Polymer Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/polymers

Sequence-controlled multi-block copolymerization of acrylamides *via* aqueous SET-LRP at 0 °C

Fehaid Alsubaie,[a] Athina Anastasaki,[a] Paul Wilson[a,b] and David M. Haddleton[a,b]*

[a] Department of Chemistry, University of Warwick, Coventry, UK.

[b] Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Australia.

Abstract

Aqueous single electron transfer living radical polymerization (SET-LRP) has been employed to synthesize multi-block homopolymers and copolymers of a range of acrylamide monomers including *N*-isopropylacrylamide (NIPAM), 2-hydroxyethyl acrylamide (HEAA), *N,N*-dimethyl acrylamide (DMA) and *N,N*-diethylacrylamide (DEA). Disproportionation of Cu(I)Br in the presence of Me_6TREN in water was exploited to generate reactive Cu(0) and $[Cu^{II}(Me_6TREN)]Br_2$ in situ resulting in unprecedented rates of reaction whilst maintaining control over chain lengths and molecular weight distributions ($Đ$ < 1.10). Kinetic studies enabled optimization of iterative chain extensions or block copolymerizations furnishing complex compositions in a matter of minutes/hours. In the multi-block copolymer system, the monomer sequence was successfully varied and limiting effects on the polymerization have been comprehensively examined through a series of control experiments which imply that the rate of ω-Br chain end loss is enhanced in tertiary acrylamides (DMA, DEA, *N*-acryloylmorpholine NAM) relative to secondary acrylamides (NIPAM, HEAA).

Introduction

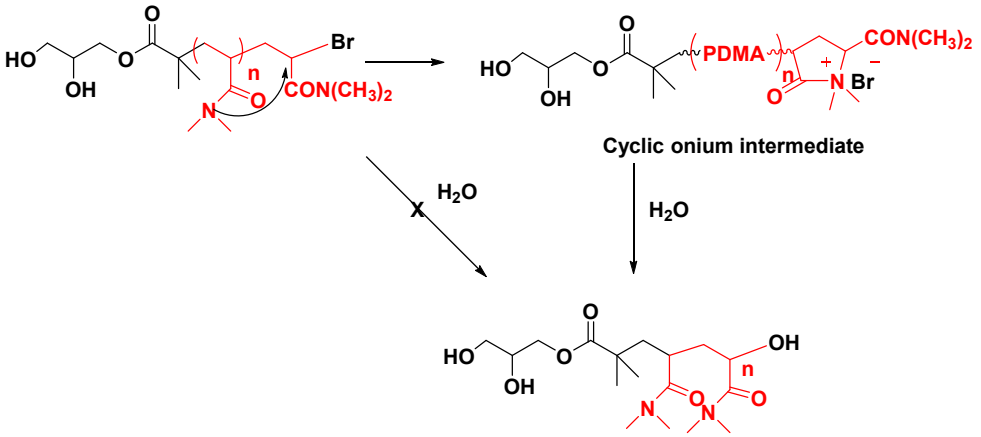
Control over monomer sequence, polymer composition and thus ensuing material properties is a key challenge facing polymer scientists. Natural polymers such as peptides, proteins, nucleic acids and carbohydrates are precisely constructed, at the cellular level, according to their intended application and function. Synthetically, this level of precision is some way off, though progress over the last 30-40 years has significantly improved the limits of control now possible over the polymer primary sequence.[1-6] Various approaches to precision polymers and materials, including single monomer addition,[7] tandem monomer addition and modification,[8, 9] kinetic control,[10-13] solution[14-20] and segregated[21] templating have been explored.

Single monomer addition *via* radical chain-growth polymerization techniques is challenging given the reactive nature of the radical intermediates involved. This has given rise to a new field in synthetic polymer science, focusing on controlling the sequence of multiple discrete regions within the polymer. The retention of chain-end functionality is often critical in the design of materials and to this end, Whittaker and co-workers exploited Cu(0)-mediated living radical polymerization in a one-pot synthesis of multi-block copolymers via iterative monomer addition.[22-24] Multi-block (up to decablock) copolymers containing discrete block lengths (2-10) were attained and the versatility of the protocol was emphasized by preparation of copolymers in both linear and star architectures as well higher molecular weight block lengths.[25] However, a limitation of this exemplary work was recognized during the synthesis of linear decablock copolymers, whereby molecular weight distributions were found to gradually increase, indicative of the accumulation of terminated chains. The same technique was employed to synthesize a number of multi-block glycopolymers with a good degree of monomer sequence control in various compositions containing mannose, glucose, and fucose moieties in the presence and absence of spacer comonomers.[26, 27] Higher molecular weight multi-blocks with narrower dispersities have also been attained but the yield of the intermediate blocks was often < 95%, compromising the integrity of the multi-block structures.[25]

Despite the progress made in the field of controlled living radical polymerization (CLRP) over the last 20 years, controlled polymerization in pure aqueous media has remained a challenge. Control in radical polymerization protocols such as nitroxide-mediated polymerization (NMP),[28, 29] reversible activation fragmentation chain transfer (RAFT)[30, 31] and transition metal mediated controlled radical polymerization (TMM-CRP)[32-35] relies on careful manipulation of an equilibrium existing dormant (P_n-X) and active (P_n-$^{\cdot}$) species. In Cu-mediated polymerization this equilibrium is largely controlled by Cu-ligand complexes. Higher rates of activation and propagation compared to less polar organic media can result in uncontrollable radical concentrations resulting in enhanced termination. The polymerization of acrylamide based monomers is further complicated by deleterious side reactions and chain transfer that lead to loss of ω-Br chain end functionality and branching.[36-38]

The TMM-CRP of acrylamide (and its derivatives) has proved to be problematic with respect to the control of the polymerization when water was employed as the only solvent at, or below, ambient temperature.[39, 40] Furthermore, to the best of our knowledge, only a few publications have reported controlled diblock copolymerization of acrylamides via TMM-CRP. Brittain et. al reported attempts to polymerise dimethacrylamide using a range of

copper salts with different ligands and solvents.[36] They concluded that the Cu salts complex to the amide group of the chain ends stabilizing the radical leading to an unacceptably high concentration of radicals which leads to 'spontaneous' termination reactions. They reported indirect evidence for a cyclization reaction involving nucleophilic bromide displacement to undergo hydrolysis to form a hydroxy-terminated polymer (Scheme 1). This was in agreement with previous work by Matyjaszewski.[37, 38] Even the use of amide initiators in place of esters has been problematic.[41] Homopolymerization of acrylamide (AA) and subsequent block copolymerization with *N*-isopropylacrylamide (NIPAM) in aqueous media at 25 °C resulted in polymers with broad molecular weight distribution ($Đ$ > 1.40).[42] Narrower distributions have been reported in mixed organic-aqueous solvent systems[43, 44] but again overall control was found to be variable. Thus it is apparent that polymerization of acrylamides mediated via copper(I) has been unsuccessful and where good control has indeed been reported it is apparent that these reactions were carried out under conditions where copper(I) is unstable relative to disproportionation.[45]



Scheme 1: Termination via formation of a cyclic onium species as described by Brittain[36] and Teodorescu.[37]

Perrier and co-workers reported the synthesis of multi-block copolymers comprising of acrylamide monomers using RAFT. Under optimized conditions they achieved up to an icosa-block (20 block) copolymer in both organic (dioxane) and aqueous media.[46-49] However, the high temperature (~70 °C) that was utilized potentially limits the possibility of simultaneous biological applications whilst at the same time limiting the monomer pool to acrylamides as polymerization of other monomers (*e.g.* acrylates) at these temperature would result in increased unavoidable termination and side reactions (backbiting, chain transfer).[50] This has been somewhat addressed by the use of a *fac*-[Ir(ppy)$_3$] photoredox catalyst,

previously employed by Hawker *et al.* to induce photomediated ATRP of methacrylates.[51] Boyer *et al.* have reported RAFT polymerization of activated and unactivated vinyl monomers at ambient temperature, highlighting the utility of the photoredox catalysis via recycling in iterative chain extension experiments.[52] Haddleton and Junkers have also reported the successful synthesis of sequence-controlled multi-block copolymers in a one-pot polymerization at ambient temperature via a Cu-mediated light induced system[53, 54].

