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Aqueous Copper-Mediated Living Polymerization: Exploiting Rapid Disproportionation of CuBr with Me_6TREN

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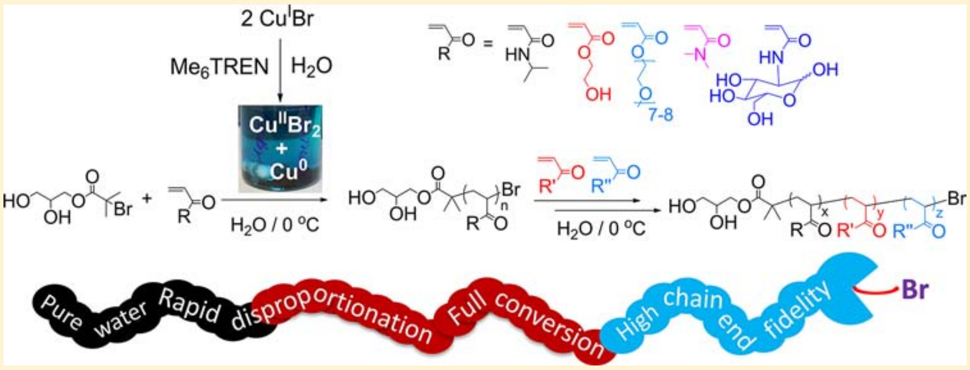
Supporting Information



ABSTRACT: A new approach to perform single-electron transfer living radical polymerization (SET-LRP) in water is described. The key step in this process is to allow full disproportionation of CuBr/Me_6TREN (TREN = tris(dimethylamino)ethyl amine to Cu(0) powder and $CuBr_2$ in water prior to addition of both monomer and initiator. This provides an extremely powerful tool for the synthesis of functional water-soluble polymers with controlled chain length and narrow molecular weight distributions (polydispersity index approximately 1.10), including poly(*N*-isopropylacrylamide), *N*,*N*-dimethylacrylamide, poly(ethylene glycol) acrylate, 2-hydroxyethyl acrylate (HEA), and an acrylamido glyco monomer. The polymerizations are performed at or below ambient temperature with quantitative conversions attained in minutes. Polymers have high chain end fidelity capable of undergoing chain extensions to full conversion or multiblock copolymerization via iterative monomer addition after full conversion. Activator generated by electron transfer atom transfer radical polymerization of *N*-isopropylacrylamide in water was also conducted as a comparison with the SET-LRP system. This shows that the addition sequence of L-ascorbic acid is crucial in determining the onset of disproportionation, or otherwise. Finally, this robust technique was applied to polymerizations under biologically relevant conditions (PBS buffer) and a complex ethanol/water mixture (tequila).

■ INTRODUCTION

Controlled and living radical polymerization methods have evolved to become almost routine. However, in the majority of cases, they still prove problematic in water. Given the expanding interest in hydrophilic and biocompatible polymers in an ever-widening array of applications, this deficiency in the synthetic toolbox needs to be addressed.

Copper-mediated living polymerization remains one of the most widely applied and useful methods of controlling vinyl polymerization. Thus, a greater understanding and development of very well controlled Cu-mediated polymerization in water and other aqueous media is required. All existing protocols are encumbered by important, and often overlooked, competing reactions that can reduce the polymerization control, broadening polydispersity index (PDI) values which can generally fall between 1.2 and 1.4. However, living anionic polymerization, a standard bearer in living polymerization, allows facile access to polymers with PDI values <1.10. As many applications are increasingly in biological and therapeutic fields, there is a pressing requirement for better control over both PDI and end group fidelity.

As polymerization initiators and propagating chains are usually secondary or tertiary alkyl halides in Cu-mediated radical polymerization (typically bromide or chloride, X), hydrolysis or elimination of HX can occur at an appreciable rate, leading to chain termination. Although conceptually a simple reaction, hydrolysis usually requires a base, and as a result, this reaction is seldom used for synthetic organic purposes. However, it has been reported that tertiary alkyl α-halocarbonyls can be efficiently converted to alcohols with silver oxide in aqueous acetonitrile.[1]

The use of copper complexes—as polymerization catalysts—extends the likelihood of competing side reactions via possible removal of a halide anion or homolytic bond cleavage. With respect to controlled polymerization reactions in aqueous

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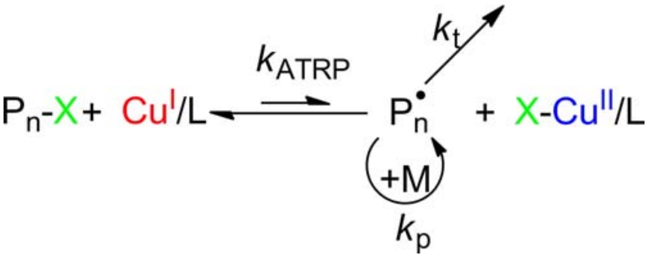
media, any such aqua-mediated side reactions which occur at an appreciable rate relative to initiation and/or propagation will lead to loss of active species, low initiation efficiency, and/or premature termination. The overall consequence of this is a loss of both molecular weight control and the inability to chain extend to block copolymers and introduce desirable chain end functionality. Despite Cu(I) retaining a full complement of d-electrons (d^{10}), it is very unstable with respect to oxidation and readily undergoes rapid disproportionation to Cu(0) and Cu(II) in aqueous and polar media. The equilibrium constants for the disproportionation vary considerably depending on the ligands, temperature, counteranions, and solvent composition. Unless there is a stabilizing effect such as a π-acceptor orbital on the ligand, as in pyridine imines,[2−4] diazabutadienes,[5] tripyridylmethylamine (TPMA),[6] and bipyridine,[7,8] or other stabilizing effects such as solvation by acetonitrile, these equilibrium constants can be high, particularly in water (approaching 10^6).

The occurrence, or not, of disproportionation is also highly dependent on ligand geometry. Many sterically constrained ligands, such as Me_6TREN (TREN = tris(2-aminoethyl)-amine), cause deviations away from a preferred geometry, exposing coordination sites to water, monomer, and other ligation. Although this does not seem to be fully understood, it is ascribed in inorganic textbooks to be in part due to greater lattice and solvation energetics as well as higher formation constants for Cu(II) complexes relative to Cu(I). Thus, there is a very large thermodynamic driving force toward disproportionation under appropriate conditions, e.g., in water. Matyjaszewski et al. have reported that atom transfer radical polymerization (ATRP)[7,9] can be influenced by a conditional disproportionation constant.[10] This knowledge, they suggest, can be used to select an appropriate ligand for ATRP which should exhibit high activity toward activation and deactivation processes but remain stable with respect to disproportionation.[11] Using this rationale, it is clear that aqueous ATRP employing Cu(I) in conjunction with tertiary amine ligands that distort complex geometry (Me_6TREN or *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA)) is not a favored approach.

