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High Molecular Weight Block Copolymers by Sequential Monomer Addition via Cu(0)-Mediated Living Radical Polymerization (SET-LRP): An Optimized Approach

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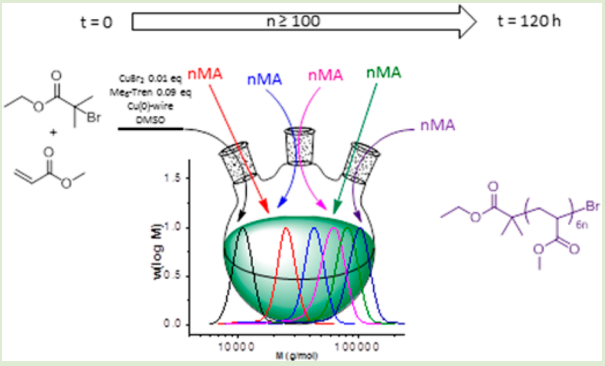
Supporting Information

ABSTRACT: The synthesis of well-defined high molecular weight block copolymers by sequential in situ chain extensions via Cu(0)-mediated living radical polymerization is reported. Optimal conditions for iterative high molecular weight block formation were determined using model homopolymer quasiblock systems, including methyl acrylate (MA), ethyl acrylate (EA), and *n*-butyl acrylate (*n*BA; each block $DP_n \approx 100$). The PDI after each chain extension was below 1.2, with good agreement between theoretical and experimental molecular weights, while the conversion of monomer incorporation into each distinct block was 95−100% (up to 6 blocks). To demonstrate this approach for true block copolymer materials, well-defined block polymers containing MA, ethylene glycol methyl ether acrylate (EGMEA), and *tert*-butyl acrylate (*t*BA) were prepared in high purity: diblock P(MA-*b*-EGMEA) and triblock P(MA-*b*-*t*BA-*b*-MA). These were prepared in high yields, on multigram scales, and with purification only required at the final step. To the best of our knowledge, this is the first time that high molecular weight block copolymers have been reported using this novel technique.



Block copolymers display a wide range of interesting and useful properties due to the fact that the combination of monomers with different physicochemical properties, confined in block sequences, allows these systems to undergo self-assembly and phase separation into higher ordered structures.[1−8] The synthesis of AB or ABA amphiphilic block copolymers of high molecular weight is of particular interest for the formation of micelles, vesicles, and so on, in solution, and various morphologies in the solid state.[1−8] The morphology of these self-assembled constructs depends upon a well-controlled synthetic protocol allowing preordained molecular weights and volume fractions (ϕA/ϕB) to be obtained.[9−12] However, while there are many polymerization techniques that have been used to produce block copolymers, a number of drawbacks exist. For example, living anionic polymerization[13] is extremely labor intensive, and the number of functional monomers that can be polymerized using this technique is limited. The development of controlled radical polymerization (CRP) techniques, such as ATRP,[14,15] NMP,[16] and RAFT,[17] has expanded this monomer library but experimental and synthetic limitations remain. The most significant limitation is the loss of "livingness", or end group fidelity, as the polymerization proceeds due to unwanted side reactions.[18,19] This loss of "livingness" of the chain end, leads to a drift in PDI, which can be reflected in the structural polydispersity of resulting higher order polymers.

Cu(0)-mediated living radical polymerization[20,21] has recently been demonstrated to yield polymers with extremely high livingness at quantitative conversions and extending into post-polymerization conditions.[22] The versatility of the approach has been demonstrated in a diverse range of polar solvents such as DMSO,[23] DMF,[24] ionic liquids,[25] water,[26,27] alcohols,[28] and even in biologically complex media.[29] Exploiting this high livingness at high conversion, the one-pot synthesis of high-order multiblock linear and star copolymers was initially reported by Whittaker et al.[30−32] More recently, Haddleton et al. have used the approach for the synthesis of structurally complex glycopolymers, to impart biologically recognized motifs.[33] However, these successful examples are confined to small blocks, $DP_n \leq 25$: clearly the routine application of this technique to higher molecular weight blocks ($DP_n \geq 100$) would represent a significant advance.