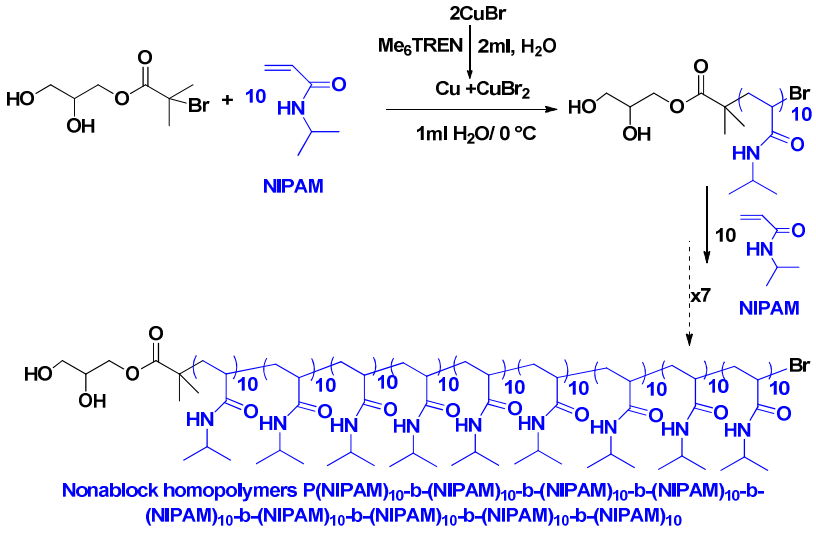
Herein, water has been utilized as the solvent for the preparation of multi-block copolymers of various acrylamides at or below ambient temperature implying compatibility with biological systems. An unprecedented level of control is achieved by the catalyst system which is prepared in situ via disproportionation of Cu(Me_6TREN)Br *prior* to introduction of monomer and initiator. Enhanced rates of homo and copolymerization are reported relative to preceding TMM-CRP protocols, without detrimental effects on the polymerization control. Following homopolymerization, up to eight chain extensions are possible furnishing multi-block compositions within 3.5 hours. In addition, we have investigated the undesirable side reaction which sequesters the ω-Br chain end of poly(acrylamides) in water offering an insight into the importance to monomer selection and sequence in poly(acrylamide)s.

Results and Discussion

We recently introduced a Cu-mediated polymerization protocol enabling preparation of poly(acrylamide)s and poly(acrylate)s in aqueous,[55, 56] biological[57] and complex alcoholic[58] media. Within this study the successful in situ chain extension and block copolymerization of P(NIPAM) prepared by aqueous SET-LRP was reported. However, in this original work the reaction was not optimized and termination was evident following each chain extension either through increasingly broad dispersities or low molecular weight shoulders detected in SEC chromatograms. The termination was attributed to a deleterious side reaction leading to loss of the ω-Br chain end of the poly(acrylamides) in water.[36-38] Cu-mediated polymerization in aqueous media had previously been difficult to control owing to enhanced rates of activation and propagation and potential dissociation of deactivating CuX_2 species. Additional complexity is introduced by the rate of the competing side reaction, namely the nucleophilic substitution of the ω-Br by H_2O. Experimentally, at high monomer concentration the rate of propagation dominates, thus substitution of the chain end is negligible. However, as the polymerization proceeds the monomer concentration, and therefore the rate of propagation decreases, and thus the substitution of the bromine becomes more prevalent relative to propagation and the affected chains are unable to undergo further activation and propagate.

Moreover, in previous work, the rate of the competing side reaction was effectively suppressed by performing the homo- and block copolymerizations at 0 °C but no further optimization was sought.[55]

Investigating the potential for multi-block homopolymer synthesis via homo chain extension of PNIPAM. In accordance with the previously reported procedure, CuBr was allowed to fully disproportionate in an aqueous solution of the tetradentate tertiary amine ligand Me_6TREN. An aqueous mixture of initiator and monomer was subsequently added and polymerization was allowed to proceed under a nitrogen atmosphere (Scheme S1). Upon sampling, conversions were determined by ^{1}H NMR analysis by monitoring the disappearance of the vinylic signals against appearance of the isopropyl methine signal from the NIPAM present in the side chain of the polymer (Figure S2). After one hour full conversion was attained (Table S1, entry 1) and a deoxygenated solution of NIPAM was injected into the reaction mixture. Chain extension was allowed to proceed for 4 hours at which time all of the NIPAM had been consumed (Table S1, entry 2) affording PNIPAM with narrow dispersity ($Đ$ = 1.07). Likewise, control over the polymerization was retained upon addition of a third aliquot of NIPAM which was incorporated into the polymer within an additional 5.5 hours (Table S1, entry 3). However, attempts to chain extend further after this cumulative reaction time were unsuccessful (Figure S1).



Scheme 2. Synthesis of multi-block homopolymers of NIPAM by iterative SET-LRP in pure H_2O.

The integrity of multi-block compositions is contingent on the maximal retention of the end group, thus considering the deleterious effect of the H_2O mediated side reaction, a more accurate understanding of the polymerization kinetics is required. Therefore a kinetic study on the homopolymerization of NIPAM was performed. During homopolymerization, regular sampling and analysis by ^{1}H NMR and SEC revealed that full monomer conversion was reproducibly attained within 11 min with retention of the narrow, symmetrical, monomodal molecular weight distributions ($Đ$ = 1.06, Table 1, entry 1, Figure S3).

Table 1: Optimization of multi-block homopolymers prepared by sequential addition of deoxygenated aliquots of aqueous NIPAM (10 eq) to PNIPAM during SET-LRP at 0°C in H_2O. $[M]_0 : [I]_0 : [CuBr] : [Me_6TREN] = [10] : [1] : [0.04] : [0.04]$.

Entry	Block number	Conv. (%)	Time per block (min)[a]	$M_{n,th}$ g.mol^{-1}	$M_{n,SEC}$[b] g.mol^{-1}	$Đ$[b]
1	Block 1	100	11 (11)	1400	2500	1.06
2	Block 2	99	8 (19)	2500	4300	1.06
3	Block 3	100	15 (34)	3600	6500	1.05
4	Block 4	98	16 (50)	4700	8900	1.05
5	Block 5	100	16 (66)	5900	11000	1.07
6	Block 6	99	20 (86)	7000	13300	1.06
7	Block 7	99	30 (116)	8200	15700	1.06
8	Block 8	99	40 (156)	9300	18700	1.06
9	Block 9	99	50 (206)	10400	22800	1.08

[a] Cumulative time in parentheses. [b] DMF SEC, calibrating with PMMA standard.

We hypothesised that in order to maximize the integrity of targeted multi-block systems, monomer additions should occur at, or as close to full conversion as possible, and certainly higher than 95%, with minimal exposure to [M] ≈ 0. The homopolymerization of NIPAM was therefore repeated and after 11 min a second aliquot of NIPAM, deoxygenated in water, was injected into the system. Pleasingly, ^{1}H NMR analysis confirmed quantitative conversion of the second NIPAM feed within an additional 8 min (19 min total, Table 1, entry 2) at which point the polymerization was stopped, and SEC analysis revealed successful chain extension with a narrow dispersity ($Đ$ = 1.06, Figure 3b). This process was repeated for each chain extension until a nonablock PNIPAM was obtained via iterative chain extension in a total reaction time of ~ 3.5 h (Table 2). Successive extensions were confirmed by ^{1}H NMR (Figure 3a) and narrow dispersities were retained throughout ($Đ$ < 1.08, Figure 1b), implying

the potential for precise control over discrete monomer sequences within the final polymer composition. However, it is noted that attempts prepare a decablock or beyond were unsuccessful, rendering the nonablock PNIPAM as the current limit in this system.

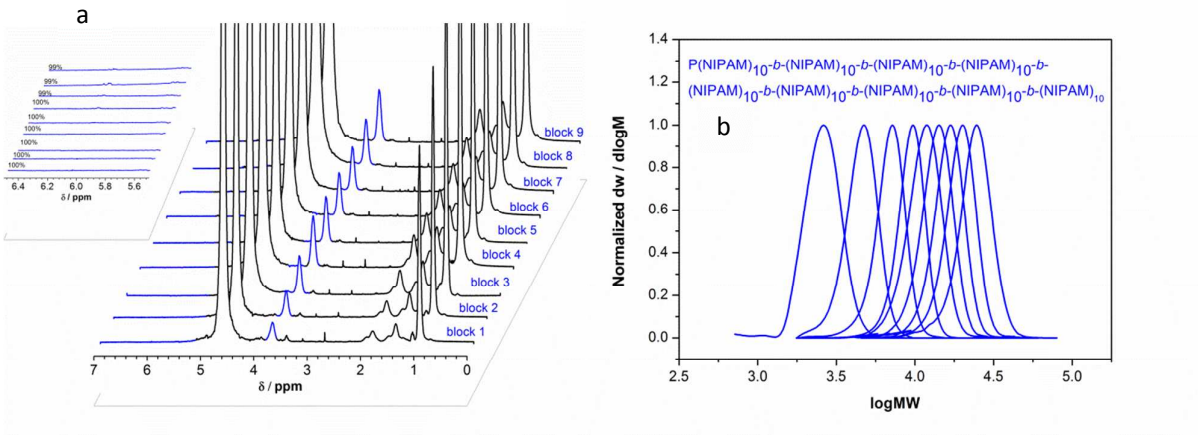


Figure 1. ^{1}H NMR spectra for multi-block homopolymers prepared by sequential additon of deoxygenated aliquots of aqueous NIPAM (10 eq) to PNIPAM via SET-LRP at 0°C in D_2O (a) and evolution of block molecular weight by DMF SEC (b) $[M]_0$: $[I]_0$: [CuBr] : [Me_6TREN] = [10] : [1] : [0.04] : [0.04].

