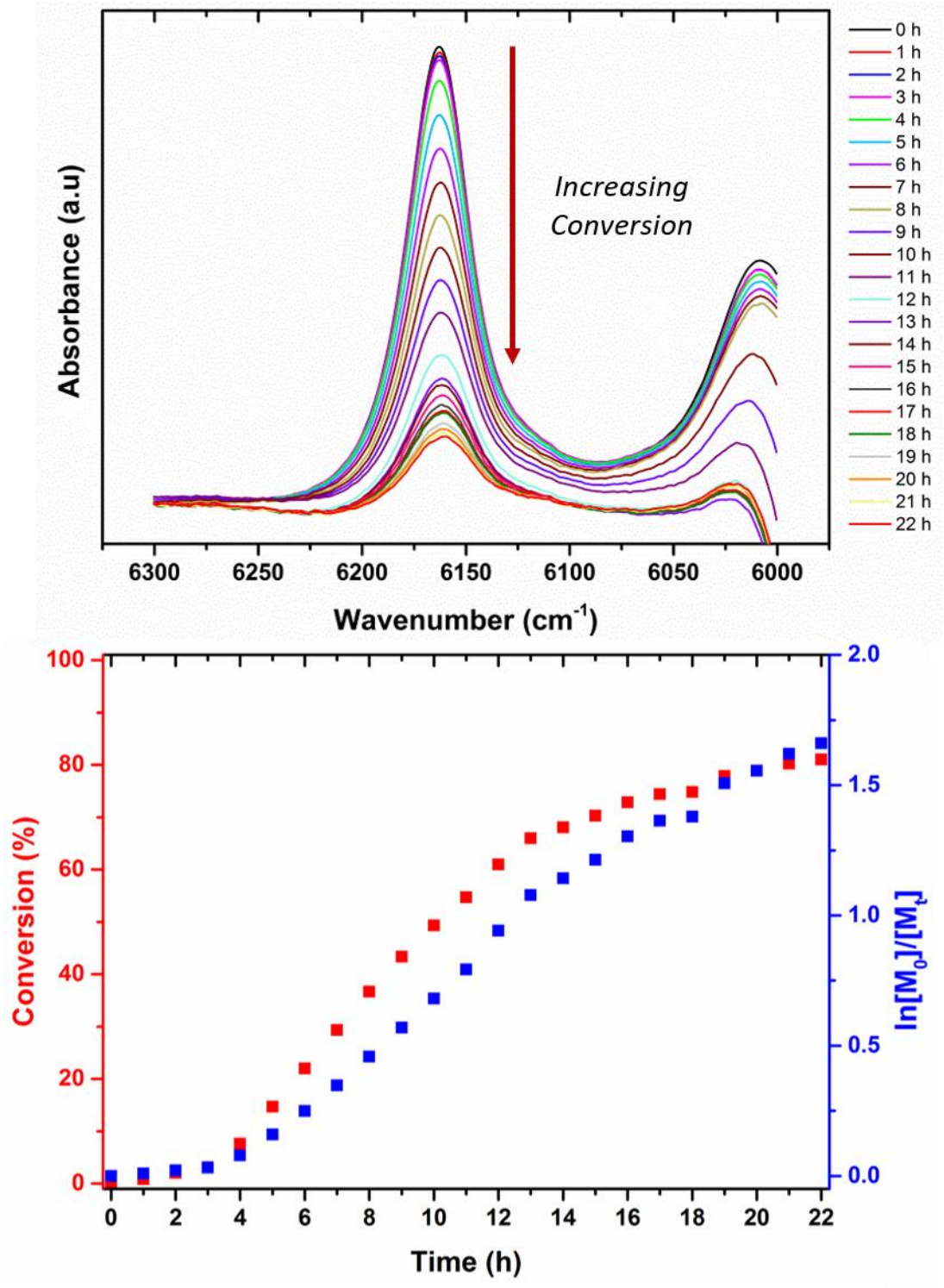


Figure 4.7: *Top: FT-NIR data showing a decrease in =CH2 absorption over time for the polymerisation of MMA with MBPA. Bottom: kinetic plots from the FT-NIR data.*

4.2.5 Higher Molecular Weight PMMA

To probe the potential of these optimized conditions to deliver polymers with narrow MWDs for higher MW polymers, a series of PMMAs were synthesized targeting

higher degrees of polymerisation ((DP_n = 100-400), table 4.6). In all cases these experiments yielded polymers with low dispersity (1.10-1.24) up to 73 000 Da (figure 4.8).

Table 4.6: *Polymerisation of methyl methacrylate with increasing target DP. MBPA : Cu(II)Br_2 : Me_6Tren; 1 eq. : 0.05 eq. : 0.18 eq.*

Entry	**Target DP_n**	**Time (hours)**	**Conv. (%)**	**$M_{n\ (Theo)}$ (Da)**	**$M_{n\ (SEC)}$ (Da)**	***Đ***
1	50	24	90	4700	8200	1.10
2	100	24	84	8600	15100	1.19
3	200	24	82	17000	32900	1.24
4	400	24	75	30200	73400	1.24

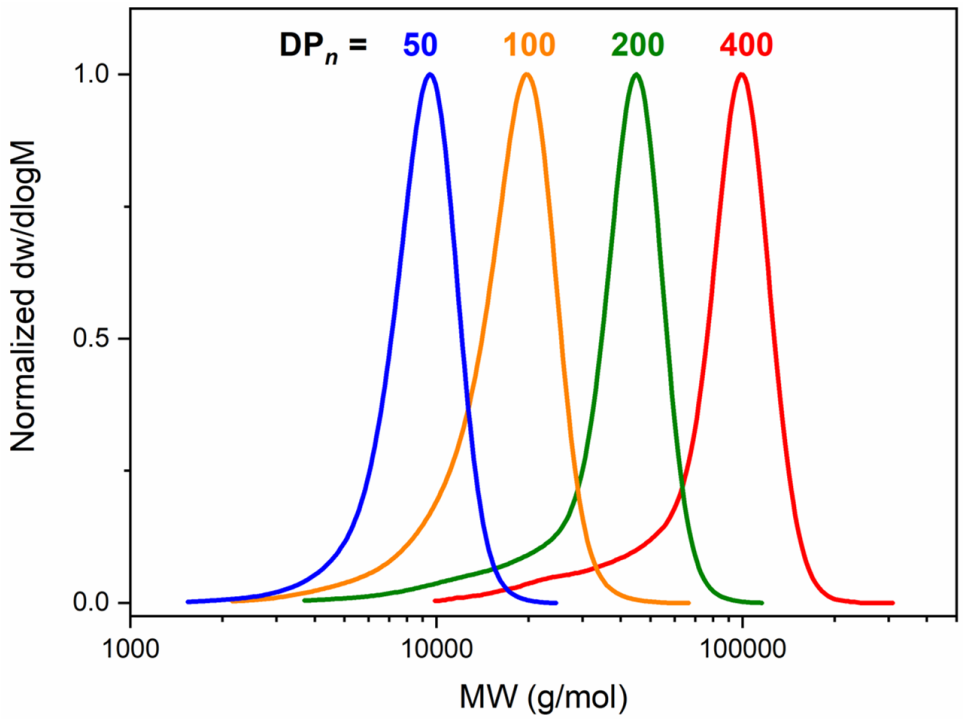


Figure 4.8: *SEC chromatograms of PMMA of different targeted degrees of polymerisation.*

4.2.6 Monomer Scope

A range of other methacrylates were also found to be compatible with these polymerisation conditions including ethyl methacrylate (EMA), benzyl methacrylate (BzMA), ethylene glycol methyl ether methacrylate (EGMA), poly(ethylene glycol methyl ether methacrylate) (PEGMA) and glycidyl methacrylate (GMA) (table 4.7, figure 4.9).

GMA is an important monomer as it allows for further post polymerisation modification; in this case conversion reached 99% furnishing the desired PGMA with a final dispersity of 1.10. Polymerisation of GMA exhibits similar control to that of MMA, despite the added chemical functionality of the epoxide group. This could be due to a previously reported synergistic effect of epoxide groups on copper mediated polymerisations.[48,49]

Table 4.7: *Polymerisation of various methacrylate monomers, target DP = 50 for all polymerisation. MBPA : Cu(II)Br$_2$: Me$_6$Tren; 1 eq. : 0.05 eq. : 0.18 eq.*

Entry	**Monomer**	**Time (hours)**	**Conv. (%)**	**$M_{n\ (Theo)}$ (Da)**	**$M_{n\ (SEC)}$ (Da)**	***Đ***
1	Ethyl methacrylate	24	95	5600	11700	1.13
2	Benzyl methacrylate	24	92	8300	10900	1.22
3	Glycidyl methacrylate	24	>99	7300	8800	1.10
4	Ethylene glycol methyl ether methacrylate	24	>99	7400	7000	1.18
5	Poly(ethylene glycol) methyl ether methacrylate	24	92	23200	36300	1.21
6	Butyl methacrylate	24	65	4700	9100	2.06

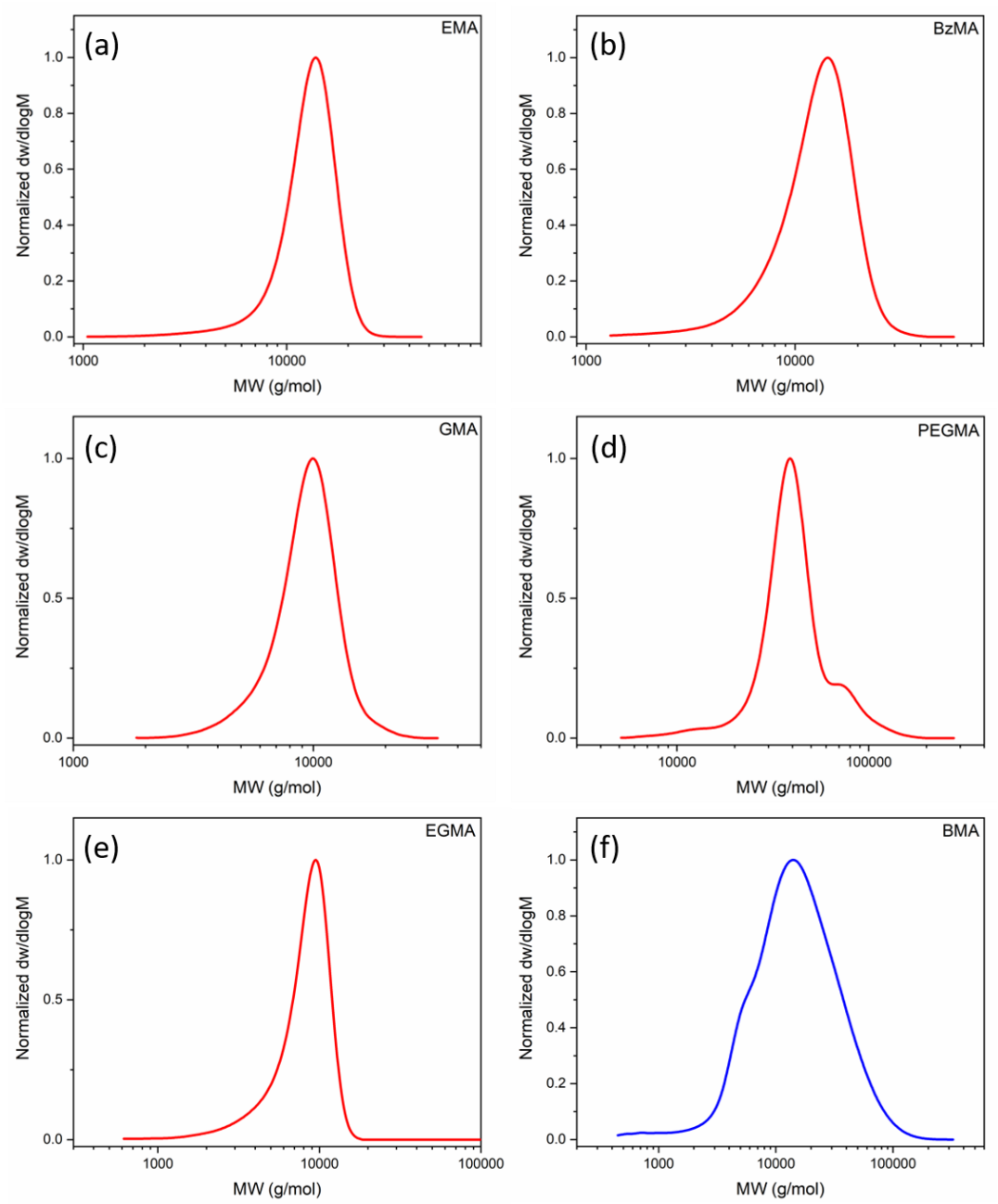


Figure 4.9: *SEC chromatograms for a range of methacrylate polymers synthesized under optimized conditions (table 4.7). Target DP of 50 for all polymerisations.*

The polymerisation of butyl methacrylate was attempted under identical conditions however the control of the polymerisation was found to be totally lacking ($Đ > 2$, figure 4.9 (f)). When stirring of the polymerisation was ceased it was noted there were two distinct phases in the reaction (figure 4.10, right): a polymer phase which was colourless (indicating low amounts of copper) and a green solvent phase containing monomer and copper catalyst. The concept of a self-generating biphasic polymerisation was first reported for Cu(0)-RDRP by Haddleton and Whittaker and coworkers in 2013.[17] In this work butyl acrylate (BA) was polymerised in DMSO

under similar conditions to the above polymerisation of BMA, except with EBiB as initiator instead of MBPA. The polymer was found to separate into a colourless phase (figure 4.10, left.) A distinction between the two systems can be seen in the control over the molecular weight distribution: poly(butyl acrylate) was furnished with dispersities around 1.2.