Herein we report for the first time the extension of this Cu(0)-mediated technique to the synthesis of high molecular

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weight multiblock polymers, model quasiblock homopolymers and true block copolymers, with each block typically comprising more than 100 monomer units. Each block formation cycle was taken to quasi-full conversion (95−100%), and therefore, purification was only required at the final step. The potential scope of this technique was demonstrated by application to a variety of monomers for which the polydispersities were kept low (1.1−1.2). The amount of Cu(II) and ligand employed was found to be crucial for optimal polymerization conditions and differentiates this synthetic route from previously reported syntheses of lower molecular weight multiblock copolymers with much shorter block lengths.

Initial attempts to synthesize higher molecular weight polymers via sequential monomer addition were conducted using conditions previously reported by Whittaker et al.,[30−32] which allowed the successful iterative chain extension of the high order multiblock copolymers with short block lengths. In this approach, each iterative chain extension cycle was taken to quasi full conversion before the addition of an aliquot of degassed monomer/DMSO solution, and as a result intermediate polymer purification was not necessary.

The polymerizations were initiated at 25 °C by ethyl 2-bromoisobutyrate (EBiB) in the presence of methyl acrylate (MA, $DP_{n,th}$ = 125), Me_6-Tren, $Cu(II)Br_2$, and Cu(0)-wire (5 cm) to generate the first block ([EBiB]/[$Cu(II)Br_2$]/[Me_6-Tren] = [1]/[0.05]/[0.18]). It is important to note that one ligand will bind to one $Cu(II)Br_2$ and, therefore, the ratio of "free" ligand is 0.13 (relative to initiator). High monomer conversion (>95%) at the end of the first chain extension cycle was confirmed via ^{1}H NMR. The evolution of the GPC molecular weight distributions of the iterative in situ chain extension cycles of methyl acrylate (MA; two chain extension cycles, each cycle generating a block length of M_n = 10000 g/mol) reveals that M_n of the model diblock PMA homopolymer is in reasonable agreement with the theoretical molecular weight ($M_{n,th}$), however, the significant increase of PDI reflects a loss of living chain ends. This loss of livingness is manifested as a low molecular weight shoulder which we attribute to dead polymer chains formed during initial polymerization (Figure S1). Semiquantitative GPC analysis has been previously used to assess livingness of block copolymer chain extensions. Applied here, the chain extension of the first block revealed that approximately 70% of the chains (by number) were living (Figure S1). This is in contrast to results reported for lower molecular weight blocks where after 4 chain extension cycles over 70% of chains where still "living."[31,32] It has been previously demonstrated using these experimental conditions that the livingness is higher in the systems where shorter blocks are targeted (~500 g/mol) rather than larger blocks (~2000 g/mol), in agreement with well-established theory.[34] It is not surprising then that under the conditions described, nonideal results have been obtained when higher molecular weight blocks of 10 kDa have been targeted.

In an effort to increase the livingness, the amount of deactivator was increased 2-fold with the addition of extra ligand to maintain a constant "free" ligand concentration ([EBiB]/[$Cu(II)Br_2$]/[Me_6-Tren] = [1]/[0.10]/[0.23]). Increasing the Cu(II) concentration to improve the control in similar systems is widely demonstrated.[22,30,35] High conversion was confirmed via ^{1}H NMR in each of chain extension cycles 1−4. The livingness after the first chain extension was improved: M_n is in good agreement with $M_{n,th}$ and the PDI decreased from 1.24 (Cu(II) = 0.05 equiv) to 1.09 (Cu(II) = 0.010 equiv). Semiquantitative GPC analysis indicated that the livingness of the diblock has increased from approximately 70% to almost 90% after the first chain extension. However, there remains significant low molecular weight tailing as the chain extension cycles are repeated with livingness decreasing to <70% after four chain extension cycles and PDI of the final tetrablock increasing to 1.40 (Figure 1, Table S1).