The current data points to an apparent sudden cessation of polymerisation during chain extension from a nona- to decablock polymer with NIPAM. It is unlikely that such an abrupt transition occurs for a chemical reason and we attribute this observation to a number of factors. Competing termination reactions can result in a gradual accumulation of 'dead' chains. Though this is not obvious by NMR and SEC analyses, it is illustrated in plot of $M_{n,exp}$ and $M_{w,exp}$ verse block number which initially shows an increase molecular weight cumulatively deviating from $M_{n,th}$ (Figure 2). Likewise the number of manipulations heightens the chance of termination through introduction of unwanted reagents such as oxygen. This combination of termination events also confers a global increase in the concentration of deactivating species which causes the equilibrium to shift towards dormant chains, an observation which has been noted in a number of related systems. We are confident that this could be overcome via automated monomer addition for example.

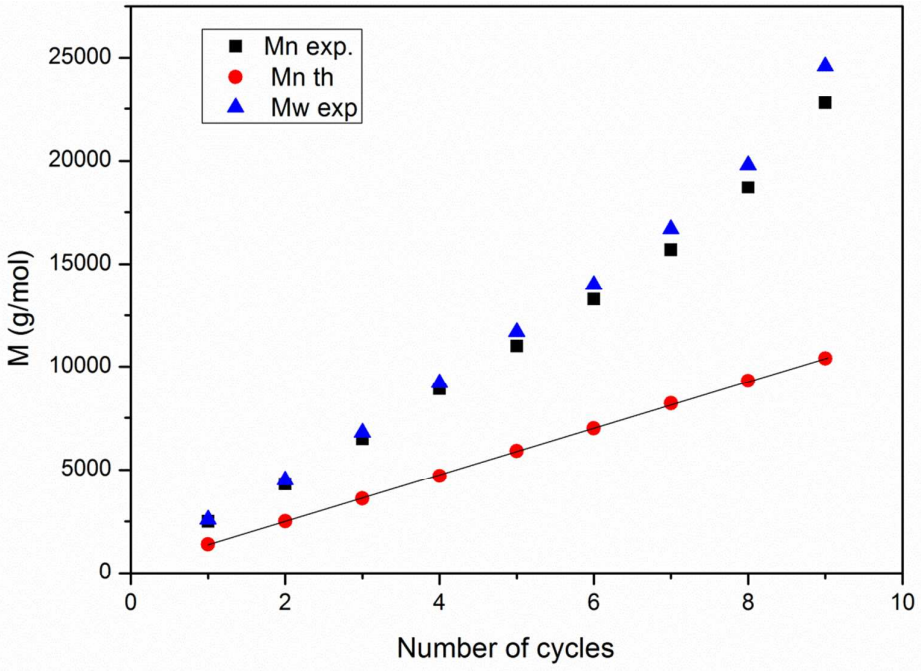
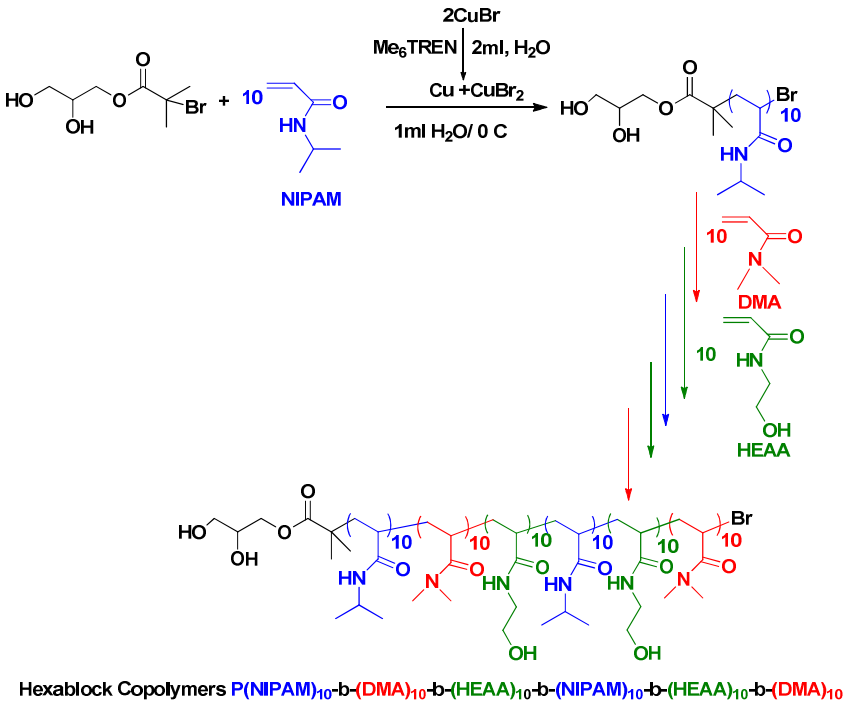


Figure 2: Relative increase in molecular weight as a function of block number (cycles).

Sequence controlled multi-block copolymerization via aqueous SET-LRP. The precise sequence of monomer units present in the biomolecules such as proteins, polysaccarides and nucleic acids determines the natural properties and function of these biomacromolecules. Therefore, the control over monomer sequences in polymerization is an interesting target in order to synthesize sequence-controlled macromolecules with different ordered monomer sequences and potentially tuneable properties. Preceding examples of Cu-mediated multi-block copolymerization of acrylates have been relatively slow with the rate of polymerization increasing with each iterative addition culminating in reaction times of up to 48 hours per block in DMSO.[22-26, 53] Using three commercially available, hydrophilic, acrylamide monomers, we applied the conditions described for the PNIPAM polymerization to synthesize a true hexablock copolymer P(NIPAM)$_{10}$-*b*-(DMA)$_{10}$-*b*-(HEAA)$_{10}$-*b*-(NIPAM)$_{10}$-*b*-(HEAA)$_{10}$-*b*-(DMA)$_{10}$ in a pure aqueous system at 0 °C (Scheme 3). These conditions address some of the challenges facing synthetic chemists particularly those working close to the interface of biology/medicine. The conditions are conducive to biological applications, in particular grafting-from strategies of protein/peptide/nucleic acid conjugation.[59, 60] Previously, this has been difficult in pure aqueous solution, requiring binary mixtures with, or, pure polar organic solvents, which can have a detrimental effect on the biomolecules employed and complicate the polymerization process.



Scheme 3. Synthesis of multi-block copolymers composed of NIPAM, DMA and HEAA by iterative SET-LRP in H_2O.

Table 2: Preparation of multi-block copolymers composed of NIPAM DMA and HEAA by iterative aqueous SET-LRP at 0° C in H_2O. $[M]_0 : [I]_0 : [CuBr] : [Me_6TREN] = [10] : [1] : [0.04] : [0.04]$.

Entry	Block number	Monomer	Conv. (%)	Time per block (min)[a]	$M_{n,th}$ g.mol^{-1}	$M_{n,SEC}$[b] g.mol^{-1}	$Đ^b$
1	Block 1	NIPAM	99	11 (11)	1400	2700	1.09
2	Block 2	DMA	99	6 (17)	2400	4800	1.11
3	Block 3	HEAA	99	25 (42)	3500	8300	1.09
4	Block 4	NIPAM	99	40 (82)	4600	10200	1.07
5	Block 5	HEAA	100	45 (127)	5800	14500	1.09
6	Block 6	DMA	97	70 (197)	6800	17400	1.11
7	Block 7	NIPAM	0	24 (221)	-	-	-

[a] Cumulative time in parentheses. [b] DMF SEC, calibrating with PMMA standard.

In line with the PNIPAM investigation, each polymerization and chain extension was screened to identify the optimum reaction time per block (Table 2). The conversion of each block extension was quantitative according to integration of the vinyl protons (~6.50–5.70

ppm) of the monomer with the isopropyl methine proton of NIPAM (-C<u>H</u> $(CH_3)_2$) (~3.50–3.90 ppm), the methyl signal of DMA (N($C\underline{H}_3$)$_2$ (~ 3.0 ppm)) and the *N*-methylene signal of HEAA (NH(-$C\underline{H}_2$-) (~3.3 ppm)) (Figure 3a). SEC analysis showed that the molecular weight evolution and distributions were controlled as confirmed by the narrow final dispersity ($Đ$ = 1.11) (Figure 3b). The total reaction time for synthesis of this hexablock was 3h, which is considerably faster than any previously reported Cu-mediated multi-block systems in organic media.