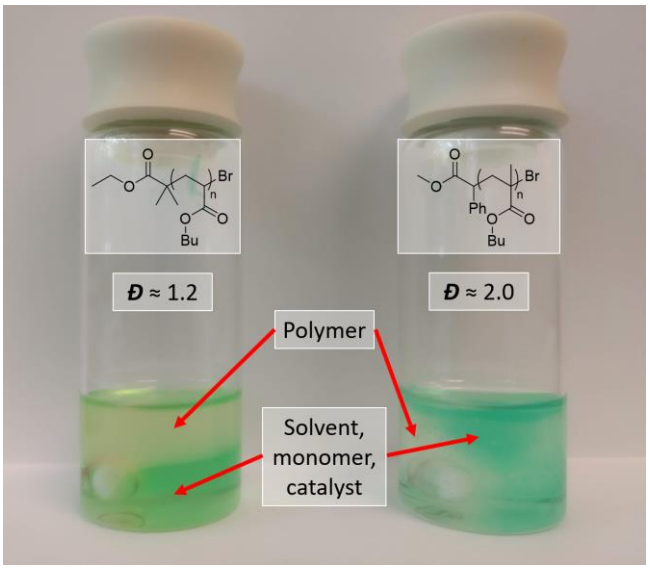


Figure 4.10: *Cu(0)-RDRP of butyl acrylate (left) and butyl methacrylate right) in DMSO, showing two distinct phases.*

Further work which resulted from the observation that Cu(0)-RDRP of hydrophobic methacrylates is uncontrolled in DMSO led to the discovery of a 'universal' set of conditions capable of polymerizing acrylates, methacrylates and styrene.[50] This system utilizes temperatures between 40-60 °C, isopropyl alcohol (IPA), and PMDETA to afford controlled polymerisation. Under these conditions poly(butyl methacrylate) is soluble in IPA and the control over molecular weight is good. It is postulated that the discrepancy between the polymerisation of BA and BMA in DMSO is due to the physical differences between the polymers: the T_g of PBMA is much higher than PBA, meaning that monomer cannot penetrate as easily and the surface area is lower because stirring cannot disperse the two phases as easily.

4.2.7 Chain extension and Block Copolymerisation

A key advantage of Cu(0)-mediated polymerisations is that upon reaching high conversions, chain extensions can be carried out *in-situ*, by addition of a second degassed aliquot of monomer. This avoids time consuming purification procedures and improves atom efficiency. It can also serve as a way to determine the end group

fidelity of the polymer. Poly(methacrylate) was synthesized under the optimized conditions and an *in-situ* chain extension of PMMA was attempted. Polymerisation of MMA was carried out with a targeted degree of polymerisation of 50. The conversion was determined to be 90% after 18 hours, at which point addition of a second aliquot of MMA (25 eq.) led to a complete shift of the molecular weight distribution after 18 hours while maintaining low dispersity (entries 1 & 2 table 4.8, figure 4.11), thus indicating high end group fidelity even at high monomer conversion.

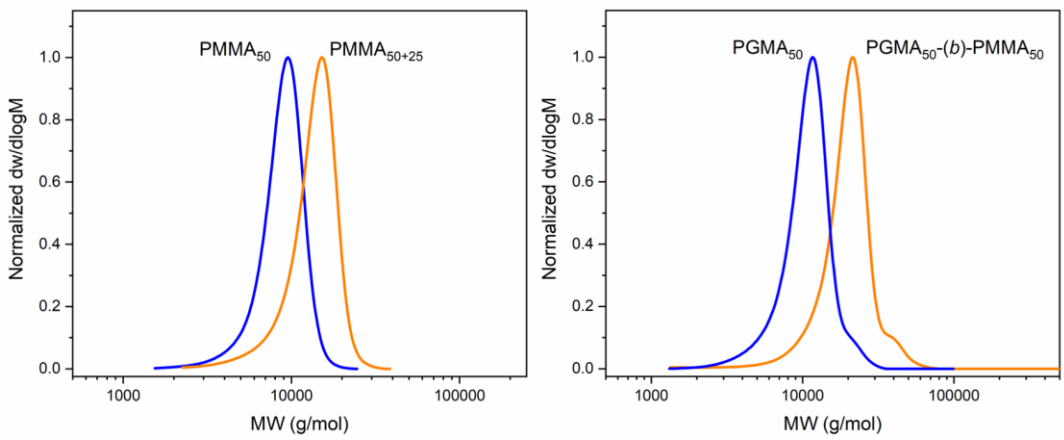
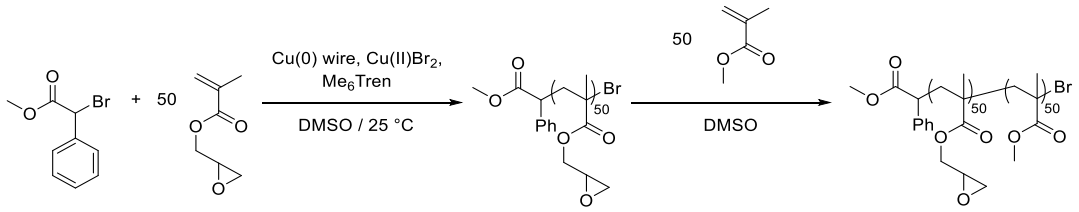


Figure 4.11: *SEC chromatograms of chain extension experiments; left: PMMA chain extended with MMA. Right: PGMA chain extended with MMA.*

Table 4.8: *Polymerisation and subsequent chain extension of methacrylates. Number in brackets in the target DP column indicates the DP of both blocks in total.*

Entry	**Monomer**	**Target DP_n**	**Time (hours)**	**Conv. (%)**	**$M_{n\ (Theo)}$ (Da)**	**$M_{n\ (SEC)}$ (Da)**	***Đ***
1	MMA	50	18	90	4700	8200	1.10
2	MMA	25 (75)	18	91	7700	12400	1.13
3	GMA	50	18	>99	8200	9800	1.16
4	MMA	50 (100)	24	90	13200	17400	1.18

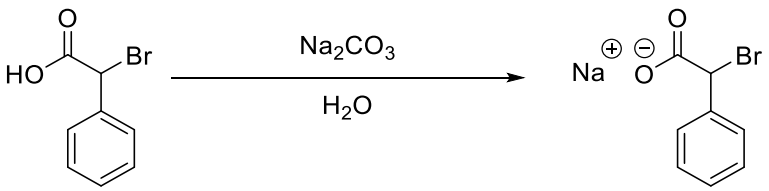
The ability of this synthetic protocol to synthesize block copolymers in a one-pot process was exemplified by polymerizing GMA (target DP_{50}) and subsequently chain extending with 50 eq. of MMA in DMSO (scheme 4.4), yielding a well-defined PGMA-PMMA diblock copolymer with M_n = 17400 g mol^{-1} and a final dispersity of 1.18 (entries 3 & 4, table 4.8.)



Scheme 4.4: *Block copolymerisation of glycidyl methacrylate and methyl methacrylate via in-situ chain extension.*

4.2.8 Cu(0)-RDRP of Methacrylates in Aqueous Media

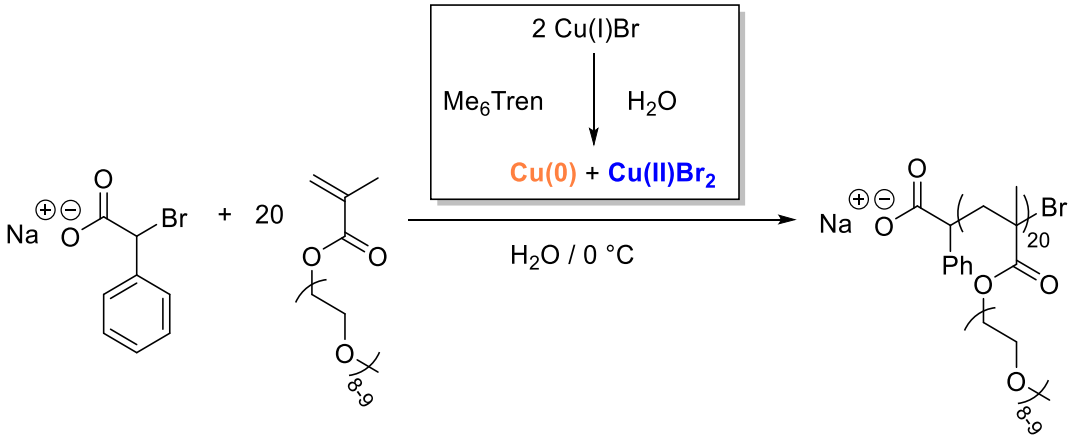
Highly controlled aqueous copper mediated polymerisation of methacrylates has been reported for a large number of systems; including activators regenerated by electron transfer (ARGET) ATRP,[51] initiators for continual activator regeneration (ICAR) ATRP,[52] Photo ATRP[53] and electro chemical ATRP (*e*ATRP).[54] Polymerisation of methacrylates in aqueous media *via* Cu(0) ATRP is much more challenging, with results to date showing a reasonably well controlled polymerisation but poor chain reinitiation, most likely due to poor end group fidelity.[38] Due to the promising advances made in organic media utilizing a phenyl acetate initiator as described in this chapter, a water soluble bromophenylacetate derivative was prepared and polymerisation of PEGMA was attempted *via* aqueous Cu(0)-RDRP (predisproportionation).



Scheme 4.5: *Synthesis of a water soluble bromophenyl acetate derivative for initiation of aqueous polymerisations.*

A water soluble bromophenylacetate initiator was initially targeted by esterification of solketal with bromophenyl acetic acid. However upon deprotection it was found that the dihydroxypropyl group was not sufficient to solubilize the initiator. Instead an approach was adopted whereby a base was used to neutralize the acid, forming a sodium salt. The acid itself is unsuitable as an initiator as it could lead to protonation of the tertiary amine ligand, Me_6Tren, thus poisoning the catalyst. Initial attempts using sodium hydroxide proved challenging due to a side reaction of nucleophilic substitution of the bromine by the hydroxide ion. A weaker base, sodium carbonate, was used instead to overcome this (scheme 4.5). The formation of the salt in aqueous

media occurs with the generation of carbon dioxide, leaving an aqueous solution of salt initiator with no side products.



Scheme 4.6: *Polymerisation of poly(ethylene glycol) methyl ether methacrylate via aqueous Cu(0)-RDRP.*

Polymerisation of PEGMA (scheme 4.6) under the standard reported conditions for aqueous Cu(0)-RDRP (0.4 :0.4 eq. of Cu(I)Br and Me_6Tren to initiator) yielded an uncontrolled polymerisation (entry 1, table 4.9.) The copper and ligand ratio then varied in a similar manner to the optimization of acrylamide polymerisation described in chapter 2. A twofold increase in Cu(I)Br concentration resulted in a much more controlled process (entry 2, table 4.9) with a final dispersity of 1.27. By increasing the ligand concentration to 0.6 equivalents polymerisation proceeded to high conversion (99%, entry 3, table 4.9) whilst maintaining a relatively narrow molecular weight distribution ($Đ$ = 1.30). It is important to note that the molecular weights obtained from SEC are drastically higher than the calculated theoretical values. This deviation cannot be attributed to the radius of gyration of these polymers as similar acrylate derivatives of PEG synthesized in chapter 3 generally have good agreement between theoretical and experimental values. It is more likely that the initiator efficiency of this reaction is very low. A reason for the low initiator efficiency could be that both the formation of the initiating radical and its associated radical-radical termination reaction is accelerated in aqueous media.

Table 4.9: *Aqueous Cu(0)-RDRP of PEGMA with varying catalyst concentration. Target DP = 20.*

Entry	**[I] : [Cu(I)Br] : [Me_6Tren]**	**Time (hours)**	**Conv. (%)**	**$M_{n\ (Theo)}$ (Da)**	**$M_{n\ (SEC)}$ (Da)**	***Đ***
1	1 : 0.4 : 0.4	20	91	9300	43200	2.15
2	1 : 0.8 : 0.4	20	97	9900	19200	1.27
3	1 : 0.8 : 0.6	20	99	10100	25200	1.30

Attempts at higher degrees of polymerisation to obtain high molecular weight P(PEGMA) in this system proved challenging, with dispersities greater than 2 in all cases, suggesting the limits of the system had been reached.

4.3 Conclusions

This work presents the a Cu(0) based system capable of controlled polymerisation of a range of hydrophobic, hydrophilic and functional methacrylates utilizing one set of conditions. It is demonstrated that appropriate choice of initiator is a vital parameter in controlling the Cu(0) mediated polymerisation of methacrylates, with a more active initiating species achieving a greater degree of control, as evidenced by narrow molecular weight distributions and pseudo-linear first order kinetics as observed by online monitoring with Near IR spectroscopy. Optimized conditions were also shown to be applicable to higher molecular weights and high end group fidelity could be maintained even at very high conversions (>99%), as exemplified by the *in-situ* chain extension of PGMA with MMA to form the desired block copolymer with low dispersity. Attempts to use a bromophenylacetate type initiator for aqueous Cu(0)-RDRP yielded very low initiator efficiency and limited molecular weight scope.

4.4 Experimental

4.4.1 Materials

Ethyl 2-bromopropionate (EBP), ethyl α-bromoisobutyrate (EBiB), methyl α-bromophenyl acetate (MBPA) and all other materials were purchased from Sigma Aldrich and used as received unless otherwise stated.

