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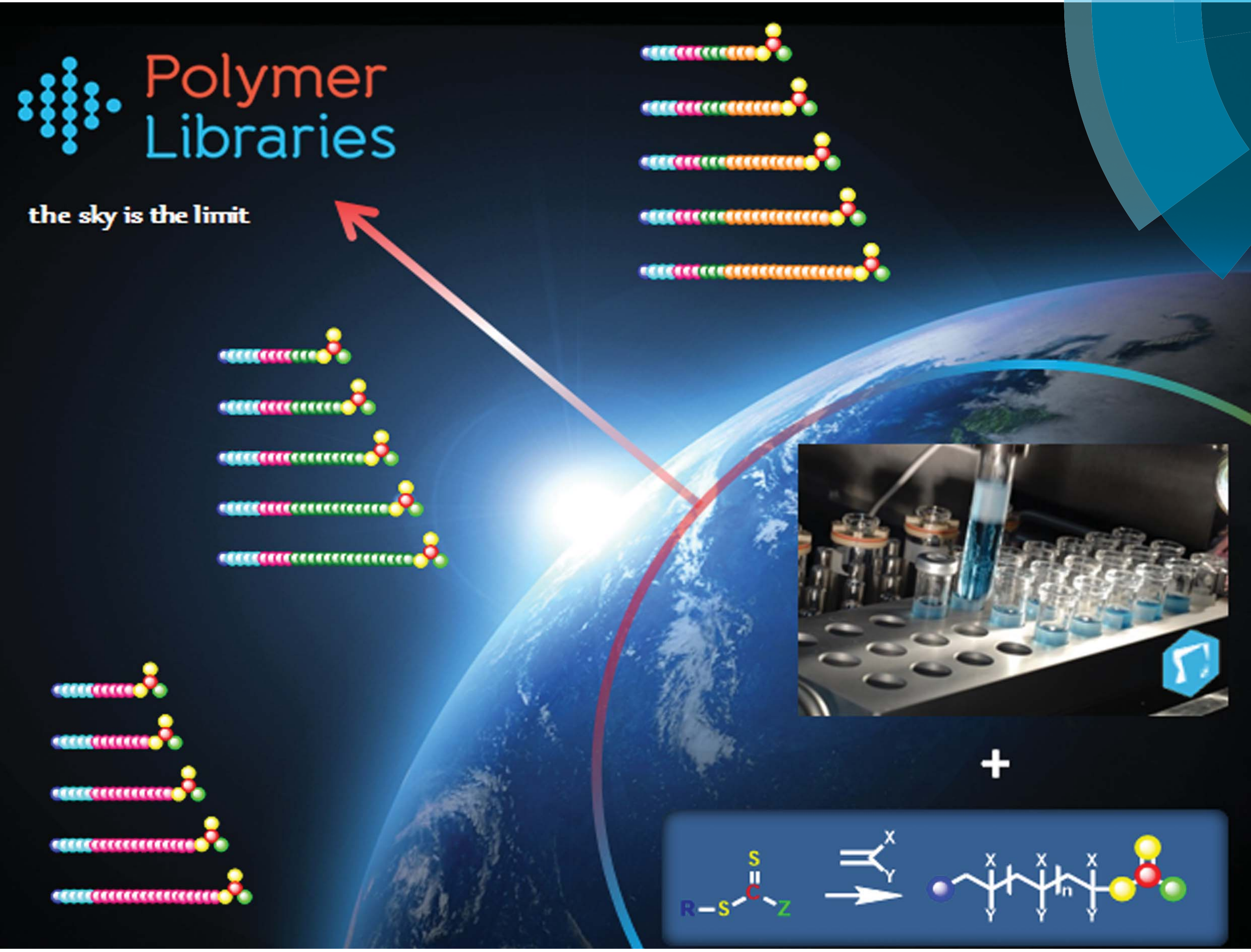

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One pot synthesis of higher order quasi-block copolymer libraries *via* sequential RAFT polymerization in an automated synthesizer†

