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Synthesis of sequence-ordered polymers *via* sequential addition of monomers in one pot†

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Sequence-ordered polymers can be simply prepared in one pot *via* sequential monomer addition.

Nature is an expert at easily controlling properties of biopolymers (DNA, proteins), including tacticity and the monomer sequence, and producing biopolymers with unrivaled properties and functionalities, which cannot be matched with synthetic polymers.[1–4] Disorder of units in a biopolymer can result in physical function imbalance, denaturation of the organism's proteins, and even fatal diseases.[5] Compared with DNA replication and protein synthesis, the methods for producing synthetic polymers are still primitive. It is very difficult to control the monomer sequence in chain-growth or step-growth processes when a polymer is made from more than one different type of monomers[6–8] although polymer chemists can now design and build intriguing compounds such as dendrimers, star-shaped polymers, macromolecular bottle-brushes and macrocycles. Sequence regulation of synthetic polymers is therefore one of the goals of polymer chemists,[4] and some new methods have recently been developed for constructing sequence-controlled copolymers. For example, Liu *et al.* reported a potential method for successfully preparing sequence-defined polymers using DNA-templated polymerization.[9] Thomas *et al.* reported an important strategy for controlling monomer sequences using ring-opening polymerization of β-lactones.[10,11] Sawamoto *et al.* described a method for preparing sequence regulated copolymers using tandem catalysis of living-free radical polymerization.[12,13] Kamigaito *et al.* prepared sequenced copolymers using sequence living-free radical chain copolymerization of naturally occurring limonene with maleimide.[14] Li *et al.* synthesized periodic vinyl copolymers using acyclic diene metathesis polymerization with built-in sequences.[15] Very recently, Zamfir and Lutz used kinetically controlled sequential addition of donor and acceptor monomer feeds to accomplish precise insertion.[7] Although these methods are very useful for preparing sequence-ordered copolymers, they rely on the development of polymerization techniques, catalysts, different comonomer reactivities, and the use of templates. And most of them involve multi-pot processes. Here, we report a sequential monomer addition method for preparing sequence-ordered polymers *via* quantitative and highly selective reactions in a one-pot process.

The Michael addition reaction of an acrylate with an amine has few side reactions and requires mild reaction conditions.[16] The reaction has been used to synthesize high-molecular-weight poly(amino ester)s in high yields.[17] In contrast, methacrylates do not react with amines without a catalyst, but they react quantitatively with thiols, even without a catalyst.[18] The reaction of a methacrylate with a thiol is therefore highly selective. Using this highly selective reaction, we prepared ABC-sequenced copolymers simply by sequentially adding ABC monomers to a polymerization system, as shown in Scheme 1. In the experiments, 2-aminoethanethiol (**B** unit) was first added to a solution of allyl methacrylate (**A** unit) in methanol at a molar equivalent feed ratio. A thiol quantitatively reacts with methacrylate at room temperature (as shown in Scheme 1), but it does not react with an alkene without a catalyst, the amino group in 2-aminoethanethiol does not react with methacrylate without a catalyst either. NMR spectroscopy verified that all the methacrylate reacted with thiol *via* Michael addition in 1 h at room temperature, because the signals at 5.65 (vinyl protons) and 1.92 ppm (methyl protons) shifted completely to 2.6 and 1.15 ppm, respectively (see Fig. S5, ESI†). The ^{13}C NMR results showed that there was no byproduct from methacrylate reacting with an amine unit or a thiol reacting with an alkene unit (Fig. S5, ESI†). Adding 2-aminoethanethiol to a solution of allyl methacrylate therefore quantitatively yields an AB sequence containing amine and alkene units (as shown in Scheme 1). Primary amines are good ring-opening reagents for aminolysis of thiolactones.[19,20] Consequently, when *N*-acetylhomocysteine thiolactone (1 equiv., **C** unit) was added to the above reaction mixture, the amine in the AB sequence can ring-open

