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RAFT emulsion polymerization for (multi)block copolymer synthesis: Overcoming the constraint of monomer order

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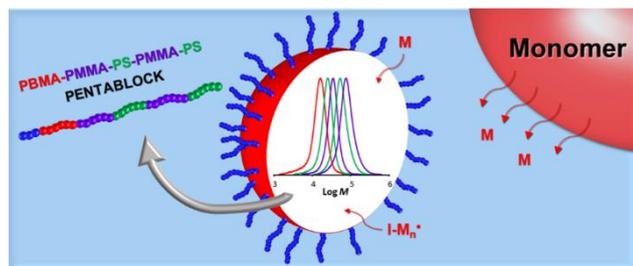
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Graphical Abstract



Abstract

Synthesis of (multi)block copolymers using reversible addition fragmentation chain transfer (RAFT) polymerization generally suffers from the limitation that the order of the blocks must be considered. Herein, syntheses of block copolymers by RAFT polymerization using trithiocarbonate RAFT species are conducted as solution, miniemulsion and emulsion polymerizations to demonstrate that the issue of monomer order for styrene and butyl methacrylate can be largely overcome in emulsion polymerization under carefully chosen conditions. The presence of monomer droplets in emulsion polymerization - in addition to polymer particles that constitute the locus of polymerization - leads to a reduction in the ratio of RAFT end groups to monomer at the locus of polymerization. Consequently, fragmentation of the RAFT adduct radical in the “backwards” (“wrong”) direction is associated with fewer monomer additions, thus minimizing the impact of this undesired kinetic event. It is demonstrated that RAFT emulsion polymerization can be exploited to prepare an alternating pentablock copolymer composed of methacrylates (with 10 mol% styrene) and styrene without consideration of monomer order, thereby significantly broadening the scope of multiblock copolymer synthesis.

Introduction

Reversible Addition-Fragmentation chain Transfer (RAFT)¹⁻² polymerization is arguably the most widely employed and versatile Reversible Deactivation Radical Polymerization (RDRP) technique, enabling synthesis of a wide range of well-defined macromolecular architectures. Implementation of RAFT polymerization in dispersed systems provides access to numerous types of polymeric nanoparticles of complex internal structure and morphology,³⁻⁴ most notably via Polymerization-Induced Self-Assembly (PISA).⁵⁻⁷

One of the most important features of RDRP and RAFT is the ability to prepare a wide range of block copolymers.⁸ Such polymers are of interest for a multitude of reasons, which include potential applications in *e.g.* nanotechnology⁹⁻¹¹ and nanomedicine.¹²⁻¹⁴ Multiblock copolymers constitute a particularly fascinating family of polymers with endless possibilities in terms of material design.¹⁰ Until 2011, which saw the first publication on multiblock copolymer synthesis via RDRP (Cu(0)-mediated radical

polymerization, also known as SARA-ATRP and SET-LRP),¹⁵ multiblock copolymer synthesis was fraught with difficulty due to the issue of the livingness (chain end fidelity) typically decreasing significantly at high monomer conversion. In the seminal work in 2011,¹⁵ a system with very high livingness to high conversion was exploited, thereby enabling multiblock copolymer synthesis via iterative polymerizations without intermediate polymer purification.¹⁶⁻¹⁷ This principle has since been exploited also for RAFT polymerization,¹⁸⁻²³ made possible via careful optimization of the system in terms of polymerization rate and livingness. The key concept in maximizing livingness in RAFT using a radical initiator is to use conditions/systems such that high conversion can be reached with a minimum number of radicals being generated from the initiator during the course of the polymerization.¹⁸⁻²⁰ As such, monomers with high propagation rate coefficients, as well as rate enhancement in compartmentalized systems (emulsion, miniemulsion), create favourable conditions for multiblock copolymer synthesis. Multiblock copolymer synthesis via RAFT in emulsion polymerization has been realized²⁴⁻²⁹ by exploiting intrinsic compartmentalization effects³⁰⁻³¹ in such dispersed systems to maximize polymerization rates³² and enable use of monomers with low propagation rates such as styrenes and methacrylates.

One intrinsic limitation of RAFT polymerization with regard to (multi)block copolymer synthesis is that, depending on the monomer type, the order of block synthesis needs to be considered, which thus restricts the range of accessible block copolymer architectures. The monomer sequence distribution can impact the molecular, supramolecular and macroscopic properties as these properties are strongly sequence dependent.³³ For successful synthesis of an AB diblock copolymer using RAFT polymerization, it is a requirement that the propagating radical of the first block is a sufficiently better leaving group during RAFT fragmentation than the propagating radical of the second block.³⁴⁻³⁷ If this is not the case, the RAFT adduct (intermediate) radical tends to fragment “backwards” to regenerate the propagating radical that added to the RAFT end group. For example, monomers such as methacrylates and methacrylamides correspond to relatively stable tertiary propagating radicals with better leaving group ability than propagating radicals of styrenes, acrylates and acrylamides (secondary radicals). Consequently, in the specific case of a block copolymer of butyl methacrylate (BMA) and styrene (S), BMA must be polymerized first.

The issue of the RAFT adduct radical fragmenting “backwards” can be largely overcome by using conditions of low monomer concentration of the monomer of the second (“next”) block. This concept has been demonstrated by Moad et al.³⁴ in a starved-fed emulsion polymerization, as they prepared PS-*b*-PMMA-dithioacetate in the wrong order (MMA second). We have recently demonstrated how methacrylate polymerization can be conducted successfully using a RAFT agent with a chain transfer constant (C_{tr}) that is “too low” (*i.e.* not suitable for methacrylates) by using emulsion polymerization without starved-feed of monomer, relying exclusively on the intrinsic nature of an emulsion polymerization.²⁹ The presence of monomer droplets in an emulsion polymerization - polymerization occurs in polymer particles - means that some monomer is effectively excluded from the locus of polymerization,³⁸ thus increasing the ratio [RAFT]:[monomer]. If the monomer concentration is low, it means that fewer monomer units are added each time a propagating radical is released by backward fragmentation, and eventually fragmentation occurs as desired, thereby generating a block comprising the next monomer. The same concept was also exploited both by Moad and coworkers³⁹⁻⁴⁰ and Haddleton and coworkers⁴¹⁻⁴² using methacrylate macromonomer type sulfur-free RAFT agent in emulsion polymerization, thereby causing the system to proceed via a controlled/living mechanism (not possible under “normal” monomer concentrations due to C_{tr} values being too low).

In the present work, we have investigated in detail to what extent RAFT emulsion polymerization can be exploited (as opposed to RAFT in bulk/solution) to prepare block copolymers irrespective of monomer order. Polymerizations to prepare blocks copolymers comprising S and BMA were conducted in solution, miniemulsion and emulsion polymerization under equivalent conditions, clearly demonstrating that emulsion polymerization can be exploited to overcome the constraint of monomer order. It is shown that this approach can be used for synthesis of an alternating pentablock copolymer composed of methacrylates and styrene without consideration of monomer order, thereby significantly broadening the scope of multiblock copolymer synthesis.

Experimental

Materials. Methyl methacrylate (MMA, Sigma-Aldrich), butyl methacrylate (BMA, Sigma-Aldrich), and styrene (S, Sigma-Aldrich) were passed through a column of basic alumina (Ajax Chemical, AR) to remove inhibitor. Methacrylic acid (MAA, Sigma-Aldrich), 1,4-dioxane (Chem-Supply), tetrahydrofuran (Chem-Supply), cyclohexane (VWR International) and 1,3,5-trioxane (Sigma-Aldrich) were used as received. Azobisisobutyronitrile (AIBN, Sigma-Aldrich) was purified by recrystallization from methanol, potassium persulfate (KPS, Sigma-Aldrich) and 4,4'-azobis (4-cyanopentanoic acid) (ACPA, Sigma-Aldrich, $\geq 97\%$) were used with no further purification. RAFT agent 4-cyano-4- [(dodecylsulfanylthiocarbonyl) sulfanyl] pentanoic acid (CDTPA, Boron Molecular $>97\%$), sodium dodecyl sulfate (SDS, Ajax Chemical), hexadecane (HD, Sigma-Aldrich), and methylation agent tri(methylsilyl)diazomethane (Sigma-Aldrich) were used as received. Deuterated solvents chloroform (CDCl_3 , Novachem) and acetone (acetone- d_6 , Novachem) were used as received. Distilled de-ionized water was obtained from a Milli-Q water purification system. Dimethylacetamide (DMAc, stabilized with 0.05% w/v 2,6-dibutyl-4-methylphenol (BHT), HPLC, Sigma Aldrich) was used for size exclusion chromatography (SEC).