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Recently developed sequential reversible addition–fragmentation chain transfer (RAFT) polymerization protocols allow the rapid, fully unattended preparation of quasi-block copolymer libraries that cover a wide range of copolymer compositions in an automated synthesizer. This contribution explores the scope and limitations of this sequential approach for the synthesis of higher order quasi-multiblock copolymers (including copolymer sequences of BAB, CBABC, ABC and ABCD). These syntheses illustrate the utility of this high-throughput approach for the one pot synthesis of functional polymers of increased complexity. Additionally, the use of this experimental technique for method development is highlighted.

Introduction

One of the major benefits to stem from reversible addition–fragmentation chain transfer (RAFT) polymerization[1] is ready access to block copolymers.[2] However, the protocol for polymer synthesis, requiring multiple isolation and purification steps, can be demanding. Thus the development of one-pot methods for the synthesis of block copolymers using RAFT polymerization[3–5] and other reversible-deactivation radical polymerization (RDRP)[6] methods, such as nitroxide mediated polymerization (NMP)[7] and atom transfer radical polymerization (ATRP),[8] is currently a research topic of substantial interest to industry and academia. The adoption of such protocol inevitably leads to lower production costs through avoidance of expensive and time-consuming intermediate purification steps.[3–5,7,8]

During RAFT polymerization, every mole of initiator decomposed will produce between one and two moles of dead chains. Those formed during synthesis of a first block of an A–B block will constitute a homopolymer A impurity in the block copolymer. It will also produce between one and two moles of initiator-derived chains. Those formed during synthesis of the second block of an A–B block will constitute a homopolymer B impurity in the block copolymer. Thus to minimize impurity one should minimize the amount of initiator consumed and take the polymerization to form block A to <100% conversion.[9]

In the synthesis of multi-block copolymers from high k_p monomers such as acrylates and acrylamides near quantitative monomer conversions can be achieved rapidly with very low initiator concentrations and thus minimal formation of dead chains and/or homopolymer impurities.[5,10] The fraction of living chains at any stage of RAFT polymerization can be easily estimated with knowledge of the concentrations of RAFT agent and initiator and readily available kinetic parameters.[2b]

For lower k_p monomers, which include methacrylates and styrenes, where high conversions require longer polymerization times and/or higher initiator concentrations, a different strategy is required.

Two main strategies have been utilized to achieve the synthesis of block-like copolymers using one pot techniques *via* RDRP: (1) exploitation of differing monomer reactivity (*i.e.*, reactivity ratios) in limited comonomer systems[3a,7] and (2) utilizing sequential monomer addition.[3b,c,4,5,8] This latter approach yields quasi-block copolymers when <100% of the first monomer has been consumed prior to a second monomer being incorporated. This approach is necessary with the low k_p monomers where relatively high initiator concentrations are required to obtain acceptable rates of polymerization.[3,4]

The term quasi-block was introduced to refer to block copolymers formed by sequential addition of monomers A, B, … where the second (and subsequent) blocks are, in the general case, some form of gradient copolymer poly(A)-*block*-

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poly(A-*grad*-B)… due to the incorporation of residual first block monomer(s).[4] For the case of an all methacrylate quasi-block where reactivity ratios are close to unity the product will be a poly(A)-*block*-poly(A-*ran*-B); *i.e.*, the ratio of A : B will remain essentially constant. The determination of composition is not trivial from an experimental point of view. Nevertheless, it can be estimated by simulation using the appropriate monomer reactivity ratios.[11]

In this work, we use high-throughput polymer synthesis[12] and build upon our previously developed one pot high-throughput synthetic strategy to develop protocols for the rapid synthesis of quasi-multiblock copolymer libraries based on methacrylates.[4,13] Furthermore, we utilize this experimental technique for the optimization of the reaction conditions of the investigated systems. This method allows the rapid and systematic preparation of higher order (multi) quasi-block copolymer libraries with "new" block combinations that expand over a comprehensive copolymer composition range. Rapid access to these new materials is particularly pertinent for rapid screening of structure–property relationships and development of novel applications. These are areas where quasi-block copolymers are ideally suited and are currently being applied.[14,15]