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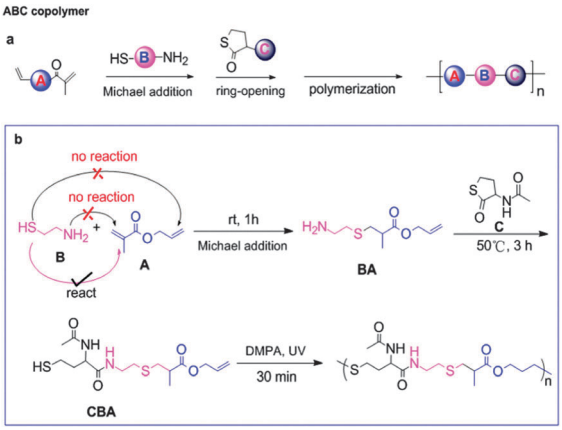
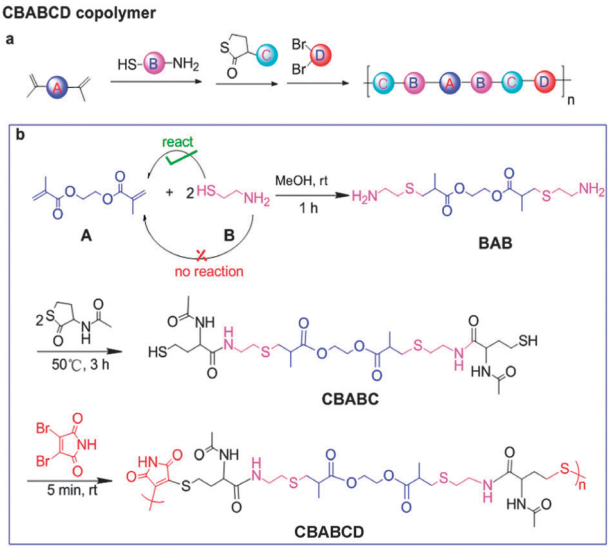


Scheme 1 (a) Schematic outline of one-pot synthesis of an ABC-sequenced copolymer *via* sequential addition of A, B, and C monomers and (b) detailed reactions for preparing an ABC-sequenced copolymer.

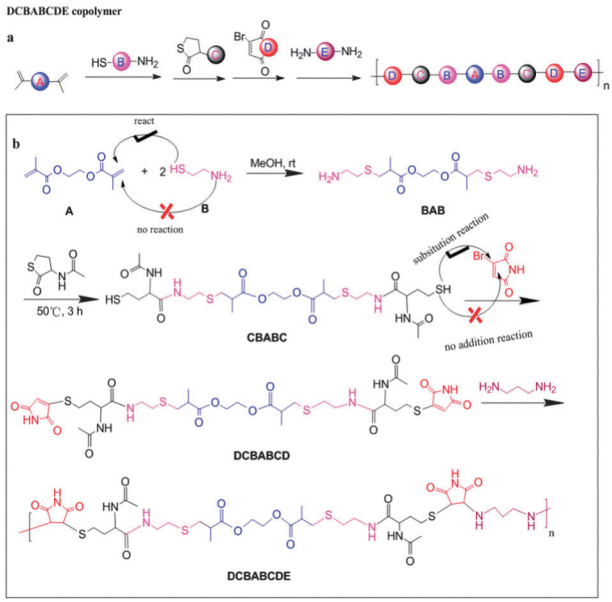


Scheme 2 (a) Schematic outline of one-pot synthesis of a CBABCD-sequenced copolymer *via* sequential addition of A, B, C, and D monomers and (b) detailed reactions for preparing a CBABCD-sequenced copolymer.

the thiolactone, generating an ABC-sequence containing thiol and alkene units from the AB sequence. We monitored the ring-opening reaction using NMR spectroscopy, and the results showed that it took 3 h to complete the ring-opening of thiolactone at room temperature. After complete ring-opening of the thiolactone, the signal (methene protons) at 2.1 ppm shifted completely to 1.85 ppm (see Fig. S6, ESI†). Amine ring-opening of the thiolactone was further verified by transformation of the lactone unit (**10**, chemical shift at 207 ppm) to amide (**10′**, chemical shift at 173 ppm) as shown by the ^{13}C NMR spectrum (see Fig. S6, ESI†) after complete ring-opening of the thiolactone. A thiol–ene click reaction (as shown in Scheme 1 and Fig. S7, ESI†) then occurred when the mixture was subjected to UV irradiation, and a polymer with the ABC sequence, a M_n of 5160 and a PDI of 1.57 was obtained after UV irradiation for 30 min. The NMR results show that only trace (<1%) signals of a double bond, between 5.5 and 6.5 ppm, were detected (see Fig. S7, ESI†). The ABC sequenced copolymer can therefore be simply prepared *via* ABC sequential monomer additions in a one-pot process.