Synthesis of macroRAFT agents. Poly(butyl methacrylate)-*b*-poly(styrene) trithiocarbonate macroRAFT agent (PBMA₂₅-*b*-PS₁₅-TTC (MacroRAFT1); Scheme 1): BMA (8.0 g, 56.3 mmol), CDTPA (0.90 g, 2.2 mmol), ACPA (0.03 g, 0.11 mmol), 1,3,5-trioxane (0.40 g, 0.44 mmol) and 1,4-dioxane (4.8 mL) were introduced in a round-bottom flask. The flask was purged with nitrogen for 30 min, sealed and immersed in an oil bath at 80°C. After 20 h of polymerization, a sample was collected and a degassed mixture of S (11.7 g, 11.2 mmol), ACPA (0.03 g, 0.11 mmol), and 1,4-dioxane (10 mL) was added to the polymerization. Polymerization was subsequently performed for an additional 17h at 80°C, after which the product was obtained by precipitating twice in cyclohexane. The polymerization scheme, experimental conditions and results are presented in Scheme S1 and Table S1.

Poly(methacrylic acid)-*b*-poly(methyl methacrylate) trithiocarbonate macroRAFT agent (PMAA₆₂-*b*-PMMA₁₁-TTC (MacroRAFT2); Scheme 1): MAA (6.50 g, 75.7 mmol), CDTPA (0.75 g, 1.86 mmol), ACPA (26 mg, 0.09 mmol), 1,3,5-trioxane (0.55 g, 6.13 mmol) and 1,4-dioxane (22 mL) were introduced

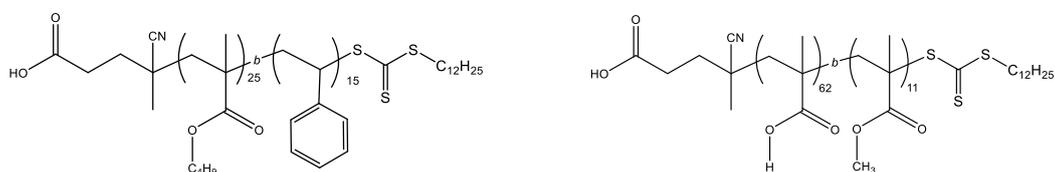
in a round-bottom flask. The flask was purged with nitrogen for 30 min, sealed and immersed in an oil bath at 80°C. After 5 h, a sample was collected and a degassed mixture of MMA (1.80 g, 18.0 mmol) and 1,4-dioxane (5 mL) was added. The polymerization was continued for an additional 17h at 80°C, and the product was obtained by precipitating twice in cyclohexane (Scheme S2; Table S2).

Individual monomer conversions were calculated by ¹H NMR and number-average molecular weights (M_n) and dispersities (\mathcal{D}) were determined by SEC. The theoretical molecular weights ($M_{n,th}$) were calculated using eq 1:

$$M_{n,th} = \frac{(X_A \cdot [\text{Mon}_A]_0 \cdot M_{\text{Mon A}}) + (X_B \cdot [\text{Mon}_B]_0 \cdot M_{\text{Mon B}})}{[\text{RAFT}]_0} + M_{\text{RAFT}} \quad (1)$$

where $[\text{Mon}]_0$, $[\text{RAFT}]_0$, M_{Mon} , and M_{RAFT} , are the initial concentrations and the molar masses of the monomers and the RAFT agent, respectively, and X is the individual monomer conversion. The minor contribution of initiator-derived chains is neglected in this calculation. The number of monomer units for each block in MacroRAFT1 (PBMA₂₅-*b*-PS₁₅-TTC) was calculated from the monomer conversion (Table S1) while for MacroRAFT2 (PMAA₆₂-*b*-PMMA₁₁-TTC) from the ¹H NMR of the purified polymer (Fig. S2).

Scheme 1. Chemical structures of macroRAFT agents used in this work.



MacroRAFT1: PBMA₂₅-*b*-PS₁₅-TTC

MacroRAFT2: PMAA₆₂-*b*-PMMA₁₁-TTC

Solution polymerization. In a typical experiment (SP1, Table S3), BMA (2.08 g, 14.7 mmol), MacroRAFT1 (PBMA₂₅-*b*-PS₁₅-TTC) (0.40 g, 7.3 x 10⁻² mmol), ACPA (4 mg, 1.46 x 10⁻² mmol), 1,3,5-trioxane (0.1 g, 1.23 mmol) and 1,4-dioxane (9.1 mL) were introduced in a round-bottom flask. The flask was purged with nitrogen for 30 min, sealed and immersed in an oil bath at 80°C. Samples were periodically

withdrawn to calculate monomer conversion by ^1H NMR. M_n and \bar{D} were determined by SEC. The $M_{n,th}$ were calculated using eq 1. Detailed recipe, experimental conditions and results are in Table S3.

Emulsion polymerization. In a typical experiment (EP1; Table S4), BMA (4.30 g, 30.2 mmol), MacroRAFT2 (PMAA₆₂-*b*-PMMA₁₁-TTC) (0.90 g, 1.5×10^{-4} mol) (critical aggregate concentration = 3.84×10^{-6} M),⁴³ KPS (5 g of 1 mg L^{-1} stock solution in water, 5.02×10^{-3} mmol) and water (18.0 g) were added to a 300 mL double wall reactor equipped with a mechanical stirrer, N₂ inlet tubing, reflux condenser, and external water bath circulator to control the reactor temperature. The polymerization mixture was degassed by bubbling nitrogen for 30 min. The stirrer was turned on at 200 rpm and the reactor was heated at 80 °C. After 45 min of polymerization, 1.6 g of NaOH solution (3.8 M) was added to the reactor to deprotonate the MAA block of the macroRAFT agent (molar ratio NaOH/macroRAFT= 40). The polymerization was conducted for an additional 75 min to reach a total of 2 h of polymerization. The PBMA₂₀₀-TTC seed latex was chain extended with S to synthesize a PBMA₂₀₀-*b*-PS₂₀₀-TTC diblock seed latex: PBMA₂₀₀-TTC seed latex (30 g), S (3.16 g, 30.3 mmol), water (12.6 g) and KPS (2.5 g of 0.82 g L^{-1} stock solution in water, 7.60×10^{-3} mmol) were added to the reactor, degassed and polymerized at 80 °C for 3 h to reach 100% conversion of S. A degassed mixture of BMA (4.13 g, 29.0 mmol) and water (18 g) was then added to the reactor, followed by 2 h polymerization to generate a PBMA-*b*-PS-*b*-PBMA-TTC triblock copolymer.

Emulsion polymerizations were also performed under so-called “swelled conditions” by allowing all the monomer present in the form of monomer droplets to diffuse to the particles before the polymerization. In a typical swelled emulsion polymerization (EP4, Table S5), the procedure of PBMA₂₀₀-*b*-PS₂₀₀-TTC diblock seed latex synthesis was the same as described above. For triblock copolymer synthesis: PBMA₂₀₀-*b*-PS₂₀₀-TTC diblock seed latex (40 g), BMA (3.6 g, 25.3 mmol), and water (19.5 g) were stirred overnight on a magnetic stirrer to swell the particles with the monomer. KPS (2 g of 1.41 g L^{-1} stock solution in water, 1.04×10^{-2} mmol) was then added and the polymerization mixture was transferred to the reactor. The reactor was degassed for 30 min by bubbling nitrogen and subsequently heated at 80 °C for 2 h.