Tris[2-(dimethylamino)ethyl]-amine (Me_6Tren) was synthesized according to the procedure in chapter 2 and stored under nitrogen and refrigerated prior to use.

N,N,N′,N″,N″-pentamethyldiethylenetriamine (PMDETA) was purchased from Sigma Aldrich and distilled prior to use.

Cu(0) (gauge 0.25 mm) wire was purchased from Comax Engineered wires and was treated by immersion in 12 M HCl for 15 minutes followed by rinsing with water and acetone and dried prior to use.

4.4.2 Instrumentation

^{1}H NMR spectra were recorded on Bruker AV-300 MHz, HD-300 MHz and HD-400 MHz spectrometers at 25 °C using deuterated chloroform as the solvent.

SEC analysis was conducted on an Agilent 390-LC MDS instrument equipped with differential refractive index (DRI) and dual wavelength UV detectors. The system was equipped with 2 x PLgel Mixed C columns (300 x 7.5 mm) and a PLgel 5 μm guard column. The eluent was either THF with 2 % TEA (triethylamine) and 0.01 % BHT (butylated hydroxytoluene) additives run at 1 ml/min at 30 °C or DMF with 5 mmol NH_4BF_4 additive run at 1 ml/min at 50 °C. Poly(methyl methacrylate) (Agilent Polymethyl Methacrylate EasiVials between 550 and 1.5 million g mol^{-1}) and polystyrene standards (Agilent Polystyrene Medium EasiVials between 162 and 364,000 g mol^{-1}) were used for calibration and fitted with a second order polynomial. Analyte samples were filtered through a GVHP membrane with 0.22 μm pore size before injection. Respectively, experimental molar mass ($M_{n\ SEC}$) and dispersity ($Đ$) values of synthesized polymers were determined by conventional calibration using Agilent SEC software.

4.4.3 Experimental Procedures

Example Cu(0) mediated polymerisation of MMA in DMSO

Cu(II)Br_2 (8.4 mg, 0.037 mmol, 0.05 eq.) was charged to a 25 mL glass vial and dissolved in 4 mL of DMSO. MMA (4 mL, 37.4 mmol, 50 eq.) was added and MBPA (118 µL, 0.75 mmol, 1 eq.) was carefully transferred into the reaction vessel *via* microliter syringe. Concurrently, in a separate vial, a stirrer bar wrapped with 5 cm of copper wire was immersed in 37% HCl, stirred for 15 minutes, washed sequentially with water and acetone, and dried. The stirrer bar was then placed into the reaction vessel, sealed with a rubber septum, and degassed by bubbling with nitrogen for 15 minutes in an oil bath at 25 °C. After this time a degassed aliquot of Me_6Tren (36 µL, 0.13 mmol, 0.18 eq.) was injected into the vial *via* microliter syringe. The reaction was left to proceed overnight and samples were taken and analysed *via* ^{1}H NMR (figure 4.12) and SEC.

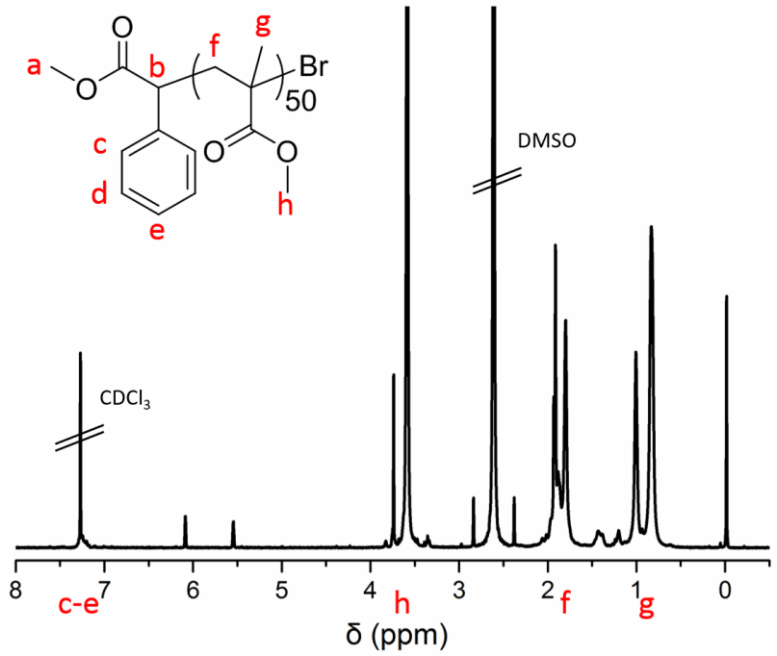


Figure 4.12: *Crude ^{1}H NMR spectra of PMMA synthesized with MBPA initiator 400 MHz, $CDCl_3$.*

Example of Cu(0) mediated polymerisation of MMA in DMSO with online FT-NIR monitoring

Cu(II)Br_2 (16 mg, 71 µmol, 0.05 eq.) was charged to a 25 mL Schlenk tube and dissolved in 7.5 mL of DMSO. MMA (7.5 mL, 71 mmol, 50 eq.) was added and Me6Tren (68 µL, 0.25 mmol, 0.18 eq.) was added *via* microliter syringe. Finally, MBPA (223 µL, 1.41 mmol, 1 eq.) was added. Concurrently, in a separate vial, a stirrer bar wrapped with 10 cm of copper wire was immersed in 37% HCl, stirred for 15 minutes, washed sequentially with water and acetone, and dried. The stirrer bar was

then placed in the Schlenk tube, suspended above the reaction mixture using a magnet (figure 4.13 (a)). The Schlenk tube was sealed using a ground glass stopper fitted with a septum through which the fibre optic FT-NIR probe was fitted. The reaction mixture was then degassed by three freeze-pump-thaw cycles, placed into an oil bath at 25 °C and the magnet removed, resulting in the stirrer bar dropping into the monomer/DMSO mixture and the reaction starting (figure 4.13 (b)). Online monitoring of polymerisations *via* Fourier transform near-infrared (FT-NIR) spectroscopy was conducted on a Bruker vector 22/N-F spectrometer equipped with a HELLMA fibre-optic probe (3 mm) with 64 scans performed sequentially every 30 minutes between 6000 and 6300 wavenumbers. Conversions were calculated *via* integration of the γ(=CH2) absorption peak (6170 cm^{-1}), in comparison to the integration at time zero.

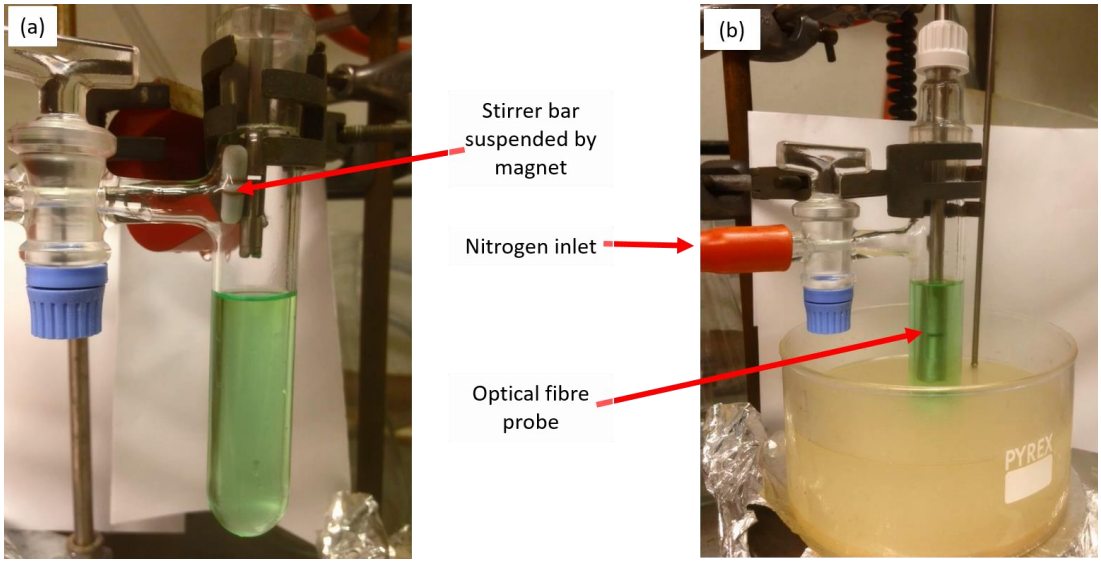


Figure 4.13: *Experimental set up for in-situ monitoring of polymerisations. (a) Reaction during free-pump-thaw procedure prior to polymerisation: stirrer bar suspended with magnet. (b) Reaction set up during polymerisation: NIR probe in submerged in the solution, stirrer bar has been dropped in the solution and the Schlenk tube is under an inert atmosphere.*

Block copolymerisation of PGMA-PMMA

Cu(II)Br_2 (5.6 mg, 0.025 mmol, 0.05 eq.) was charged to a 25 mL glass vial and dissolved in 4 mL of DMSO. GMA (4 mL, 24.9 mmol, 50 eq.) was added and MBPA (78.6 μL, 0.75 mmol, 1 eq.) was carefully transferred into the reaction vessel *via* microliter syringe. Concurrently, in a separate vial, a stirrer bar wrapped with 5 cm of copper wire was immersed in 37% HCl, stirred for 15 minutes, washed sequentially with water and acetone, and dried. The stirrer bar was then placed into the reaction

vessel, sealed with a rubber septum, and degassed by bubbling with nitrogen for 15 minutes in an oil bath at 25 °C. After this time a degassed aliquot of Me_6Tren (24 µL, 0.09 mmol, 0.18 eq.) was injected into the vial *via* microliter syringe. The reaction was left to proceed for 18 hours and samples were taken and analysed *via* ^{1}H NMR and SEC (>99%, M_n = 9800 Da, $Đ$ = 1.16). A degassed solution of MMA (2.67 mL, 24.9 mmol, 50 eq.) in DMSO (2.67 mL) was then transferred into the reaction vial *via* deoxygenated syringe. After 24 hours the reaction was sampled and analysed (90% conversion, M_n = 9800 Da, $Đ$ = 1.18).

Example polymerisation of PEGMA via aqueous Cu(0)-RDRP

H_2O (2 mL) and Me_6Tren (17.7 µL, 66.1 µmol, 0.6 eq.) were charged to a 25 mL Schlenk tube with a magnetic stirrer bar and a rubber septum. The solution was deoxygenated by bubbling with nitrogen for 2 minutes. Cu(I)Br (12.6 mg, 88.1 µmol, 0.8 eq.) was added with rapid stirring, disproportionation was seen to occur after a few seconds. The disproportionated solution was placed in an ice bath and deoxygenated for a further 15 minutes. Simultaneously, a vial was charged with sodium bromophenylacetate (26.1 mg, 110 µmol, 1 eq.), poly(ethylene glycol) methyl ether methacrylate (M_n = 500) (1 mL, 2.2 mmol, 80 eq.) and 7 mL of H_2O. The vial was fitted with a septum, stirred and deoxygenated with nitrogen in an ice bath for 15 minutes. Subsequently the degassed monomer/initiator solution was transferred into the Schlenk tube containing the disproportionated solution *via* degassed syringe. The polymerisation mixture was allowed to react for 15 minutes, after which a sample (~0.1 mL) was taken for analysis. The sample for SEC was filtered through a plug of neutral alumina to remove catalyst residues prior to analysis. The sample for ^{1}H NMR analysis was diluted with D_2O. Monomer conversion was calculated by comparison of vinyl protons with the methyl ether protons. Conversion >99%, $M_{n\,(SEC)}$ 25200 Da, $Đ$ = 1.30.

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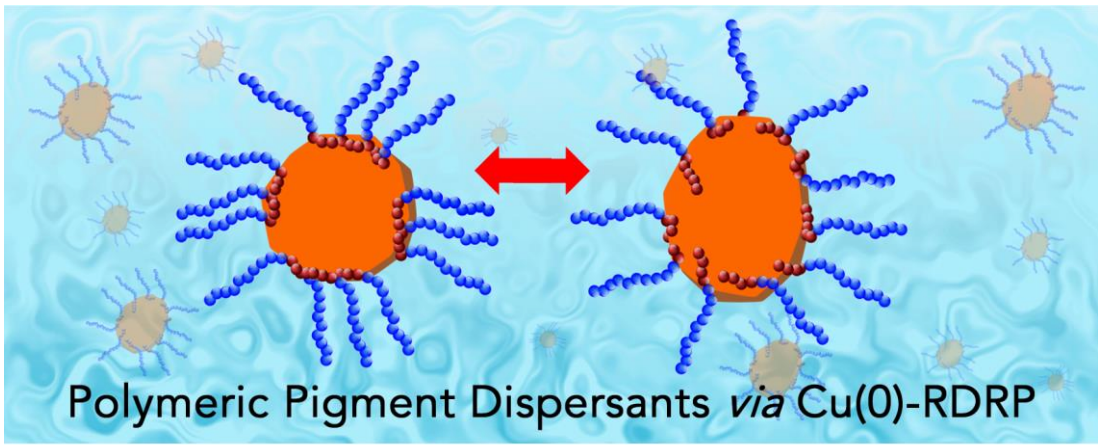
Chapter 5: Pigment Dispersants for Waterborne Coatings *via* Reversible Deactivation Radical Polymerisation



5.1 Introduction

Prior to 1950 almost all commercially available coatings were solventborne. The introduction of latex architectural paints was the first major step towards adoption of waterborne coatings. A number of driving forces has pushed the coatings industry towards more waterborne coatings: they are easier to clean up, often exhibit better performance, and have reduced hazards relative to solventborne systems. In more recent years the trend towards waterborne coatings has been further driven by efforts to reduce the volatile organic compounds (VOC) content of coatings in order to comply with increasingly stringent United States (US) and European Union (EU) regulations. Water presents no toxicity hazards, is odourless and non-flammable. In addition to this there are no disposal problems. Economically, water is the cheapest solvent to use for a process and associated decreases in insurance costs and permits/licences further reduces costs.

