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Synthesis of Complex Multiblock Copolymers via a Simple Iterative Cu(0)-Mediated Radical Polymerization Approach

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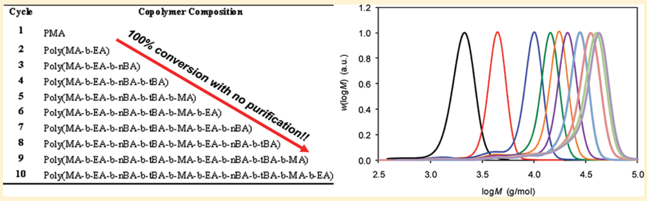
S *Supporting Information*

ABSTRACT: Controlled/living radical polymerization is an efficient technique for the synthesis of well-defined polymeric architectures, including copolymers, block copolymers, stars, graft, and variations thereof. In this article, we report for the first time the synthesis of a decablock copolymer via a simple and efficient iterative Cu(0)-mediated radical polymerization technique. In this approach, purification is not required between the iterative chain extension steps, as each block formation is taken to full conversion. The final decablock copolymer can be obtained with a yield in mass of ∼90%. Using traditional controlled/living radical polymerization techniques, including reversible addition−fragmentation chain transfer (RAFT) polymerization, nitroxide-mediated polymerization (NMP), or atom transfer radical polymerization (ATRP), synthesis of decablock copolymer in such high yield is very difficult (and may be impossible) and requires numerous purification steps. The synthesis of the final complex copolymers required the concomitant synthesis of 16 architecturally discrete block copolymers.



Cycle	Copolymer Composition
1	PMA
2	Poly(MA-b-EA)
3	Poly(MA-b-EA-b-nBA)
4	Poly(MA-b-EA-b-nBA-b-tBA)
5	Poly(MA-b-EA-b-nBA-b-tBA-b-MA)
6	Poly(MA-b-EA-b-nBA-b-tBA-b-MA-b-EA)
7	Poly(MA-b-EA-b-nBA-b-tBA-b-MA-b-EA-b-nBA)
8	Poly(MA-b-EA-b-nBA-b-tBA-b-MA-b-EA-b-nBA-b-tBA)
9	Poly(MA-b-EA-b-nBA-b-tBA-b-MA-b-EA-b-nBA-b-tBA-b-MA)
10	Poly(MA-b-EA-b-nBA-b-tBA-b-MA-b-EA-b-nBA-b-tBA-b-MA-b-EA)

INTRODUCTION

Block copolymers possess fascinating properties due to their ability to self-assemble in solution to form higher order structures (micelles, liposomes, etc.) and undergo phase separation in the solid state (for example, thin films).[1,2] Because of these properties, they have found application in a range of very diverse areas, including adhesion, microelectronics, and drug delivery.[3−9] The synthesis of block copolymers has traditionally only been possible using anionic living polymerization.[10−13] This polymerization technique presents several limitations due to the rigorous nature of the synthetic requirements and the limited range of applicable monomers. With the emergence of controlled/living radical polymerization (CLRP),[14] including copper-mediated polymerization (such as atom transfer radical polymerization (ATRP/ARGET)[15−19] and single electron transfer polymerization (SET-LRP)),[20−22] reversible addition−fragmentation chain transfer polymerization (RAFT),[23,24] and nitroxide-mediated radical polymerization (NMP),[25,26] the routine synthesis of such complex polymeric architectures (block copolymers, multiblocks, and others) has been realized.[27] To produce complex structures via a living free radical process, it is crucial to maintain high end-group fidelity in each block formation step. For most CLRP techniques it has been established that the end-group fidelity continually decreases during the polymerization process. To preserve the end-group functionality, the polymerization is usually quenched before high conversion is reached, typically around 50−60%.[28] Indeed, a significant loss of end-group fidelity has been observed at high conversion due to a variety of competing side reactions.[29,30] For example, the loss of end-group (halide) in ATRP has been associated with transfer to ligand at high conversion and to radical−radical termination reactions.[31,32] In the case of RAFT, due to the addition−fragmentation mechanism which requires a constant radical source (usually AIBN), a significant decrease in end-group fidelity during the polymerization process is characteristic, and at full conversion (or in the absence of monomer) the RAFT end-group can be replaced by residual radical initiator moieties (as exploited by Perrier and coworkers).[33] In contrast, SET-LRP has been demonstrated by the Percec and Haddleton groups[22,34−38] to preserve the end-group fidelity until high conversion. However, it is important to note there is some debate in the literature regarding the exact mechanism of SET-LRP.[20,21,39−43]