Samples were withdrawn from the reactor after each block synthesis for ^1H NMR and SEC analysis. Detailed recipes, experiment conditions and results can be found in Table S4 and S5. Particle size and distributions were measured by DLS and $M_{n,\text{th}}$ values calculated using eq 1.

Miniemulsion polymerization. In a typical polymerization (ME1, Table S3), BMA (2.5 g, 17.5 mmol), MacroRAFT2 (PBMA₂₅-*b*-PS₁₅-TTC) (0.48 g, 8.7×10^{-2} mmol) and 0.125 g of HD were mixed to form an organic phase. The aqueous phase was prepared separately by mixing 0.125 g of SDS and 9.5 g of distilled de-ionized (DDI) water. The two phases were mixed in a 25 mL flask and subsequently ultrasonicated using a Branson 450 probe (maximum output power of 500 W) at an amplitude of 50% for 10 min. The KPS (0.5 g of 0.24 g L^{-1} stock solution in water, 4.44×10^{-3} mmol) was then added and the flask was purged with nitrogen for 30 min, sealed and immersed in an oil bath at 80°C. Samples were periodically withdrawn to calculate monomer conversion by ^1H NMR. M_n and \mathcal{D} were determined by SEC. $M_{n,\text{th}}$ were calculated using eq 1. Detailed recipe, experimental conditions and results can be found in Table S3.

Multiblock copolymer synthesis. Multiblock copolymer synthesis was performed in the 300 ml double wall reactor described above (B1-B5, Table 2 and Table S7). PBMA₂₀₀-TTC seed latex (40 g) synthesized previously, AIBN (3.1 mg, 1.88×10^{-2} mmol) dissolved in MMA (2.03 g, 20.3 mmol) and water (26 g) were added to the reactor, degassed with nitrogen for 30 min and heated at 80 °C for 1 h to generate a diblock copolymer. S (2.06 g, 19.8 mmol) was then transferred to the reactor via a degassed syringe and polymerization was continued for 1.5 h resulting in a triblock copolymer. Subsequently, AIBN (2.4 mg, 1.46×10^{-2} mmol) dissolved in 1.72 g of MMA (17.2 mmol) and 0.2 g of S (1.9 mmol) mixture was degassed and added to the reactor. The addition of AIBN was necessary to maintain the concentration of initiator-derived radicals in the subsequent blocks similar to the preceding blocks. The polymerization was conducted for an additional 1 h to generate a tetrablock copolymer. Degassed S (1.93 g, 18.5 mmol) was subsequently added to the reactor and polymerization was continued for 1.5 h to generate a pentablock copolymer (Scheme 2). Samples were withdrawn after each block for ^1H NMR and SEC analysis. Detailed

recipe, experiment conditions and results can be found in Table S7. Particle size and distributions were measured by TEM and $M_{n,th}$ were calculated by eq 1.

Results and discussion

A number of RAFT polymerizations were conducted to elucidate to what extent “wrong block order” has an impact on the control over the molecular weight distribution (MWD): Solution polymerizations (SP1, SP2), emulsion polymerizations (EP1, EP2, EP3, EP4), and miniemulsion polymerizations (ME1, ME2). For synthesis of multiblock copolymers comprising BMA and S, current understanding is that BMA should be polymerized as the first block.⁴⁴⁻⁴⁸ In homogeneous systems (solution/bulk), the opposite order results in unsuccessful chain extension of the S block with BMA due to the poor leaving group ability of a PS radical compared to a PBMA radical.^{35, 49} The overall strategy in the present work was to first chain extend PBMA with S to generate the diblock copolymer PBMA-*b*-PS-TTC (correct order), which was subsequently chain extended with BMA to generate the triblock copolymer PBMA-*b*-PS-*b*-PBMA-TTC (wrong order). In solution (SP1, SP2) and miniemulsion (ME1, ME2), the PBMA-*b*-PS-TTC diblock copolymer is referred to as MacroRAFT1 (prepared in a separate solution polymerization), whereas in emulsion polymerization (EP1, EP2, EP3, EP4) each block (1st PBMA (seed), 2nd PS and 3rd PBMA) was synthesized in emulsion polymerization starting with the amphiphilic macroRAFT agent PMAA₆₂-*b*-PMMA₁₁-TTC (MacroRAFT2). In the solution and miniemulsion polymerizations, the “wrong order” extensions with BMA were conducted using a PBMA-*b*-PS-TTC macroRAFT species as opposed to a PS-TTC macroRAFT species to make these systems consistent with the emulsion polymerizations, which started from a PBMA seed prepared using MacroRAFT2.

Solution polymerization. PBMA₂₅-*b*-PS₁₅-TTC macroRAFT (MacroRAFT1, synthesized in two step solution polymerization of BMA and S, respectively, with $\mathcal{D} = 1.17$ and 1.14 for the 1st and 2nd step, respectively (Table S1; Fig. S1)), was chain extended with BMA in solution polymerization in 1,4-dioxane to confirm unsuccessful chain extension for the wrong monomer order. The polymerization was performed at 80°C using ACPA as initiator with a targeted degree of polymerization (DP) of 200 at full monomer

conversion (SP1; Table 1; Table S3). As expected, this chain extension was unsuccessful with a bimodal MWD (Fig. 1a and 2a). The low molecular weight peak in the region of MacroRAFT1 is consistent with PBMA₂₅-*b*-PS₁₅-TTC (MacroRAFT1) not being extended. SEC-UV analysis (Fig. 2a) revealed that the RAFT end group was not present in the high molecular weight peak, thus confirming uncontrolled homopolymerization of BMA. PBMA• would add to the RAFT end group, but “backward” fragmentation would result in regeneration of PBMA• (possibly several such cycles) and eventual bimolecular termination.

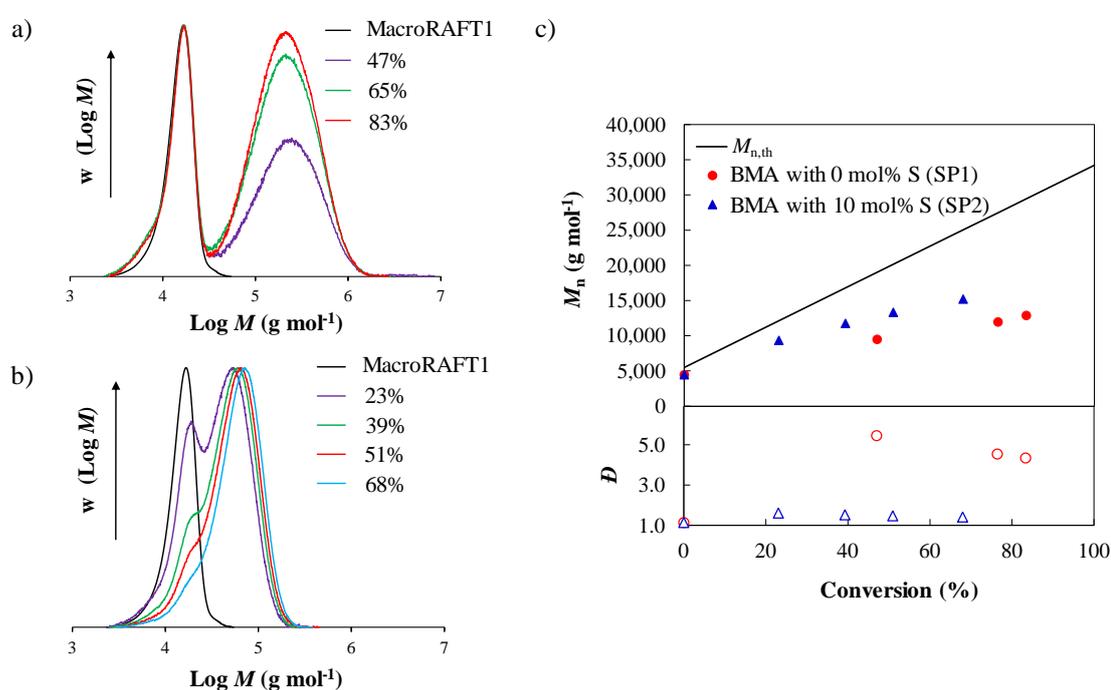


Figure 1. MWDs for PBMA-*b*-PS-*b*-PBMA-TTC obtained by chain extension of MacroRAFT1 (PBMA₂₅-*b*-PS₁₅-TTC) with BMA with (a) 0 mol% S (b) 10 mol% S (SP1 and SP2, respectively; Table 1) in solution polymerization (1,4-dioxane); Theoretical and experimental M_n values and \bar{D} (c). Legends in (a) and (b) show BMA conversions.