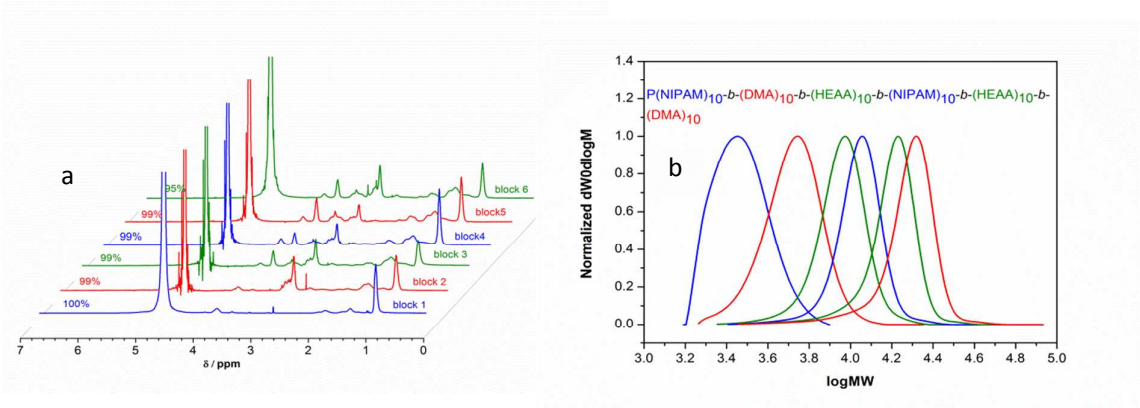


Figure 3. ^{1}H NMR spectra for multi-block copolymers composed of NIPAM, DMA and HEAA by iterative aqueous SET-LRP at 0 °C in D_2O (a) and evolution of block molecular weight by DMF SEC (b) $[M]_0 : [I]_0 : [CuBr] : [Me_6\text{-TREN}] = [10] : [1] : [0.04] : [0.04]$.

Unfortunately, attempts to form a hepta-block copolymer were unsuccessful in this case, presenting a significant deviation from the results obtained when just NIPAM was employed as monomer. It was thought that this may have been due to consumption of the activating species as the Cu(0) formed during disproportionation are visibly consumed as the reaction proceeds.[61, 62] In an attempt to circumvent this, a new aliquot of Cu(0) and Cu(Me_6TREN)Br_2 was fed into the reaction mixture prior to the fifth addition of monomer (Scheme S2). Upon addition of NIPAM as the 7th monomer the reaction mixture was allowed to stir overnight, affording 70% conversion (Table S2, entry 7, Figure S4). However, although an expected shift in molecular weight distribution was observed by SEC, the bimodality of the resulting peak indicated that significant loss of chain-end, rather than consumption of activating species, was responsible for limiting the number of possible chain extensions (Figure S5).

Considering that it was possible to prepare a nona-block homopolymer when NIPAM alone was employed as monomer, the effect of monomer structure was investigated as a possible cause for these observations. Comparing these monomers, it was recognized that a

notably difference arose from the nature of substitution at the amide bond. Both secondary (NIPAM, HEAA) and tertiary (DMA) amide based acrylamides have been employed throughout this and previous studies with little insight into differences in chain-end fidelity and relative rates of deleterious side reactions. Therefore, two copolymerizations were conducted in which NIPAM was block copolymerized, in an alternating sequence, with HEAA and DMA respectively.

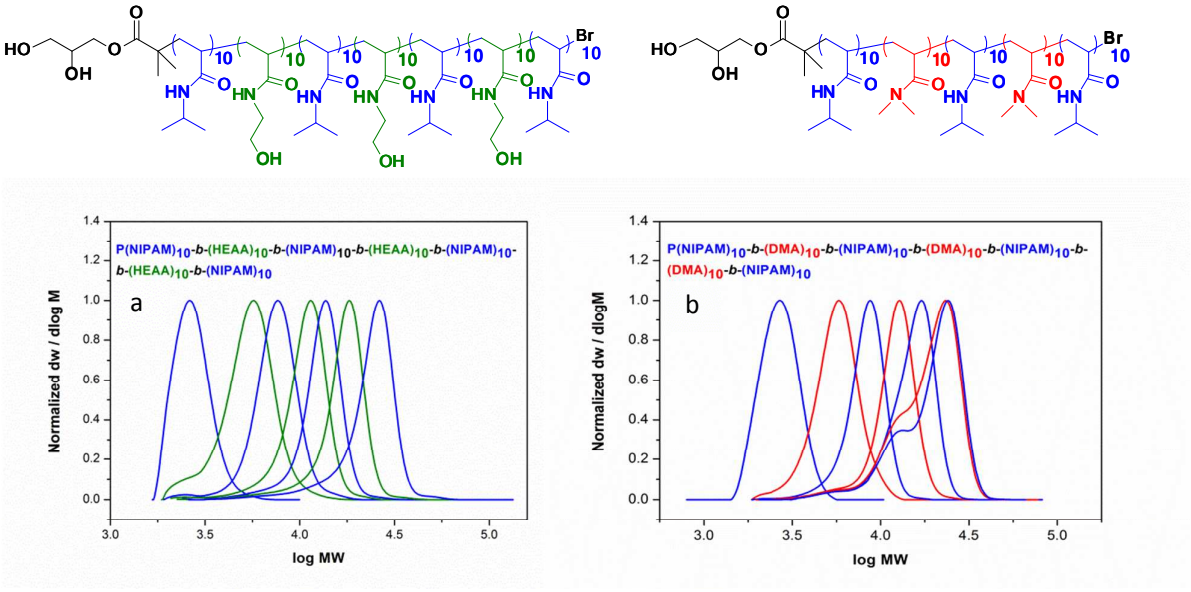


Figure 4. DMF SEC for alternating mulitblock copolymers of NIPAM and HEAA (a) and NIPAM and DMA (b) in H_2O at 0 °C. $[M]_0 : [I]_0 : [CuBr] : [Me_6TREN] = [10] : [1] : [0.04] : [0.04]$.

A heptablock copolymer of NIPAM and HEAA was prepared by sequential, alternating additions of NIPAM and HEAA to the aqueous polymerization mixture at 0 °C in a total reaction time of 3.5 hours (Scheme S3). The conversion after each iteration was quantitative (Table S3, Figure S6) and narrow dispersities were retained throughout ($Đ$ = 1.07, Table S3, Figure 4a). Surprisingly, when the tertiary acrylamide DMA was employed as comonomer, the copolymerization was compromised following addition of the second aliquot of DMA (Table S4). Conversion, according to ^{1}H NMR (Figure S7), ceased upon addition of the 7th monomer feed (Table S4, entry 7) and evidence for premature termination was manifest as low molecular weight shoulder peak which was found to increase during subsequent monomer additions (Figure 4b).

This suggests that the limiting factor for chain extension is the lifetime of the ω-Br chain end, and that the rate of loss of this end group is faster in the presence of tertiary acrylamides such as DMA.

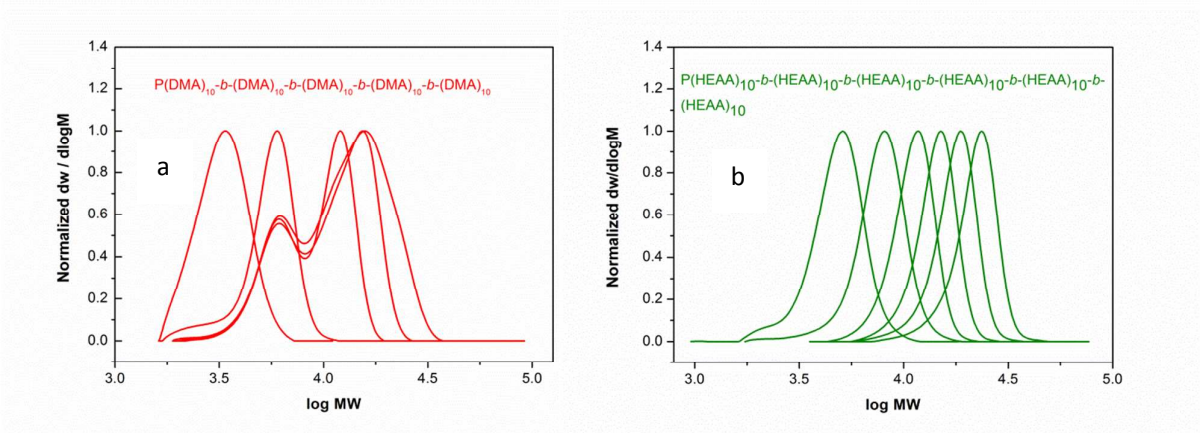


Figure 5. DMF SEC analyses for aqueous SET-LRP of multi-block homopolymers of HEAA and DMA (a, b). $[M]_0 : [I]_0 : [CuBr] : [Me_6TREN] = [10] : [1] : [0.04] : [0.04]$.

