

# Sequence Control of Macromers via Iterative Sequential and Exponential Growth

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**S** Supporting Information

**ABSTRACT:** A general strategy through the use of direct azidation of alcohols allowed the sequence control of macromers via both the iterative sequential growth and iterative exponential growth methods. The chemistry was highly efficient in building polymers from a sequence of compositionally different macromers tethered together in close proximity. Using the DPPA/DBU method for near quantitative azidation of the benzyl alcohol moiety, sequence controlled polymers were made via a direct and one-step procedure for CuAAC activation. With four different macromers, spherical miktoarm star-like polymers of 50 000 molecular weight were prepared with a low dispersity, and the polymer coil size depended on the type of added macromer. Polymers made via the iterative methods opens the way for the design of advanced materials with predictable properties.

Building complex polymer architectures has been driven by the quest to obtain new and predictable solution and bulk properties. Incorporating sequence control into these architectures through the judicious choice of monomer or macromers will have the potential to create advanced polymer materials<sup>1</sup> with unique properties and functions that are commonly found in biological proteins. This will lead to material design with potential applications as adaptive materials, catalysts, and use in vaccine and drug delivery.

The iterative growth approach through either iterative sequential addition (ISG)<sup>2</sup> or iterative exponential growth (IEG)<sup>3</sup> of monomer provides precise control over the monomer sequence, chain length and in some cases stereocontrol depending on the monomer and chemistry used. The iterative growth chemistry for the addition of each monomer unit and reactivation of the chain end must be highly efficient. Reactivation usually occurs through coupling of a second molecule containing a different R-group, with most examples of ISG utilizing a solid support to grow the chain sequentially.<sup>4</sup> For example, Lutz and co-workers used the nitroxide radical coupling method<sup>5</sup> to synthesize a digitally encoded polymer sequence.<sup>6</sup> The IEG method<sup>7</sup> and the IEG+ strategy<sup>8,9</sup> allows doubling of the chain length with each coupling reaction, resulting in a significantly fewer number of coupling reactions.

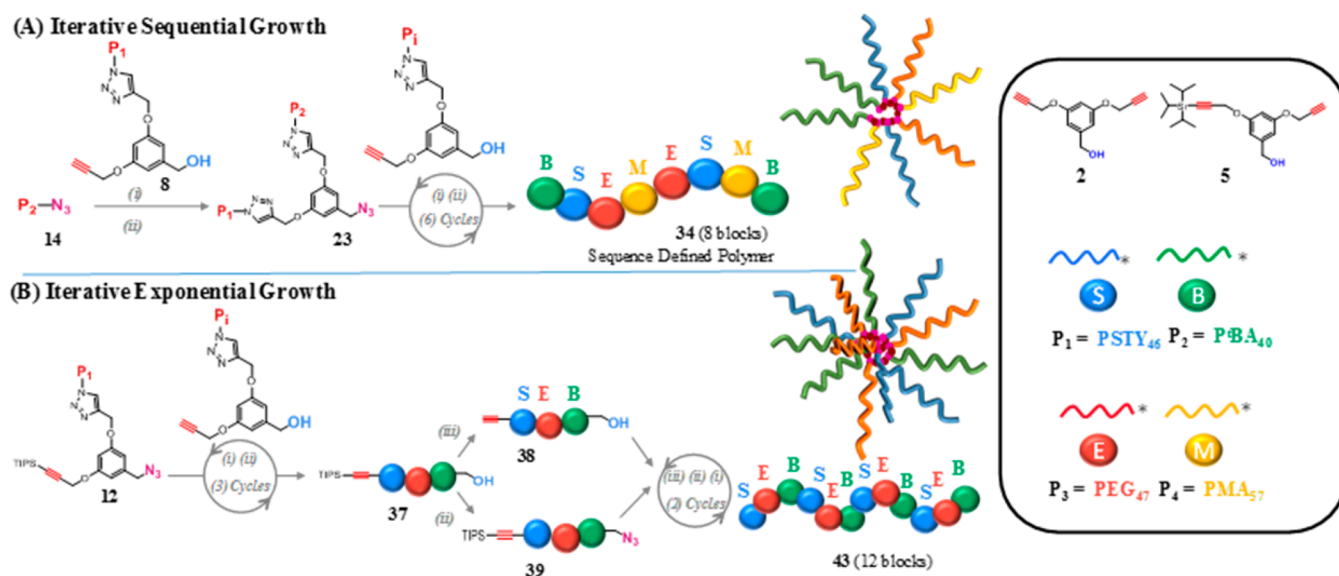
The copper-catalyzed azide–alkyne cycloaddition (CuAAC) “click” reaction via an iterative approach provided near quantitative conversion of the halide end-group to an azide for further coupling and continued growth.<sup>9,10</sup> Activation of alcohol end-groups to azides in one-step would represent a straightfor-