It is well-established that the addition of a small amount of S to a homopolymerization of a methacrylate monomer can significantly improve the level of control when using a RAFT agent with a C_{tr} value that is too low, such as 2-(dodecylthiocarbonothioylthio)-2-methylpropanoic acid⁵⁰ and PS-dithioacetate (PS-dithioacetate adduct).⁴⁸ This can be explained based on (i) the higher value of the rate coefficient for

addition of an S-terminated propagating radical to the RAFT end group compared to a methacrylate-terminated propagating radical, and (ii) a poly(methacrylate) species with a terminal S unit as the radical species would not tend to undergo “backward” fragmentation (unlike a poly(methacrylate) radical), thus making “forward” fragmentation and expulsion of the desired radical more likely. It is also important to note that there is no penultimate unit effect (PUE) on the fragmentation rates, *i.e.* the presence of S does not change the fact that methacrylate-terminated species fragment faster than S-terminated species.⁴⁸ The addition of 10 mol% S (SP2; Table 1; Table S3) resulted in the MWDs shifting towards high molecular weight with increasing conversion (Fig. 1b), with a linear increase in M_n and final \bar{D} of 1.42 (Fig. 1c). However, some low molecular weight tailing was present, which can be attributed to poor chain extension of MacroRAFT1. SEC-UV analysis revealed that some chains were not capped with the RAFT end group (Fig. 2b). The presence of S resulted in a slight decrease in polymerization rate, which would be at least partially caused by the reduction in the overall propagation rate coefficient due to the implicit PUE on the radical reactivity ratios s_1 and s_2 (Fig. 3).⁵¹⁻⁵² In general, the strategy of adding a comonomer to improve the control over RAFT polymerization and also nitroxide-mediated radical polymerization (NMP) has been employed previously also for other monomer pairs.^{25, 50, 53-56}

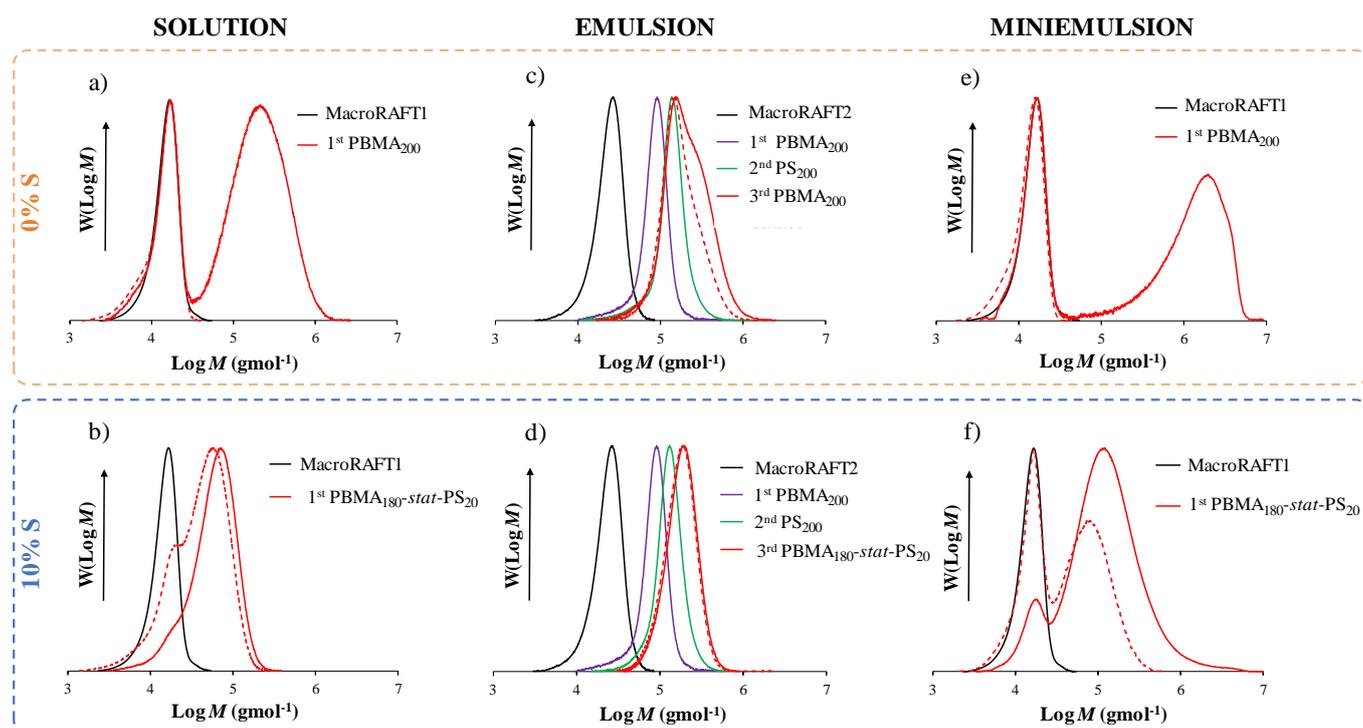


Figure 2. MWDs for PBMA-*b*-PS-*b*-PBMA-TTC triblock copolymer by chain extension of MacroRAFT1 (PBMA₂₅-*b*-PS₁₅-TTC) with BMA with (a) 0 mol% S (b) 10 mol% S in solution (SP1 and SP2 respectively in Table 1); by chain extension of PBMA₂₀₀-*b*-PS₂₀₀-TTC diblock seed latex with BMA with (c) 0 mol% S (d) 10 mol% S in emulsion polymerization (EP1 and EP2 respectively in Table 1); by chain extension of MacroRAFT1 with BMA with (e) 0 mol% S (f) 10 mol% S in miniemulsion (ME1 and ME2 respectively in Table 1). MacroRAFT1 is PBMA₂₅-*b*-PS₁₅-TTC and MacroRAFT2 is PMAA₆₂-*b*-PMMA₁₁-TTC. Subscripts in legends represent number of repeating units for each block at full monomer conversion (Table 1, Table S3 and Table S4). Dashed lines represent UV detection at 325 nm (full lines: RI detection).

Emulsion polymerization. Emulsion polymerization was conducted using the amphiphilic macroRAFT agent PMAA₆₂-*b*-PMMA₁₁-TTC (MacroRAFT2) generating the seed latex PBMA₂₀₀-TTC (*i.e.* PMAA₆₂-*b*-PMMA₁₁-*b*-PBMA₂₀₀-TTC). Two sequential *seed* emulsion polymerizations were then conducted with first S and subsequently BMA resulting in a triblock copolymer (not counting MacroRAFT2 as blocks) comprising 200 repeating units of each block (EP1; Table 1; Table S4). The MWDs in Fig. 2c show a clear shift towards higher molecular weight for the extension of the PBMA block (the seed) with S (correct order). However, the chain extension of the PS block with BMA (wrong order) resulted in a significant portion of the MWD not shifting, with a high molecular weight shoulder appearing. SEC-UV analysis (Fig. 2c) revealed that a significant fraction of chains at high molecular weight did not possess the RAFT end group. However, this chain extension was more successful than the corresponding chain extension in solution (SP1; Fig. 1a and 2a).