The synthesis of multiblock copolymer requires multiple polymerization steps, where in each step the polymerization is stopped well before full conversion and the polymer purified from the excess monomer prior to the next block formation step. Because of the current synthetic limitations of this approach, high order multiblock copolymers have rarely been reported. In the literature, there are a few examples of pentablock copolymer,[44] and the maximum block number we could ascertain is a block copolymer containing 7 blocks, prepared via ATRP.[45] The synthesis of such copolymers containing 7 blocks via CLRP would require 14 steps, i.e., 7 polymerizations and 7 purifications, with a significant loss of product (reflecting a loss of livingness) occurring at each step. Clearly, for the synthesis of higher order block copolymers

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Scheme 1. Schematic Representation of the Synthesis of Multiblock Copolymer via Copper(0)-Mediated Radical Polymerization

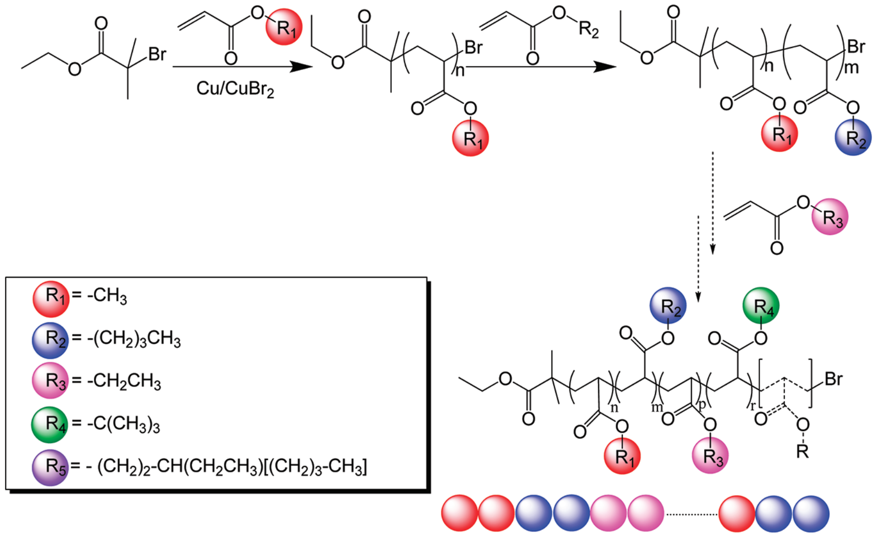

Table 1. Summary of the Copolymers Presented in This Study

		final copolymer				
series	sequence distribution	$M_{n,th}$ (g/mol)	$M_{n(GPC)}$ (g/mol)	PDI	$M_{n(NMR)}$ (g/mol)	wt % living chains
1	poly(MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA)	20 200	19 800	1.29	21 200	80
2	poly(MA-*b*-EA-*b*-*n*BA-*b*-*t*BA-*b*-MA-*b*-EA-*b*-*n*BA-*b*-*t*BA-*b*-MA-*b*-EA)	22 500	24 000	1.72	21 000	90
3	poly(MA-*b*-*n*BA-*b*-EA-*b*-EHA-*b*-EA-*b*-*n*BA-*b*-*n*BA-*b*-MA)	3 800	7 700	1.20	3 900	80

and for widespread industrial applications, such a process is not viable.