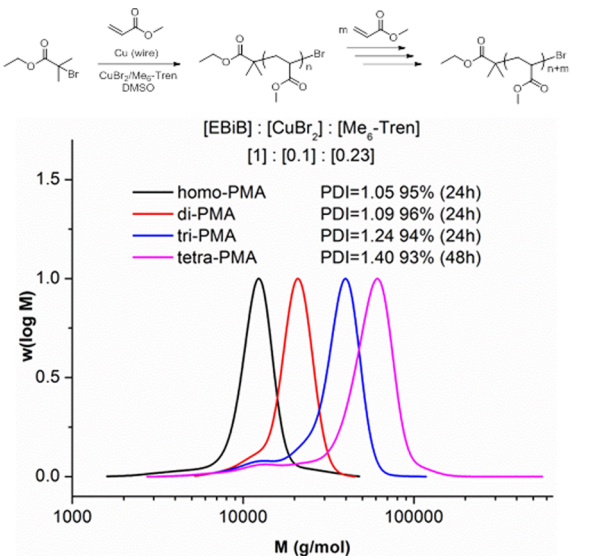

Figure 1. Molecular weight distributions for the synthesis and in situ chain extension of PMA: [MA]/[EBiB]/[$CuBr_2$]/[Me_6-Tren] = [125]/[1]/[0.1]/[0.23].

Recently published work by Haddleton et al. reports the importance of the careful optimization of [initiator]/[ligand] (Me_6-Tren) ratios to achieve optimum polymerization of acrylates. Adventitious ligand mediated side reactions were found to cause termination reactions if the ligand concentration was not optimized.[36] Also, simply lowering the ligand concentration may lead to a prohibitive reduction in polymerization rate, as demonstrated by Haddleton et al.[36] Consequently, further optimization of the [EBiB], [Cu(II)], and [ligand] was undertaken.

Percec et al. have shown excellent results for Cu(0)-mediated polymerization in the absence of added Cu(II).[37−39] Therefore, we decided to reduce the [$CuBr_2$] from 0.05 to 0.01 equiv and for comparison we conducted a reaction without adding $CuBr_2$. In the absence of [$CuBr_2$], using [Me_6-Tren] (0.18 equiv) as ligand and activated Cu(0)-wire, the EBiB initiated homopolymerization of MA reached high conversion (99%) within 2 h with good agreement between theoretical and experimental M_n and PDI = 1.05. Chain extension resulted in a well-defined block polymer (95% conversion, PDI = 1.10) in 5.5 h. Additional chain extensions required longer times (24, 48, and 100 h, respectively), yielding a final polymer with overall final conversion of 94% and PDI = 1.14 (Figure S2a). When a small amount of $CuBr_2$ (0.01 equiv) was introduced at the beginning of the reaction, the chain extensions proceeded without a significant decrease in polymerization rate and near quantitative conversion (>99%) with PDI = 1.10 (Figure S2b). Under both sets of conditions the initial inability to efficiently chain extend was remediated by an overall reduction in [$CuBr_2$]. However, the data attained was not ideal, with lower conversions for

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polymerizations in the absence of $CuBr_2$ and, in both cases, low molecular weight shoulders were observed (Figure S2).

In consideration of our previous work,[36] these experiments were repeated using a reduced Me_6-Tren concentration (0.09 equiv). In the absence of $CuBr_2$, a significant decrease in the polymerization rate was observed, and the chain extension seldom reached >90% conversion. In contrast, when [EBiB]/[$CuBr_2$]/[Me_6-Tren] = [1]/[0.01]/[0.09], the homopolymerization of MA reached 99% conversion in 2 h with a PDI as low as 1.04, while the first chain extension was equally successful furnishing a well-defined polymer (95%, PDI = 1.06). A total of five iterative additions of degassed MA in DMSO were successfully performed. Excellent agreement between theoretical and experimental M_n was observed for each chain extension cycle (Figure 3), and the final polymer had a PDI of 1.11 and