A well-accepted mechanism for Cu(I)-mediated ATRP, which is reproduced in many papers, is shown in Scheme 1.[12]

Scheme 1. Accepted Mechanism for ATRP



The mechanism is often discussed in terms of the equilibrium constant, K_{ATRP}, which has been measured during polymerization of methyl acrylate (MA) under a range of conditions and in a variety of polar solvents. Considering the contrasting stability of Cu(I) under these conditions, it is notable that the additional equilibrium between Cu(I) and Cu(0)/Cu(II) is often omitted from reaction schemes. As the equilibrium lies very much to the left, with measured K_{ATRP} values on the order of 10^{-9}−10^{-8}, there should be very significant amounts of Cu(I) in solution. In DMSO, in the presence of Me_6TREN, there is a significant level of disproportionation;[13,14] thus, there are many different complexes present during propagation. The removal of Cu(I) from this equation via disproportionation increases complexity and should not be ignored when considering the reaction mechanism.

The ATRP of acrylamide monomers has proven problematic, with Brittain concluding that ATRP of *N,N*-dimethylacrylamide (DMA) was not controlled.[15] This was purported to be due to complexation of the amido group at the chain ends, which stabilized the propagating radicals. It was suggested that this retarded the deactivation step in ATRP, giving an unacceptably high concentration of radicals and leading to bimolecular termination. Additionally, cyclization involving nucleophilic Br displacement by the penultimate amide nitrogen was invoked, and hydrolysis of the resulting onium intermediate furnished hydroxyl-terminated polymers.

Greater success has been achieved in the polymerization of *N*-isopropylacrylamide (NIPAM) under apparent ATRP conditions.[16] It is worthwhile to note that most Cu-mediated living radical polymerizations (LRPs) of NIPAM have usually been performed using chloro-based initiators with CuCl/$CuCl_2$/Me_6TREN catalyst in high-polarity organic solvents (alcohol, DMF, or DMSO) or binary mixtures of water and organic solvents.[17−25] The only example of ATRP of NIPAM in water with no added cosolvent required a high ratio of Cu(II) salts for effective deactivation to retain good control.[26] Likewise, in the expanding field of nanomedicine, NIPAM-containing (block) copolymers are desirable for the formation of responsive, dynamic assemblies. Statistical copolymerization and in situ chain extension of NIPAM have been conducted, however, due to the complex nature of (meth)acrylamide systems; examples of block copolymerizations via Cu-mediated methods are limited.[22,25,27] Nitroxide-mediated polymerization (NMP) and reversible addition−fragmentation chain transfer polymerization (RAFT) are therefore often employed for the (co)polymerization of NIPAM.[28−31]

Single-electron transfer living radical polymerization (SET-LRP) employs Cu(0) as the activator and cites the disproportionation of in situ formed Cu(I) into highly active "nascent" Cu(0) and Cu(II) as a key step in the mechanism.[32−35] Percec et al. have conducted numerous investigations toward identifying the degree, rate, location, and effect of the disproportionation phenomenon under assumed SET-LRP conditions, and the mechanism has been discussed at length in these papers.[13,35−40] The presence of nascent Cu(0) has been microscopically verified,[41] and the enhanced activity of these species has been demonstrated via polymerization mediated by Cu(0) particles prepared in situ from disproportionation [L_nCu^IX] in polar solvents and their binary mixtures in water.[42] Intentional termination and reactivation experiments have also been used to ascertain the activating species and highlight the "living" nature of this process.[43,44] It is not the purpose of the present work to repeat this mechanistic investigation but to extend the use to efficient use in water and aqueous media as a solvent.

Thus, there are currently conflicting reports in the literature regarding the effectiveness and mechanism of Cu-mediated polymerization in aqueous media (particularly for acrylamide monomers). Herein, we report the SET-LRP polymerization of a variety of water-soluble monomers using Cu(0) and $CuBr_2$ as the activator and deactivator, respectively. The catalyst is prepared, for the first time, by in situ disproportionation of CuBr/Me_6TREN in pure water prior to addition of monomers and initiator. Careful experimental design allowed the use of hydrolytically labile bromine-containing initiator and propagating species. Optimization of the reaction conditions, according to the published mechanism, also provides near-quantitative end-group fidelity which is exemplified by iterative chain extension toward the synthesis of well-defined multiblock copolymers.

■ RESULTS AND DISCUSSION

Disproportionation of Cu^IX (X = Br, Cl)/*N*-Ligand Complexes in Water. Cu^IX/*N*-ligand complexes are frequently employed in living radical polymerization, either as catalysts in ATRP or as activator precursors in SET-LRP.[45,46] The disproportionation of Cu^IX/*N*-ligand complexes into nascent Cu(0) and Cu(II) is considered the crucial step in SET-LRP, which has been demonstrated to occur in a series of polar solvents and monomers.[35] Many papers report that the disproportionation is a *slow* process relative to propagation and overall chain formation. As such, SET-LRP has also been considered in some of the literature as ARGET ATRP (activator regenerated by electron transfer atom transfer radical polymerization) or SARA ATRP (supplemental activator and reducing agent atom transfer radical polymerization).[47] To conduct successful polymerization in water, it is important to define more precisely the nature of Cu^IX/*N*-ligand complexes in water.

Disproportionation of Cu(I) in water in the absence of *N*-donor ligands proceeds efficiently (with an equilibrium constant of ~10^6) when noncoordinating ClO_4^- and SO_4^{2-} counterions are present.[48] However, copper(I) halides, which are widely used in both ATRP and SET-LRP, have low solubility in water. Consequently, the disproportion to copper(0) and copper(II) halides, which should lead to a slightly blue color in water, is not significant at ambient temperature when ligands are absent (S Figure 1, Supporting Information).