Pigment dispersion is the process of breaking up pigment particles and dispersing them in liquid (water in the case of waterborne coatings). These liquid concentrates of dispersed pigments are known as mill bases, which are then mixed with resins and other ingredients and additives to form a coating. High quality dispersions are a key requirement for good colourfastness and high gloss in the final coating.[1] The process of pigment dispersion can be broken down into 3 steps, as shown in figure 5.1.

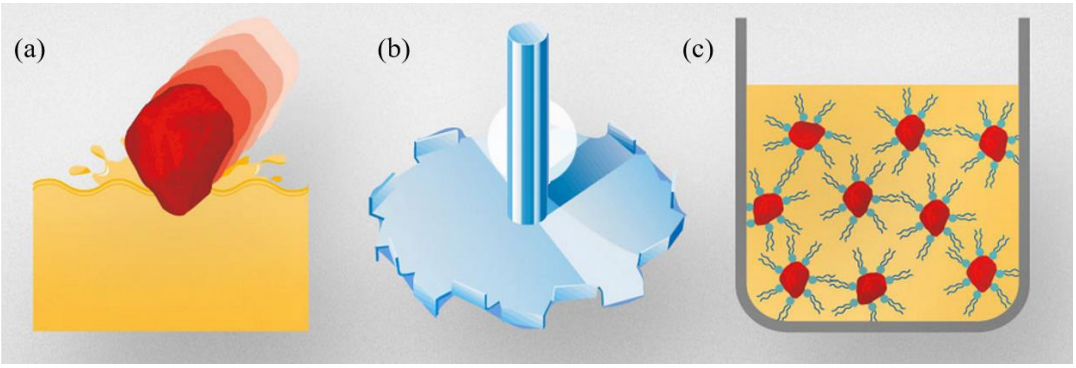


Figure 5.1: *Steps to achieving pigment dispersion: (a) pigment wetting, (b) milling, (c) stabilization.*

The first step, shown in figure 5.1 (a), is called pigment wetting. This is the process of the displacement of air and moisture on the surface of pigment particles with the dispersing medium. The high surface tension of water combined with the hydrophobicity of many organic pigments means that wetting can sometimes be

problematic in waterborne systems. Wetting agents and surfactants are sometimes used to help overcome this.

The second step in pigment dispersion is milling, sometimes called separation. Pigments are manufactured in such a way as to give a particle size distribution which strikes a balance between various properties. These particles can often become fused together into aggregates during processing. Milling is the process of inputting mechanical energy (represented by a high-shear mixer in figure 5.1 (b)) in order to separate aggregates of pigments into primary particles. Bead mills, which utilize the shear forces generated by the movement of ceramic or zirconium beads are often used to mill pigments to their primary particle size.

Stabilization (figure 5.1 (c)) is the means of maintaining a dispersion. If a dispersion is not stabilized, pigments particles will be attracted to each other and undergo a process known as flocculation. Similar to aggregation, this leads to larger particle sizes which in turn will reduce colour strength and gloss.[2] There are two mechanisms for stabilization of a pigment dispersion: electrostatic repulsion and steric repulsion. Electrostatic repulsion works by introducing charge at the pigment particle surface which leads to particles repelling each other hence preventing flocculation. Steric repulsion is achieved through use of a polymeric pigment dispersion: polymer chains around the pigment particle provide steric bulk to prevent flocculation as shown in figure 5.2. Although electrostatic mechanisms of repulsion can be important in aqueous millbases the work in this chapter will focus on the synthesis of mainly non-ionic dispersants, as anionic dispersants have been shown to stabilize foam formation, which can lower the quality of a coating.[2]

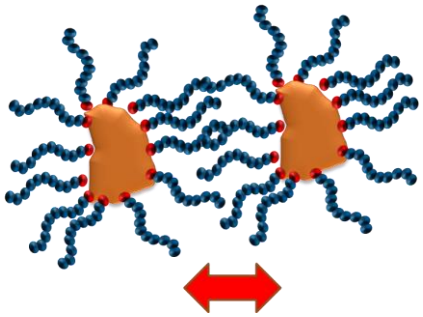


Figure 5.2: *Steric repulsion between two pigment particles with polymeric dispersant.*

Polymeric pigment dispersants typically have a segmented structure containing both functional groups which bind to the pigment particles (pigment affinic groups), and

polymeric chains which are readily soluble in the dispersing media. Dispersants can have a range of different macromolecular architectures, some common examples of which are shown in figure 5.3. Changing the degree of polymerisation of each block allows for fine tuning of pigment affinity and solubility of the dispersing medium. The amphiphilic nature of many of these polymeric structures also aid in the wetting stage of dispersion by acting in a similar way to a surfactant.

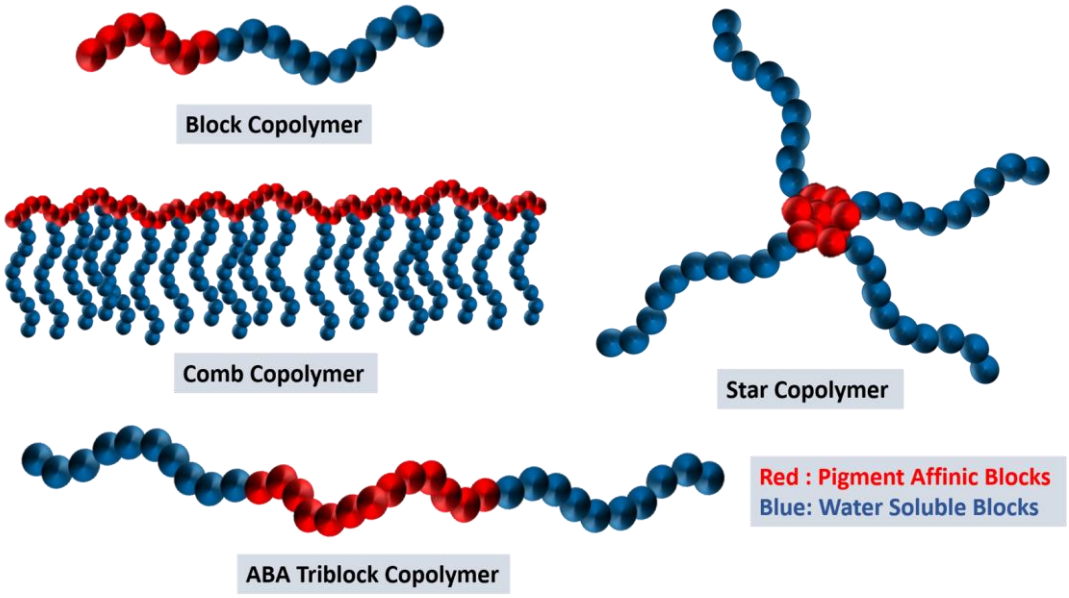


Figure 5.3: *Examples of macromolecular architectures used in polymeric pigment dispersants for waterborne coatings. Pigment affinic groups are shown in red and water soluble blocks in blue.*

Well defined block copolymers and other higher order macromolecular architectures were traditionally only accessible *via* anionic polymerisation methods, which requires stringent reaction conditions and has limited applicability to functionalized (meth)acrylic monomers. The advent of reversible-deactivation radical polymerisation (RDRP) techniques such as atom transfer radical polymerisation (ATRP)[3] and nitroxide mediated polymerisation (NMP)[4] has allowed for the synthesis of complex functional macromolecular architectures under much less stringent conditions and has accordingly been utilized to synthesize a range of different polymeric pigment dispersants. Retention of active chain ends after polymerisation has reaches high conversions allows for the facile preparation of block copolymer architectures through sequential addition of monomers.

In a 2002 report by Auschra and coworkers block copolymers of butyl acrylate (BA) and dimethylaminoethyl acrylate (DMAEA) were synthesized by NMP and used to

disperse Pigment Red 254 in a solvent mill base.[5] It was found that addition of the block copolymer gave improved gloss of the final cured coating as well as dramatically reduced flocculation. In this case the tertiary amine of the second block is able to interact with the pigment surface through hydrogen bonding and acid-base interactions. The butyl acrylate block is soluble in the dispersing media and acts as the steric stabilization chain.

ATRP has been used to prepare amphiphilic triblock copolymers by Lokhande and Jagtap.[6] Triblocks comprised of butyl acrylate, hydroxyethyl methacrylate and methyl methacrylate were modified with cyclic ethylene chlorophosphate and triethylamine to give a centre block of zwitterionic polymer. These charged polymers were then used to disperse a yellow pigment in water. It was found that the polymers act as an efficient wetting agent and dispersant which provide improved optical properties of resultant coatings.

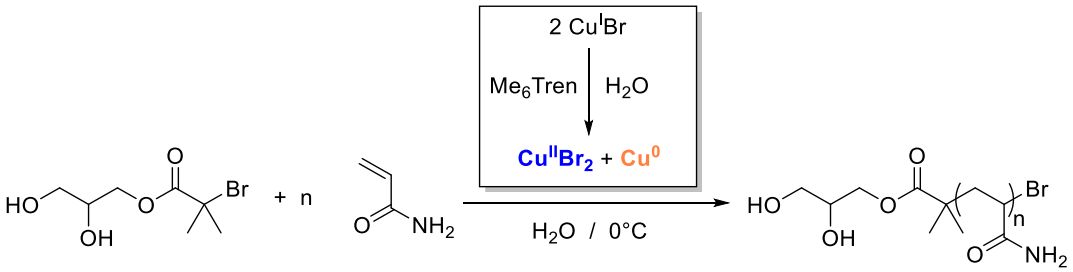
5.2 Acrylamide Block Copolymers – Results and Discussion

Polyacrylamides are a group of polymers of which many are very water soluble due to the presence of a high number of amide bonds. These amide groups are also responsible for the high glass transition temperatures (T_g) of many polyacrylamides. Free radical polymerisation of acrylamides usually results in molecular weights on the order of 10^6 Da. This is due to the very high K_p of acrylamides, which has been reported to be over two orders of magnitude higher than methacrylates.

Polymeric pigment dispersants for waterborne coatings based on acrylamide architecture could be beneficial due to their high water solubility and high T_g. High water solubility means that polyacrylamides could act as good steric stabilization chains in aqueous mill bases. The high glass transition means that coatings won't be softened by the presence of the dispersant, which can be problematic when using aqueous stabilization chains such as polyethers, which typically have low T_g's.

However, synthetic limitations of acrylamide polymerisation have limited the exploration of these materials as aqueous pigment dispersants. The high K_p means that is it relatively difficult to prepare low molecular weight polymers. This is problematic as high molecular weight polyacrylamides are commerically used as flocculating agents[7,8]: the complete opposite effect to that which is desired from a pigment dispersant.

5.2.1 Acrylamide block copolymer synthesis



Scheme 5.1: *Homopolymerisation of acrylamide by aqueous Cu(0)-RDRP via predisproportionation of Cu(I)Br with Me_6Tren, as optimized in chapter 2.*

An optimization of the polymerisation of acrylamide by aqueous Cu(0)-RDRP (scheme 5.1) is detailed in full in chapter 2. Well defined polyacrylamide can be prepared with quantitative monomer conversion (>99% by NMR), with excellent control over molecular weight distributions.[9] In addition, *in-situ* chain extension

experiments proved that end group fidelity was very high, and as a result well defined hydrophilic block copolymers could be prepared in a one pot process.

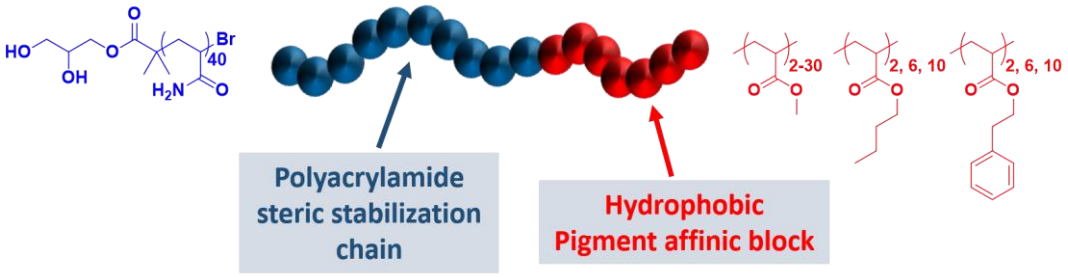


Figure 5.4: *Design of block copolymer dispersants from polyacrylamide synthesized by aqueous Cu(0)-RDRP.*

In order to synthesize an effective block copolymer pigment dispersant from polyacrylamide the second block must contain pigment affinic groups. Pigment affinic groups include hydrophobic and aromatic groups. With this in mind *in-situ* chain extension of polyacrylamide (target DP = 40) was attempted with methyl acrylate, butyl acrylate and phenylethyl acrylate.