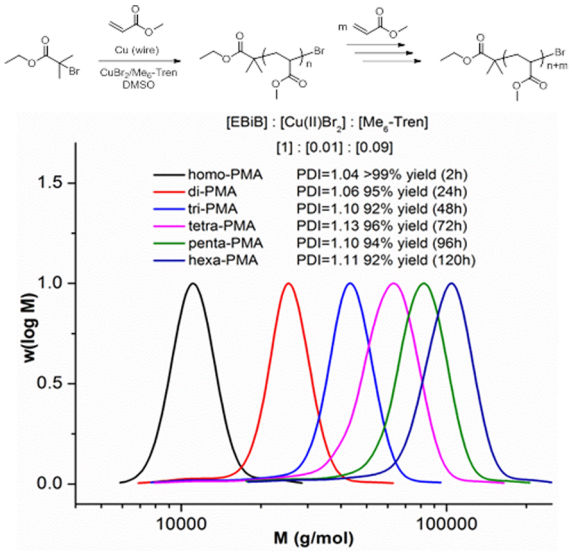

Figure 2. Molecular weight distributions for the synthesis and in situ chain extension of PMA: [MA]/[EBiB]/[$CuBr_2$]/[Me_6-Tren] = [100]/[1]/[0.01]/[0.09].

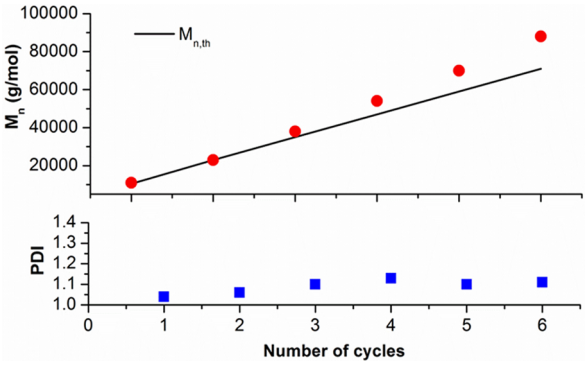

Figure 3. $M_{n,th}$, M_n (red circle), and PDI (blue square) values for five successive chain extension cycles of PMA using [MA]/[EBiB]/[$CuBr_2$]/[Me_6-Tren] = [100]/[1]/[0.01]/[0.09].

conversion of 92%. GPC analysis revealed symmetrical distributions for each chain extension without low molecular weight tailing (Figure 2).

It is clear that [Cu(II)] and [ligand] must be optimized w.r.t. [EBiB] to maximize livingness and polymerization rate. The ratio of free ligand w.r.t. to initiator has perhaps the most significant effect on overall "livingness" of the system. In the presence of an excess concentration of Me_6-Tren (e.g., 0.18 equiv) unwanted side reactions occur at the propagating chain end, resulting in premature termination, manifest as low molecular weight shoulders in GPC analysis. This is alleviated when the free ligand ratio is comparable to previous work (e.g., 0.09 equiv, cf. 0.07−0.10 equiv)[32,36] at which point side reactions are minimized without compromising the rate of polymerization.

Subsequently, EA and *n*BA were homopolymerized using the same methodology. The homopolymerization of the first block of EA was complete within 8 h: conversion >99, $M_n \approx M_{n,th}$, and PDI = 1.04. Subsequent chain extensions again required longer reaction times, but high conversions and low PDI were retained throughout. The target "pentablock" of PEA was realized with final conversion of 96%, $M_n \approx M_{n,th}$ and PDI = 1.11 (Figure S3).

The Cu(0)-mediated polymerization of *n*BA in DMSO was recently reported to proceed with high livingness in a self-generated biphasic system.[40,41] Consequently, we decided to investigate whether such a biphasic system could sustain the synthesis of high molecular weight P(*n*BA) by the sequential monomer addition route. The targeted molecular weight was higher than previously reported (∼10000 g/mol per monomer addition), thus, phase separation was evident during the early stages of the initial homopolymerization. The associated increase in viscosity, coupled with phase separation, did not have a detrimental effect with high conversion (98%), good agreement between $M_{n,th}$ and M_n (11000 g/mol) and low PDI (1.10). A further four additional chain extensions of *n*BA furnished a "pentablock" P(*n*BA) while maintaining the desired high conversions and low PDI at each step, with $M_n \approx M_{n,th}$ (50000, cf. 53000 g/mol) and final PDI <1.10 (Figure S4). The current data points to an extremely controlled process with minimal termination for this phase-separated high molecular weight P(*n*BA) system.

