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High-Order Multiblock Copolymers via Iterative Cu(0)-Mediated Radical Polymerizations (SET-LRP): Toward Biological Precision

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Supporting Information

ABSTRACT: We report a new approach for the facile synthesis of high-order multiblock copolymers comprising very short blocks. The approach entails sequential addition of different monomers via an iterative single electron transfer−living radical polymerization technique, allowing nearly perfect control of the copolymer microstructure. It is possible to synthesize high-order multiblock copolymers with unprecedented control, i.e., A-B-C-D-E-etc., without any need for purification between iterative 24 h block formation steps. To illustrate this concept, we report the synthesis of model P(MA-*b*-MA...) homopolymer and P(MA-*b*-nBuA-*b*-EA-*b*-2EHA-*b*-EA-*b*-nBuA) copolymer in extremely high yield. Finally, the halide end-group can be modified via "click chemistry", including thiol−bromide click chemistry, sodium methanethiosulfonate nucleophilic substitution, and atom transfer radical nitroxide coupling reaction, to yield functional, structurally complex macromolecules.

Biopolymers, including DNA, peptides, and proteins, exhibit exceptional structural, chemical, and biological properties compared to synthetic polymers. It is the specific distribution/placement of monomer units in the biomolecules that confers the remarkable properties of these polymers, and it is therefore the ultimate goal of macromolecular scientists to reproduce these structural features. Perhaps the most successful attempt to synthesize polymers with predetermined and highly controlled sequence distributions has been the synthesis of artificial peptides, obtained by the sequential condensation steps of different amino acids onto a solid support.[1−5] This has allowed the preparation of oligopeptides with good control of the monomer sequence distribution. However, this multistep approach is only suitable for the preparation of relatively short peptides. The less-than-quantitative reaction yields and time-consuming deprotection/purification processes routinely result in milligram-scale yields due to the complexity of this process. All these difficulties are present in other iterative synthetic techniques used for other large macromolecules, e.g., dendrimers.[1,6] The translation of this concept of sequential control to the widely used free radical polymerization techniques for the synthesis of polymers is nontrivial.

Anionic and controlled radical polymerization (CRP) techniques[7−14] have allowed the routine preparation of block copolymers with two or three different monomer blocks. However, anionic polymerization is only suitable for a specific range of monomers and must be performed under a rigorous set of polymerization conditions. For CRP, after each block addition, the copolymer requires purification to eliminate unreacted monomers prior to the next chain-extension step with another monomer. Due to the experimental process, the synthesis of multiblock copolymers is usually time-consuming and generally allows the synthesis of only a small number of relatively large blocks with limited synthetic control. If taken to high conversion, CRP techniques inevitably result in significant loss of "livingness" (end-group fidelity), which prohibits synthesis of multiblock copolymers in high yield.[8,11,15,16] Higher order and structurally complex block structures are therefore rarely reported.[11,17,18] To circumvent these difficulties, different teams have reported the synthesis of multiblock copolymers using the copolymerization of monomers exhibiting a large differences in relative reactivity.[19−22] These copolymerizations yield pseudoblock copolymers or gradient copolymers. Unfortunately, this method is limited to co-monomers that have a large disparity in their reactivity ratios. In all the above examples, side reactions such as chain termination events reduce both structural control and yield. Another synthetic route to multiblock copolymers involves linking several preformed short blocks, which has been reported by use of a "polyinitiator" species as well as by exploiting click chemistry.[17,18,23−25] Again, side reactions limit the synthesis of well-defined structures.

In this Communication, we present an original approach for the facile synthesis of high-order multiblock copolymers via sequential Cu(0)-mediated living radical polymerization (LRP) inspired by the previous works of Haddleton, Percec, and Matyjaszewski and co-workers.[11,12,14,26−34] It has been shown previously that, by the judicious choice of solvent used in copper(0)-mediated polymerizations, chain end functionality can be highly conserved until high monomer conversions. When carried out in a solvent that promotes disproportionation, such as dimethylsulfoxide (DMSO, as in the work here), the polymer synthesis shows very high chain end fidelity, leading to polymers with low polydispersity index (PDI) and increased livingness. This is in contrast to polymerizations carried out in non-disproportionating solvents which give rise to polymers with much poorer end-group fidelity and therefore a greater proportion of dead polymer chains.[35−37] We demonstrate that this technique can be employed for the preparation of high-order multiblock copolymers, where each block constitutes a very small number of monomer units (ideally two monomer units), with unprecedented control and minimal loss of end-group fidelity.