The chain extensions of EP1 were subsequently repeated with two alterations in the conditions: (i) the chain extension with BMA was conducted with 10 mol% S added as comonomer; (ii) the S chain extension was not pushed to full conversion in contrast to EP1 (1h polymerization with S conv. = 95%), and the remaining S was thus present during the subsequent chain extension with BMA (EP2; Table 1; Table S4). The evolution of SEC traces (Fig. 2d) shows clear shifts towards high molecular weight both for the extension of PBMA₂₀₀-TTC with S (2nd block) and the subsequent extension of PBMA₂₀₀-*b*-PS₂₀₀-TTC with BMA (3rd block), demonstrating that the chains were successfully extended irrespective of the

monomer sequence. The MWDs were narrow and monomodal, consistent with good control. In addition, a linear increase in M_n and a low dispersity ($\mathcal{D} = 1.16$ and 1.25 for 1st and 2nd chain extension, respectively) were observed (Fig. 4). DLS results showed an increase in the particle diameters consistent with particle growth (Fig. S3). The polymerizations proceeded rapidly in both emulsion systems (EP1 and EP2) due to the compartmentalization effect, whereby isolation of propagating radicals in different particles reduces the termination rate (Table S4).³⁰⁻³¹

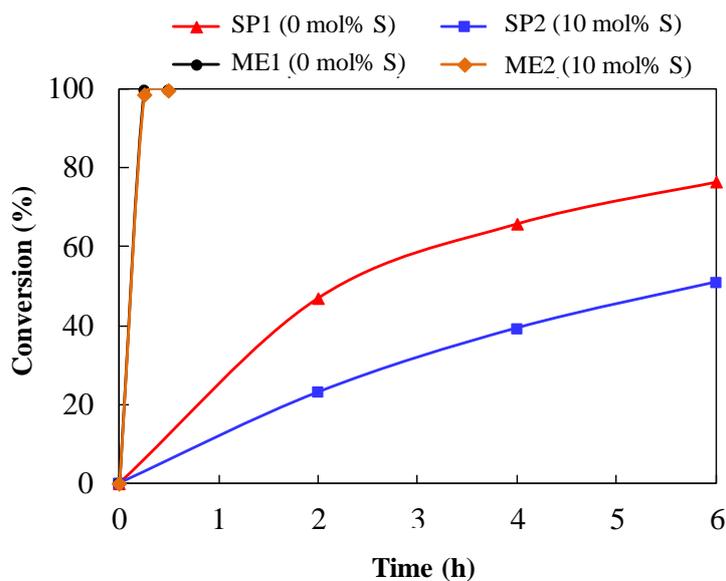


Figure 3. Conversion vs time data for BMA polymerizations mediated by MacroRAFT1 (PBMA₂₅-*b*-PS₁₅-TTC) in solution and miniemulsion with 0 mol% S (SP1 and ME1 in Table 1, respectively) and 10 mol% S (SP2 and ME2 in Table 1, respectively). Lines are guides to the eye only.

Table 1. Recipes, experimental conditions and results for the synthesis of PBMA-*b*-PS-*b*-PBMA-TTC triblock copolymer in solution (SP1, SP2) and miniemulsion (ME1, ME2) using PBMA₂₅-*b*-PS₁₅-TTC (MacroRAFT1) and emulsion polymerization (EP1-EP4) using PBMA₂₀₀-*b*-PS₂₀₀-TTC diblock seed latex.

Exp.	Mon	[Mon] ₀ (mol L ⁻¹) ^a	[RAFT]/ [I]	X (%)/ t (h)	<i>M</i> _{n,th} (g mol ⁻¹)	<i>M</i> _{n,exp} (g mol ⁻¹)	<i>D</i>	<i>Z</i> _{av} (nm) / PDI
<i>Solution polymerization</i>								
SP1	BMA	1.28	5	83/20	29,440	12,850	4.34	-
SP2	BMA/S	1.34	5	^b 70/20	24,770	15,200	1.42	-
<i>Emulsion polymerization</i>								
EP1	BMA	0.42	20	99.1/2	83,680	49,970	1.42	122.8/0.03
EP2	BMA/S	0.43	20	^b 99.2/2	83,450	50,320	1.25	119.4/0.02
EP3 ^c	BMA	0.41	20	99.0/2	83,920	45,650	1.90	119.1/0.02
EP4 ^c	BMA/S	0.41	20	^b 99.4/2	83,650	47,830	1.36	116.5/0.03
<i>Miniemulsion polymerization</i>								
ME1	BMA	1.82	20	100/0.5	33,900	9,260	26.7	73.6/0.08
ME2	BMA/S	1.75	20	^b 100/0.5	33,500	19,340	2.73	72.0/0.08

T = 80°C; ACPA was used for solution and KPS was used for emulsion and miniemulsion polymerizations; [M]/[RAFT]= 200; Conversion determined by ¹H NMR; *M*_{n,th} calculated by eq 1; *M*_n and *D* determined by DMAc-SEC using PMMA calibration. ^a Concentration based on total volume; ^b Overall conversion of BMA and S; ^c Polymerizations performed in swelled emulsion polymerization (see text for details).

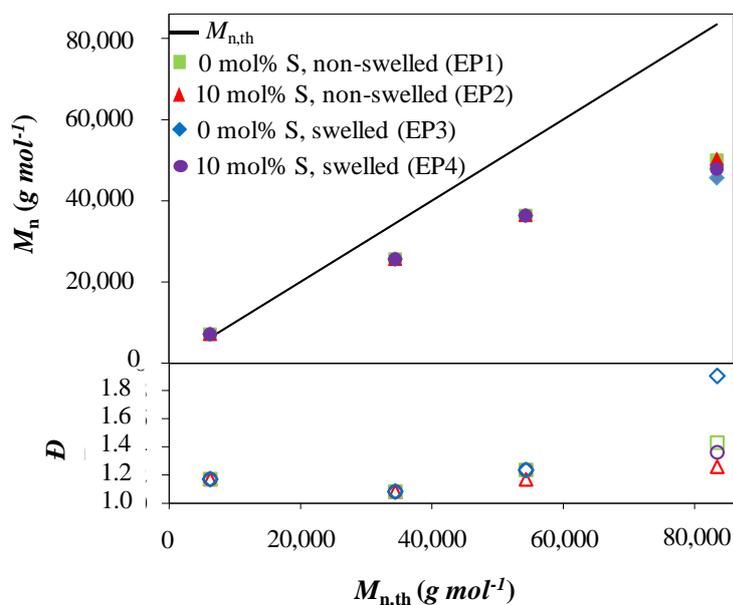


Figure 4. Theoretical (line) and experimental (filled symbols) M_n and \bar{D} (empty symbols) for PBMA-*b*-PS-*b*-PBMA-TTC triblock copolymer synthesis by the chain extension of PBMA₂₀₀-TTC seed latex with S and subsequently with BMA with 0 mol% S and 10 mol% S in non-swelled emulsion polymerization (EP1 and EP2 in Table 1, respectively); 0 mol% S and 10 mol% S in swelled emulsion polymerization (EP3 and EP4 in Table 1, respectively) via PMAA₆₂-*b*-PMMA₁₁-TTC mediated emulsion polymerization.

Miniemulsion polymerization. In miniemulsion polymerization, submicron-size monomer droplets are directly converted to polymer particles.⁵⁷ This is in sharp contrast with an emulsion polymerization, where monomer diffuses from monomer droplets through the aqueous phase to polymer particles where polymerization takes place.³⁸

MacroRAFT1 (PBMA₂₅-*b*-PS₁₅-TTC; the macroRAFT agent used in the solution polymerizations above) was chain extended with BMA in miniemulsion polymerization targeting 200 repeating units at full conversion using KPS at 80°C (ME1; Table 1; Table S3). The PBMA₂₅-*b*-PS₁₅-TTC (MacroRAFT1) used in miniemulsion has a lower DP for both the PBMA and the PS blocks than the corresponding diblock copolymer extended in emulsion polymerization to avoid solubility issues (when preparing the miniemulsion, MacroRAFT1 needs to be dissolved in BMA). The resulting MWD of the chain extension in miniemulsion was bimodal with the initial MacroRAFT1 peak remaining plus a second broad high molecular weight peak (Fig. 2e), indicating the formation of BMA homopolymer similar to the

corresponding solution polymerization (SP1; Fig. 2a). SEC-UV analysis revealed that the high molecular weight peak comprised polymer without RAFT end group (Fig. 2e).