Experimental

Materials

n-Butyl methacrylate (BMA), methyl methacrylate (MMA), di(ethylene glycol) methyl ether methacrylate (DEGMA) and benzyl methacrylate (BzMA) monomers were purchased from Sigma-Aldrich and purified by stirring in the presence of inhibitor-remover for hydroquinone or hydroquinone monomethyl ether (Aldrich) for 30 minutes prior to use. RAFT agent: 4-cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl]pentanoic acid was purchased from Strem Chemicals and utilized as received. Bis-RAFT agent: 4-cyano-4((dodecylthiocarbonothioylthio)pentanoyloxy)butyl 4-cyano-4-(dodecylthiocarbonothioylthio)pentanoate was prepared according to the reported literature procedure.[14] 1,1′-Azobis(cyclohexanecarbonitrile) (ACHN) initiator (DuPont VAZO-88) was used as received. *N,N*-Dimethylformamide (DMF) (AR grade) was purchased from Merck.

Automated parallel synthesizer

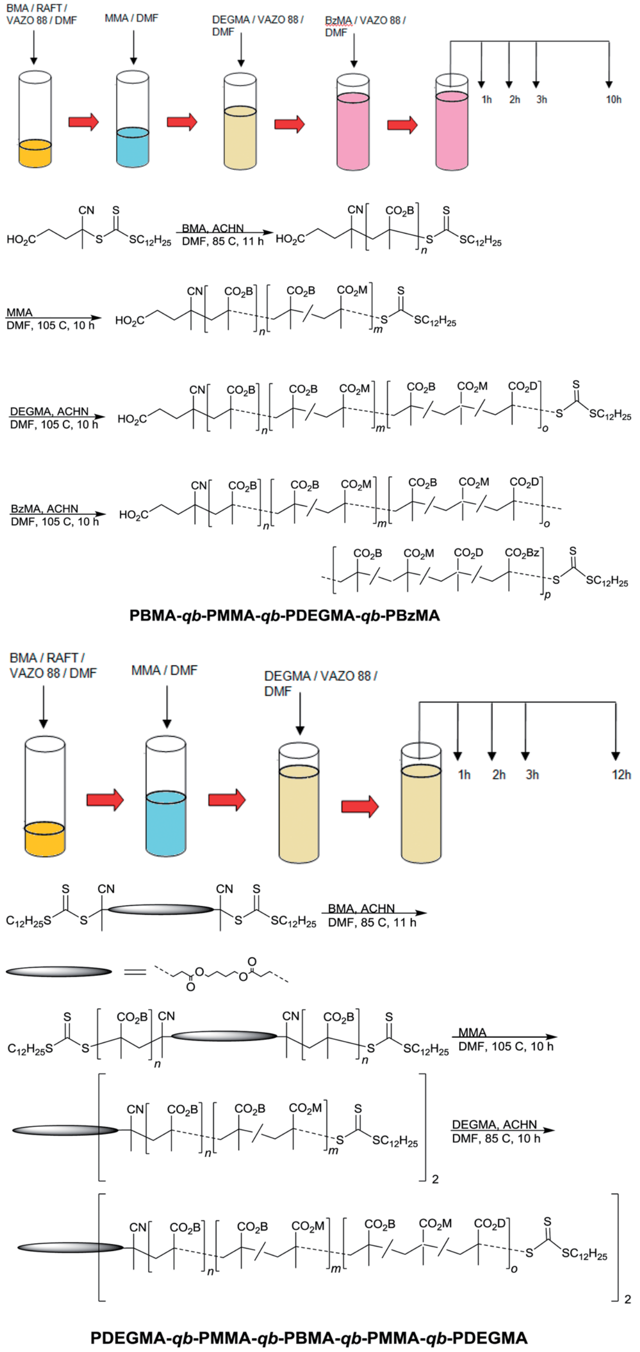
The commercially available synthesizer utilized in this work was a Chemspeed Swing-SLT automated parallel synthesizer.[13] The synthesizer was equipped with a glass reactor block consisting of 16 reaction vessels (13 mL) with thermal jackets connected in series through the reaction block to a heating/cooling system (Hüber, −90 °C to 140 °C). In addition, all reaction vessels were equipped with cold-finger reflux condensers (∼7 °C). Mixing was achieved by vortex agitation (up to 1400 rpm). Liquid transfers were handled by a 4-needle head (4-NH) capable of four simultaneous sample transfers. The 4-NH was connected to a reservoir bottle (degassed DMF solvent) for needle rinsing after each liquid transfer step. This DMF solvent reservoir was degassed by continuous sparging with nitrogen and was also utilized to prime the tubing lines of the 4-NH. When experiments were carried out, the synthesizer was maintained under an inert atmosphere by supplying a constant flow of nitrogen to the hood of the synthesizer. A nitrogen atmosphere was also applied to reactors and stock solutions at all times. Prior to the experiments, the reaction vessels were heated to 135 °C and subjected to 10 cycles of vacuum (2 min each) and filling with nitrogen (2 min each) to ensure the elimination of oxygen. After this pre-treatment, the RAFT polymerization experiment was carried out following similar procedures to those reported elsewhere.[4,13] It is worth mentioning that the characteristics of the RAFT-synthesized polymers prepared in the automated parallel synthesizer are very similar to those obtained in conventional batch polymerization performed in sealed ampoules as demonstrated in a previous contribution.[13a]