In order to probe this assumption block homopolymerizations of both HEAA and DMA were carried out. Secondary acrylamide HEAA was polymerized under the conditions described previously with chain extension afforded by sequential addition of degassed aliquots of HEAA at full converision. Comparable conversions to NIPAM were obtained (98-100%, Figure S9) and narrow dispersities were retained throughout ($Đ$ = 1.07, Table S5, Figure 5d). However, the limit to chain extension was found to be the hexablock polymer which was syntheized in 3.5 hours (Table S5, entry 6). The rate of reaction was slower than that observed for NIPAM, which could furnish a nonablock polymer in 3.5 hours, explaining, at least in part, the limited number of blocks possible for HEAA. Interestingly, homopolymerization and a single chain extension of DMA were found to proceed in comparable rate and with comparable control to that observed for NIPAM (Table S6, entry 1-2). However, following injection of a second aliquot of DMA, towards yielding a triblock homopolymer, significant low molecular weight termination was observed, indicative of ω-Br chain end loss (Figure 5a). It should be noted that this is apparent after only 30 minutes in the presence of the tertiary acrylamide, as opposed to 3.5 hours in the presence of secondary acrylamides.

The effect of monomer on chain-end fidelity. Being intrigued by the apparent enhancement of premature termination present during polymerization of DMA, an investigation into the relative rates of ω-Br chain end loss for secondary (NIPAM, HEAA)

and tertiary (DMA, NAM) acrylamides was conducted. Each monomer was homopolymerized via aqueous SET-LRP and then subsequently in all experiments NIPAM was employed as the model monomer and added at different time-delayed feeds. The extent of chain extension was evaluated by ^{1}H NMR and SEC analyses as standard.

We reported earlier that the homopolymerization of NIPAM was complete within 11 minutes. During this investigation, in order to assess the retention of end group fidelity as a function of time, the homopolymerization was allowed to proceed for 2-8 hours before addition of the second aliqout of NIPAM required for chain extension (Figure 6, Table S7). Despite the fast rate of the initial homopolymerization, successful chain extension was seperately achieved upon addition of the second portion of NIPAM after 2, 3, 4 and 5 hours respectively, further evidence against the sudden cessation of polymerisation as indicated above. ^{1}H NMR analysis confirmed the 100% conversion (Figure S10) for the chain extension and SEC analysis confirmed retention of the ω-Br chain end by a complete shift in the molecular weight distribution (Figure 6a, S11-S13). When addition of NIPAM was delayed for 8 hours, ^{1}H NMR revealed that the conversion was limited to 55%, as confirmed by SEC, which revealed minimal shift in the molecular weight distribution imposed by loss of the ω-Br chain end (Figure 6b).

In the original work describing aqueous SET-LRP, comprehensive compositional and end group analysis was conducted on poly(acrylamides) using low molecular weight PNIPAM (DP_n = 8). It was found that even at 0 °C, two modes of termination were operational. Hydrolysis of the ω-Br end group via a cyclic onium species (Scheme 1) and elimination of HBr to furnish either an OH or internal vinylic ω-end group. The present data suggests that the extent of termination increases as a function time and monomer structure.

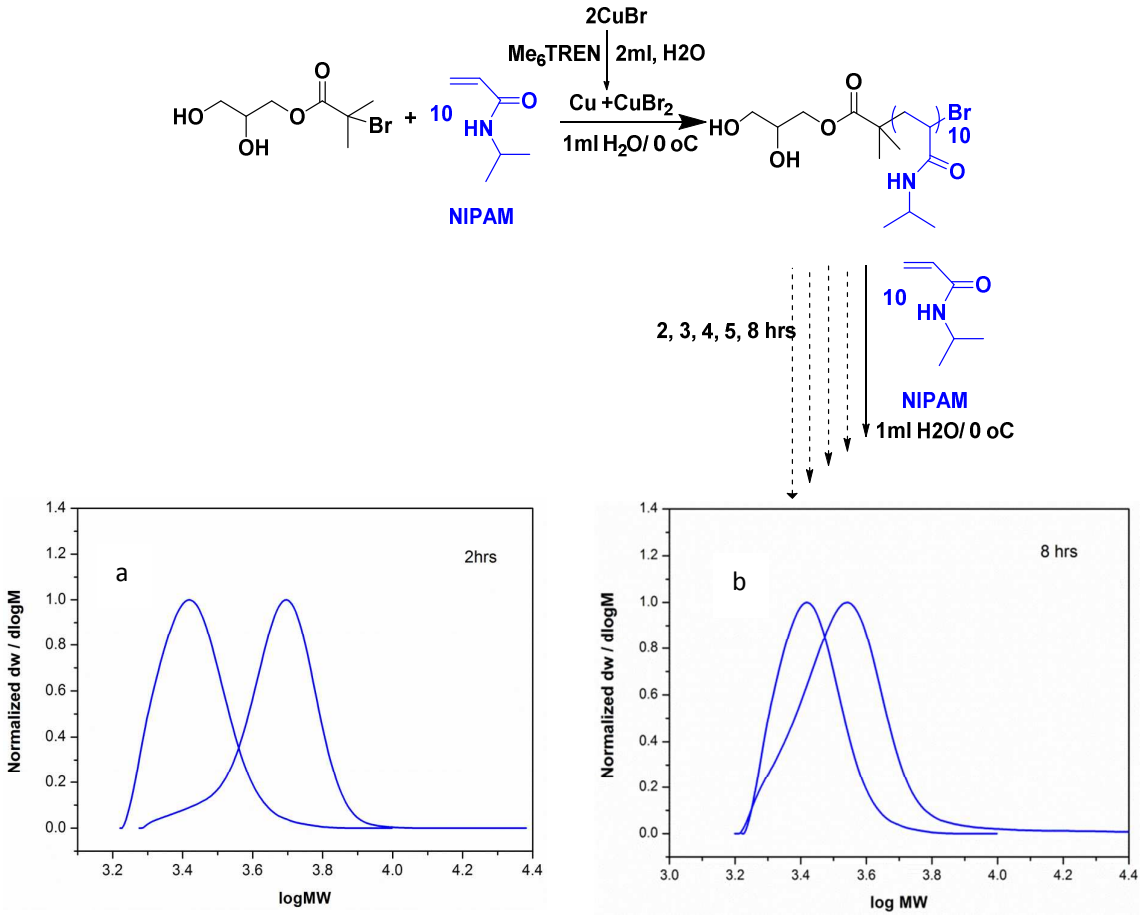


Figure 6. Assessment of the chain end fidelty of PNIPAM by in situ chain extension using deoxygenated NIPAM (10 eq). DMF SEC (a, b) following chain extension at delayed feed times. $[M]_0 : [I]_0 : [CuBr] : [Me_6TREN] = [10] : [1] : [0.04] : [0.04]$.

Similar results were obtained when alternative secondary acrylamide HEAA was homopolymerized with chain extension conducted via addition of NIPAM. Retention of the ω-Br chain end was evident when chain extension was delayed for up to 4 hrs (Table S8, Figure S14-S19). However, after a 5 hour delay, conversion was again limited (75 %, Table S7, Figure S18) and SEC revealed that chain extension and therefore end group fidelity had been compromised (Figure S17). Attempts to chain extend tertiary acrylamides DMA (Figure 7, Figure S19, Figure S20, Table S9) were successful when the aliquot of NIPAM was injected into the reaction mixture after a delay of up to 30 minutes. With delay times of an hour, or more, conversions and molecular weight shifts were significantly compromised, implying an enhancement in the loss of end group, in line with results obtained above.