With the addition of *N*-donor ligands, copper(I) halides coordinate to form water-soluble complexes.[49] As Cu(I) can be stabilized in water by ligands that have π-acceptor orbitals, both *N*-ethyl-2-pyridylmethanimine and CuBr were added to water to form a stable water-soluble complex which is dark brown in color due to metal to ligand charge transfer. No precipitate or color change resulting from disproportionation was observed even when the mixture was heated to 50 °C for 1 h (S Figure 5, Supporting Information).

Me_6TREN is a widely used tetradentate tertiary amine-based ligand in both ATRP and SET-LRP. Previously it has been reported that this ligand does not stabilize Cu(I) in aqueous solution, with disproportionation proceeding with an equilibrium constant of ~1.4×10^3.[13,49] In our hands, when CuBr was added to an aqueous solution of Me_6TREN, the solution instantly became blue and Cu(0) powder was formed even in the presence of air (S Figure 1, Supporting Information). Under oxygen-free conditions, disproportionation of CuBr/Me_6TREN in water is fast and significant, yielding an obvious purple-red-colored Cu(0) precipitate and a bright blue solution (S Figure 2, Supporting Information). Careful separation of the blue solution from the Cu(0) precipitate and UV/vis characterization, by way of comparison with known concentrations of $CuBr_2$/Me_6TREN/H_2O solutions (Figure 1), confirmed the existence of $CuBr_2$ from disproportionation, and the results were in accordance with the literature.[13,50] Concurrent mass measurement of Cu(0) precipitate and concentration calculations via UV/vis showed that the extent of disproportionation is close to 100% (S Figures 3 and 4, Supporting Information), implying that stable, detectable CuBr/Me_6TREN complexes cannot exist in a water solution for any significant period of time. Indeed, visual and quantitative analysis of the suspension formed after mixing CuBr with Me_6TREN in water revealed the existence of newly formed Cu(0) powder and $CuBr_2$/Me_6TREN/H_2O complexes.

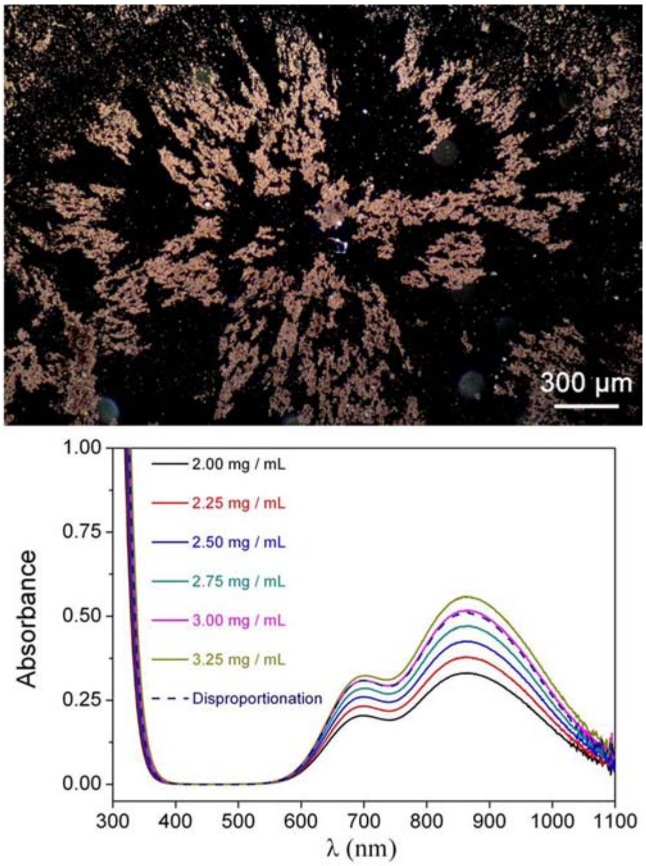


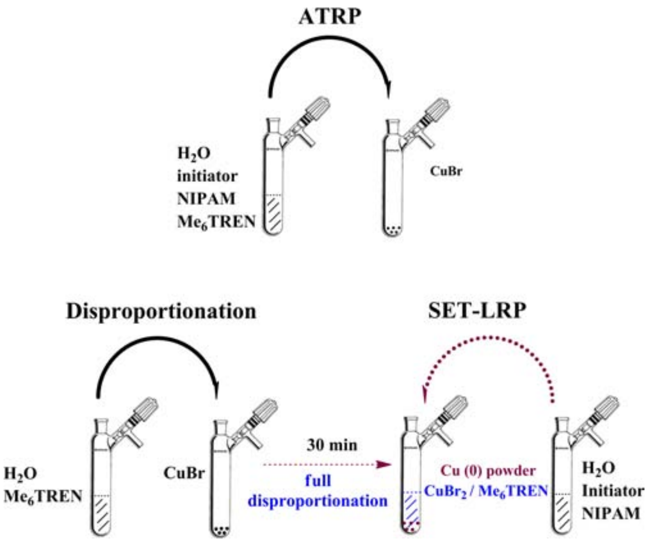
Figure 1. Optical microscopy image (top) of copper powder from disproportionation of CuBr/Me_6TREN in H_2O and UV−vis spectra (bottom) of the solution of $CuBr_2$/Me_6TREN and filtered disproportionation solution (dashed line).

In a previous report regarding the ATRP of NIPAM, a catalyst stock solution of CuCl/Me_6TREN in water was used without reference to any observation of this disproportionation reaction.[17] However, upon addition of CuCl to aqueous Me_6TREN, we predictably observed significant existence of purple-red-colored Cu(0) precipitate and a blue solution, indicative of rapid disproportionation.

Synthesis of Poly(*N*-isopropylacrylamide) (PNIPAM) by ATRP in Water. The challenges in performing ATRP in protic media are often attributed to inefficient deactivation, relative to activation and propagation, and the existence of side reactions with both the catalyst and chain end.[51] As a useful reference point for the present study, we first investigated the ATRP of NIPAM in water using a traditional experimental approach.

To avoid the direct disproportionation of Cu^IBr promoted by Me_6TREN in water, a degassed initiator/NIPAM/Me_6TREN aqueous solution was transferred to a second Schlenk tube containing CuBr under nitrogen for ATRP (Scheme 2). In a polymerization using a ratio of [initiator]:[CuBr]:[Me_6TREN] = 1:1:1 at ambient temperature, fast polymerization resulted in a gel precipitate with PDI = 2.60 and 100% conversion in 30 min (S Figure 7, Supporting Information). CuBr was observed to diminish during the polymerization as exemplified by the blue color of the solution becoming more intense (S Figure 6, Supporting Information). Optimization of polymerization conditions with a lower ratio of [initiator]:[CuBr]:[Me_6TREN] = 1:0.8:0.4 in an ice/water bath allowed polymerization without gel formation, attaining 100% conversion in 30 min, but the PDI was still high (2.70) (Figure 2) (S Figure 8, Supporting Information). The high molecular weight tail may be caused by the fast initiation and propagation due to the highly reactive catalyst in water and also ineffective deactivation due to the absence of additional copper(II) halides. To summarize, the ATRP of NIPAM in water via the traditional ATRP approach of adding degassed ligand, monomer, and initiator to CuBr under an inert blanket does not yield a controlled/living system.