ward iterative method to produce sequence-defined polymers in a facile manner. Alcohol end-groups represent an alternative to halides as they are more stable to hydrolysis and unreactive to copper species used in the CuAAC reaction. There are only a few methods for the direct conversion of HO-groups to azides: the first, the Mitsunobu displacement,<sup>11</sup> and the second, the diphenyl phosphorazidate (DPPA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) method (i.e., DPPA/DBU method).<sup>12</sup> The DPPA/DBU method is operationally simple resulting in excellent yields and if required allows high enantioselectivity. Here, we advance the CuAAC iterative concept by using macromers with molecular weights ranging from 3 to 5.5 k coupled either via ISG or IEG. The macromer end-group was directly reactivated using the DPPA/DBU method in one-step (Scheme 1). By coupling compositionally different macromers via either the ISG or IEG strategies, molecular weights of up to 50 000 could be reached forming spherical miktoarm star-like structures. The novelty of our synthetic strategy is that by using the same linker attached to the macromer, sequence-defined polymers can be produced in a facile manner by either ISG or IEG.

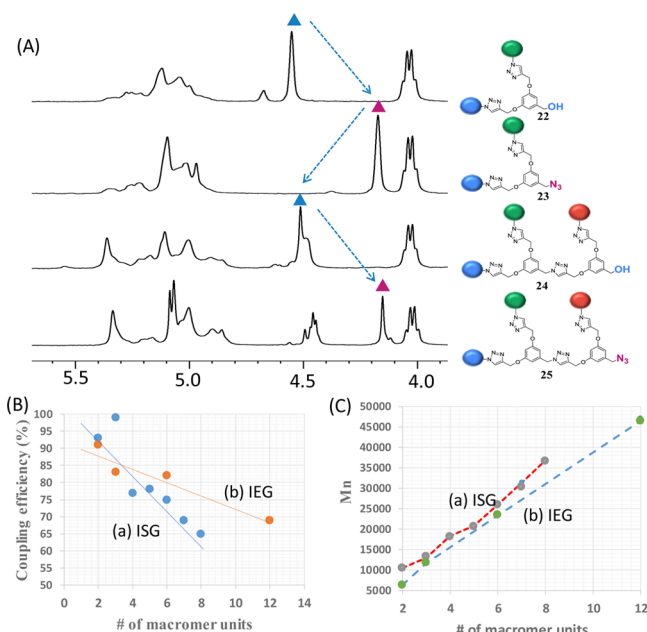
The ISG method was used to grow a chain of four low molecular weight macromers of polystyrene (PSTY, **S**;  $M_n = 5130$  for ISG, and 3800 for IEG), poly(*t*-butyl acrylate) (P<sup>t</sup>BA, **B**;  $M_n = 5690$ ), poly(ethylene glycol) (PEG, **E**;  $M_n = 2490$ ), and poly(methyl acrylate) (PMA, **M**;  $M_n = 5230$ ). This tool box of functional macromers (Scheme 1) was also used in the IEG procedure. These polymers were made by either ATRP or SET-LRP with low dispersity values (see Table S1 in SI), the halide end-group was azidated and then coupled to linker **2**. The HO-end-group of purchased PEG was functionalized to the azide. The first step in the ISG process was the coupling of P<sup>t</sup>BA<sub>40</sub>-N<sub>3</sub> (**14**) to PSTY<sub>46</sub>-(OH)-≡ (**8**) to produce the first diblock **22** (BS-OH). The alcohol group was then directly azidated using DPPA/DBU in DMF at 50 °C for 24 h to form **23** in near quantitative yields as shown from the shift of the methylene protons at 4.5 to 4.1 ppm in the <sup>1</sup>H NMR given in Figure 1A. The size exclusion chromatograms (SEC) using refractive index (RI) detection with PSTY calibration curve showed a shift toward a higher molecular weight (Figure S21 in SI). Analysis of the CuAAC coupling efficiency required simulation of the refractive index SEC using the Log-normal distribution (LND) model with known  $dn/dc$  values for the macromers and sequential product.<sup>13,14</sup> The  $dn/dc$  values for the homopolymers were taken from the literature<sup>15</sup>

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Scheme 1. Methodology for the Sequence Control of Macromers via ISG and IEG Using the Direct Activation Chemistry of Alcohols by DPPA/DBU<sup>a</sup>

<sup>a</sup>Conditions. (i) CuAAC “click” reaction: CuBr, PMDETA in toluene at 25 °C; (ii) azidation, DPPA/DBU in DMF at 50 °C (dark); (iii) deprotection, TBAF in THF at 25 °C.