To demonstrate the versatility of this approach, well-defined P(MA-*b*-EGMEA) and P(MA-*b*-*t*BA-*b*-MA) were prepared. Polymers containing a PEG block are of wide interest due to the antifouling, temperature responsiveness and "stealth" properties the PEG component confers. For the purpose of self-assembly, preparation of amphiphilic block copolymers using *t*BA is well established, with amphiphilicity installed postpolymerization by facile removal of the *tert*-butyl group to unmask a pH responsive, hydrophilic acrylic acid (AA) block.[42−44]

P(MA-*b*-EGMEA): The PMA block was first synthesized using the optimized conditions ([MA]/[EBiB]/[$CuBr_2$]/[Me_6-Tren] = [100]/[1]/[0.01]/[0.09], 2 h, 98%, PDI = 1.07) and chain extended by addition of degassed EGMEA in DMSO. A well-defined diblock copolymer, P(MA-*b*-EGMEA), with 94% conversion, $M_n \approx M_{n,th}$ and PDI = 1.08 was achieved after 7 h (Figure S5). P(MA-*b*-*t*BA-*b*-MA): The MA block was synthesized as above (98%, PDI = 1.05). The chain extension with *t*BA resulted in an extremely viscous gel-like mixture. However, upon dilution with degassed DMSO, the viscosity was reduced, refuting the possibility of gel formation. A well-defined diblock copolymer, P(MA-*b*-*t*BA), with 100% conversion, $M_n \approx M_{n,th}$ and PDI = 1.05 was realized. The diblock was chain extended to give P(MA-*b*-*t*BA-*b*-MA) with a final conversion of 100%. There was also excellent agreement between M_n and $M_{n,th}$ (Figure 4) with narrow, symmetrical MWDs (Figure 5, final PDI = 1.06), indicating minimal termination in each chain extension cycle.

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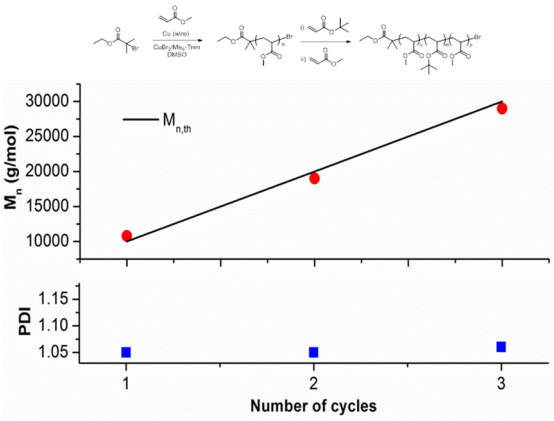

Figure 4. $M_{n,th}$, M_n (red circle), and PDI (blue square) values for the one-pot Cu(0)-mediated synthesis of P(MA-*b*-*t*BA-*b*-MA) via three chain extension cycles.

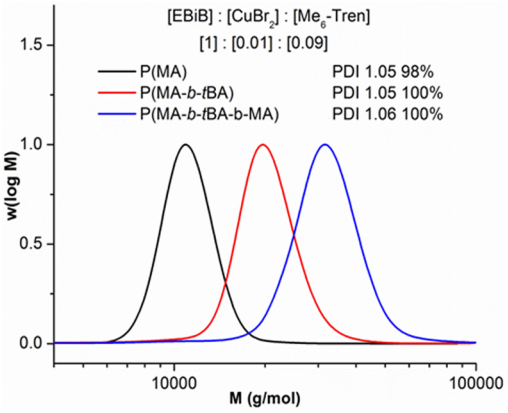

Figure 5. Molecular weight distributions for the one-pot Cu(0)-mediated polymerization yielding P(MA-*b*-*t*BA-*b*-MA) via sequential monomer addition.

In summary, we report for the first time the successful synthesis of model block homopolymers and block copolymers of high molecular weight via Cu(0)-mediated living radical polymerization at room temperature. No purification steps are required between the monomer additions while near quantitative conversions and low polydispersities are obtained in all cases. The amounts of Cu(II) and ligand proved to be crucial for maintaining the balance between excellent control, livingness and high polymerization rate. This work provides a facile route for accessing high molecular weight blocks and thus their associated applications, opening the path for well-defined copolymers in an extremely controlled and robust way.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and supplementary data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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