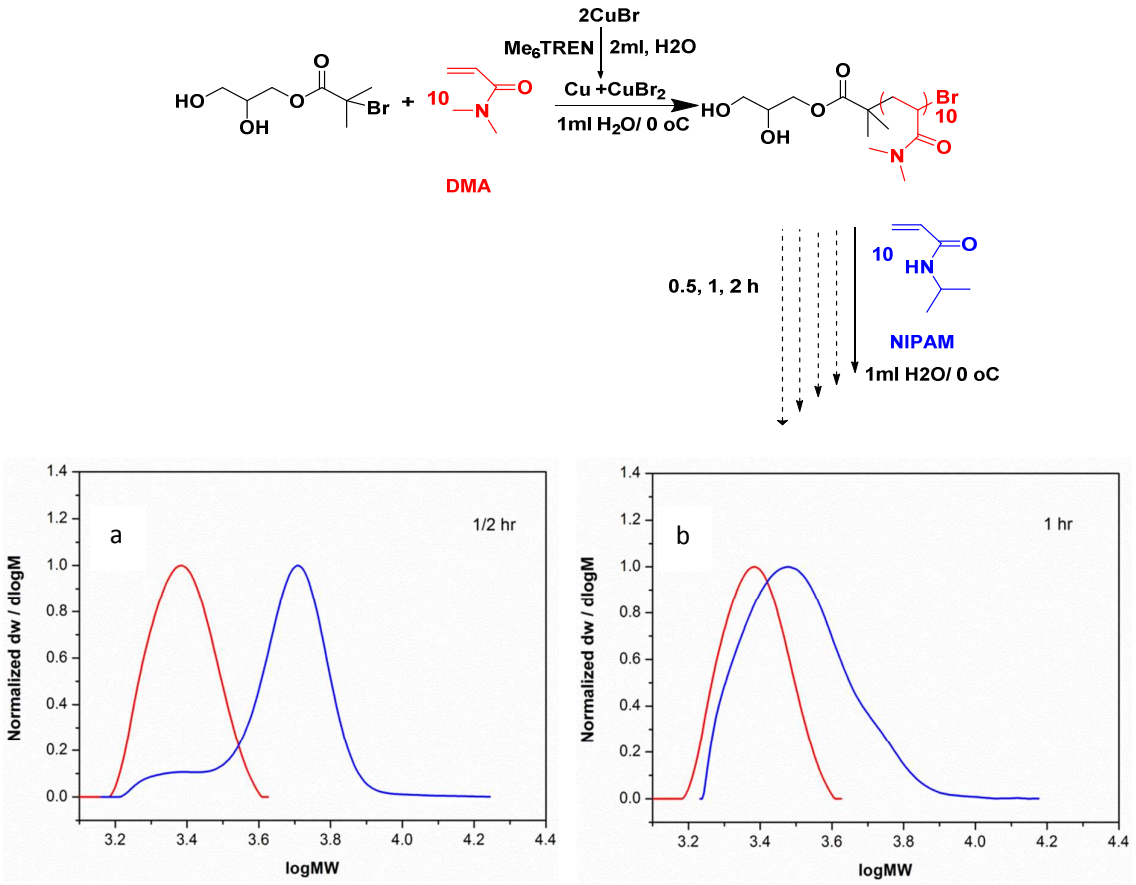


Figure 7: Assessment of the chain end fidelty of PDMA by in situ chain extension using deoxygenated NIPAM (10 eq). DMF SEC (a, b) and ^{1}H NMR (c) following chain enxtension at delayed feed times. $[M]_0 : [I]_0 : [CuBr] : [Me_6\text{-TREN}] = [10] : [1] : [0.04] : [0.04]$.

A second tertiary acrylamide, *N*-acryloylmorpholine, NAM, was also investigated. Homopolymerization of NAM via aqueous SET-LRP was recently reported with comment on the inability to successfully chain extend from a NAM macroinitiator via sequential monomer addition.[63] Therefore, to complete this investigation, NAM was screened to establish if this was due to an enhanced rate of chain end loss (Table S10). Following homopolmerization of NAM, addition of NIPAM after 30 minutes resulting in 100 % conversion according to ^{1}H NMR (Figure S24). However, even after just 30 minutes, SEC revealed a bimodal mass distribution (Figure S21), whereby a degree of the homopolymer was unable to chain extend following addition of NIPAM. Increasing the delay time resulted in an increase in chain end loss (Figure S22) until after a 2 hour delay, no chain extension was detected by SEC (Figure S23). Similarly, *N,N*-diethylacrylamide, DEA, showed same behaviour when identical conditions and procedures were used (Table S11, Figure S25-28). Though consistent with the

results obtained for DMA, NAM and DEA, this represents the fastest rate of ω-Br chain end loss for the tertiary acrylamides screened and offers an explanation for the results in the earlier publication.

Finally, to confirm the effect of the tertiary acrylamide on the loss of end group fidelity, homopolymers of PNIPAM and PDMA were synthesized and chain extension was attempted using a feed of DMA at the timed intervals reported above. According to ^{1}H NMR (Figure S31) and SEC (Figure 8a), PNIPAM was successfully chain extended upon addition of DMA following a delay of up to 3 hours (Table S12). Monomer injection after 4 hours furnished only limited conversion (28 %), and after a delay time of 24 hours, no conversion or chain extension was detected in ^{1}H NMR of SEC analysis (Figure 8b). Changing the homopolymer macroinitiator to PDMA invoked an increase in the rate of loss of ω-Br with a bimodal mass distribution apparent after a 30 minute delay prior to chain extension (Figure 8c-d, Table S13, Figure S32-S33).

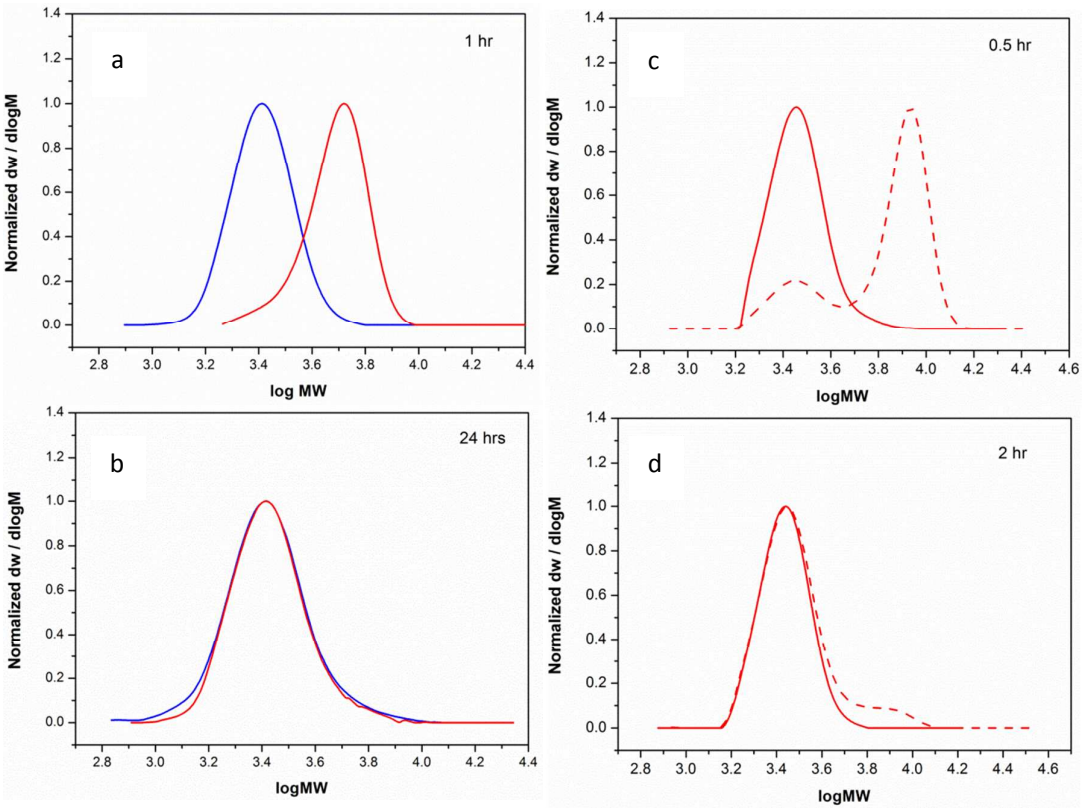


Figure 8: DMF SEC illustrating the effect of time on chain end retention during homopolymerization of NIPAM (a, b) and DMA (c, d). Chain extension attempted using deoxygenated DMA (10 eq). $[M]_0 : [I]_0 : [CuBr] : [Me_6TREN] = [10] : [1] : [0.04] : [0.04]$.

It has been proposed that one of the reasons for loss of control during the aqueous Cu-mediated polymerisation of (meth)acrylamides is substitution of the terminal bromine to form a cylic onium species.[36, 37] Teodorescu and Matyjaszewski have used small molecule models to show that substitution can occur through both the nitrogen and oxygen of the penultimate acrylamide monomer unit. Our results suggest that increasing the alkyl substitution and therefore the electron density of the amide group through inductive effects, increases the rate of this cyclisation reaction resulting in an enhanced rate of termination and loss of active chains.