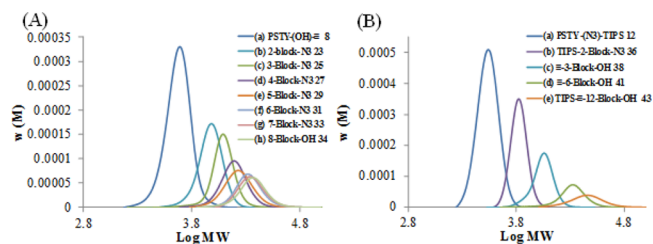
**Figure 1.** (A) <sup>1</sup>H NMR of azidation of benzyl alcohol end-group using DPPA/DBU in ISG. (B) CuAAC coupling efficiency for ISG (curve a) and IEG (curve b) processes. (C) Absolute  $M_n$  determined by NMR, triple detection SEC and theory for ISG (curve a) and IEG (curve b); all  $M_n$  data points were nearly the same with theory  $M_n$  represented as dashed lines.

and those for the block copolymers determined by a weighted average of the homopolymers.<sup>14</sup>

Simulating the SEC traces by the LND method has been described previously to obtain the true weight fractions of each polymer species in the reaction.<sup>14</sup> The coupling efficiency by this method gave a purity of 92% (Figure S21D in SI) and coupling efficiency of 93% for the two-block 22 (Figure 1B, curve a). Apart from the product, only the starting macromers remained (7% of 14 and 1% of 8). Azidation to form 23, then purification by

preparative SEC and subsequent CuAAC “click” with PEG-(OH)-≡ (18) to produce 24 (BSE-OH) showed near quantitative loss of the azide end-group by <sup>1</sup>H NMR (Figure 1A) and a shift to a higher molecular weight from SEC (Figure S22A in SI) with a purity of 98% and coupling efficiency of 99%. It can also be seen that the absolute molecular weight by both NMR and triple detection SEC was in excellent agreement with theory (Figure 1C, curve a) not only for two and three blocks but also for higher block units. The purity of all the blocks after preparative SEC and simulation was greater than 95% (Table S2 in SI). With the sequential addition of more macromers, the purity after the CuAAC coupling reaction decreased with each subsequent addition, a similar trend found for the coupling efficiency (Figure 1B, curve a). To increase the coupling efficiency, an excess of the macromer was added, especially when coupling to reach a high number of block units (Table S2 in SI). After the addition of 8 blocks, the coupling efficiency was greater than 65%, suggesting that the DPPA/DBU chemistry used was efficient to overcome the large steric crowding of coupling large macromolecules in a confined conformation (see miktoarm pictorial in Scheme 1).

Good resolution was found between the molecular weight distributions (MWDs) as the block number increased to 4 (Figure 2A). At higher block numbers, the difference between



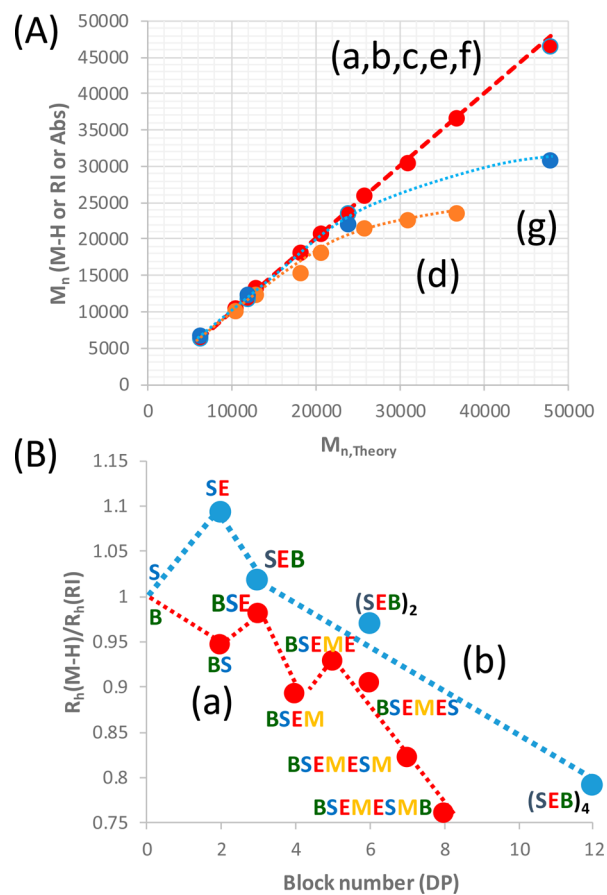
**Figure 2.** Molecular weight distributions from SEC(RI) after purification by preparative SEC. (A) ISG process, and (B) IEG process. See Tables S1–S3 in SI for  $M_n$  and  $D$  values.