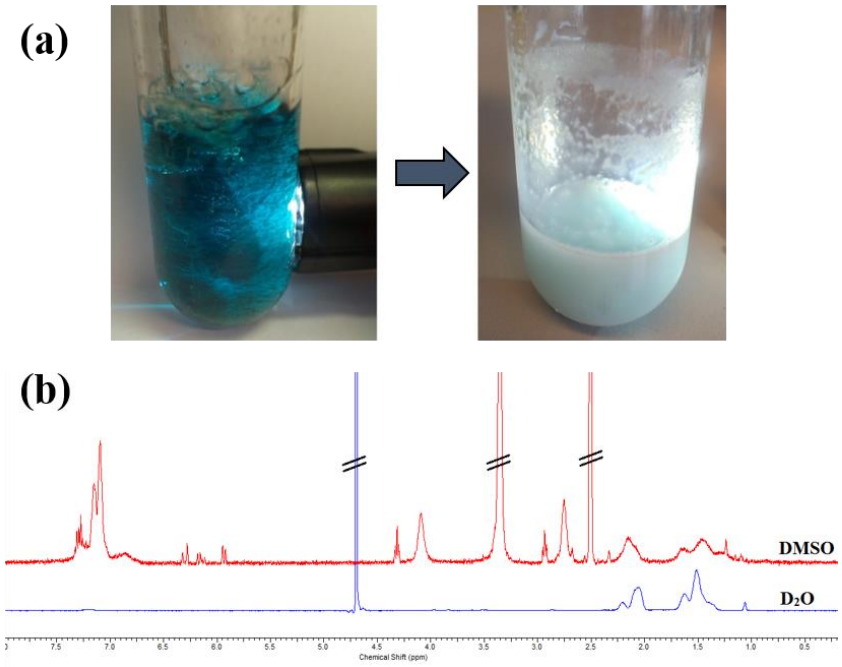


Figure 5.5: *(a) reaction before and after addition of hydrophobic monomer (PhEA), (b) NMR of resultant polymer in DMSO-d_6 and D_2O.*

Characterization of the materials prepared through reaction of these hydrophobic monomers with polyacrylamide was challenging due to their amphiphilic nature, figure 5.5 (a) shows the polymerisation before and after the addition of the

hydrophobic monomer phenylethyl acrylate. SEC characterization proved impossible as the copolymers were not fully soluble in any solvent. Figure 5.5 (b) shows typical ^{1}H NMR's for a phenylethyl acrylate block copolymer. When D_2O is used as the solvent the NMR spectrum shows only polyacrylamide, whereas DMSO-d_6 shows only poly(phenylethyl acrylate), indicative of self-assembly.

5.2.2 Milling Tests

Table 5.1: *Particle sizes for acrylamide block copolymer dispersants from milling with Raven 5000 Ultra carbon black pigment.*

Entry	Polymer Dispersant	D_{50} (nm)	D_{90} (nm)	z-average (nm)
1	*blank*	711	818	1604
2	$P(Am)_{40}$	512	618	420
3	$P(Am)_{40}$-$P(MA)_2$	298	488	141
4	$P(Am)_{40}$-$P(MA)_6$	194	431	84
5	$P(Am)_{40}$-$P(MA)_{10}$	204	310	215
6	$P(Am)_{40}$-$P(MA)_{20}$	176	309	169
7	$P(Am)_{40}$-$P(MA)_{30}$	227	391	229
8	$P(Am)_{40}$-$P(BA)_2$	640	874	399
9	$P(Am)_{40}$-$P(BA)_6$	568	705	411
10	$P(Am)_{40}$-$P(BA)_{10}$	763	1020	436
11	$P(Am)_{40}$-$P(PhEA)_2$	1070	1290	863
12	$P(Am)_{40}$-$P(PhEA)_6$	1020	1260	825
13	$P(Am)_{40}$-$P(PhEA)_{10}$	493	579	1077

Milling tests were performed by mixing polymeric dispersant, water, glass beads and Raven 5000 Ultra carbon black pigment. After being milled for 16 hours on a low frequency horizontal shaker the samples were diluted and pigment particle size was determined by dynamic light scattering (DLS). Interestingly, the particle size data in table 5.1 indicated that the smallest pigment particle size (and hence the best

dispersions) were achieved using polyacrylamide-poly(methyl acrylate) block copolymers, followed by butyl and then phenylethyl. It is expected that aromatic groups should be the most pigment affinic and hence give the best dispersions, opposite to what is actually found.

The reason for the unexpected result of block copolymers containing strongly hydrophobic or aromatic groups not efficiently dispersing pigment if most likely due to the poor solubility of the second block. It is well known that amphiphilic block copolymers will aggregate in aqueous media to form polymeric micellar structures due to association of the hydrophobic block.[10] In a 2010 review by Nicolai, Colombani, and Chasseniux,[11] it is explained that for many cases in aqueous media the exchange between unimer (a single polymer chain) and micelle is almost imperceptibly slow. In such cases it is proposed that polymeric nanoparticle is a better descriptor than polymeric micelle. One of the factors that governs unimer exchange is the interfacial tension between the hydrophobic block and water. This is expected to be higher (and hence have a higher energy barrier to exchange) in more hydrophobic blocks.[12] In terms of pigment dispersion the lack of significant unimer exchange means that the hydrophobic block will never actually 'see' the surface of the pigment, as it is shielded by the polyacrylamide corona of the formed nanoparticle.

5.2.3 Further Synthesis of Block Copolymer

A series of water soluble block copolymers were synthesized in order to test the hypothesis that soluble copolymers would provide better dispersion due to the pigment affinic block being more available at the surface of the pigment. Poly(acrylamide)$_{40}$ was chain extended with 10, 20, and 30 equivalents of *N*-acryloylmorpholine (NAm)[13] and the resultant block copolymers were milled with Raven 5000 Ultra carbon black in an identical manner to the previous experiments.

Table 5.2: *Particle sizes for acrylamide-acryloylmorpholine block copolymer dispersants from milling with Raven 5000 Ultra carbon black pigment.*

Entry	Polymer Dispersant	D_{50} (nm)	D_{90} (nm)	z-average (nm)
1	$P(Am)_{40}$-$P(NAm)_{10}$	269	389	258
2	$P(Am)_{40}$-$P(NAm)_{20}$	231	341	221
3	$P(Am)_{40}$-$P(NAm)_{40}$	211	372	201

The z-average particle size for these dispersions are all much lower than those of the phenylethyl acrylate block copolymers, further suggesting that solubility of a polymeric dispersant is key to achieving efficient dispersion.

5.3 Molecular Weight Distribution and Dispersion – Results and Discussion

Although RDRP is undoubtedly a very useful technique for the synthesis of polymeric pigment dispersants due to its ability to synthesize well-defined macromolecular architectures, the effect of molecular weight distribution on pigment dispersion is relatively unexplored.

In a free radical polymerisation initiating radicals are formed throughout the reaction usually through thermal or photolytic decomposition of peroxide or azo compounds. Due to this continued formation of radicals the radical concentration is relatively high. As a result of this many termination and chain transfer events can occur, giving a broad molecular weight distribution, as represented in figure 5.6. In a controlled radical polymerisation all polymer chains initiate at the start of the reaction and radical concentration is kept low by a predominance of dormant states. As a result of this all chains have very similar probability of propagating with monomer, hence chains are similar in length, giving a narrow molecular weight distribution.

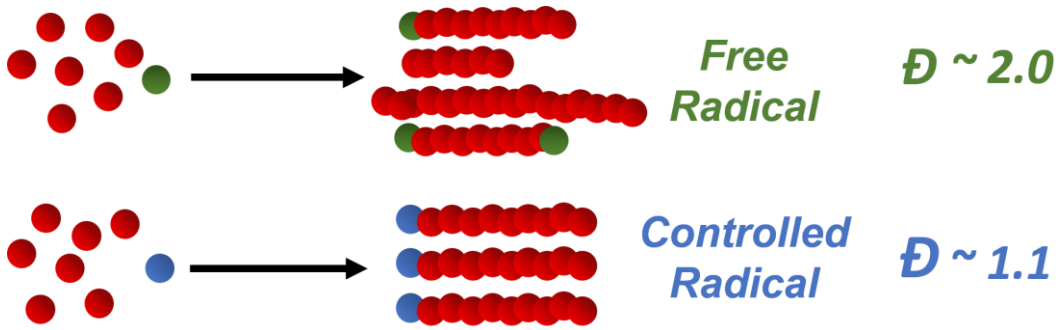


Figure 5.6: *Cartoon representations of initiation in free radical and controlled radical polymerisation and its effect on molecular weight distribution.*

In 2016 Fors and coworkers introduced a simple method of manipulating the shape and breadth of the molecular weight distribution obtained from a controlled polymerisation.[14] Feeding the initiator (in the case of ATRP and anionic polymerisation[15]) or CTA (RAFT) or nitroxide (NMP) means that the first molecule to reach the reaction will have a longer time to react (propagate) than the last molecule. This means that not all chains have the same probability of reacting with monomers and therefore a range of molecular weights are obtained (figure 5.7). Slower feeding rates result in broader molecular weight distributions.

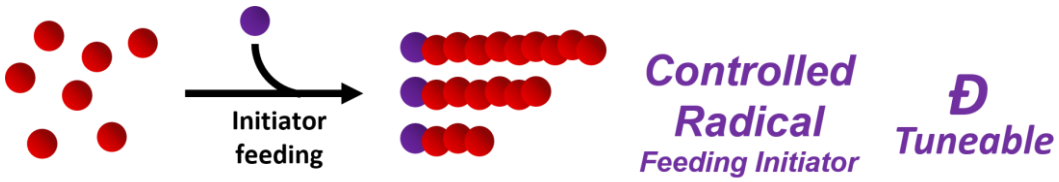
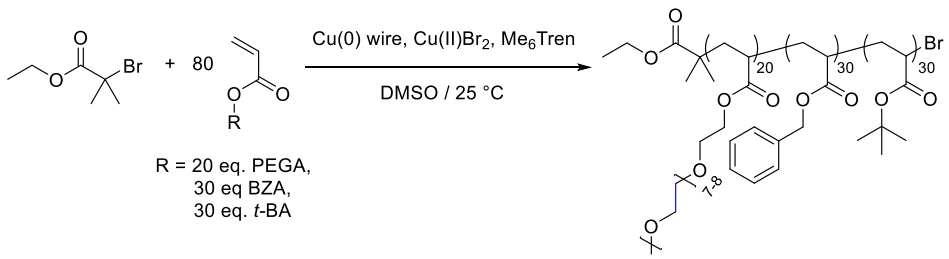


Figure 5.7: *Cartoon representation of controlled radical polymerisation with initiator feeding.*

5.3.1 Design of a model polymeric dispersant

In order to investigate the effect of molecular weight distribution on pigment dispersion it was necessary to design a synthesis of a model polymeric pigment dispersant. It was decided that the dispersion tests would focus on dispersing a carbon black pigment in aqueous media. For this reason the pigment affinic groups should contain aromatic groups and a charged species to give good pigment affinic properties. In terms of molecular architecture a comb type dispersant was chosen because they can be prepared by a relatively simple one step polymerisation procedure and are well known to act as efficient dispersants. If a block copolymer was chosen then further complications would arise: both blocks have an associated dispersity, e.g. the first block could be essentially monodisperse whereas the second block could be polydisperse and vice versa. By copolymerizing PEGA (an acrylate functionalized with a low dispersity PEG chain) with BzA and *t*BA a model comb type dispersant can be prepared. Cu(0)-RDRP of PEGA (20 eq.), BzA (30 eq.) and *t*BA (30 eq.), proceeded to high conversion (>99%) with excellent control over molecular weight ($Đ$ = 1.13, figure 5.8, scheme 5.2).



Scheme 5.2: *Polymerisation of PEGA, BzA and tBA to give a comb type pigment dispersant.*

A comparison of the vinyl protons by ^{1}H NMR as polymerisation progressed (figure 5.9) revealed that the consumption of each monomer is equal throughout (the ratio between the integrations remains constant). This confirms that the polymerisation is essentially random, and therefore the resultant polymer has comb architecture with water soluble PEG chains distributed along the polymer backbone.