Scheme 2. Schematic Representation of Procedures for ATRP and SET-LRP via Prior Disproportionation of CuBr/Me_6TREN in Water



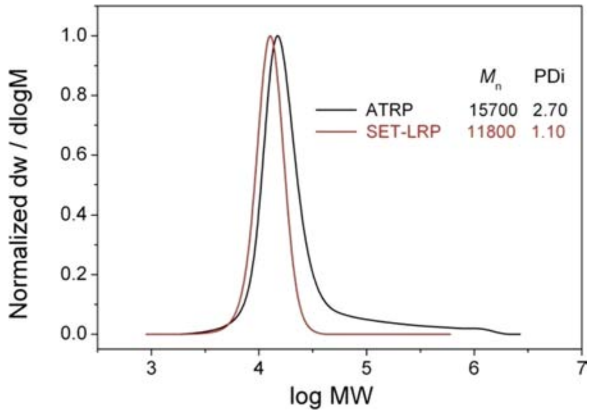


Figure 2. Molecular weight distributions of PNIPAM by ATRP and SET-LRP with [NIPAM]:[initiator]:[CuBr]:[Me_6TREN] = 80:1:0.8:0.4 at 0 °C as measured via SEC employing DMF as the eluent.

Cu(0)-Wire-Mediated SET-LRP of NIPAM and $PEGA_{480}$ (PEGA = Poly(ethylene glycol) Acrylate) in Water. Cu(0)-wire-mediated SET-LRP of NIPAM and $PEGA_{480}$ was performed in both dipolar aprotic and protic solvents.[14,40,42] Addition of Cu(II) halides proved to be required for deactivation and suppression of an induction period. As a further reference point, the SET-LRPs of NIPAM and $PEGA_{480}$ were performed using a Cu(0) wire/$CuBr_2$/Me_6TREN catalyst system in water. For NIPAM polymerization, there tends to be an induction period of >2 h prior to monomer conversion reaching >99% in a further 2 h, resulting in a final polymer with M_n = 7200 and a dispersity of 1.13 (S Figure 12, Supporting Information). For the analogous polymerization of $PEGA_{480}$, the polymerization rate is moderate without a significant induction period, reaching approximately 99% conversion in 5 h and resulting in a final polymer with M_n = 6500 and a dispersity of 1.11 (S Figure 13, Supporting Information). The results obtained are in accordance with a previous report.[40]

Generation of Cu(0) Powder and $CuBr_2$ via Disproportionation of CuBr/Me_6TREN in Water for SET-LRP of NIPAM under Apparent ATRP Conditions. Disproportionation of CuBr promoted by Me_6TREN in water yields a purple-red-colored precipitate of Cu(0) powder and $CuBr_2$/Me_6TREN aqua complexes (S Figure 9, Supporting Information). The fine Cu(0) powders should be highly active toward reaction with the initiator, while $CuBr_2$ in solution is necessary in mediating the deactivation step, particularly at the beginning of the polymerization.

Previous work describing ATRP using stock solutions of CuCl/Me_6TREN and in situ SET-LRP of NIPAM either seem to have ignored the above phenomena or did not discuss the occurrences or consequences. This could be due to the use of mixed water/organic solvents where the organic solvents act as dispersants for the Cu(0) or the additional complexity associated with employing mixed initiator/Cu(I) halogen/ligand/monomer/solvent systems together, which likely has an effect on the rate and extent of disproportionation.[17,22,25]

To investigate the potential of the suspension arising from disproportionation to control polymerization, we injected a degassed solution of initiator and NIPAM into the obtained blue suspension and left the mixture to react in an ice/water bath for 30 min. It is noteworthy that the reagent quantities and conditions used mirror those applied to the ATRP procedure discussed above, with the only change being the precursory disproportionation reaction. ^{1}H NMR analysis confirmed full conversion according to the disappearance of the vinyl peaks. Surprisingly, size exclusion chromatography (SEC) characterization revealed a very symmetrical Poisson-shaped distribution with M_n = 11 800 and a dispersity of 1.10 without tailing at either high or low molecular weight (MW) (Figure 2).

To identify the synergistic nature of the disproportionation products, the Cu(0) precipitate was carefully separated from the blue solution, washed with water repeatedly, and added to equivalent amounts of Me_6TREN/H_2O (S Scheme 8, Supporting Information). Initiator/NIPAM solutions were then injected separately into both the Cu(0)/Me_6TREN and $CuBr_2$/Me_6TREN systems to test for polymerization activity.

The polymerization catalyzed by the separated Cu(0) (and additional Me_6TREN) reached 96% conversion in 15 min according to ^{1}H NMR (S Figure 16, Supporting Information). However, the reaction solution had an observable high viscosity, and SEC showed a very broad peak with M_n = 5400 and a dispersity of 13.25 (Figure 3). Addition of an initiator/NIPAM solution to the bright blue $CuBr_2$/Me_6TREN solution showed no detectable polymerization after 24 h according to both ^{1}H NMR and SEC analysis (S Figures 15 and 16).

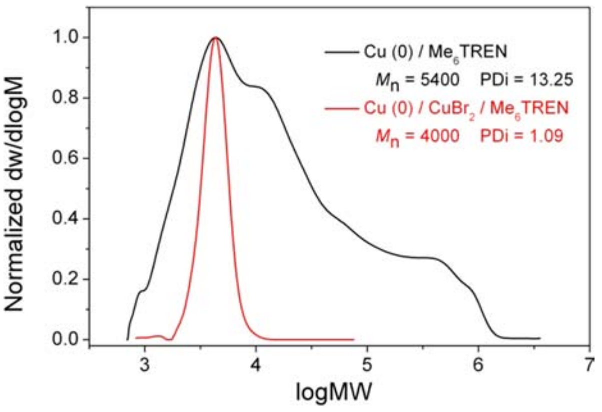


Figure 3. Molecular weight distributions of PNIPAM (DP = 20) catalyzed by separated Cu(0) powder/Me_6TREN (black) or Cu(0) powder/$CuBr_2$/Me_6TREN (red) in H_2O at ambient temperature as measured via SEC employing DMF as the eluent.