the MWD of the previous block and a higher block number was small if not indistinguishable due to the conformational change to a star-like polymer topology. Both  $^1\text{H}$  NMR and triple detection SEC showed the expected increase in the number-average molecular weight ( $M_n$ ) in agreement with theory (curve a in Figure 1C). The dispersities for all blocks after purification by preparative SEC were low and below 1.11, suggesting that the DPPA/DBU and subsequent “click” strategy produced well-defined blocks in sequence; in this case, to an  $M_n$  of 37 000 after 8 separate “click” reactions. The yields for the ISG process given in Table S2 were above 68%, and the highest yield of 87% found for 23.

IEG is an alternative method to produce high molecular weight polymer with a repeating sequence in fewer steps through molecular doubling. To build the 3-macromer sequence for the IEG process, we first used the ISG method starting from 12 to make SEB (Scheme 1B). This building block was then split into two parts: in the first part deprotection resulted in the alkyne moiety, and in the second part the alcohol was directly activated to the azide using the DPPA/DBU reaction. After two cycles, a 12-block sequence-defined polymer was made. The key building compound is linker 5 in Scheme 1. The free alkyne was coupled to PSTY- $\text{N}_3$  to form 11, and after the DPPA/DBU reaction produced 12 (Scheme 1B). Polymer 12 was then coupled to 18 with a coupling efficiency of 91% (curve b in Figure 1B) and after azidation and purification by preparative SEC gave 36 with >99% purity (Table S3 in SI). Coupling 15 to 36 produced SEB-(OH)- $\equiv$ -TIPS (37), the starting building block for the IEG process. A portion of 37 was then reacted with TBAF to form the free alkyne on 38, and the other portion activated with the DPPA/DBU reaction to form 39. The purity of 38 and 39 after preparative SEC increased from 90% to 95% and 99%, respectively. There was no evidence for alkyne–alkyne coupling of 38 as shown from the SEC (see Figure S29 in SI). Polymers 38 and 39 were then coupled using the CuAAC to form a 6-macromer block (i.e.,  $(\text{SEB})_2$ ), and the same procedure as above was used to produce a 12-macromer block 43 (i.e.,  $(\text{SEB})_4$ ). From Figure 1B, the coupling efficiency decreased with the number of cycles (curve b) but at a lower rate than the ISG method (curve a). This suggests that the IEG process is far more efficient for building high molecular weight polymers in which the macromers were tethered in close proximity to each other. The increase of the narrow MWD ( $\mathcal{D} < 1.15$ ) after each cycle is shown in Figure 2B. The increase in absolute  $M_n$  was in agreement with theory (curve b in Figure 1C). The yields for the IEG process given in Table S3 decreased from 79 to 35% after two cycles. The reason for the lowering in the yield with increasing blocks was due to the small differences between the starting and product MWDs during preparative SEC. Our strategy to produce sequence-defined polymers allows not only such polymers to be generated via the ISG process but also excellent control of the polymer sequence through the IEG process.

Ring-opening metathesis polymerization (ROMP) of macromers was shown to form bottle brush structures due to the close proximity of the macromers.<sup>16</sup> These solution coil conformations remain near spherical until a degree of polymerization (DP) of approximately 120, after which the coil drives toward a cylindrical structure.<sup>17</sup> Therefore, in our system where the DP (maximum) was 12, the sequential addition of macromers in such close proximity will be preferentially spherical in a good solvent like THF and its coil conformation will change with an increase in block number and change in the composition of the macromer sequence. There is a difference between the  $M_{n,\text{RI}}$  (determined

from a PSTY calibration curve in THF) and both theory and  $M_{n,\text{abs}}$  (determined from triple detection SEC), in which the deviation increased with block number (Tables S2 and S3 in SI). This resulted from the different hydrodynamic volumes of each macromer when forming denser miktoarm star-like structures in THF (see Scheme 1). Using the Mark–Houwink (M-H) constants for the macromers (see Table S4 in SI), the expected  $M_{n,\text{RI}}$  could be determined by calculating the hydrodynamic volume ( $V_h$ ).<sup>18</sup> A comparison between  $M_{n,\text{theory}}$  (i.e., true  $M_n$ , curve a in Figure 3A),  $M_{n,\text{M-H}}$  (curve b), and  $M_{n,\text{abs}}$  (curve c)