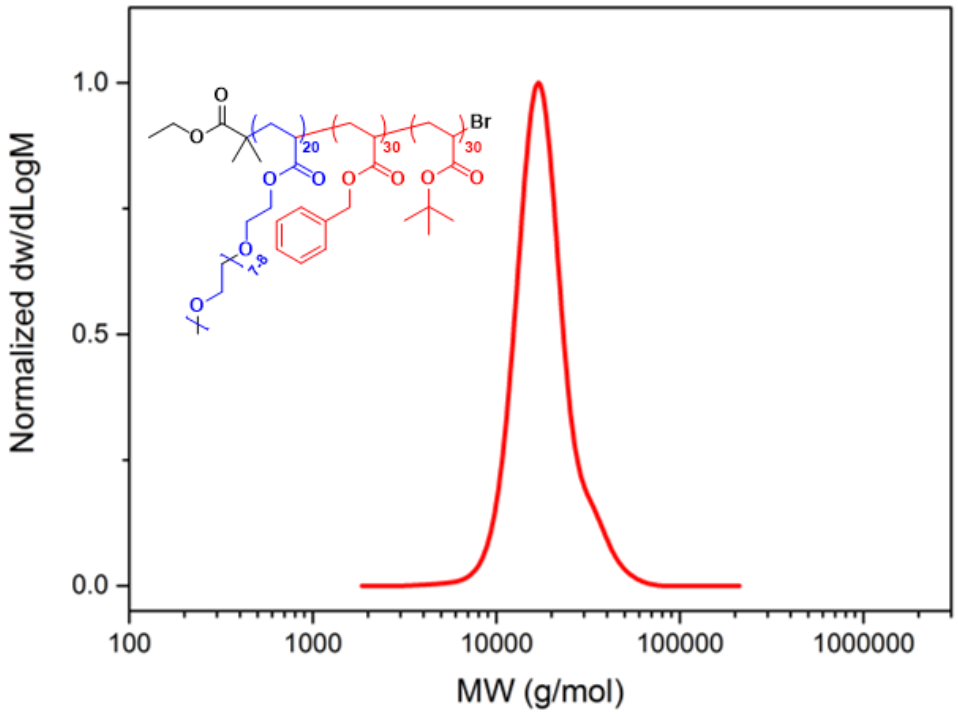


Figure 5.8: *SEC chromatogram of copolymerisation of PEGA, BZA and tBA.*

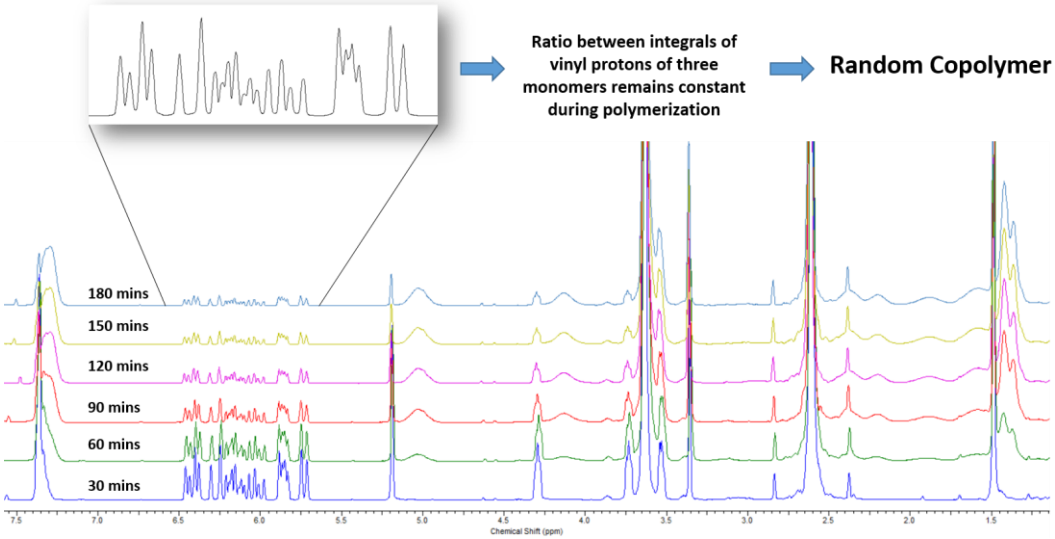


Figure 5.9: *^{1}H NMR spectra as polymerisation progresses showing equal consumption of all 3 monomers.*

5.3.2 Tailoring molecular weight distribution

The polymerisation was repeated with slow addition of initiator. A syringe pump was used to feed a stock solution of initiator over a predetermined time. Table 5.3 shows that the conversion of each fed polymerisation reached >99% monomer conversion within 6 hours. M_n, as determined by SEC remained between 15000-18800 Da. It can be seen that increasing the time over which initiator is added increases the dispersity of the polymer.

Table 5.3: *Copolymerisation of PEGA, BzA, and tBA with different rates of initiator feeding.*

Entry	**Addition Time (hours)**	**Time (hours)**	**Conv. (%)**	**$M_{n\ (Theo)}$ (Da)**	**$M_{n\ (SEC)}$ (Da)**	***Đ***
1	***Instant***	24	>99	18500	16700	1.13
2	**1**	24	>99	18500	15900	1.19
3	**2**	24	>99	18500	15000	1.33
4	**3**	24	>99	18500	16800	1.50
5	**4**	24	>99	18500	16400	1.68
6	**5**	24	>99	18500	17700	1.84
7	**6**	24	>99	18500	18800	2.00

Figure 5.10 shows the molecular weight distributions of the polymers as measured by SEC in THF. As feeding time is increased the M_p increases and the molecular weight distribution broadens. The shape of the molecular weight distributions tail to the low molecular weight region, which is in agreement with similar experiments conducted by Fors and coworkers on nitroxide mediated and anionic polymerisation of styrene.[14] The relationship between dispersity (*Đ*) and addition time is linear, as shown in figure 5.11.

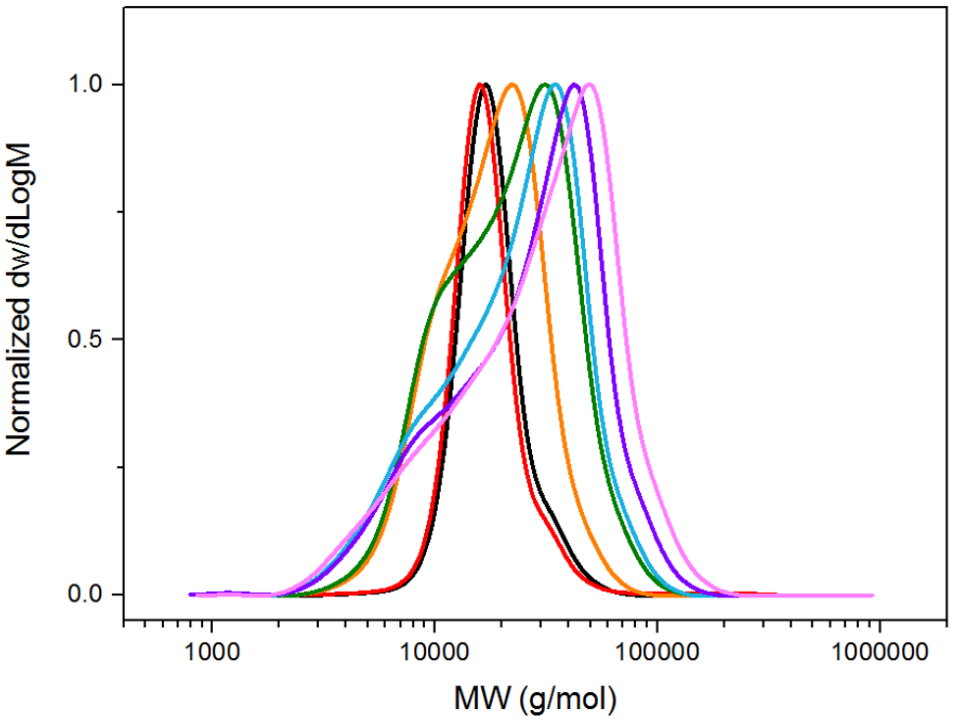


Figure 5.10: *SEC chromatograms of initiator fed polymerisations (table 5.3).*

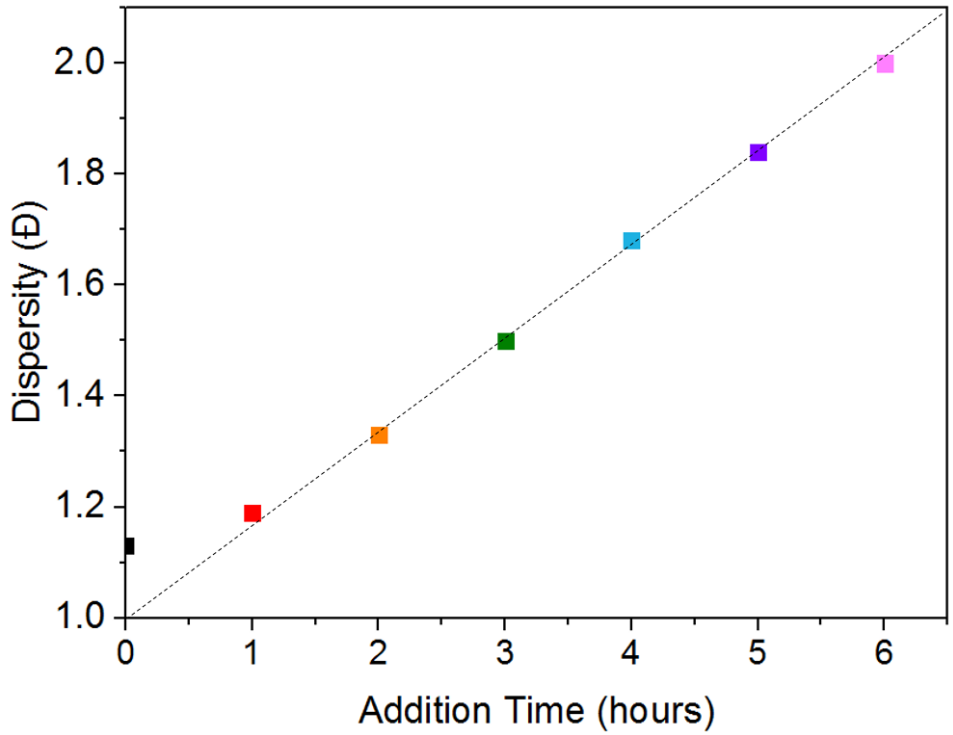


Figure 5.11: *Plot of dispersity (Đ) vs. addition time of initiator.*

5.3.3 Milling Tests

Table 5.4: *Polymers used in milling tests.*

Entry	Ref.	[I] : [PEGA] : [BzA] : [*t*BA]	Time (hours)	Conv. (%)	$M_{n\ (SEC)}$ (Da)	$M_{w(SEC)}$ (Da)	*Đ*
1	**A**	1 : 20 : 30 : 30	24	>99	23200	26500	1.13
2	**B**	1 : 40 : 60 : 60	24	>99	45000	53900	1.18
3	**C**	1 : 20 : 30 : 30	24	>99	27400	34300	1.27
4	**D**	1 : 20 : 30 : 30	24	>99	18800	36100	1.94
5	**E**	1 : 20 : 30 : 30	24	>99	15200	52400	3.49

Table 5.4 shows the polymers synthesized to be used in milling tests with carbon black pigments. Entry 1 represents a polymer of relatively low M_n (23200 Da by SEC) with a narrow molecular weight distribution (*Đ* = 1.13). Entry two was synthesized in a similar manner, with twice the targeted molecular weight (M_n = 45000, *Đ* = 1.18). entries 3-5 in table 5.4 are polymerisations carried out with initiator feeding to broaden the molecular weight distribution (feeding times 1.5, 6, and 12 hours).

Figure 5.12 shows the molecular weight distributions of these polymers as measured by size exclusion chromatography (SEC) in tetrahydrofuran (THF). Combined with the molecular weight data in table 5.4 it becomes clear that many points of comparison can be drawn between the polymer samples which should allow for differentiation between different molecular weight parameters when testing their efficacy as pigment dispersants. For example, entry 1 (red) and entry 2 (green) both have similar *Đ* but entry 2 has an M_n around twice as high.

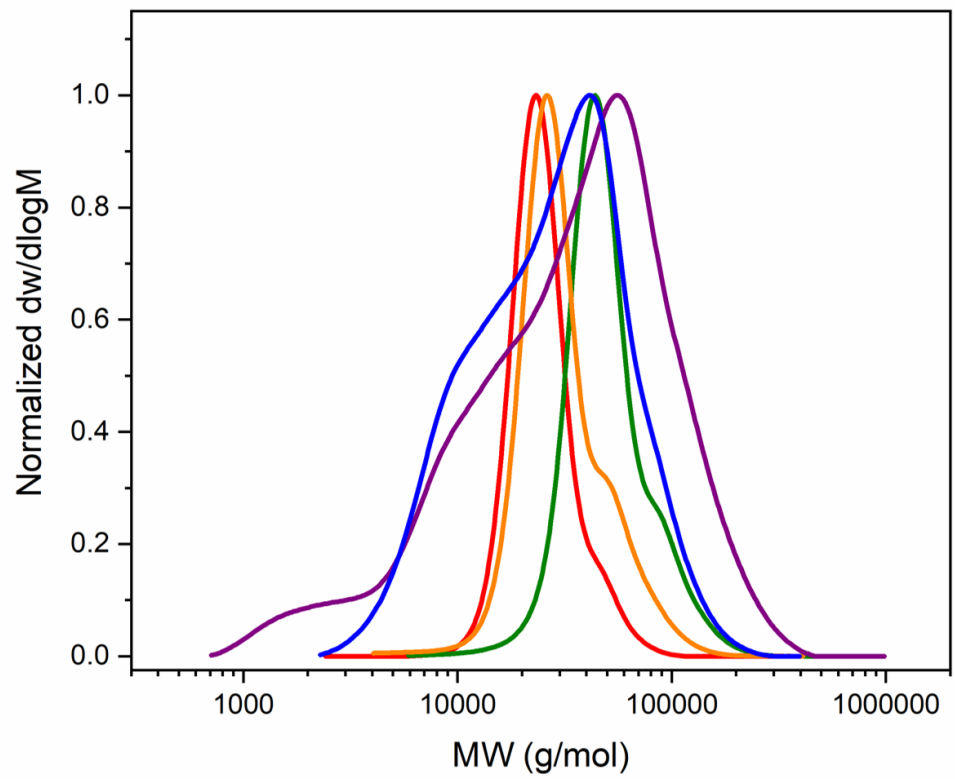
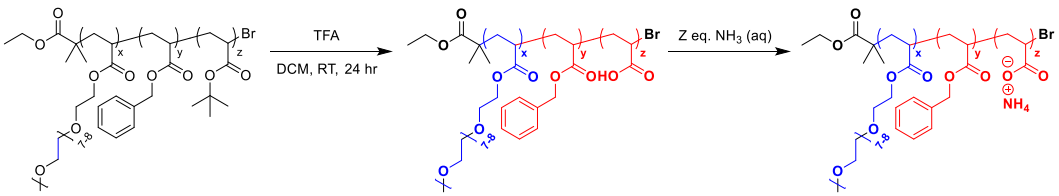


Figure 5.12: *SEC chromatograms (THF) of polymers from table 5.4*

Efficient pigment dispersion is heavily reliant on the solubility of the polymeric dispersant in the dispersing media, as demonstrated in the acrylamide copolymer dispersants tested in section 5.2. Although the pendant PEG chains copolymerised into the backbone afford good water solubility, the functionality along the backbone is very hydrophobic, containing aromatic and tertiary butyl groups. In order to improve both water solubility and pigment affinity, the *t*BA was deprotected to carboxylic acid by treatment with trifluoroacetic acid in dichloromethane. These acid groups were then neutralized using a stoichiometric amount of ammonia to give a highly water soluble pigment affinic salt (scheme 5.3).