Recently, Baker and Haddleton *et al.* reported that bromomaleimides can react rapidly (<10 min) and selectively with thiols to form thiomaleimides. The reaction between the thiol and the maleimide proceeded *via* a thiol substitution reaction, and was highly efficient and quantitative.[21–25] Polymers can be easily linked with proteins *via* this reaction. We used this quantitative thiol substitution reaction in the preparation of sequence-ordered copolymers. Using sequential Michael addition, amine ring-opening of thiolactone, and thiol substitution reactions (as shown in Scheme 2), a CBABCD-sequenced copolymer was easily obtained in one pot *via* ABCD sequential monomer addition as follows. First, 2-aminoethanethiol (**B** unit) was added to a solution of ethylene dimethacrylate (**A** unit), yielding a BAB sequence with an amine at each end *via* Michael addition of the thiol and the methacrylate (amine did not react with the methacrylate because no catalyst was added). After 1 h, signals at 5.5–6.1 ppm, assigned to vinyl protons, shifted to 2.6 ppm, and the signal at 1.85 ppm, assigned to methyl protons (next to the vinyl unit), shifted to 1.2 ppm in the ^{1}H NMR spectrum (as shown in Fig. S9, ESI†). The ^{13}C NMR results also verified the quantitative reaction of 2-dimethacrylate with 2-aminoethanethiol, as the vinyl carbon signals (**1** and **2**) at 126 and 137 ppm completely shifted to 40 and 34 ppm, respectively (as shown in Fig. S9, ESI†). *N*-acetylhomocysteine thiolactone (**C** unit) was added to the mixture, and the amines in the BAB sequence can quantitatively ring-open thiolactones, giving the CBABC sequence with a thiol at each end (as shown in Scheme 2). This was verified by NMR, because the signal at 2.1 ppm (methene protons of thiolactone) shifted completely to 1.85 ppm (see Fig. S10, ESI†), and the lactone unit (**8**, 207 ppm) was completely transformed to an amide (**8′**, 173 ppm) (see Fig. S10, ESI†), after complete ring-opening. Finally, 2,3-dibromomaleimide (**D** unit) was added to the reaction mixture. The reaction solution immediately changed from colorless to bright yellow. The coupling of 2,3-dibromomaleimide with the thiol was almost complete in only 5 min, and the viscosity of the polymerization mixture increased noticeably. 2,3-Dibromomaleimide underwent rapid and highly efficient conjugation with a thiol *via* a thiol substitution reaction, yielding a CBABCD-sequenced copolymer with a M_n of 8460 and a PDI of 1.17 only in a one-pot process.

Bromomaleimide can not only react with a thiol *via* a thiol substitution reaction, but can also react with a thiol or an amine *via* nucleophilic addition. Compared with the thiol substitution reaction, the nucleophilic addition reaction of thiomaleimide with a thiol or an amine is very slow, so it can only occur after complete substitution of the bromide in bromomaleimides.[21–25] Inspired by this, we prepared a DCBABCDE-sequenced copolymer *via* ABCDE sequential monomer addition as follows. A BAB sequence with an amine at each end was formed *via* quantitative Michael addition of a thiol with a methacrylate (the amine did not react with the methacrylate in the absence of a catalyst) when 2-aminoethanethiol (**B** unit) was added to a solution of ethylene dimethacrylate (**A** unit) (as shown Scheme 3). The signals at 5.5–6.1 ppm, assigned to vinyl protons, shifted to 2.6 ppm, and the signal at 1.85 ppm, assigned to methyl protons



Scheme 3 (a) Schematic outline of one-pot synthesis of a DCBABCDE-sequenced copolymer *via* sequential addition of A, B, C, D, and E monomers and (b) detailed reactions for preparing a DCBABCDE-sequenced copolymer.

(next to the vinyl unit), shifted to 1.2 ppm in the ^{1}HNMR spectrum (as shown in Fig. S13, ESI†). The ^{13}C NMR results also verified quantitative reaction of 2-dimethacrylate with 2-aminoethanethiol, shown by the vinyl carbon signals (**1** and **2**) at 126 and 137 ppm shifting completely to 40 and 34 ppm, respectively (Fig. S13, ESI†). *N*-acetylhomocysteine thiolactone (**C** unit) was added to the mixture, and amine ring-opening of the thiolactone gave a CBABC sequence with a thiol at each end (as shown in Scheme 3). This was verified by the NMR spectrum, in which the signal (methene protons of thiolactone) at 2.1 ppm shifted completely to 1.85 ppm (see Fig. S14, ESI†), and complete transformation of the lactone unit (**8**, 207 ppm) to an amide (**8′**, 173 ppm) occurred (see Fig. S14, ESI†), after complete ring-opening of the thiolactone. When a bromomaleimide (**D** unit) was added to the above CBABC sequence reaction mixture, the bromomaleimide underwent rapid and highly efficient conjugation with the thiols *via* a substitution reaction, yielding a DCBABCD sequence with a thiomaleimide at each end. Based on the NMR results, it is clear that thiomaleimides are present at both ends after the substitution reaction (see Fig. S15, ESI†). Finally, a diamine was added, and the mixture underwent nucleophilic addition of amine and thiomaleimide, yielding a DCBABCDE-sequenced copolymer with a M_n of 25600 and a PDI of 1.24. It is clear that the signals for the double bond of the thiomaleimide were absent from the NMR spectrum (Fig. S16, ESI†), indicating complete nucleophilic addition of the thiomaleimide with the amine, and the formation of the DCBABCDE-sequenced copolymer.

In this study, we have reported a novel method for preparing sequence-ordered copolymers *via* quantitative or highly selective one-pot reactions. *Via* this method, ABC-, CBABCD-, and DCBABCDE-sequenced copolymers were easily obtained by sequentially adding ABC monomers, ABCD monomers, and ABCDE monomers.

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