**Figure 3.** (A) Number-average molecular weight ( $M_n$ ) vs  $M_{n,\text{theory}}$ : curve a,  $M_{n,\text{theory}}$  for ISG; curve b,  $M_{n,\text{M-H}}$  for ISG; curve c,  $M_{n,\text{abs}}$  (TD-SEC) for ISG; curve d,  $M_{n,\text{RI}}$  (PSTY calibration curve) for ISG; curve e,  $M_{n,\text{M-H}}$  for IEG; curve f,  $M_{n,\text{abs}}$  (TD-SEC) for IEG; curve g,  $M_{n,\text{RI}}$  for IEG. (B) Ratio of  $R_h(\text{M-H})/R_h(\text{RI})$  vs block number: curve a, ISG process; curve b, IEG process.

showed that  $M_{n,\text{RI}}$  in theory would be very close to absolute molecular weight for the ISG process and independent of the macromer sequence. This trend was the same for the IEG process (curves e and f). Comparing the  $M_{n,\text{RI}}$  obtained from SEC for the ISG, there was good agreement up to block 3, after which the  $M_n$  deviated toward a lower molecular weight (curve d). The deviation was less pronounced for the IEG process with good agreement of the  $M_n$  to 6 blocks for both processes (curve g).

The data suggest that tethering macromers within close proximity decreased the polymer coil size attributed to hydrodynamic volume adjustments upon addition of macromers or macromer sequences in forming the miktoarm star-like structures. This hydrodynamic coil radius change can be calculated based on the equivalent hydrodynamic radius of

PSTY standards.<sup>18,19</sup> The ratio of  $R_{h,RI}/R_{h,M-H}$  gives the normalized change in the coil radius with block length and sequence (Figure 3B). For the ISG-made polymer, the ratio for BS was close to 0.95 suggesting a smaller hydrodynamic volume to what would be expected if the polymer chain could adopt its theoretical linear coil dimension (curve a). The addition of an E macromer to BS increased the ratio back to a value close to 1 (BSE), whereas a further addition of M decreased the ratio to ~0.89 (i.e., BSEM). Subsequent addition of E (BSEME), like that observed for the third block BSE, again increased the ratio from 0.89 to 0.92. The sequential addition of S, M, and then B resulted in a decrease in the ratio from 0.92 to 0.76. The rate of decrease in the ratio with block length was similar when S, B, and M were sequentially added regardless of the order.

In the case of the making the starting 3-block polymer for the IEG process (Scheme 1), the addition of E to S (i.e., SE) resulted in an increase in the ratio to 1.1 (curve b, Figure 3B), a similar increase found when E was added to the sequence above. Further addition of B to form SEB decreased the ratio to approximately 1.02. Regardless of the sequence, i.e., either BSE or SEB, the final ratios for the 3-blocks were similar as both polymers would form the same 3-arm star polymer. SEB was then added to itself via the IEG to make the 6- and 12-block polymers. The ratio decreased linearly with each IEG reaction but at a slower rate than the ISG-made polymer. The data demonstrated that the sequential growth method provided a greater change in coil dimension, suggesting that the dimension of both the starting coil and the subsequent macromer dictated the coil dimension. For example, the addition of E increased the ratio whereas all other macromers decreased the ratio, and thus the coil dimension could be manipulated with the type of macromer added. It was found that ratio for the 8-macromer block made by ISG was of a similar coil size to that found for cyclic PSTY ( $R_{h,RI}/R_{h,M-H}$  ratio ~ 0.84).<sup>20</sup>

In summary, we have developed a strategy to prepare polymers with sequence control using a direct and one-step procedure for CuAAC activation. The DPPA/DBU method for near quantitative azidation of the benzyl alcohol allowed us to produce polymers built from a sequence of compositionally different macromers tethered together in close proximity to form mikoarm stars-like structures via both ISG and IEG methods. With four different macromers, an 8-block polymer was synthesized using the ISG method, and a 12-block polymer made by IEG (a quantitatively more efficient reaction process). These methods allowed polymers of 50 000 molecular weight to be made with a low dispersity. We postulate that our strategy could be used to build sequence controlled polymers from small molecule building blocks and for reactions where halides or other groups may be unstable. We have demonstrated that sequence control of polymers does provide a more advanced way to drive toward a predictable structure–function relationship.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b10869.

Materials, synthetic procedures, characterization of compounds and polymers (PDF)

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## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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