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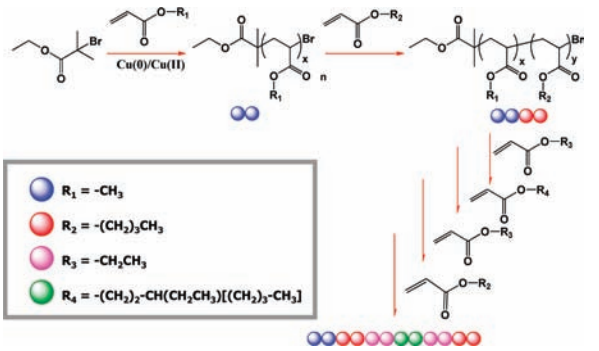
Scheme 1. Schematic Representation of the Synthesis of Multiblock Copolymers by Sequential Addition of Monomers without Intermediate Purification



The method involves no purification between the successive block formation steps because each step is taken to full monomer conversion. To demonstrate the feasibility of this process, the syntheses of a multiblock homopolymer and a structurally complex copolymer are reported in high yields.

Scheme 1 illustrates the process used for the synthesis of multiblock copolymers containing very short blocks, typically two or three monomer units. The synthesis of each block was achieved via iterative Cu(0)-mediated single electron transfer—living radical polymerization (SET-LRP) at room temperature (25 °C) in DMSO, carried out to full conversion by successive monomer addition. Importantly, there is no need to purify the polymer after the formation of each block.

Full conversion is usually not recommended in CRP techniques [reversible addition—fragmentation chain transfer (RAFT), atom-transfer radical polymerization (ATRP), and nitroxide-mediated polymerization (NMP)] due to the accumulation of dead polymer formed throughout the polymerization via termination events or loss of end-groups due to side reactions (transfer to ligand, to polymer, to monomer, and to solvent).[11,38,39] Recently, Percec and co-workers reported that Cu(0)-mediated SET-LRP allows the synthesis of polymers with exceptionally high end-group fidelity.[27,35−37] Inspired by these findings, we decided to investigate whether high end-group fidelity can be achieved at full monomer conversion in the SET-LRP of methyl acrylate (MA) initiated by ethyl 2-bromoisobutyrate (EBiB) at 25 °C in DMSO. Polymerizations were carried out in the presence of different amounts of initially added Cu(II) (Figure S1 in the Supporting Information (SI)), and in all cases, full conversion was obtained after 2 h, as determined by ^{1}H NMR. The polymerizations were allowed to "continue" (despite all monomer having been consumed) for 3 days. Aliquots were taken periodically and analyzed by mass spectroscopy (MS) to evaluate end-group fidelity. Mass spectroscopic analysis revealed high end-group fidelity even after 3 days for polymerization in the presence of Cu(II) (Figure S1). Gel permeation chromatography (GPC) analysis confirmed the absence of significant bimolecular termination via coupling. In the absence of initially added Cu(II), the formation of a significant amount of dead polymer was clearly detected by MS.

The apparent high end-group fidelity in the presence of Cu(II), despite full monomer conversion, suggests it is possible to prepare multiblock copolymers by an iterative approach. We therefore decided to explore the synthesis of high-order multiblock copolymers with very short blocks (A-B-C-D-E-etc.), each