The above chain extension in miniemulsion was repeated in the presence of 10 mol% S (ME2; Table 1; Table S3), again resulting in a bimodal MWD (Fig. 2f). SEC-UV analysis (Fig. 2f) revealed that the low molecular weight peak in the region of MacroRAFT1 comprised non-extended MacroRAFT1, and the high molecular weight peak only partially comprised chains with RAFT end groups. The polymerization rates in both miniemulsion experiments (ME1, ME2) were much higher than in the corresponding solution polymerizations due to the compartmentalization effect on the kinetics (particle diameters approx. 70 nm (Table 1)).³⁰⁻³¹ However, different initiators were used in solution (ACPA) and miniemulsion (KPS), and a direct comparison cannot be made.

Mechanistic discussion. The far superior control in emulsion polymerization (EP1; Fig. 2c and EP2; Fig. 2d) compared to both solution polymerization (SP1; Fig. 2a and SP2; Fig. 2b) and miniemulsion polymerization (ME1; Fig. 2e and ME2; Fig. 2f) in the case of “wrong order” of block synthesis has its origin in the mechanism of emulsion polymerization. In emulsion polymerization, the locus of polymerization is the polymer particles, with monomer droplets functioning as monomer reservoirs feeding monomer to the particles via diffusion through the aqueous phase. As such, only a fraction of the total monomer in the system is present at the polymerization locus. This is fundamentally different from the situation in solution and miniemulsion polymerizations, where all monomer in the system is available for polymerization at any time. In the presence of monomer droplets in an emulsion polymerization, it thus follows that the monomer concentration is lower and the RAFT end group concentration is higher than in the corresponding solution/miniemulsion systems.²⁹ The low $[M]/[RAFT]$ in the particles results in the addition of fewer monomer units during each activation/deactivation cycle and therefore improved control over the MWD.⁵⁸ We have previously reported that the low $[M]/[RAFT]$ in emulsion polymerization can be exploited to improve the performance of RAFT/monomer systems that perform poorly in homogeneous systems due to the C_{tr} value being too low.²⁹

The issue of “wrong order” is related to the poor leaving group ability of the preceding block (PS•) relative to the propagating radical (PBMA•) in the fragmentation of the initial adduct radical (pre-equilibrium step). However, if the concentration of BMA is low (as in emulsion polymerization due to the inherent emulsion polymerization mechanism), only few monomer units are added when fragmentation to release PBMA• occurs (*i.e.* when the initial adduct radical fragments “backwards” to simply regenerate PBMA•). Consequently, the problem of BMA homopolymerization is minimized before expulsion of PS• eventually occurs after perhaps several “attempts”. This feature of a lower [M]/[RAFT] in emulsion polymerization has previously been used to tweak the limitation of monomer order. Moad et al.³⁴ demonstrated that the monomer order is not important in the case of semi-continuous emulsion polymerization. The authors synthesized PS-*b*-PMMA-TTC using a feed pump to add MMA, thereby achieving low [M]/[RAFT]. This is in contrast to the present work, where we rely exclusively on the self-regulatory emulsion polymerization mechanism to achieve low [M]/[RAFT] (*i.e.* batch addition of monomer with no use of a syringe pump monomer feed).

Swelling experiment. The instantaneous monomer concentration inside the particles is related to the rate of diffusion of monomer from monomer droplets to particles and the extent of swelling at phase transfer equilibrium, the latter dictated by the Morton equation.⁵⁹⁻⁶⁰ In the present case, it is of interest to know whether addition of BMA to the latex leads to formation of BMA monomer droplets, or whether all BMA is absorbed by the existing particles. Assuming that all BMA swells the existing particles, the BMA concentration in the particles is calculated to be 2.32 M (based on the total particle volume and the total amount of BMA added). Under the present conditions, maximum swelling of the particles (*i.e.* in presence of excess monomer) would result in a concentration of 3.8 M based on previous experimental work for the particle diameter of 80 nm at 50°C.⁶⁰ Consequently, it can be deduced that in the present system, the polymer particles are capable of swelling to the extent that there would be no BMA droplets present once swelling is complete (*i.e.* 3.8 M > 2.32 M). This would imply that there is no benefit of a reduced [monomer]/[RAFT] in the particles, unless the swelling process is sufficiently slow relative to the rate of polymerization.

To explore the time scale of the swelling, a swelling test was performed with the same recipe and experimental conditions as EP1 for the chain extension of the PBMA₂₀₀-*b*-PS₂₀₀-TTC seed latex with BMA (no initiator added). The hydrophobic dye magnesium phthalocyanine,⁶¹ only soluble in the monomer (Fig. S4; clear aqueous phase and dark blue monomer phase), was dissolved in the monomer and added to the reaction mixture. A pool of monomer initially forms as an upper layer (Fig. S5a-S5c). As time progresses, this pool gradually disappears as the monomer diffuses to the particles (video available in SI). After 4 min and 50 s, the monomer layer disappeared completely and the dye precipitated (Fig. S5d). The swelling time is to be compared with the polymerization time of 2h for the BMA chain extension in emulsion – the conversion of BMA was >99% in 2 h, but intermediate/high conversion would have been reached in much shorter than 2 h. It can thus be concluded that significant polymerization would occur during the time it takes for swelling to occur.

To further investigate this matter, we removed the effect of low monomer concentration in the particles during the initial stage of the polymerization due to the presence of monomer droplets in EP1 and EP2 in the synthesis of the 3rd block (wrong order) by allowing the PBMA₂₀₀-*b*-PS₂₀₀-TTC seed latex to swell with monomer for 14 h before polymerization, *i.e.* BMA (0 mol% S) (EP3; Table 1; Table S5) and BMA (10 mol% S) (EP4; Table 1; Table S5). The chain extension with BMA (0 mol% S; EP3) showed significantly poorer control compared to EP1 (Fig. 5a; Fig. S6a), resulting in a bimodal MWDs. Similarly, the chain extension with BMA (10 mol% S; EP4) did not result in a complete MWD shift as compared to EP2 (Fig. 5b; Fig. S6b). The peak was monomodal, but broadening of the MWD had occurred. SEC-UV analysis (Fig. 5) shows that the swelled cases (EP3, EP4) exhibit poorer agreement between RI and UV detection than the non-swelled cases (EP1, EP2) (although the difference is quite small for 10 mol% S), indicative of the presence of a significant number of chains without RAFT end group in the swelled cases.

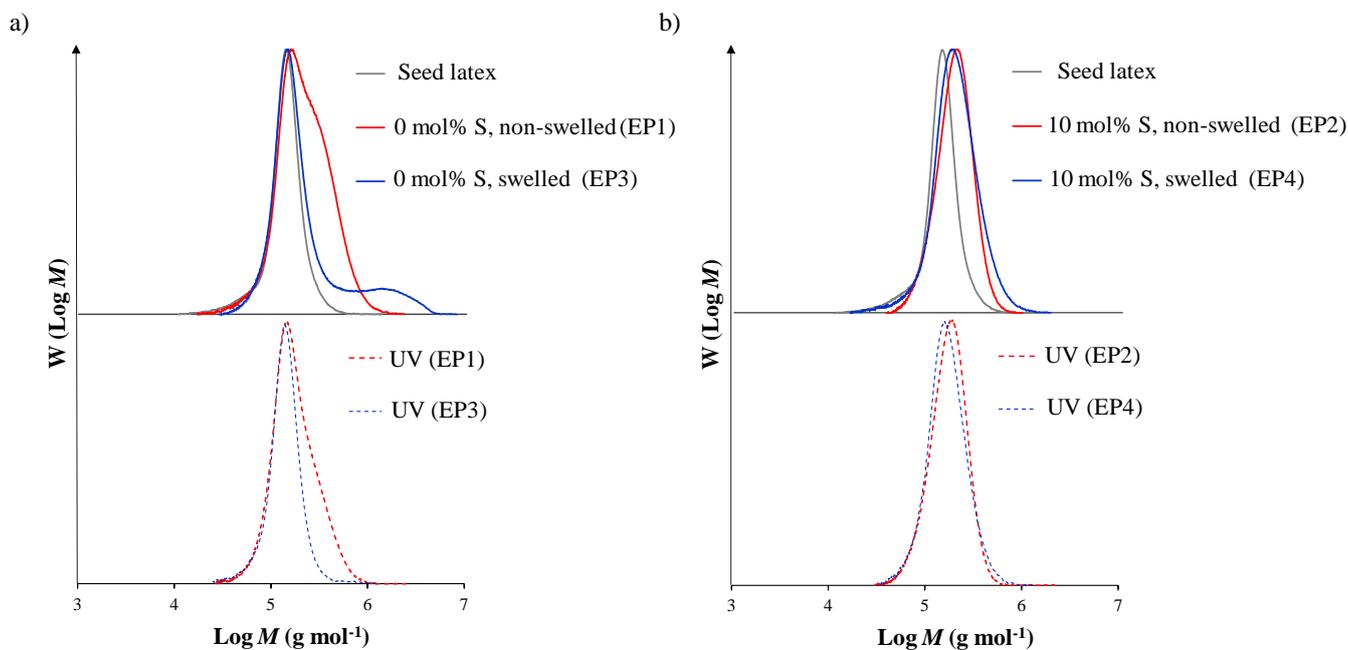
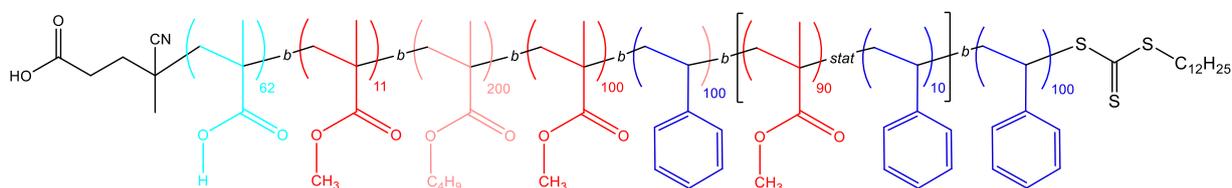