Recently, we have demonstrated that it is possible to generate short highly controlled macromolecular block copolymer chains via Cu(0)-mediated radical polymerization (SET-LRP).[46] This structurally complex macromolecule was synthesized in high yield and consisted of six small blocks with each block comprising two monomer units on average. In this article, we have extended the scope of this simple approach to demonstrate the synthesis of a model decablock poly(MA) homopolymer and two complex block copolymers, poly(MA-*b*-EA-*b*-*n*BA-*b*-*t*BA-*b*-MA-*b*-EA-*b*-*n*BA-*b*-*t*BA-*b*-MA-*b*-EA) and poly(MA-*b*-*n*BA-*b*-EA-*b*-EHA-*b*-EA-*b*-*n*BA-*b*-*n*BA-*b*-MA), with near perfect control of the architecture in extremely high yield. The block chain length has been varied, and both the sequence and monomer type have also been changed to show the high versatility of this approach. As far as we can ascertain, this is the first example of the synthesis of such complex high-block copolymer via CLRP. It is important to underline that this approach is extremely simple, carried out at room temperature, and can be implemented in a general laboratory setting without recourse to complex equipment. Finally, NMR and GPC data analysis of the model decablock poly(MA) homopolymer and the two complex block copolymers has allowed quantitative monitoring of the livingness after each synthetic cycle.

RESULTS AND DISCUSSION

Block Copolymer Synthesis. The synthesis of high-order multiblock model decablock PMA homopolymer poly(MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA) and copolymer poly(MA-*b*-EA-*b*-*n*BA-*b*-*t*BA-*b*-MA-*b*-EA-*b*-*n*BA-*b*-*t*BA-*b*-MA-*b*-EA) with each block designed to be 2000 g/mol was achieved as outlined Scheme 1 and detailed in the Supporting Information. A block copolymer was also synthesized comprising shorter blocks of ~500 g/mol, poly(MA-*b*-*n*BA-*b*-EA-*b*-2EHA-*b*-EA-*b*-*n*BA-*b*-*n*BA-*b*-MA), to facilitate electrospray mass spectrometry (ESI-MS) analysis and demonstrate the versatility of this technique. Table 1 provides a summary of the different homo/copolymers prepared in this study. All these polymer syntheses were achieved via an iterative Cu(0)-mediated radical polymerization process carried out at 25 °C in DMSO,[40] inspired by previous works of Percec, Haddleton, and Matyjaszewski.[20−22,37,38,47−52] In this approach, each block formation cycle is taken to full conversion, and as a result polymer purification is not necessary until the final isolation of the predesigned block copolymer. The polymerizations were initiated by ethyl 2-bromoisobutyrate in the presence of methyl acrylate and Cu(II) to generate the first block in all cases: either a 2000 g/mol or 500 g/mol A-block. Importantly, high monomer conversion (>95%) was assessed via ^{1}H NMR spectroscopy (see Figure S1 in Supporting Information using the following equation: $\alpha^{M} = \int \mathrm{CH{=}CH}^{5.5-6.5\,\mathrm{ppm}} / \int \mathrm{OCH_3}^{3.6\,\mathrm{ppm}}$) in less than 2 h, but the polymerization was continued for 24 h to attain full monomer conversion (>99%). Aliquots were taken for analysis by GPC, NMR, and ESI-MS. GPC analysis reveals the formation of well-defined block polymers with PDI < 1.2, while ^{1}H NMR confirms the presence of the CH-Br signal at 4.2 ppm (Figures S1 and S2). The CH-Br functionality, calculated based on % CH-Br = $(2 \times \int \mathrm{CH{-}Br}^{4.2\,\mathrm{ppm}} / \int \mathrm{CH_2O}^{4.0\,\mathrm{ppm}}) \times 100$, with the CH_2O