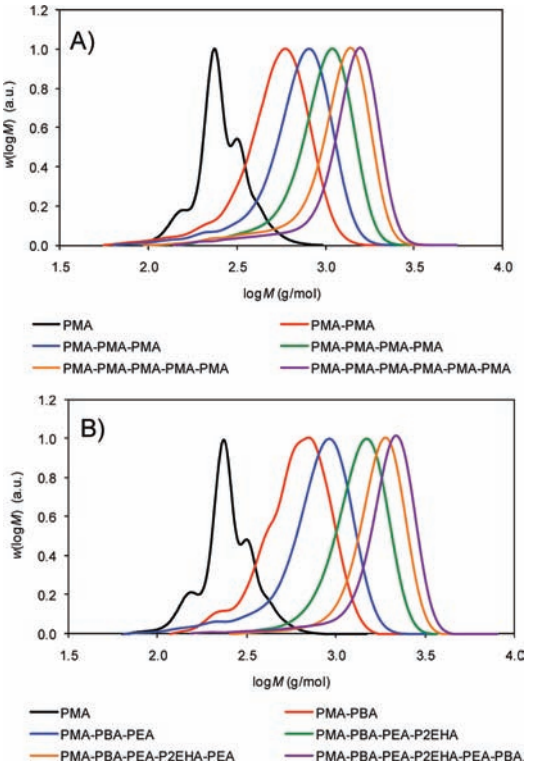


Figure 1. Molecular weight distributions (normalized to peak height) of (A) multiblock homopolymer and (B) multiblock copolymer obtained by Cu(0)-mediated polymerization via iterative chain extensions.

block typically comprising only twoor three monomer units. Cu(0)-mediated LRP was thus employed in tandem with the sequential monomer addition technique to synthesize a model multiblock P(MA) homopolymer and a multiblock copolymer comprising different acrylates. In both cases, we first synthesized a P(MA) macroinitiator by polymerization for 24 h at room temperature (25 °C) in DMSO. NMR analysis confirmed full monomer conversion in this first step (SI). The second monomer, MA or ethyl acrylate (EA) (a degassed 50 vol % solution in DMSO), was then added under nitrogen without purification of the first block. The polymerization was allowed to continue for a further 24 h. This process was repeated several times until the formation of the high-order multiblock copolymers was achieved. Each block addition was characterized by a range of analytical techniques, including GPC, NMR, and MS. GPC analysis of the molecular weight distributions confirmed successful chain extensions as manifested by clear shifts to higher molecular weights in each step (Figure 1). In addition, the molecular weight distributions remained narrow after several steps, confirming that the polymerizations are well controlled (PDI^{final} = 1.2 and 1.1 for poly(MA) and block copolymer, respectively). The number-average molecular weights (M_n) were in good agreement with the theoretical values for each monomer addition (Tables S3 and S4, SI). The molecular weight distributions (assessed by GPC) reveal some low-molecular-weight tailing, the extent of which increases with increasing number of cycles. However, these presumably dead chains constitute <7 wt % of the total weight of polymer after six steps. The quantitative interpretation of these molecular weight distributions is subject to the limitations of the GPC system.

Mass spectroscopy was also performed for each chain extension to investigate the degree of livingness for the syntheses of

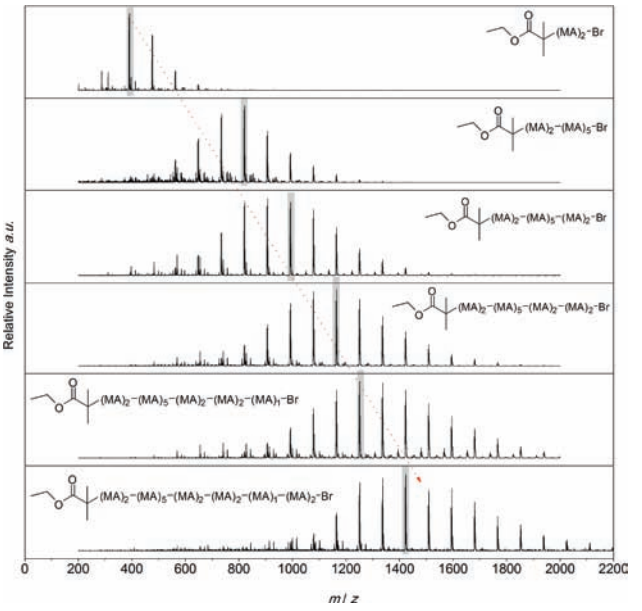
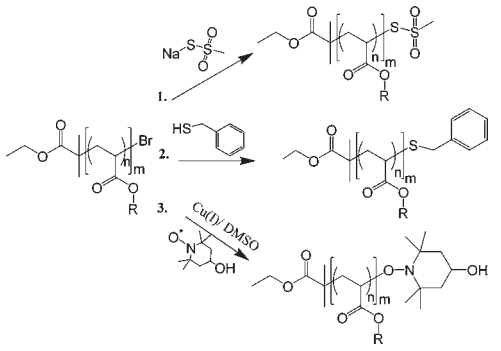


Figure 2. Mass spectra of P(MA) homopolymer obtained by Cu(0)-mediated polymerization via iterative chain extensions.