Figure 5. MWDs of PBMA-*b*-PS-*b*-PBMA-TTC triblock copolymer by chain extension of PBMA₂₀₀-*b*-PS₂₀₀-TTC diblock seed latex (grey) with BMA with (a) 0 mol% S in non-swelled emulsion (red) and swelled emulsion polymerization (blue) (EP1 and EP3 respectively in Table 1; see text for details); and (b) 10 mol% S in non-swelled emulsion (red) and swelled emulsion polymerization (blue) (EP2 and EP4 respectively in Table 1). The seed latex is PBMA₂₀₀-*b*-PS₂₀₀-TTC. Dashed lines represent UV detection at 325 nm (full lines: RI detection).

Comparison of emulsion polymerizations without swelling time (EP1, EP2) and emulsion polymerizations with swelling time (EP3, EP4) thus demonstrates that the low monomer concentration at the reaction locus does have an effect on the chain extension of PBMA₂₀₀-*b*-PS₂₀₀-TTC with BMA (wrong monomer order). It may seem surprising that the swelling step has such an impact given that the dye swelling experiments indicate it only takes ~5 min for complete swelling of the polymer particles. However, what is of utmost importance for a successful chain extension is the early (initiation) stage of the chain extension – once the adduct radical resulting from addition of PBMA• to the initial macroRAFT agent PBMA-*b*-PS-TTC has fragmented in the “forward” direction to generate an S-terminated propagating radical (PBMA-*b*-PS•), the “wrong order” problem is solved once this radical undergoes a single propagation step with BMA to convert it to PBMA-*b*-P(S)(BMA)•. The low [BMA] at the initial stage of

the chain extension polymerization allows the adduct radical resulting from addition of PBMA• to PBMA-*b*-PS-TTC to fragment back to PBMA• several times without significant “punishment” in terms of excessive addition of BMA to PBMA• (which is what is seen as uncontrolled growth if [BMA] is high). This explains why a relatively short time window (*i.e.* the swelling time) with low monomer concentration at the beginning of the polymerization can have a significant impact on the chain extension for conditions of “wrong” monomer order.

PMMA/PS alternating multiblock copolymer synthesis. Block copolymers of PMMA and PS are of great interest due to their unique self-assembly behaviour,⁶²⁻⁶⁵ making them attractive for applications in polymer films,⁶⁶⁻⁶⁷ nano stamping,⁶⁸ and magnetic data storage.⁶⁹ There are numerous examples of PMMA-*b*-PS diblock copolymer syntheses via RAFT polymerization.⁷⁰⁻⁷¹ However, it is difficult to prepare alternating multiblock copolymers comprising PMMA and PS blocks by RAFT polymerization due to the necessity of “wrong order” arising from the alternating sequence arrangement. Alternating sequence arrangement of two different monomers in the polymer backbone often provides superior properties compared to a simple diblock copolymer.⁷² For example, the ability of a diblock copolymer to compatibilize polymer blends is far less effective than a multiblock copolymer comprising two monomers.⁷²⁻⁷³ Having successfully demonstrated in the present work that the constraint of “wrong order” can be overcome in emulsion polymerization, such alternating multiblock copolymers can now be readily prepared.



Scheme 2. Synthesis of pentablock copolymer (PBMA₂₀₀-*b*-PMMA₁₀₀-*b*-PS₁₀₀-*b*-(PMMA₉₀-*stat*-PS₁₀)-*b*-PS₁₀₀-TTC, Exp B1-B5 in Table 2) by emulsion polymerization using PMAA₆₂-*b*-PMMA₁₁-TTC (MacroRAFT2).

We decided to extend the application of our work by synthesizing a pentablock copolymer comprising alternating segments of methacrylates and S. A seed of PBMA₂₀₀-TTC (same seed as in emulsion polymerizations EP1-EP4, prepared using MacroRAFT2) was used as first block. This was subsequently chain extended with four blocks (each with DP = 100 at full monomer conversion) of MMA and S in an alternating fashion using KPS at 80°C. This synthetic route thus comprises one chain extension that is in “the wrong order”, *i.e.* the 4th block (BMA block). In order to improve the level of control for the 4th chain extension, 10 mol% S was added for reasons outlined above. The final pentablock copolymer exhibited a monomodal MWD but a somewhat high dispersity ($D = 1.59$; Fig. S7, Table S6).

RAFT emulsion polymerization using an amphiphilic macroRAFT as in the present study results in the RAFT moiety being predominantly located in the core region of the particles. As such, in order for the RAFT mechanism to be operative, *z*-mer radicals⁶⁰ entering from the aqueous phase must be able to diffuse to the particle core (while propagating) before bimolecular termination occurs. We have recently exploited this feature to nanoengineer multiblock copolymer particles with an onion-like multilayered internal morphology.²⁵ In the present multiblock system, the radical penetration depth⁷⁴ is less likely to be sufficient compared to the systems described above due to an increase in the number of blocks and the high glass transition temperature (T_g) of both PMMA and PS. To overcome the issue of limited radical penetration depth, which would have caused the relatively high dispersity of the alternating multiblock copolymer structure prepared above (Fig. S7, Table S6), we adopted the strategy of using the oil-soluble initiator AIBN (B1-B5, Table 2, Table S7). The mechanism of organic phase initiation to achieve improved control will be addressed in detail in future publications.

**Table 2. Recipe, experimental conditions and results for the synthesis of PBMA-*b*-PMMA-*b*-PS-*b*-
(PMMA-*stat*-PS)-*b*-PS-TTC pentablock copolymer via PMAA₆₂-*b*-PMMA₁₁-TTC mediated emulsion
polymerization**

Exp.	Mon	[Mon] ₀ (mol L ⁻¹) ^a	[RAFT]/ [I]	X (%)/ t (h)	<i>M</i> _{n,th} (g mol ⁻¹)	<i>M</i> _{n,exp} (g mol ⁻¹)	<i>D</i>	<i>Z</i> _{av} (nm) / PDI
B1	BMA	1.0	30	100/2	34,440	24,200	1.18	100.3/0.03
B2	MMA	0.30	20	95/1	44,430	26,440	1.16	101.7/0.02
B3	S	0.29	-	94/1.5	54,360	32,300	1.14	104.8/0.01
B4	MMA/S	0.28	20	^b 91/1	64,540	37,380	1.17	107.6/0.02
B5	S	0.27	-	95/1.5	744,70	41,590	1.23	111.7/0.02

T = 80°C; AIBN initiator; SC = 20%; [M]/[RAFT] = 100 except for seed latex B1= 200; conversion determined by ¹H NMR; *M*_{n,th} calculated by eq 1; *M*_n and *D* determined by DMAc-SEC using PMMA calibration. ^a concentration based on total volume; ^b Overall conversion of BMA and S.