Scheme 5.3: *Deprotection of tBA to poly(acrylic acid) followed by reaction with aqueous ammonia to form a salt used in pigment dispersion.*

Milling tests were performed on a low frequency horizontal shaker. Polymeric dispersant was dissolved in water and Raven 5000 Ultra carbon black pigment was added along with 3mm diameter glass beads. After mechanical agitation on the shaker

overnight the samples were diluted and the particle size measured using a Nanotrac particle size analyzer (figure 5.13).

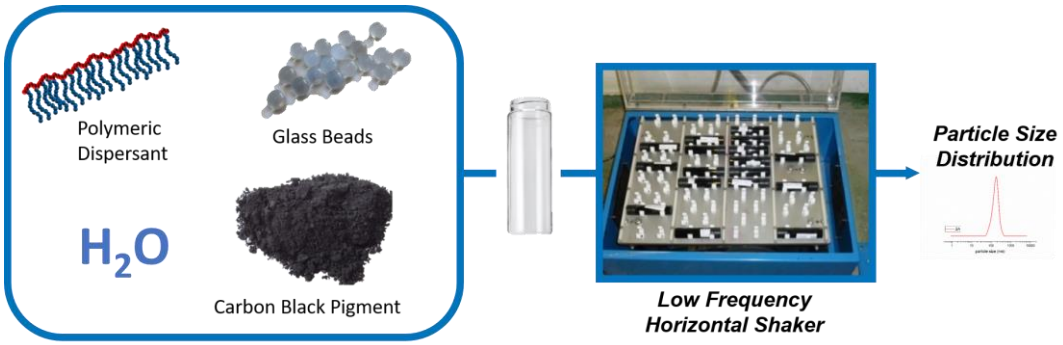


Figure 5.13: *Aqueous milling studies of polymeric comb dispersants with carbon black pigment on a low frequency horizontal shaker.*

Table 5.5: *Particle sizes for comb polymers A-E from milling with Raven 5000 Ultra carbon black pigment.*

Entry	Ref.	D_{50} (nm)	D_{90} (nm)
1	**A**	217	591
2	**B**	454	840
3	**C**	386	590
4	**D**	611	997
5	**E**	697	3600

Table 5.5 shows the particle size analysis data for the milling of Raven 5000 Ultra carbon black with polymeric dispersants A-E. D_{50} and D_{90} are defined as the particle diameters at which 50% and 90% of the samples mass is comprised; so for sample A (entry 1) 50% of particles are 217 nm or smaller and 90% are 591 nm or smaller. By this analysis it can be said that dispersants A and C (both with low dispersity) give the best dispersions, as they achieve the smallest pigment particle size. Referring back to table 5.4 shows that these polymers are both of relatively low dispersity (1.13 and 1.27) and low targeted M_n.

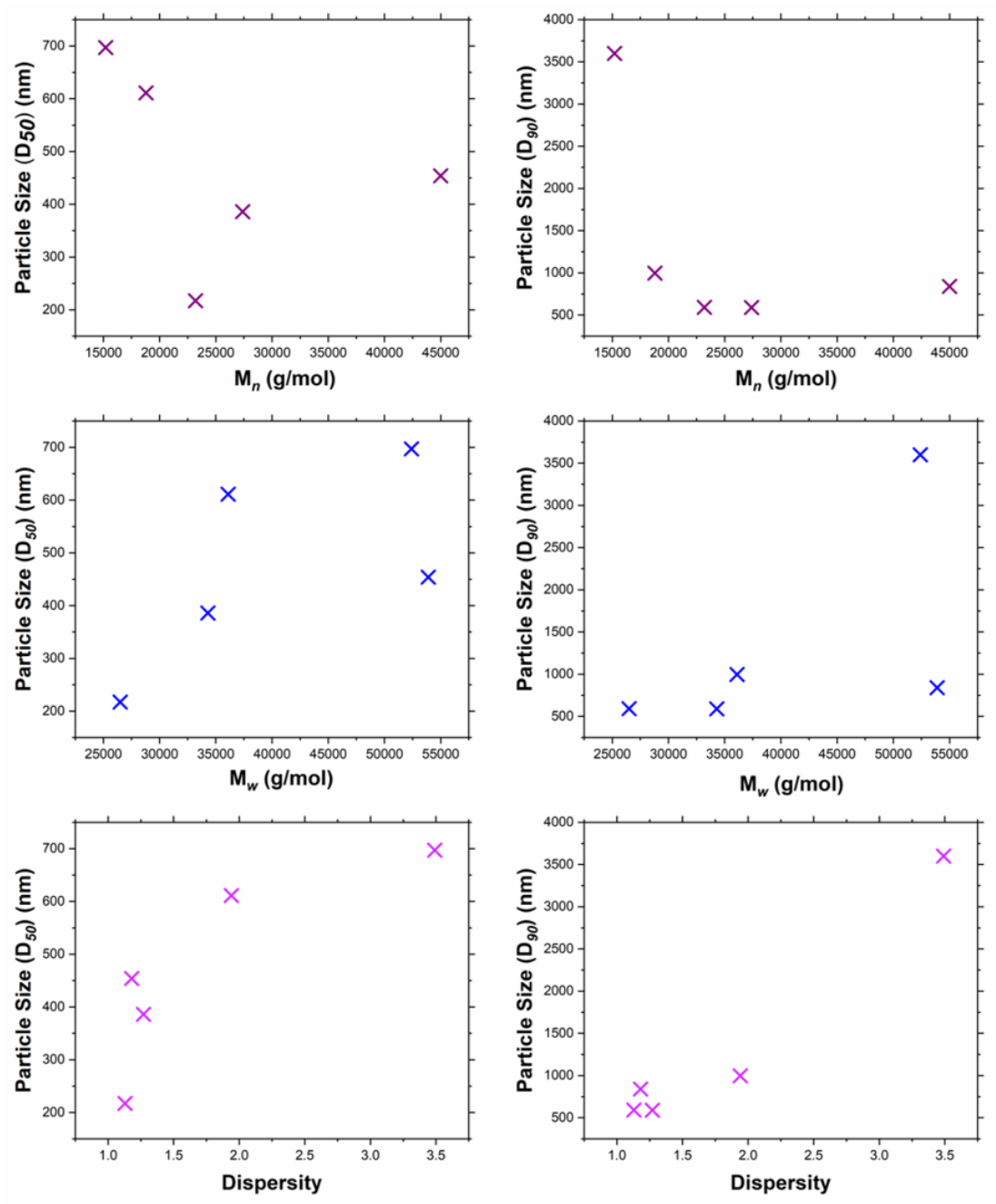


Figure 5.14: *Particle size data from milling experiments plotted against M_n, M_w, and Đ. D_{50} is shown on the left and D_{90} on the right.*

Plotting the pigment particle sizes determined by DLS against different molecular weight parameters (M_n, M_w, and *Đ*) gives the graphs shown in figure 5.14. Trends associated with M_n and M_w appear to have a number outliers, but generally it can be said that pigment particle size is minimized at high M_n and low M_w respectively. Dispersity appears to have a much clearer effect on pigment dispersion: lower dispersity (i.e. a narrow molecular weight distribution) gives much lower pigment particle sizes in milling tests than high dispersity. One possible reason for this

enhanced dispersion for narrow molecular weight dispersants could be due to enhanced pigment affinity: a more uniform polymer chain size could allow for more efficient packing on the surface of a pigment particle, thus allowing for more dispersant molecules to bind. Following on from this, the presence of much longer chains (as in the case of a high dispersity polymer) could result in dispersant chains bridging between two pigment particles, which could have a flocculating effect on the mill base, as shown in figure 5.15 (b).

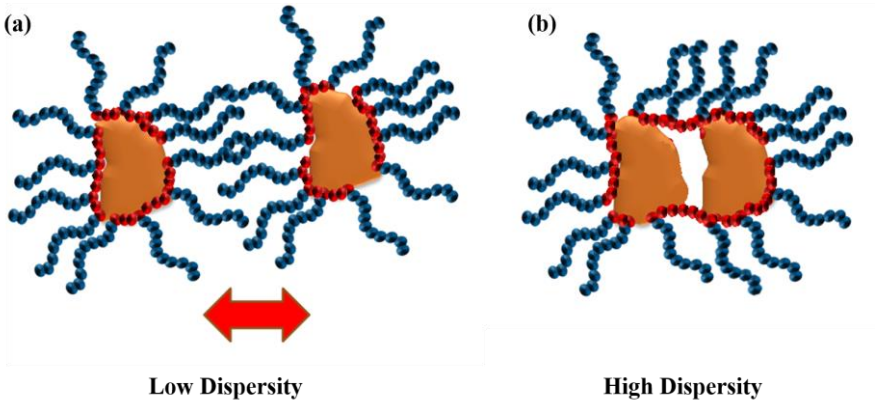


Figure 5.15: *cartoon representation of the effect of dispersity on flocculation: (a) low dispersity causing steric repulsion, (b) High dispersity causing flocculation.*

5.4 Conclusions

In summary, aqueous Cu(0)-RDRP has been exploited to prepare a number of amphiphilic block copolymers from a water soluble polyacrylamide macroinitiator. The efficacy of these polymers as pigment dispersants were determined by milling with Raven 5000 Ultra carbon black pigment. It was found that dispersants which contain aromatic and highly hydrophobic groups do not disperse pigment as well as those which contain water soluble pigment affinic portions. It is proposed that this is due to the non-dynamic nature of the self-assembly of these amphiphiles in aqueous media: resulting in the pigment affinic portion never coming into contact with the surface of the pigment.

In addition, Cu(0)-RDRP was also successfully employed to synthesize comb dispersants with different molecular weight distributions. The breadth of the molecular weight distributions could be systematically varied by changing the time over which initiator was fed. Milling tests with these polymers found that low dispersity (narrow molecular weight distributions) are the best dispersants.

5.5 Experimental

5.4.1 Materials

Acrylamide (≥99% for electrophoresis), *N*-hydroxyethyl acrylamide (97%) and all other monomers were obtained from Sigma-Aldrich and used as received. and *N*-isopropyl acrylamide (97%) were obtained from Sigma-Aldrich and purified by recrystallization from hexanes.

Tris[2-(dimethylamino)ethyl]-amine (Me_6Tren) was synthesized according the procedure in chapter 2 and stored under nitrogen and refrigerated prior to use.

Water soluble initiator, 3-dihydroxypropyl 2-bromo-2-methylpropanoate was synthesized according to the procedure in chapter 2.

Copper(I) bromide (Cu(I)Br, 98%) and copper (II) bromide (Cu(II)Br_2, 99%) was purchased from Sigma-Aldrich. Cu(I)Br was purified by sequentially washing with acetic acid and ethanol and dried *in vacuo* to remove Cu(II)Br_2 impurities. Purified Copper(I) bromide was stored in a foil wrapped vial in a desiccator to prevent oxidation.

Cu(0) (gauge 0.25 mm) wire was purchased from Comax Engineered wires and was treated by immersion in 12 M HCl. prior to use.

HPLC grade water (H_2O, VWR international, LLC) was used as the solvent for all polymerisations in section 5.2. Analytical grade dimethyl sulfoxide (DMSO, Fisher Scientific) was used as the solvent for all polymerisations in section 5.3.

5.4.2 Instrumentation

NMR spectra were recorded on Bruker AV-250 MHz, DPX-400 MHz, HD-300 MHz and HD-400 MHz spectrometers using deuterated solvents purchased from Sigma-Aldrich and Cambridge Isotope Laboratories Inc. Monomer conversion was calculated by comparison of vinyl protons (5.5-7.0 ppm) with polymer backbone protons (1.3-2.5 ppm.)

Aqueous SEC was conducted on an Agilent Technologies Infinity 1260 MDS instrument equipped with a differential refractive index (DRI), light scattering (LS) and viscometry (VS) and UV detectors. The column set used was 2 Agilent PL Aquagel OH 30 and a 5 μm Aquagel guard column. The mobile phase used was 0.1 M $NaNO_3$. Column oven and detector temperatures were regulated to 35 °C, flow rate

1 mL/min. Poly(ethylene oxide) standards (Agilent EasyVials) were used for calibration (100-30,000 g/mol.) Analyte samples were filtered through a hydrophilic membrane with 0.22 μm pore size before injection. Experimental molar mass ($M_{n\,SEC}$) and dispersity ($Đ$) values of synthesized polymers were determined by conventional calibration using Agilent GPC/SEC software.