Higher molecular weight block copolymers by aqueous SET-LRP. In order to investigate the dependence of block molecular weight upon the aqueous system, the average chain length per block was increased ten fold. Secondary acrylamides NIPAM and HEAA were polymerized with target DP_n = 100. The optimum amount of CuBr and Me_6TREN has been shown to vary with chain length.[55] Thus, the initial feed ratio was changed from $[M]_0$: $[I]_0$: [CuBr] : [Me_6TREN] = [10] : [1] : [0.04] : [0.04] to [100] : [1] : [0.08] : [0.04]. Although reactions were slower, full conversion was attained within 60 and 90 minutes respectively, and narrow dispersities were retained ($Đ \approx 1.10$, Figure S34-S35). The PNIPAM homopolymer was successfully chain extended upon two additional, sequential feeds of 100 molar equivalents (with respect to $[I]_0$) of deoxygentated aqueous NIPAM (Table S14). Diblock PNIPAM was obtained within a total reaction time of 2.5 hours ($Đ$ = 1.09), whilst the triblock was attained when the reaction was allowed to proceed overnight ($Đ$ = 1.08, Table S14, Figure S36). Furthermore, by switching the first chain extending monomer added to HEAA, a AB diblock copolymer P(NIPAM$_{100}$-*b*-HEAAm$_{100}$) was obtained with 4.5 hours ($Đ$ = 1.08, Table 3, entry 2). Addition of an aliquot of deoxygenated aqueous NIPAM to the diblock macroinitiator yielded an ABA triblock copolymer P(NIPAM$_{100}$-*b*-HEAAm$_{100}$-NIPAM$_{100}$) in a one pot process with retention of monomodal, narrow dispersity ($Đ$ = 1.14 Table 3, Figure 9).

Table 3: Preparation of higher molecular triblock copolymer prepared by sequential monomer additon during SET-LRP at 0 ℃ in H_2O. $[M]_0$: $[I]_0$: [CuBr] : [Me_6-TREN] = [100] : [1] : [0.04] : [0.04].

Entry	Block number	Monomer	Conv. (%)	Time per block (min)[a]	$M_{n,th}$ g.mol^{-1}	$M_{n,SEC}$[b] g.mol^{-1}	$Đ$[b]
1	Block 1	NIPAM	98	15 (15)	11600	13000	1.06

2	Block 2	HEAAm	99	250 (265)	23100	29000	1.08
3	Block 3	NIPAM	90	overnight	34200	42200	1.14

[a] Cumulative time in parentheses. [b] DMF SEC, calibrating with PMMA standard.

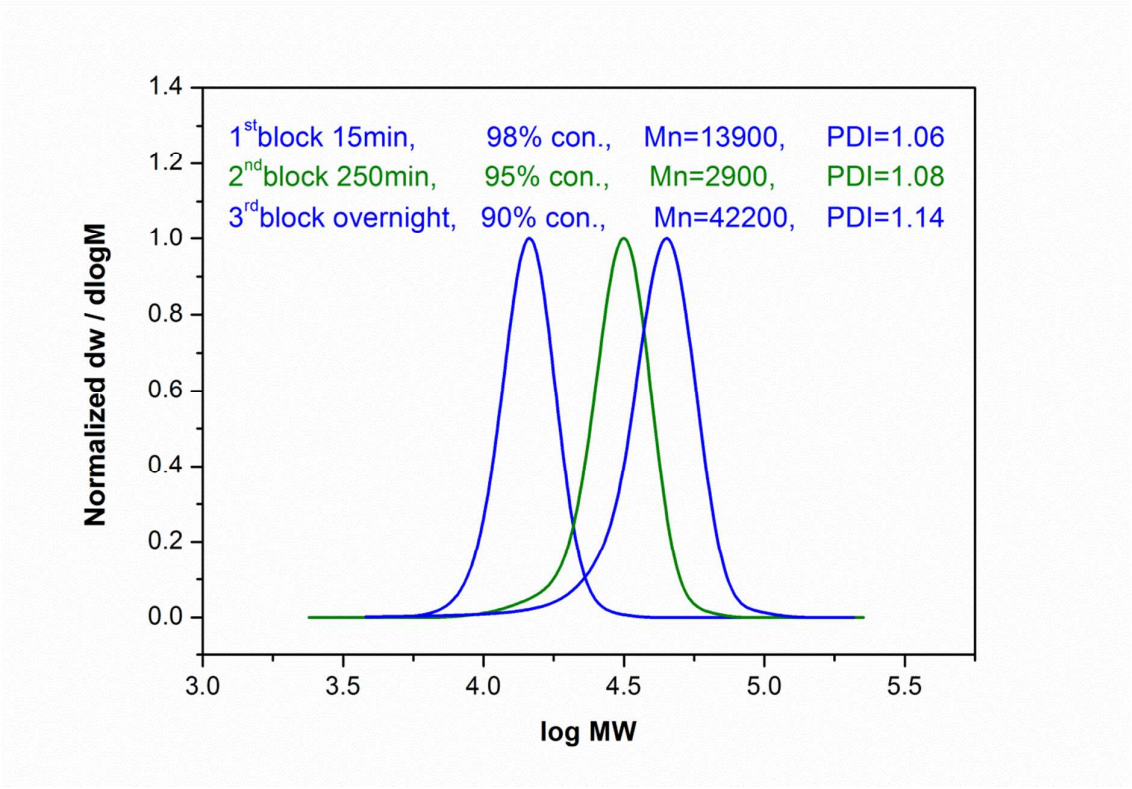


Figure 9: DMF SEC of ABA triblock copolymer P(NIPAM$_{100}$-*b*-HEAAm$_{100}$-NIPAM$_{100}$) prepared by aqueous SET-LRP with sequential monomer addition.

Conclusion

The synthesis of multi-block acrylamide copolymers via Cu-mediated radical polymerization of acrylamide monomers is reported. Disproportionation of unstable Cu(Me-$_6$TREN)Br in water results in formation of highly active Cu(0) and deactivating Cu(Me$_6$TREN)Br$_2$ *prior* to addition of initiator and monomer. Good knowledge of the rate of polymerization is required and subsequent management of the reaction can minimise the amount of termination by both conventional radical processes and adventitious side reactions. Thus, a 'nonablock' PNIPAM and a true multi-block comprised of three alternating acrylamides can be obtained within 3.5 hrs reaction time. The chain length per block can be reality increased from DP$_n$ = 10 to DP$_n$ = 100 to afford higher molecular weight block copolymers. The loss of the ω-Br chain end is a common limitation in Cu-mediated multi-block copolymerization. During aqueous polymerization it was recognized that tertiary

acrylamides (DMA, DEA, NAM) invoke an enhanced rate of chain end loss relative to secondary acrylamides (NIPAM, HEAA), as exemplified by a variety of kinetic chain extension experiments. This highlights the need for careful consideration of monomer choice and sequence when designing a multi-block copolymer composition.

Acknowledgements

We appreciate financial support from the University of Warwick. Equipment used in this research was supported by the Innovative Uses for Advanced Materials in the Modern World (AM2), with support from Advantage West Midlands (AWM), and partially funded by the European Regional Development Fund (ERDF). D.M.H. is a Royal Society/Wolfson Fellow.

Notes and references

[a] Department of Chemistry, University of Warwick, Coventry, UK

[b] Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Australia.

The data presented in this manuscript is complimented by Electronic Supplementary Information (ESI), including materials and experimental information as well appropriate supporting figures, schemes and tables. See DOI: 10.1039/b000000x/

References

1. N. Badi and J.-F. Lutz, *Chem. Soc. Rev.*, 2009, **38**, 3383-3390.
2. M. Ouchi, N. Badi, J. F. Lutz and M. Sawamoto, *Nat. Chem.*, 2011, **3**, 917-924.
3. J. F. Lutz, M. Ouchi, D. R. Liu and M. Sawamoto, *Science*, 2013, **341**, 1238149.
4. M. Ouchi, T. Terashima and M. Sawamoto, *Chem.Rev.*, 2009, **109**, 4963-5050.
5. M. Minoda, M. Sawamoto and T. Higashimura, *Macromolecules*, 1990, **23**, 4889-4895.
6. J.-F. Lutz, *Polym. Chem.*, 2010, **1**, 55-62.
7. J. Vandenbergh, G. Reekmans, P. Adriaensens and T. Junkers, *Chem. Commun.*, 2013, **49**, 10358-10360.
8. K. Nakatani, T. Terashima and M. Sawamoto, *J. Am. Chem. Soc.*, 2009, **131**, 13600-13601.
9. K. Nakatani, Y. Ogura, Y. Koda, T. Terashima and M. Sawamoto, *J. Am. Chem. Soc.*, 2012, **134**, 4373-4383.
10. S. Pfeifer and J.-F. Lutz, *J. Am. Chem. Soc.*, 2007, **129**, 9542-9543.
11. M. Zamfir and J.-F. Lutz, *Nat. Commun.*, 2012, 1138.
12. D. Moatsou, C. F. Hansell and R. K. O'Reilly, *Chem. Sci.*, 2014, **5**, 2246.
13. J.-F. Lutz, *Acc. Chem. Res.*, 2013, **46**, 2696-2705.
14. A. Khan, D. M. Haddleton, M. J. Hannon, D. Kukulj and A. Marsh, *Macromolecules*, 1999, **32**, 6560-6564.
15. A. Marsh, A. Khan, D. M. Haddleton and M. J. Hannon, *Macromolecules*, 1999, **32**, 8725-8731.
16. P. J. Milnes, M. L. McKee, J. Bath, L. Song, E. Stulz, A. J. Turberfield and R. K. O'Reilly, *Chem. Commun.*, 2012, **48**, 5614-5616.