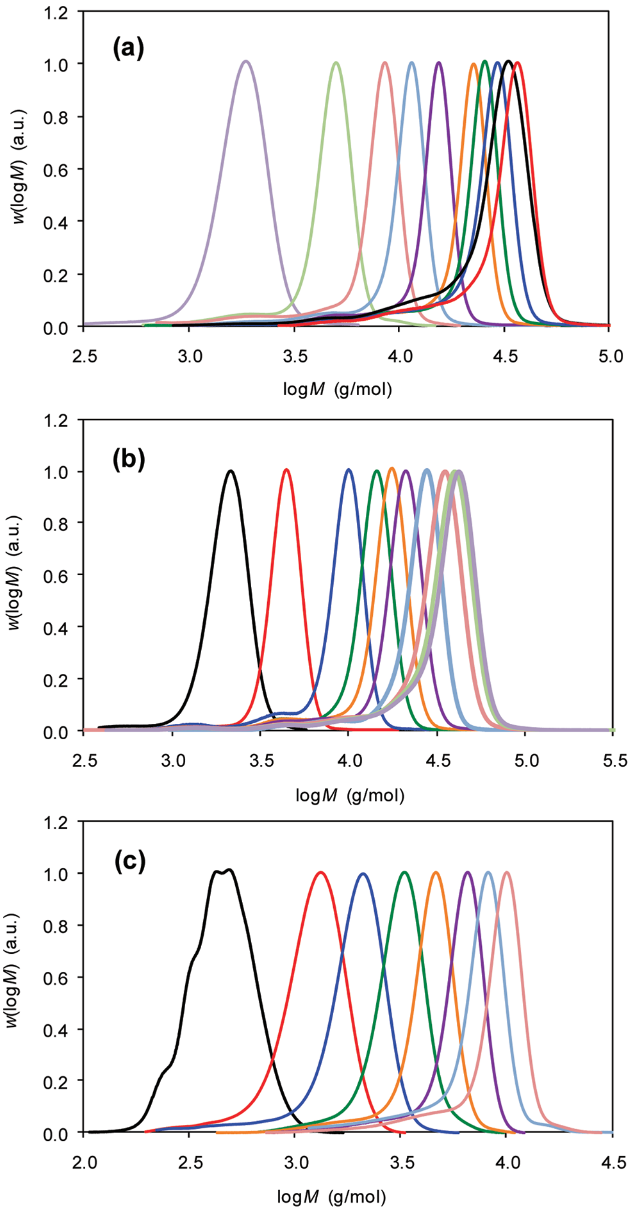

Figure 1. Evolution of $w(\log M)$ vs $\log M$ for successive cycles during synthesis of (a) decablock poly(PMA), (b) decablock poly(MA-*b*-EA-*b*-*n*BA-*b*-*t*BA-*b*-MA-*b*-EA-*b*-*n*BA-*b*-*t*BA-*b*-MA-*b*-EA), and (c) octablock poly(MA-*b*-*n*BA-*b*-EA-*b*-EHA-*b*-EA-*b*-*n*BA-*b*-*n*BA-*b*-MA).

intensity corresponding to the CH_2O-ester of the initiator at 4.0 ppm, is greater than 95%, which confirms that the majority of the polymer chains are still living. ESI-MS also confirms that the first block consists of more than 95% living chains for all three PMA A-blocks. ESI-MS analysis shows that the formation of dead polymer can be attributed to bimolecular termination by disproportionation and chain transfer (presumably to ligand). The absence of coupling termination (detected by GPC and by ESI-MS) for acrylate is surprising. The relative extents of termination by combination and disproportionation have to date not been determined with accuracy for acrylates, and the literature contains conflicting reports claiming both modes are dominant.[53] We have investigated in more detail the mechanism of termination during copper-mediated polymerization using ESI-MS, NMR, and GPC.[54] However, these side reactions have been minimized by the initial addition of Cu(II), and <5% of dead polymer (by number) can be detected by ESI-MS (Figure S3) and NMR (Figure S2).[54]

The first block (poly(MA)) was in each case chain extended without any purification by addition of degassed DMSO/monomer mixture (50/50 vol %), and the polymerization was continued for 24 h. ^{1}H NMR spectroscopy shows that full monomer conversion (as evidenced by disappearance of the acrylic bond at 5.5−6.5 ppm) was obtained after 24 h (see Figure S6a in the Supporting Information). The CH-Br signal at 4.2 ppm can be clearly detected when MA was used for chain extension, which confirms a high conservation of chain end functionality and therefore livingness (above 95%). GPC analysis confirms a significant shift of the molecular weight distribution (MWD) to higher molecular weights (Figure 1). Interestingly, residual low molecular weight polymer (low molecular weight tailing) was not observed by GPC in the first cycle. Considering the synthesis of block copolymer poly(MA-*b*-*n*BA-*b*-EA-*b*-EHA-*b*-EA-*b*-*n*BA-*b*-*n*BA-*b*-MA), it was possible to show by ESI-MS that the A-block poly(MA) has been successfully chain extended with *n*BA (B-block), and subsequently with EA (C-block) only accompanied by the formation of a small amount of dead polymer (Figure S4). Indeed, the simulated and experimental ESI-MS spectra are in strong agreement with this observation (see Figure S5 in the Supporting Information). Because of the loss of resolution of ESI-MS after three successive chain extensions, we were unable to characterize higher order copolymer by this technique.