For the polymerization catalyzed by the Cu(0)/$CuBr_2$/Me_6TREN suspension resulting from the initial disproportionation, full conversion was attained in 30 min and SEC showed a final polymer with M_n = 4000 and a dispersity of 1.09 (Figure 3). These experiments indicate it is unlikely CuBr/Me_6TREN complexes exist under these conditions or any minute quantities present are incapable of efficiently catalyzing ATRP. Crucially, the in situ generated Cu(0) powders and $CuBr_2$ are required to be present in tandem for a controlled SET-LRP polymerization.

Synthesis of PNIPAM by AGET ATRP in Water. AGET ATRP utilizes water-soluble reducing agents (typically L-ascorbic acid) to reduce higher oxidation state Cu(II)/ligand complexes and generate Cu(I)/ligand complexes which are claimed to have higher catalytic stability. This allows for reduced catalytic loadings and, hence, more applicability in heterogeneous systems.[52,53] To check the stability and behavior of the obtained Cu(I)/ligand complexes for AGET ATRP, we polymerized NIPAM using $CuBr_2$/Me_6TREN and L-ascorbic acid at ambient temperature. Initial experiments were carried out according to the literature reported procedure using slightly less reducing reagent with a ratio of [$CuBr_2$]:[Me_6TREN]:[L-ascorbic acid] = 1:1:0.4, resulting in only 60% conversion after 16 h to give a product with M_n = 2500 and a dispersity of 1.11 (S Figure 54, Supporting Information). Under more optimized conditions, with a ratio of [$CuBr_2$]:[Me_6TREN]:[L-ascorbic acid] = 1:2:0.5, the polymerization rate was increased and conversion reached 85% in 15 min, with full conversion attained with a final M_n = 4000 and a dispersity of 1.10 (S Figure 55, Supporting Information). Interestingly, the initially blue solution remained clear throughout the polymerization when L-ascorbic acid was added, and no significant visible Cu(0) precipitation was observed (S Figure 53, Supporting Information), suggesting that disproportionation of the reduced Cu(I)/ligand complexes does not occur under these conditions.

To distinguish the Cu(I)/ligand complexes from the polymerization solution, we first made a solution of Cu(I)/ligand prior to addition of initiator and monomer, either by addition of the L-ascorbic acid to the $CuBr_2$/Me_6TREN solution or addition of Me_6TREN after mixing $CuBr_2$/L-ascorbic acid. Interestingly, foaming occurred when L-ascorbic acid was added to the clear blue solution of $CuBr_2$/Me_6TREN, resulting in a turbid white suspension. Following the injection of monomer and initiator, the suspension immediately became clear (S Figure 59, Supporting Information). ^{1}H NMR showed that polymerization stopped at a conversion of 36%, and SEC analysis revealed an asymmetric peak with M_n = 1800 and a dispersity of 1.10.

A white precipitate of CuBr was obtained when L-ascorbic acid was added to the light blue solution of $CuBr_2$, disappearing when Me_6TREN was added, leaving a bright blue solution with the appearance of a red Cu(0) precipitate, indicative of disproportionation (S Figure 56, Supporting Information). Subsequently, initiator and monomer were added to start polymerization. When a ratio of [$CuBr_2$]:[Me_6TREN]:[L-ascorbic acid] = 1:1:0.4 was used, polymerization stopped at 61% conversion with a final M_n = 2500 and dispersity of 1.08 (S Figure 57, Supporting Information). With [$CuBr_2$]:[Me_6TREN]:[L-ascorbic acid] = 1:2:0.5, polymerization was fast and full conversion was attained in 15 min with a final M_n = 4000 and M_w/M_n = 1.12 (S Figure 58, Supporting Information).

These experiments further underline the complexity inherent in Cu-mediated LRP, which showed that the copper aquo ion behaves very differently from the Cu(I,II)/ligand complexes. L-Ascorbic acid has been shown to coordinate with copper even in the presence of *N*-ligands.[54−56] The reduction of $CuBr_2$ also releases HBr into the solution, and it is still not clear whether this protonates Me_6TREN or effects the disproportionation. Thus, the catalyst in this AGET ATRP system does not seem to be a CuBr/Me_6TREN/H_2O complex, or disproportionation does not proceed under such conditions. Further research is required for full understanding.

Synthesis of PNIPAM with Varying Degree of Polymerization (DP) by SET-LRP in Water. SET-LRP catalyzed by in situ generated Cu(0) and $CuBr_2$ formed via disproportionation of CuBr/Me_6TREN in water was used for the synthesis of PNIPAM with DP between 8 and 320. Polymerizations were conducted under strict degassing procedures using either repeated freeze−pump−thaw procedures or, more conveniently, nitrogen bubbling. For DP = 8, 20, and 40, polymerizations were conducted at ambient temperature (∼18 °C) using a ratio of [CuBr]:[Me_6TREN] = 1:1. ^{1}H NMR analysis of the polymerization (DP = 40) showed conversion reached 93% in 5 min, 99% in 10 min, and 99.9% in 15 min, with full conversion attained in <30 min. SEC characterization of all final polymer products revealed narrow molecular weight distributions (dispersity ∼1.10, Figure 4) with symmetrical peaks without tailing (S Figures 17−19, 33, and 34, Supporting Information).