Organic SEC analysis was conducted on an Agilent 390-LC MDS instrument equipped with differential refractive index (DRI) and dual wavelength UV detectors. The system was equipped with 2 x PLgel Mixed C columns (300 x 7.5 mm) and a PLgel 5 μm guard column. The eluent was THF with 2 % TEA (triethylamine) and 0.01 % BHT (butylated hydroxytoluene) additives run at 1 ml/min at 30 °C. Poly(methyl methacrylate) (Agilent Polymethyl Methacrylate EasiVials between 550 and 1.5 million g mol^{-1}) and polystyrene standards (Agilent Polystyrene Medium EasiVials between 162 and 364,000 g mol^{-1}) were used for calibration and fitted with a second order polynomial. Analyte samples were filtered through a GVHP membrane with 0.22 μm pore size before injection. Respectively, experimental molar mass ($M_{n\,SEC}$) and dispersity ($Đ$) values of synthesized polymers were determined by conventional calibration using Agilent GPC/SEC software.

Particles size analysis for aqueous millbases was conducted on a Microtrac Nanotrac Flex Dynamic light scatterer (DLS) fitted with a probe.

5.4.3 Experimental Procedures

Note: all milling experiments and particle size analysis was carried out at Lubrizol ltd., Manchester.

Preparation of amphiphilic acrylamide-acrylate block copolymers

H_2O (1 mL) and Me_6Tren (18.8 μL, 70.4 μmol, 0.4 eq.) were charged to a 25 mL Schlenk tube with a magnetic stirrer bar and a rubber septum. The solution was deoxygenated by bubbling with nitrogen for 2 minutes. CuBr (10.1 mg, 70.4 μmol, 0.4 eq.) was added with rapid stirring, disproportionation was seen to occur after a few seconds. The disproportionated solution was placed in an ice bath and deoxygenated for a further 15 minutes. Simultaneously, a vial was charged with 3-dihydroxypropyl 2-bromo-2-methylpropanoate (42.4 mg, 176 μmol), acrylamide (0.5 g, 1.76 mmol, 40 eq.) and 3.5 mL of H_2O. The vial was fitted with a septum, stirred, and deoxygenated with nitrogen in an ice bath for 15 minutes. Subsequently the degassed

monomer/initiator solution was transferred into the Schlenk tube containing the disproportionated solution via degassed syringe. The reaction mixture was sampled after 15 minutes and analysed by SEC and NMR. Immediately after this a deoxygenated aliquot of phenylethyl acrylate (0.31 g, 14.06 mmol, 10 eq.) was transferred into the reaction vessel by degassed syringe, upon which an emulsion was formed almost instantly. The reaction was ceased after 2 hours. Excess monomer was removed under reduced pressure and the resultant aqueous mixture was dialyzed in water with 1 kDa MWCO dialysis membrane. Water was removed by freeze-drying and the resultant polymers used without further purification.

Milling with block copolymer dispersant, Raven Ultra 500 pigment (10%, 50% agent on weight of pigment (AOWP))

0.5 g of polymeric dispersant was charged to a 21 mL tall trident vial and dissolved in 8.5 mL of water. 1 g of Raven Ultra 5000 carbon black pigment was added along with 17 g of 3 mm glass beads. The vial was fitted with a polypropylene screw-top cap and sealed tight with electrical insulation tape. Sealed vials were placed in a low frequency horizontal shaker (figure 5.16). After 16 hours the vials were removed. A small aliquot was taken and diluted with water and particle size distribution was determined by DLS.

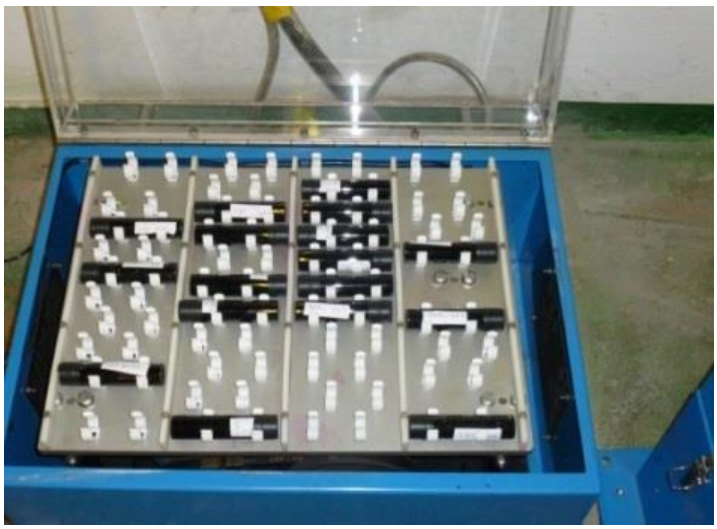


Figure 5.16: *Low frequency horizontal shakers used in all milling tests. Shown with multiple trident vials in place.*

Synthesis of comb type dispersants

$Cu(II)Br_2$ (6.3 mg, 0.028 mmol, 0.05 eq.) was charged to a 25 mL glass vial and dissolved in 10 mL of DMSO. PEGA (5 mL, 11.4 mmol, 20 eq.), *t*-BA (2.46 mL, 17 mmol, 30 eq.), and BzA (2.61 mL, 17 mmol, 30 eq.) was added and EBiB (83.3 μL, 0.568 mmol, 1 eq.) was carefully transferred into the reaction vessel via microliter syringe. Concurrently, in a separate vial, a stirrer bar wrapped with 10 cm of copper wire was immersed in 37% HCl, stirred for 15 minutes, washed sequentially with water and acetone, and dried. The stirrer bar was then placed into the reaction vessel, sealed with a rubber septum, and degassed by bubbling with nitrogen for 15 minutes in an oil bath at 25 °C. After this time a degassed aliquot of Me_6Tren (27 μL, 0.10 mmol, 0.18 eq.) was injected into the vial via microliter syringe. The reaction was left to proceed overnight and samples were taken and analysed via ^{1}H NMR (figure 5.9) and SEC (figure 5.8).

Synthesis of combs type dispersants with initiator feeding.

$Cu(II)Br_2$ (6.3 mg, 0.028 mmol, 0.05 eq.) was charged to a 25 mL glass vial and dissolved in 9 mL of DMSO. PEGA (5 mL, 11.4 mmol, 20 eq.), *t*-BA (2.46 mL, 17 mmol, 30 eq.), and BzA (2.61 mL, 17 mmol, 30 eq.) was added and Me_6Tren (27 μL, 0.10 mmol, 0.18 eq.) was carefully transferred into the reaction vessel via microliter syringe. Concurrently, in a separate vial, a stirrer bar wrapped with 10 cm of copper wire was immersed in 37% HCl, stirred for 15 minutes, washed sequentially with water and acetone, and dried. The stirrer bar was then placed into the reaction vessel, sealed with a rubber septum, and degassed by bubbling with nitrogen for 15 minutes in an oil bath at 25 °C. After this time a 1 mL aliquot of a degassed stock solution of EBiB in DMSO (83.3 μL / mL) was fed into the reaction *via* syringe pump. The reaction was left to proceed overnight and samples were taken and analysed via ^{1}H NMR (figure 5.9) and SEC (figure 5.8).

Deprotection of t-butyl groups to acrylic acid

5 g of Comb polymer was dissolved in 10 mL of DCM and stirred rapidly in a round bottom flask at room temperature. 10 mL of trifluoroacetic acid was slowly added and left to stir overnight. Solvent and excess acid were removed by rotary evaporation followed by addition of acetone to form an azeotrope. The addition and removal of acetone was repeated four times.

Milling with comb type dispersant, Raven Ultra 500 pigment (10%, 60% agent on weight of pigment (AOWP))

0.6 g of polymeric dispersant was charged to a 21 mL tall trident vial and dissolved in 5 mL of water and 3.4 mL of dilute aqueous ammonia (amount of ammonia calculated according to weight percentage of acid groups in the polymer). 1 g of Raven Ultra 5000 carbon black pigment was added along with 17 g of 3 mm glass beads. The vial was fitted with a polypropylene lid and sealed tight with electrical insulation tape. Sealed vials were placed in a low frequency horizontal shaker (figure 5.16). After 16 hours the vials were removed. A small aliquot was taken and diluted with water and particle size was determined by DLS.

5.6 References

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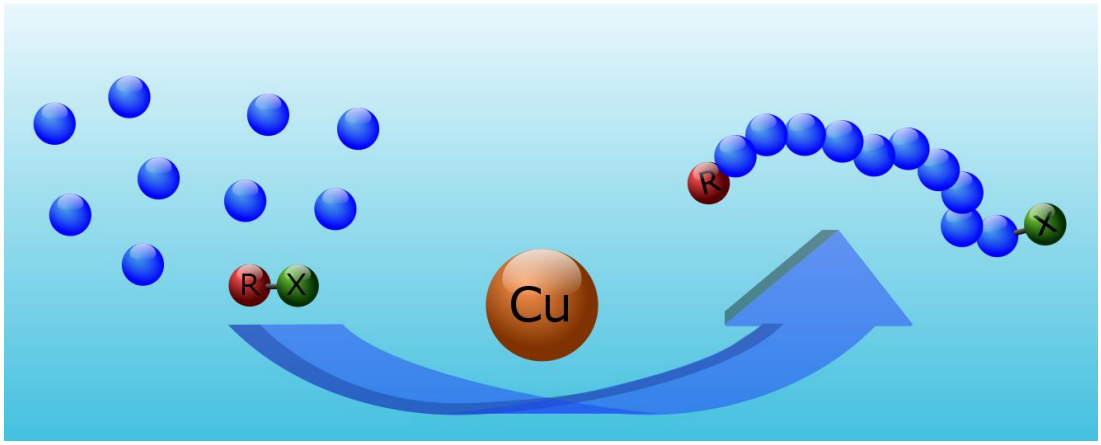
Chapter 6: Conclusions



7.1 Conclusions

The object of this work was to investigate the potential of copper mediated polymerisation for controlled macromolecular synthesis in aqueous media. Firstly the polymerisation of acrylamide by aqueous Cu(0)-RDRP was investigated. It was found that careful tuning of the Cu(I) and ligand ratio is crucial to achieving well defined polymers at high conversions over a range of molecular weights. Kinetic analysis revealed that the polymerisation proceeds rapidly in aqueous media, with conversions reaching over 90% in just 2 minutes. Depsite the rapid reaction chain end fidelity was retained even at quantiative conversion, which was exemplified by *in-situ* chain extensions to yield hydrophilic and thermoresponsive block copolymers. This optimized approach to polyacrylamide synthesis proves to be a significant advance over traditional ATRP, in which the polymerisation of acrylamide monomers is characterized by low conversions, low end group fidelity and broad molecular weight distributions.

Photo-mediated ATRP has previously been shown to be severly limited in aqueous media, exhibiting significantly less control than analoguous polymerisations in organic media, proposed to be due to insufficient deactivation due to catalyst dissociation. The second part of this thesis realizes a controlled photomedaited polymerisation in aqueous media through manipulation of the dissociation equilibrium. Increasing Cu(II) deactivator concentration led to dramatic improvements in control over polymerisation, with kinetic analysis indicating a constant concentration of radicals. In addition, it was also demonstrated that adding excess halide salt in place of extra Cu(II) also had the same effect, but without an increase in catalyst concentration. This approach was then explored and found to afford controlled polymerisation at even parts per million (ppm) catalyst loading. The scope of this aqueous photopolymerisation system was found to encompass a wide range of molecular weights and monomer functionality, although polymerisation of acrylamides was uncontrolled. Importantly, the temporal control exhibited over the reaction was found to be better than any other reported Cu-mediated polymerisation, with no conversion of monomer observed during periods in which the light source was switched off.

The polymerisation of methacrylates by Cu(0)-RDRP is not as well reported as acrylamides and acrylates in both organic and aqueous media. The third part of this

thesis investigated how a high degree of control can be achieved over the polymerisation of this monomer class. Systematic variation of the initiator found that the stability of the initiating radical plays a significant role in controlling the polymerisation. The initiating radical must be sufficiently stable in order to make initiation a more favourable process than propagation, meaning that all chains will have similar chances of propagating and will therefore be similar in length. Methyl bromophenylacetate (MBPA) was found to afford good control of methacrylate polymerisations in dimethyl sulfoxide (DMSO), with a range of monomer functionalities, block copolymers, and molecular weights sucessfully targeted. In order to test whether the same priniciple could be applied to aqueous polymerisation a water soluble bromophenylacetate was used to polymerise PEGMA in water. Although the polymerisation was reasonably well controlled, the initiator efficiency was found to be much lower, and higher degrees of polymerisation could be be successfully targeted.

Finally Cu(0)-mediated polymerisation was exploited to synthesize novel polymeric dispersants for waterborne coatings applications. Amphiphilic polyacrylamide block copolymers were prepared and tested by milling with an automotive carbon black pigment. Interestingly, it was found that strongly hydrophobic groups inhibit dispersion, despite their theoretically high pigment affinity. This was attributed to the hydrophobic groups having limited contact with the pigment particles' surface. The effect of molecular weight distribution on pigment dispersion was also investigated by preparing comb type dispersants of different dispersities; narrow molecular weight distributions appeared to give the best dispersions.

Cu-mediated radical polymerisation in aqueous media is now capable of controlled polymerisation of a wide range of monomers, and is capable of synthesizing complex macromolecular architectures such as block copolymers. Temporal control, such as that demonstrated by the photomediated polymerisation technique in chapter 2, could allow for even high degrees of precision in the synthesis of complex macromolecules. However, a number of challenges still remain: the polymerisation of acrylamides appears to be most efficient in Cu(0)-mediated reactions with other transition metal mediated techniques yielding uncontrolled polymerisation. A mechanistic investigation is currently underway and could possibly allow for the polymerisation

of other relatively unexplored monomer classes such as *N*-vinyl monomers, vinyl ethers, and charged styrenic monomers.