The process was repeated to produce the predesigned multiblock copolymers. After five chain extensions, full monomer conversion could not be obtained after 24 h (presumably a dilution effect), and the polymerization times were consequently increased to 48 h. The process was repeated several more times to yield the final decablock and octablock (co)polymers. ^{1}H NMR confirms the incorporation of monomer units in the copolymer structure in each iterative cycle (Figures S6 and S7). As far as we can ascertain, this is the first example of the synthesis of such a complex block copolymer systems. Figure 2 shows the evolution of the molecular weight (M_n and M_w) and polydispersity (PDI) versus the number of cycles for all three polymers (series 1−3). The experimental M_n of the model decablock PMA homopolymer and the decablock copolymer (series 2 in Table 1) are in good agreement with the theoretical molecular weights, while M_w starts to deviated from the theoretical line after 6−7 cycles (in the ideal case with PDI = 1, $M_w = M_{n,th}$). The deviation in M_w reflects the loss of living chain ends while the good agreement with $M_{n(GPC)}$ and $M_{n,th}$ for both series 1 and 2 in Table 1 shows that the number of chains stays approximately constant during each cycle. We attribute the deviation between $M_{n(GPC)}$ and $M_{n,th}$ for series 3 (Table 1) to the influence of the 2-ethylhexyl acrylate (EHA) block. This monomer block was specific to this copolymer, and we suspect it introduced an error to the GPC analysis by affecting the hydrodynamic volume of the copolymer. It is important to note that the analysis of the GPC data to determine $M_{n(GPC)}$ included all the polymer chains. Although the PDI increases with the number of cycles, it remains below 1.50. The increase of the PDI is attributed to the formation of dead polymer (approximately 3−5% in each cycle). If the dead polymers are not included in the GPC analysis, the PDI is approximately 1.1−1.2.

^{1}H NMR analysis can be also used to determine the molecular weight (M_n) based on the assumption that all chains have a given structure (i.e., specific end groups at α- and ω-ends) (Figure 2).