When using the same ratio of [CuBr]:[Me_6TREN] = 1:1 for polymerizations targeting higher DP (80 and 160), increased amounts of water and NIPAM were used (lower overall catalyst concentration). In this case, inefficient deactivation was observed. The dispersity observed during the early stages of polymerization was approximately 3.0, with final values >1.4 (S Figures 35 and 37, Supporting Information). Consequently, we changed the [CuBr]:[Me_6TREN] ratio to 2:1, which should provide more $CuBr_2$ and thus more efficient deactivation. Polymerization of DP = 80 under ambient temperature reached 99% conversion in 30 min with M_n = 10 300 and a dispersity of

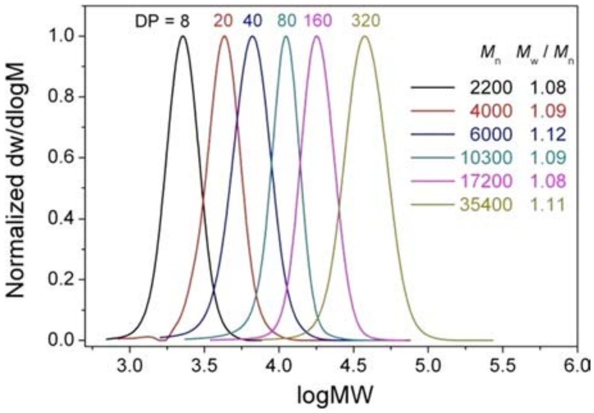


Figure 4. Molecular weight distributions of PNIPAM (DP = 8, 20, 40, 80, 160, 320) catalyzed by the in situ generated Cu(0) powders/$CuBr_2$/Me_6TREN in H_2O as measured via SEC employing DMF as the eluent.

1.08 (S Figure 36, Supporting Information), a significantly improved control. Interestingly, previous reports also suggested that a ratio of [CuBr]:[Me_6TREN] = 2:1 showed the maximum degree of disproportionation in DMSO.[13]

When applying the same conditions in a polymerization targeting DP = 160 under ambient temperature, an interesting lower critical solution temperature (LCST) phenomenon was observed after approximately 3 min. This was manifested by way of a cloudy suspension and precipitation of polymer, caused by an enhanced exotherm associated with the larger scale reaction. A temperature profile revealed that the temperature increased from ~18 to ~31 °C over the first 3 min, bringing it close to the LCST of PNIPAM. This further illustrated that there is no significant induction period and the polymerization rate was fast (S Figure 39, Supporting Information). Although conversion reached 93% in 60 min with M_n = 18 200 and a dispersity of 1.13, a tailing peak at low molecular weight was observed (S Figure 38, Supporting Information). The polymerization was repeated in an ice/water bath, which eliminated the previously observed LCST phenomenon and resulted in 99% conversion in 60 min and a final M_n = 17 200 and dispersity of 1.08 (S Figure 40, Supporting Information). Successful polymerization targeting a DP = 320 under the same reaction conditions resulted in 99.9% conversion in 60 min, with M_n = 35 400 and a dispersity of 1.11 (S Figure 42, Supporting Information). At a higher ratio of [CuBr]:[Me_6TREN] = 3:1 (DP = 160) at ambient temperature the polymerization was slower, reaching only 70% conversion in 150 min, with M_n = 12 900 and a dispersity of 1.20, indicative of increased termination during the polymerization (S Figure 41, Supporting Information).

Chain End Fidelity and Chain Extension of PNIPAM by SET-LRP in Water. It is normally difficult to maintain high chain end fidelity under aqueous polymerization conditions, mainly due to the facile hydrolysis of the terminal halogen group via a cyclic onium intermediate.[15,57] Significant termination and very broad MW distributions have been observed when employing ATRP procedures for block copolymerization of NIPAM in water.[58]

Previous reports suggested that chlorine-containing initiator/CuCl systems were preferable in invoking good control and high chain end fidelity. Interestingly, while we used a bromide initiator with CuBr for all polymerizations, we did not observe any deleterious effects in employing the more labile halide.[42,57] Narrow dispersity was maintained throughout all SET-LRP polymerizations from low conversion to full conversion. No detectable coupling peaks were observed, even when reactions were left overnight. Chain extension polymerization was initially performed at ambient temperature as a qualitative assessment of the terminal bromide. The polymerization to produce the first block was allowed to proceed for 2 h, although ^1H NMR showed 100% conversion already at 30 min. After addition of new monomer and reaction for a further 3 h, total conversion reached 87%. However, SEC revealed a bimodal peak which overlapped with the initial polymer trace, implying significant loss of the terminal bromide (Figure 5).

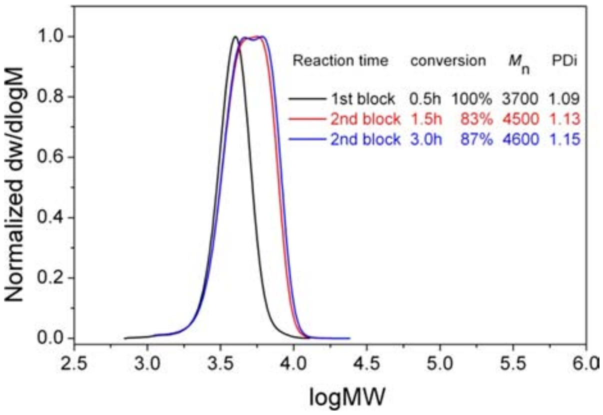


Figure 5. Molecular weight distributions of PNIPAM by SET-LRP for chain extension in H_2O under ambient temperature as measured via SEC employing DMF as the eluent.

As a more quantitative assessment of bromo functionality, high-resolution NMR and MALDI-ToF MS analyses were used to characterize low-MW PNIPAM samples (DP = 8) obtained by SET-LRP at both ambient temperature (~ 18 °C) and 0 °C (S Figures 20–32, Supporting Information). ^1H, ^{13}C, COSY, and HSQC NMR spectra showed that the bromide end groups of PNIPAM obtained at ambient temperature underwent quantitative hydrolysis to yield terminal hydroxyl (OH) groups (3.75 ppm (^1H NMR) and 69 ppm (^{13}C NMR)). The relative correlation with the polymer backbone on COSY and clear overlap with the initiator residue at 3.9 and 69 ppm on HSQC were also observed. Hydrolysis was also found in PNIPAM polymerized at 0 °C. However, in this case we were able to identify some bromo-functional PNIPAM via a resonance at 3.95 (terminal C*H*Br) and appropriate correlation with the polymer backbone from COSY. MALDI-ToF MS analysis of the same sample (0 °C) confirmed peaks of PNIPAM with terminal bromide groups, OH groups from hydrolysis, and also internal vinyl groups, as a result of HBr elimination.

From 600 MHz NMR we can conclude that the hydrolysis of bromine is the predominant termination reaction. The hydrolysis reaction becomes more obvious subsequent to full conversion, but lower reaction temperatures (i.e., ice/water bath) suppress the rate.