Scheme 2. Post-functionalization of Multiblock Copolymers by Nucleophilic Substitution with Sodium Methanethiosulfonate (Reaction 1) or Benzyl Mercaptan (Reaction 2) and by ATRC in the Presence of Nitroxide (Reaction 3)



both the multiblock P(MA) homopolymer and the multiblock copolymer (Figure 2 and Figures S2 and S4, SI). Model reactions using iterative chain extensions of P(MA) facilitate characterization by MS. The major chain population is terminated by a bromide; i.e., a high conservation of living character is achieved. For each cycle, the molecular weight (assessed by MS) increases by 2−3 units, in accord with the theoretical values (Tables S3 and S4) and GPC results.

Characterization of the multiblock copolymer comprising different acrylates was also carried out by MS. In this case the analysis is more complicated due to the presence of different families of chain populations. However, importantly, it can clearly be shown that the vast majority of chains possess a bromide end-group. The block iterations were not taken beyond six cycles because the resolution limit of the mass spectrometer had been reached.

Finally, the high fidelity of terminal bromide at the end of the synthetic cycles was exploited to introduce specific functional

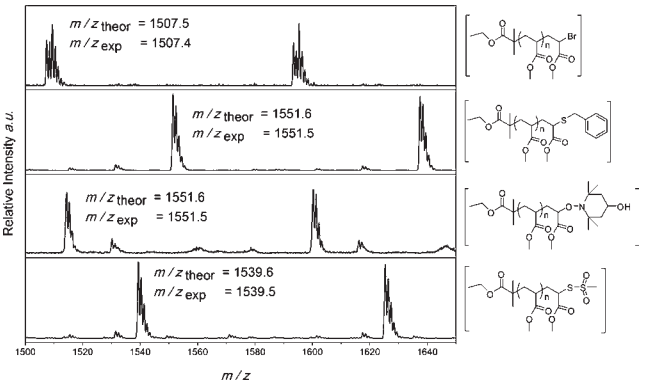


Figure 3. Mass spectra of unmodified and modified P(MA) homopolymer obtained via six iterative chain extensions.

end-groups to multiblock P(MA) homopolymer obtained after six successive chain extensions. To confirm the chemical accessibility of the bromide end-group, two different quantitative modifications were performed, based on (i) nucleophilic substitution of halide atom by thiolate compounds (in this example, methanethiosulfonate compounds)[40] or benzyl mercaptan[41−43] and (ii) atom transfer radical coupling (ATRC)[44,45] reaction (Scheme 2).

Both nucleophilic reactions 1 and 2 (Scheme 2) were performed in DMF at room temperature overnight. Figure 3 shows the mass spectra after modification, which confirms successful nucleophilic substitution without significant formation of side products. ATRC between bromide-terminated copolymer and nitroxide was performed (reaction 3, Scheme 2), whereby macroradicals are generated by Cu(0) and subsequently trapped by nitroxide.[44] Quantitative modification by radical coupling was also confirmed by MS (Figure 3). GPC analysis revealed that the molecular weight distributions for each modification remained monodisperse, although some disulfide coupling is evident in the sodium methanethiosulfonate modification due to partial hydrolysis to free thiols with subsequent oxidation to disulfide (Figure S4).

In conclusion, a new approach has been developed for the synthesis of high-order multiblock copolymers via an iterative Cu(0)-mediated SET-LRP technique featuring high yield and unparalleled control and requiring purification only at the final step. In contrast with the conventional approach to extend and purify chains, this novel technique allows facile synthesis of high-order multiblock copolymers in a manner that is amenable to scale-up. The accessibility of end-groups (bromide) to chemical modification was confirmed by three different methods to yield functional polymers.

■ ASSOCIATED CONTENT

Supporting Information. Experimental data, NMR analysis, GPC traces, and MS characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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