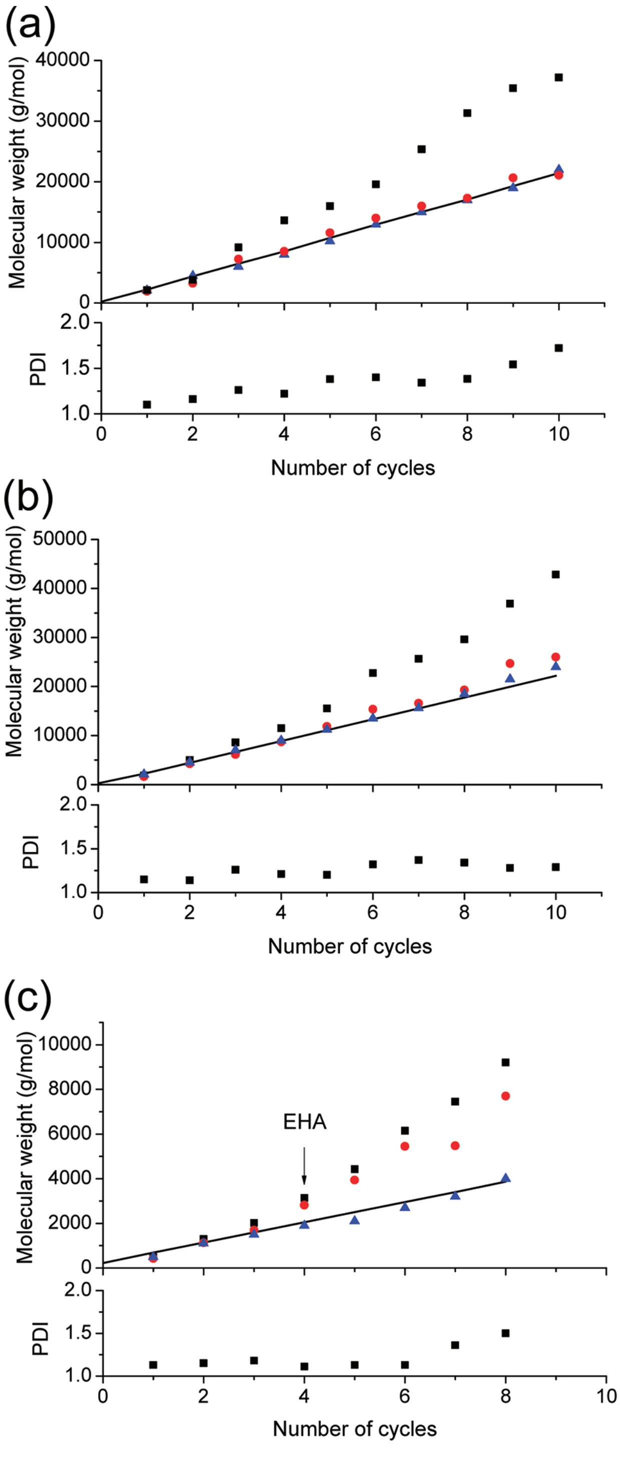

Figure 2. Evolution of theoretical (straight lines) and experimental molecular weight determined by NMR (▲) and by GPC ((●) M_n and (■) M_w) and of (■) PDI vs the number of cycle for (a) decablock poly(MA)$_{10}$ homopolymers for each cycle, (b) decablock poly(MA-*b*-EA-*b*-*n*BA-*b*-*t*BA-*b*-MA-*b*-EA-*b*-*n*BA-*b*-*t*BA-*b*-MA-*b*-EA), and (c) octablock poly(MA-*b*-*n*BA-*b*-EA-*b*-EHA-*b*-EA-*b*-*n*BA-*b*-*n*BA-*b*-MA) copolymers.

In the case of poly(MA) multiblock homopolymer, the determination of M_n by NMR ($M_{n(NMR)}$) is relatively straightforward using the equation $M_{n(NMR)} = (2 \times \int CH_3O^{3.6\,ppm}/3 \times \int CH_2O^{4.0\,ppm}) \times MW^{MA} + MW^{initiator}$, with $\int CH_3O^{3.6\,ppm}$, $\int CH_2O^{4.0\,ppm}$, MW^{MA}, and $MW^{initiator}$ corresponding to intensities from methyl acrylate (methyl ester) and initiator and molar mass of monomer and initiator, respectively. Peak assignments for the ^{1}H NMR spectra are shown in Figure S1. Estimation of M_n in the case of copolymers is slightly more complex. Figures S8 and S9 in the Supporting Information show the assignments for all the signals of the final copolymers (series 2 and 3). Using the signal at 1.1 ppm (d) attributed to CH_3 of initiator as reference, we are able to calculate M_n by successive iteration. For example, M_n of poly(MA-*b*-EA) copolymers has been calculated via the equation $M_{n(NMR)} = (2 \times \int CH_3O^{3.6\,ppm}/\int CH_3^{1.1\,ppm}) \times MW^{MA} + (2 \times \int CH_3^{1.3\,ppm}/\int CH_3^{1.1\,ppm}) \times MW^{EA} + MW^{initiator}$, with $\int CH_3O^{3.6\,ppm}$, $\int CH_3^{1.3\,ppm}$ $\int CH_3^{1.1\,ppm}$, MW^{MA}, MW^{EA}, and $MW^{initiator}$ corresponding to intensities from methyl acrylate (methyl ester), methyl of EA and methyl of initiator (d), and molar mass of MA, EA, and initiator, respectively. For both copolymers, the results calculated by ^{1}H NMR are in good accord with the theoretical values. In the case of series 3, the good agreement between $M_{n(NMR)}$ and $M_{n,th}$ supports that the deviation for $M_{n(GPC)}$ observed by GPC is due to the changes of the copolymer hydrodynamic volume in the presence of EHA.

A critical point to note in this process is that full monomer conversion is targeted in each block formation cycle. As we mentioned in the previous paragraphs, full conversion usually results in the formation of a significant amount of dead polymer.[29] We have therefore studied the livingness of this process by (i) GPC and (ii) ^{1}H NMR analysis.