17. S. Ida, T. Terashima, M. Ouchi and M. Sawamoto, *J. Am. Chem. Soc.*, 2009, **131**, 10808-10809.
18. S. Ida, M. Ouchi and M. Sawamoto, *J. Am. Chem. Soc.*, 2010, **132**, 14748-14750.
19. Y. Hibi, M. Ouchi and M. Sawamoto, *Angew. Chem. Int. Ed.*, 2011, **50**, 7434-7437.
20. Y. Hibi, S. Tokuoka, T. Terashima, M. Ouchi and M. Sawamoto, *Polym. Chem.*, 2011, **2**, 341-347.
21. R. McHale, J. P. Patterson, P. B. Zetterlund and R. K. O'Reilly, *Nat. Chem.*, 2012, **4**, 491-497.
22. C. Boyer, A. Derveaux, P. B. Zetterlund and M. R. Whittaker, *Polym. Chem.*, 2012, **3**, 117-123.
23. C. Boyer, A. H. Soeriyadi, P. B. Zetterlund and M. R. Whittaker, *Macromolecules*, 2011, **44**, 8028-8033.
24. A. H. Soeriyadi, C. Boyer, F. Nystrom, P. B. Zetterlund and M. R. Whittaker, *J. Am. Chem. Soc.*, 2011, **133**, 11128-11131.
25. A. Anastasaki, C. Waldron, P. Wilson, C. Boyer, P. B. Zetterlund, M. R. Whittaker and D. Haddleton, *ACS Macro Letters*, 2013, **2**, 896-900.
26. Q. Zhang, A. Anastasaki, G.-Z. Li, A. J. Haddleton, P. Wilson and D. M. Haddleton, *Polym. Chem.*, 2014, **5**, 3876.
27. Q. Zhang, J. Collins, A. Anastasaki, R. Wallis, D. A. Mitchell, C. R. Becer and D. M. Haddleton, *Angew. Chem. Int. Ed.*, 2013, **52**, 4435-4439.
28. C. J. Hawker, A. W. Bosman and E. Harth, *Chem. Rev.*, 2001, **101**, 3661-3688.
29. J. Nicolas, Y. Guillaneuf, C. Lefay, D. Bertin, D. Gigmes and B. Charleux, *Prog. Polym. Sci.*, 2013, **38**, 63-235.
30. J. Chiefari, Y. K. Chong, F. Ercole, J. Krstina, J. Jeffery, T. P. T. Le, R. T. A. Mayadunne, G. F. Meijs, C. L. Moad, G. Moad, E. Rizzardo and S. H. Thang, *Macromolecules*, 1998, **31**, 5559-5562.
31. G. Moad, E. Rizzardo and S. H. Thang, *Aust. J. Chem.*, 2009, **62**, 1402-1472.
32. M. Kato, M. Kamigaito, M. Sawamoto and T. Higashimura, *Macromolecules*, 1995, **28**, 1721-1723.
33. J.-S. Wang and K. Matyjaszewski, *J. Am. Chem. Soc.*, 1995, **117**, 5614-5615.
34. D. M. Haddleton, C. B. Jasieczek, M. J. Hannon and A. J. Shooter, *Macromolecules*, 1997, **30**, 2190-2193.
35. V. Percec, T. Guliashvili, J. S. Ladislaw, A. Wistrand, A. Stjerndahl, M. J. Sienkowska, M. J. Monteiro and S. Sahoo, *J. Am. Chem. Soc.*, 2006, **128**, 14156-14165.
36. J. T. Rademacher, M. Baum, M. E. Pallack, W. J. Brittain and W. J. Simonsick, *Macromolecules*, 2000, **33**, 284-288.
37. M. Teodorescu and K. Matyjaszewski, *Macromolecules*, 1999, **32**, 4826-4831.
38. M. Teodorescu and K. Matyjaszewski*, *Macromol. Rapid Commun.*, 2000, **21**, 190-194.
39. P. D. Iddon, K. L. Robinson and S. P. Armes, *Polymer*, 2004, **45**, 759-768.
40. J. Ye and R. Narain, *J. Phys. Chem. B*, 2008, **113**, 676-681.
41. A. Limer and D. M. Haddleton, *Macromolecules*, 2006, **39**, 1353-1358.
42. D. A. Z. Wever, P. Raffa, F. Picchioni and A. A. Broekhuis, *Macromolecules*, 2012, **45**, 4040-4045.
43. N. H. Nguyen, B. M. Rosen and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 1752-1763.
44. E. A. Appel, J. del Barrio, X. J. Loh, J. Dyson and O. A. Scherman, *J. Polym. Sci., Part A: Polym. Chem.*, 2012, **50**, 181-186.
45. H. D. Maynard, K. L. Heredia, R. C. Li, D. P. Parra and V. Vazquez-Dorbatt, *J. Mater. Chem.*, 2007, **17**, 4015-4017.
46. G. Gody, T. Maschmeyer, P. B. Zetterlund and S. Perrier, *Nat. Commun.*, 2013, **4**.
47. G. Gody, T. Maschmeyer, P. B. Zetterlund and S. b. Perrier, *Macromolecules*, 2014.
48. P. B. Zetterlund, G. Gody and S. Perrier, *Macromol. Theory Simul.*, 2014.

49. G. Gody, T. Maschmeyer, P. B. Zetterlund and S. Perrier, *Macromolecules*, 2014, **47**, 3451-3460.
50. J. Chiefari, J. Jeffery, R. T. A. Mayadunne, G. Moad, E. Rizzardo and S. H. Thang, *Macromolecules*, 1999, **32**, 7700-7702.
51. B. P. Fors and C. J. Hawker, *Angew. Chem. Int. Ed.*, 2012, **51**, 8850-8853.
52. J. Xu, K. Jung, A. Atme, S. Shanmugam and C. Boyer, *J. Am. Chem. Soc.*, 2014, **136**, 5508-5519.
53. A. Anastasaki, V. Nikolaou, G. S. Pappas, Q. Zhang, C. Wan, P. Wilson, T. P. Davis, M. R. Whittaker and D. M. Haddleton, *Chem. Sci.*, 2014.
54. Y.-M. Chuang, A. Ethirajan and T. Junkers, *ACS Macro Letters*, 2014, **3**, 732-737.
55. Q. Zhang, P. Wilson, Z. Li, R. McHale, J. Godfrey, A. Anastasaki, C. Waldron and D. M. Haddleton, *J. Am. Chem. Soc.*, 2013, **135**, 7355-7363.
56. Q. Zhang, P. Wilson, A. Anastasaki, R. McHale and D. M. Haddleton, *ACS Macro Letters*, 2014, 491-495.
57. Q. Zhang, Z. Li, P. Wilson and D. M. Haddleton, *Chem. Commun.*, 2013, **49**, 6608-6610.
58. C. Waldron, Q. Zhang, Z. Li, V. Nikolaou, G. Nurumbetov, J. Godfrey, R. McHale, G. Yilmaz, R. K. Randev, M. Girault, K. McEwan, D. M. Haddleton, M. Droesbeke, A. J. Haddleton, P. Wilson, A. Simula, J. Collins, D. J. Lloyd, J. A. Burns, C. Summers, C. Houben, A. Anastasaki, M. Li, C. R. Becer, J. K. Kiviaho and N. Risangud, *Polym. Chem.*, 2014, **5**, 57.
59. B. Le Droumaguet and J. Nicolas, *Polym. Chem.*, 2010, **1**, 563-598.
60. Y. Qi and A. Chilkoti, *Polym. Chem.*, 2014, **5**, 266-276.
61. D. Konkolewicz, Y. Wang, M. Zhong, P. Krys, A. A. Isse, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 8749-8772.
62. S. Harrisson and J. Nicolas, *ACS Macro Letters*, 2014, **3**, 643-647.
63. A. Anastasaki, A. J. Haddleton, Q. Zhang, A. Simula, M. Droesbeke, P. Wilson and D. M. Haddleton, *Macromol. Rapid Commun.*, 2014, **35**, 965-970.