Given the above end group fidelity, both initial polymerization and chain extension were carried out at 0 °C using a ratio of [CuBr]:[Me_6TREN] = 1:1 or 2:1. Successful chain extensions were carried out to very near full conversions (96–99%). The [CuBr]:[Me_6TREN] ratio influenced the MW distribution of the first block and also affected the reaction rate, whereby [CuBr]:[Me_6TREN] = 1:1 showed worse control but a faster reaction rate (S Figures 44 and 45, Supporting Information). Nevertheless, the clear MW shift after chain extension and only slight increase of dispersity to 1.13 (including small tailing peaks at low MW) showed that high chain end fidelity could be maintained under these conditions (Figure 6).

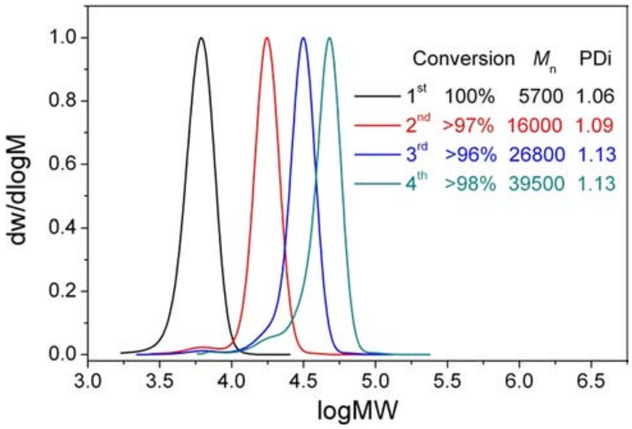
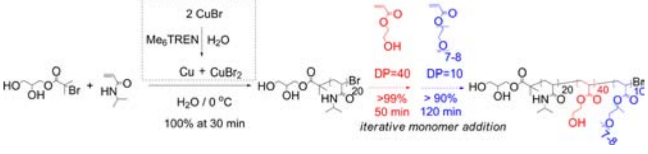


Figure 6. Molecular weight distributions of PNIPAM by SET-LRP for chain extension in H_2O under 0 °C as measured via SEC employing DMF as the eluent.

Multiblock Copolymers by SET-LRP in Water. We subsequently applied this technique for the preparation of diblock copolymer poly[$(NIPAM)_{20}$-*b*-$(HEA)_{40}$] (HEA = 2-hydroxyethyl acrylate. Block copolymerization was performed by in situ addition of monomers to the reaction solution at full conversion with respect to the first block, negating the need for purification between each block and further highlighting the high versatility of this one-pot reaction. ^{1}H NMR analysis confirmed 100% conversion of each block according to the total disappearance of vinyl groups and the expected ratios of each component in the product (S Figure 47, Supporting Information). SEC characterization revealed a clear and total MW shift after block copolymerization and a final dispersity of <1.2 (S Figure 46, Supporting Information).

Furthermore, a triblock copolymer was synthesized via iterative monomer addition (Scheme 3). Aqueous solutions of HEA and $PEGA_{480}$ were sequentially added to the reaction solution of PNIPAM at full conversion. SEC characterization again revealed an MW shift after each block polymerization with only a slight increase of disperstiy to 1.15 (Figure 7). SEC revealed a higher M_n than the theoretical target for the second poly[$(NIPAM)_{20}$-*b*-$(HEA)_{40}$] copolymer, which is likely due to the different hydrodynamic volume of the HEA block with a narrow poly(methyl methyacrylate) (PMMA) calibration standard. ^{1}H NMR of the final product confirmed the correct ratio of NIPAM to HEA to PEGA (Figure 8).

Scheme 3. Schematic Representation for Synthesis of Poly[$(NIPAM)_{20}$-*b*-$(HEA)_{40}$-*b*-$(PEGA_{480})_{10}$] by Iterative SET-LRP in H_2O



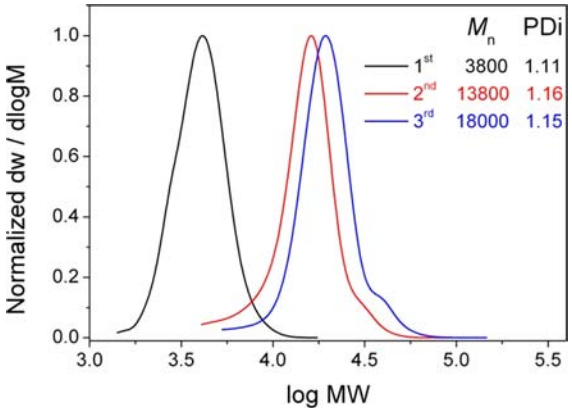


Figure 7. Molecular weight distributions of poly[$(NIPAM)_{20}$-*b*-$(HEA)_{40}$-*b*-$(PEGA_{480})_{10}$] by iterative SET-LRP in H_2O at 0 °C as measured via SEC employing DMF as the eluent.

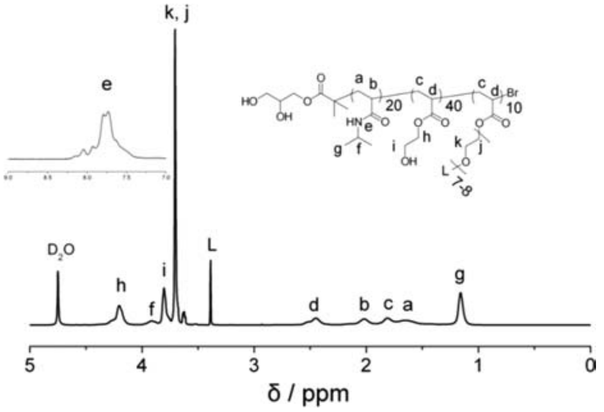


Figure 8. ^{1}H NMR spectrum of poly[$(NIPAM)_{20}$-*b*-$(HEA)_{40}$-*b*-$(PEGA_{480})_{10}$] by iterative SET-LRP in D_2O.

SET-LRP of NIPAM in PBS Buffer and Ethanol/Water (Tequila). PBS buffer is a medium used to mimic biological conditions, and alcohol/water mixtures can extend the scope of this process to less hydrophilic initiators and monomers. Accordingly, we conducted SET-LRP, with prior disproportionation, in these solvents. In PBS buffer (pH 6.2 and 6.8) disproportionation of CuBr/Me_6TREN was observed, although with a slower rate than in pure water. SET-LRP in PBS buffer tended to be slower than that in pure water and resulted in final polymers with higher dispersity (1.21 and 1.29), suggesting that the buffer affected the catalyst and polymerization (S Figures 64 and 65, Supporting Information). For SET-LRP in an alcohol/water mixture, we directly used commercial tequila (38% ethanol) as the solvent. Disproportionation of CuBr/Me_6TREN resulted in a deep green solution with insoluble Cu(0) precipitate (S Figure 61, Supporting Information). The SET-LRP of NIPAM in tequila showed results similar to those in pure water, with 99% conversion attained in 30 min (M_n = 9900 and a dispersity of 1.08 for the final polymer; S Figures 62 and 63, Supporting Information). This finding intimates that previous reports on ATRP of NIPAM using a water/alcohol mixture as the solvent, especially when stock solutions of CuCl/Me_6TREN have been employed prior to addition of initiator/NIPAM, likely proceed via SET-LRP rather than ATRP.