Estimation of Livingness from GPC Data. With the exceptions of the first iterative cycles (until three cycles), the MWDs plotted as GPC distributions ($w(\log M)$ vs $\log M$) exhibit significant low molecular weight tailing, the extent of which generally increases with increasing number of cycles (Figure 1). If the polymerization proceeds according to an ideal controlled/living radical process (negligible termination and other side reactions), no such low molecular weight tail would be present. Thus, at face value, it is reasonable to assume that the chains comprising the low molecular weight tail are dead chains. However, this is not necessarily the case; (i) chain transfer to a low molecular weight species (e.g., monomer) could for example result in a largely living low molecular weight tail,[55] and (ii) it is of course also possible that dead chains, originating for example from termination by disproportionation, may be present in the main "living" peak. Nonetheless, bearing these shortcomings and limitations in mind, estimation of the fraction of living chains based on the extent of low molecular weight tailing in the MWD can at the very least provide a useful semiquantitative estimate of the livingness.

To estimate the livingness according to this method from GPC data, it is first necessary to convert the MWDs to the corresponding number distributions. The *y*-axis values in the GPC distributions (normally what is given by the GPC software) are proportional to nM^2, where n is the number of chains and M is the molecular weight.[56,57] It follows that the number distribution, where the *y*-axis values are proportional to the number of chains, is given by $w(\log M)/M^2$. Thus, if one plots $w(\log M)/M^2$ vs M, the area under the curve between two given values of M is proportional to the number of chains within that range of M values.

To illustrate this approach, Figure S10a shows the number distribution corresponding to Cu(0)-mediated polymerization of MA via nine iterative chain extensions. In the number distribution, the low molecular weight tail of the GPC distribution (Figure S10b) appears as a distinct multimodal peak. The livingness is

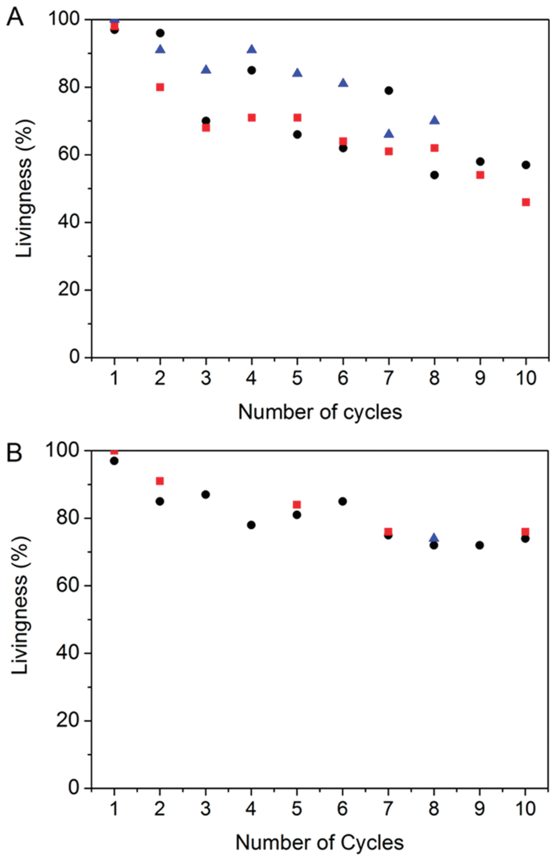

Figure 3. Livingness plotted vs number of cycles in Cu(0)-mediated polymerizations via iterative chain extensions: (a) determined by GPC analysis and (b) by ^{1}H NMR spectroscopy for (●) series 1, (■) series 2, and (▲) series 3.

estimated by assuming that all chains with molecular weights greater than the value at the minimum point (indicated in Figure S10a and also in Figure S10b for comparison, with a thick red vertical line) are living chains. Using this approach, plots of livingness vs number of cycles were constructed for the different poly(MA) "block" homopolymers and block copolymer series.

Effect of Cycle Number on Livingness. Figure 3a shows the livingness vs number of cycles for series 1−3. A number of observations can be made: (i) Despite as many as 9−10 iterative cycles, each cycle being taken to near 100% (>99%) monomer conversion, the livingness (i.e., number-, not weight-, percentage of living chains) is in excess of 54%, up to cycle 9. (ii) The loss of livingness appears to be greater in the first 4−5 cycles than the remainder of the cycles, especially for series 1. (iii) The livingness is higher in the systems where short blocks (∼500 g/mol) rather than long blocks (∼2000 g/mol) have been targeted.