The MWDs (Fig. 6a) showed that each block was successfully chain extended as evident by the shifts towards higher molecular weight with each successive block. The characteristic features of controlled/living polymerization such as a linear increase in *M*_n and low *D* for each block (Fig. 6b) were also observed. Polymerization proceeded rapidly with each block reaching high conversion (>90% conversion for MMA and S in 1h and 1.5h, respectively (Fig. 6c, Table 2). These results demonstrate the potential of emulsion polymerization in synthesizing complex multiblock copolymers comprising high molecular weights of low dispersity regardless of monomer sequence.

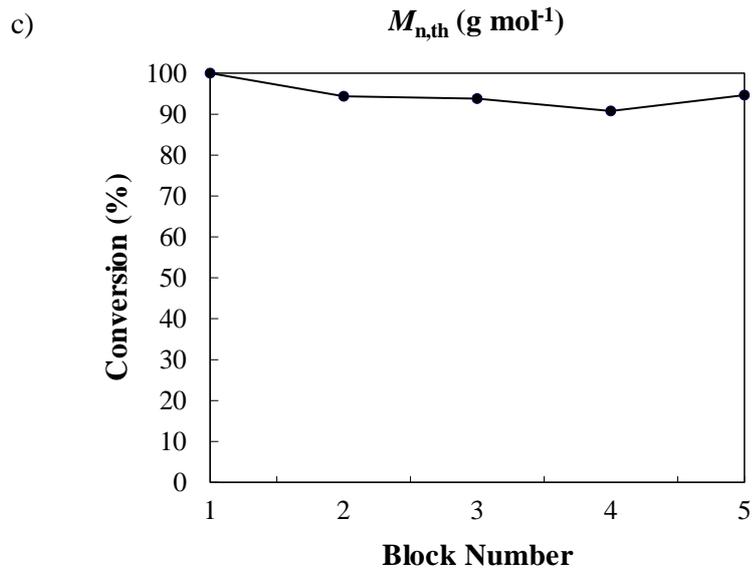
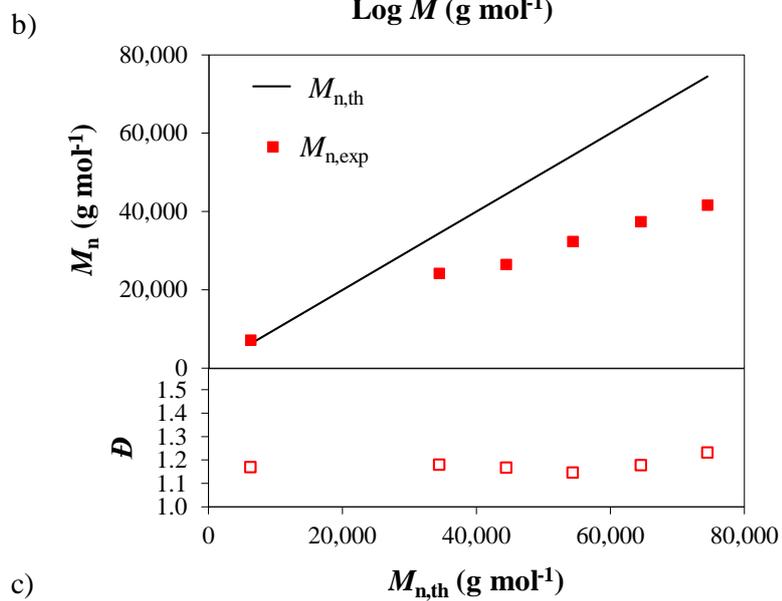
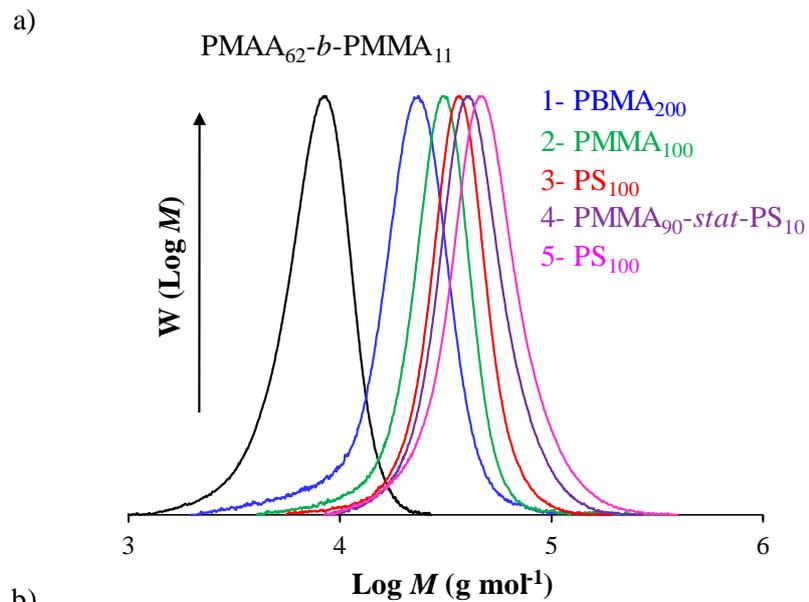


Figure 6. Evolution of (a) MWDs (y-axis normalized), (b) theoretical (straight line) and experimental M_n (filled symbol) and \mathcal{D} (empty symbol), and (c) monomer conversion for each block in pentablock copolymer synthesis (B1, B2, B3, B4 and B5, Table 2) in emulsion polymerization.

Conclusions

The issue of monomer order when preparing block copolymers via RAFT polymerization has been addressed by exploiting the monomer feeding characteristics inherent to emulsion polymerization and the use of a comonomer (10 mol% styrene). Syntheses of block copolymers of styrene and butyl methacrylate by RAFT polymerization using trithiocarbonate RAFT species were conducted under comparable conditions as solution polymerization, miniemulsion polymerization and emulsion polymerization. In emulsion polymerization, a seed latex of PBMA was first prepared using the amphiphilic macroRAFT agent PMAA₆₂-*b*-PMMA₁₁-TTC. With respect to the present work, the key difference between these systems is that the molar ratio of RAFT end group to monomer is the same in solution and miniemulsion, but significantly higher in emulsion polymerization at the locus of polymerization under conditions when a monomer phase (monomer droplets) exists, given that there is no RAFT agent present in the monomer droplets. The level of control over the MWD (low dispersity) was far superior in emulsion polymerization than in solution/miniemulsion polymerization. This can be rationalized in more detail by considering how the issue of “wrong” monomer order originates in the RAFT adduct radical fragmenting “backwards” to regenerate the propagating radical that added to the RAFT end group – this is what prevents chain extension of the preceding block. If the ratio [RAFT]:[monomer] is high, fewer monomer units are added subsequent to backward fragmentation, and as such there is less “punishment” for this undesired kinetic event.

Emulsion polymerization under suitable conditions can thus be exploited for synthesis of multiblock copolymer without consideration of monomer order. This is demonstrated by preparing an alternating pentablock copolymer composed of methacrylates (with 10 mol% styrene) and styrene without consideration of monomer order, thereby significantly broadening the scope of multiblock copolymer synthesis.

Supporting Information. Schematics, recipes, experimental conditions and results for the synthesis of MacroRAFT1 and MacroRAFT2, triblock copolymer in solution, miniemulsion, emulsion and swelled emulsion polymerization, and pentablock copolymers using KPS and AIBN; illustration of the monomer phase with dye and water phase after mixing and swelling of PBMA₂₀₀-*b*-PS₂₀₀-TTC seed with BMA at 80°C in 300 mL double jacketed reactor; and MWDs for pentablock copolymer synthesized using KPS.

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