SET-LRP of PEGA, HEA, DMA, and Glyco Monomer Mediated by Prior Disproportionation of CuBr/Me_6TREN in Pure Water. The initial scope of this approach to SET-LRP has been extended to the polymerization of common hydrophilic monomers, including PEGA, HEA, DMA, and a synthesized acrylamide-based glyco monomer, glucose acrylamide (GAm). The general procedure for NIPAM polymerization was followed, with variations in temperature and [CuBr]:[Me_6TREN] ratios dependent on the targeted DP. For each monomer, the polymerizations reached quantitative conversion within 1 h. Pleasingly, narrow molecular weight distributions and good agreement between theoretical and observed molecular weights were obtained (Table 1), indicative of controlled polymerization.

Table 1. Summary of Results Obtained from the Polymerization of Hydrophilic Monomers via SET-LRP Mediated by in Situ Disproportionation of CuBr/Me_6TREN

	[M]:[I]:[CuBr]:[L]	conversion[a] (%)	$M_{n,th}$	$M_{n,GPC}$[b]	PDI
DMA[c]	80:1:0.8:0.4	>99	8200	9700	1.18
HEA	20:1:0.4:0.4	97	2600	8800	1.07
PEGA	10:1:0.4:0.4	>99	5000	7600	1.07
PEGA	20:1:0.4:0.4	>99	10000	11300	1.09
GAm	10:1:0.4:0.4	>99	2600	2800	1.15

[a]Measured by ^{1}H NMR. [b]DMF eluent, PMMA standards. [c]Performed at $T = 0$ °C.

The deviation in M_n obtained from DMF gel permeation chromatography (GPC) analysis of poly(*N*-(hydroxyethyl)-acrylamide) (PHEA) can be explained by the differences in the hydrodynamic radius of the relatively hydrophilic PHEA polymer compared to the linear PMMA standards. A more accurate M_n of PHEA (3300) was calculated by ^{1}H NMR with careful integration of the geminal methyl groups, incorporated through the initiator (a, S Figure 67, Supporting Information), against the side chain CH_2 groups (d, S Figure 67, Supporting Information). Despite their narrow molecular weight distributions, PDMA and PGAm exhibit a degree of low molecular weight tailing. We are confident that this can be alleviated by brief optimization for each monomer. That said, the results obtained are exemplary for SET-LRP performed in aqueous media.

Exploration of Ligand and Solvent Effects on in Situ SET-LRP. Both the solvent and ligand play important roles in the disproportionation of Cu^IX to Cu(0) and $Cu^{II}X_2$.[13,34] Solvents, such as water and ethanol, do not stabilize colloidal Cu(0) and thus give large particulate precipitates. In our hands, water strongly facilitated the disproportionation of CuBr/Me_6TREN with agglomeration of Cu(0), which resulted in apparent clumps of Cu(0) particles easily separating from a blue aqueous solution (S Figures 78 and 79, Supporting Information). However, with the addition of ethanol, the Cu(0) precipitate became finer with a reduction in particle size (S Figures 80 and 81, Supporting Information).

To investigate the versatility of this system, we further investigated two ligands which have been previously widely utilized in SET-LRP, TREN (tris(2-aminoethyl)amine) and PMDETA, for the polymerization of NIPAM, HEA, and PEGA. Disproportionation tests showed that both TREN and PMDETA favor the disproportionation of CuBr in water (S Figures 70 and 74, Supporting Information). Polymerization of NIPAM using PMDETA and TREN resulted in final polymers with a dispersity of ~1.50, showing worse control relative to Me_6TREN (S Figures 71 and 75, Supporting Information). However, polymerizations of HEA and PEGA using PMDETA and TREN under similar reaction conditions gave better control, and the dispersity of the final polymer was as low as 1.16 (S Figures 72, 73, 76, and 77, Supporting Information), suggesting that NIPAM may coordinate with the copper catalyst and affect the polymerization. Thus, the choice of ligand is important to mediate a living/controlled polymerization, and further work is under way to optimize the reaction conditions.

■ CONCLUSION

The prior disproportionation of CuBr/Me_6TREN in water has been exploited for the SET-LRP of hydrophilic monomers. Reactions proceed faster and with no induction periods when compared to SET-LRP mediated by commercial Cu(0) sources without any compromise in polymerization control. Thorough analysis of the model and reaction mixtures confirmed complete disproportionation of CuBr/Me_6TREN in the water system. Attempted polymerization with the separated products of disproportionation revealed the synergistic character of the products of the disproportionation reaction. Comparison with L-ascorbic acid-mediated aqueous AGET-ATRP revealed the sensitive and complex nature of all Cu-mediated systems, as observations were found to be highly dependent on the order of reagent addition. The SET-LRP polymerization of NIPAM was investigated, and careful selection of the catalyst ratio and reaction temperature provided access to a range of molecular weights (DP = 8–320). Full characterization of the low molecular weight PNIPAM resulted in identification of the end-group functionality. Suppression of hydrolysis, leading to premature termination, permitted preparation of block copolymers. Iterative, in situ chain extension up to a triblock copolymer was also tolerated without appreciable loss of polymerization control. The robustness of this procedure has been further exemplified by performing SET-LRP of NIPAM in biologically relevant media (PBS, pH 6.2 and 6.8) and in a commercial water/alcohol mixture (tequila). A small library of acrylamide and acrylate monomers was finally polymerized to provide an indication of the potential scope of this procedure. It is our belief that this process could be applied to a wide range of hydrophilic monomers and less hydrophilic monomers in mixed solvent systems.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and supplementary data, including NMR, SEC, UV/vis, FTIR, and MALDI-ToF MS. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interests: D. M. Haddleton is a Director of Warwick Effect Polymers Ltd.

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