The high livingness after 10 consecutive polymerizations, where each cycle is taken to essentially full conversion, is extraordinary. It is also noteworthy that 54% livingness by number corresponds to 90 wt % living chains (series 3, 8 cycles). CLRP based on NMP, ATRP, and RAFT generally (depending on particular system/conditions) results in less than ∼90% livingness (by number of chains) at very high conversion (∼90%).[29,30,32,58−61] Moreover, the livingness at close to full conversion (>99% conversion) would be anticipated to be much lower, probably 60% or less, because the value of d(livingness)/d(conversion) decreases dramatically with increasing conversion in the highest conversion regime. As such, if these techniques were employed to carry out iterative polymerizations as in the present study (taking each cycle to near full conversion), the final livingness would be anticipated to be less than $(0.60^{10}) \times 100\% = 0.6\%$; i.e., the final multiblock copolymer yield would be prohibitively low and the MWD would be very broad (high PDI).

^{1}H NMR analysis can also be directly used to estimate the livingness for each cycle. In the poly(MA) block copolymer, the ratio between CH-Br (ω-end if chain is living) and CH_2O (initiator fragment at α-end) provides a good way to estimate the livingness. Figure 3b shows the evolution of the livingness vs the number of cycles. The livingness calculated by GPC and by ^{1}H NMR analysis are in relatively good agreement for the poly(MA) homopolymer. Unfortunately, direct estimation of the livingness is impossible in the case of block copolymers due to the overlap of CH-Br (4.2 pm) and CH_2O (4.0 pm) signals. To overcome this problem, we decided to modify the bromide end group by "thio-click reaction" using benzyl mercaptan.[62−64] ESI-MS data of poly(MA) (M_n = 2000 g/mol) after bromide end-group modification confirms that this reaction is quantitative, as evidenced by the absence of bromide-terminated polymers and the expected mass of the benzyl-terminated poly(MA) (Figure S11 in the Supporting Information). Having demonstrated that the reaction is quantitative, the livingness of the original polymer was estimated as a function of iterative cycle by ^{1}H NMR using the benzyl group signal at 7.20 ppm (Figure S12). The livingness was calculated by the following equation: $\%\ \text{CH-Br} = (6 \times \int \text{CH}^{7.2\ \text{ppm}}/5 \times \int \text{CH}_3^{1.1\ \text{ppm}}) \times 100$, with $\int \text{CH}^{7.2\ \text{ppm}}$ and $\int \text{CH}_3^{1.1\ \text{ppm}}$ corresponding to CH (benzyl ring) and CH_3 of initiator signal (d), respectively. The livingness decreases with increasing number of cycles for series 2 but remains as high as 75% after 10 cycles. The livingness obtained by ^{1}H NMR is somewhat higher than the livingness estimated by GPC, but the differences are relatively minor considering the expected experimental errors involved (especially in the GPC analysis). The livingness was also estimated by this ^{1}H NMR approach for series 3, resulting in 74% livingness after eight cycles (to be compared with 71% based on GPC analysis).

CONCLUSIONS

In this article, we report for the first time the synthesis of decablock copolymers by a straightforward method via iterative Cu(0)-mediated radical polymerization at room temperature without any purification for each chain extension. The approach has been demonstrated by the synthesis of poly(MA-*b*-EA-*b*-*n*BA-*b*-*t*BA-*b*-MA-*b*-EA-*b*-*n*BA-*b*-*t*BA-*b*-MA-*b*-EA), poly(MA-*b*-*n*BA-*b*-EA-*b*-2EHA-*b*-EA-*b*-*n*BA-*b*-*n*BA-*b*-MA), and a model decablock PMA homopolymer. Such (co)polymers can be successfully synthesized due to the unprecedented high level of livingness at each block formation step. As a result of the synthetic strategy used herein, during the synthesis of the final block copolymers we generated 16 structurally discrete block copolymers with systematic variation in complexity.

ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Experimental part, ^{1}H NMR spectra of copolymers and poly(MA), ESI-MS spectra of homopolymer and copolymers, summary of the copolymer (Table S1). This material is available free of charge via the Internet at http://pubs.acs.org.

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