Automated synthesis of high order (multi) quasi-block copolymer libraries

Monomers and solvent (BMA, MMA, DEGMA, BzMA and DMF), and stock solutions of ACHN (4.12 mg mL^{-1} in DMF), RAFT (136.24 mg mL^{-1} in DMF) and bis-RAFT (140 mg mL^{-1} in DMF) agents were prepared, degassed by sparging with nitrogen for 15 min, and placed inside the automated synthesizer. The sequential RAFT polymerization method utilized in this work was adapted from that previously reported[4] and is described below. Schematic representations of the followed synthetic procedures are summarized in Scheme 1.

The utilized characterization methods, *i.e.*, proton nuclear magnetic resonance (^{1}H-NMR) and size exclusion chromatography (SEC), are described in the ESI.† Fig. S1† in the ESI displays representative ^{1}H-NMR spectra and their analysis to calculate conversions for the four different monomers investigated in this work.

Synthesis of poly(butyl methacrylate) (PBMA) macro RAFT and bis-macro-RAFT agents. For each investigated case, aliquots of RAFT agent (for the ABC and ABCD cases) or bis-RAFT agent (for the BAB and CBABC cases) and ACHN stock solutions, BMA and solvent from the reservoir were transferred into different reactors (13 mL) of the synthesizer with the automated liquid handling system to provide the desired concentrations of reagents. The total reaction volume was 1.75 mL corresponding to a BMA concentration of 2.143 M (3.75×10^{-3} mol of BMA). Different degrees of polymerization (DP) – assuming 100% monomer conversion – were targeted (50, 75, 100 and 150) by utilizing different RAFT agent concentrations (4.286×10^{-2} M (7.50×10^{-5} mol of RAFT), 2.857×10^{-2} M (5.00×10^{-5} mol of RAFT), 2.143×10^{-2} M (3.75×10^{-5} mol of RAFT) and 1.429×10^{-2} M (2.50×10^{-5} mol of RAFT), respectively). A [RAFT]/[Initiator] ratio of 10, 6.667, 5 and 3.333 were used for the DP of 50, 75, 100 and 150, respectively (*i.e.*, 7.50×10^{-6} mol of initiator ACHN in all cases). After all the liquid transfers were completed, the reaction solutions were degassed through three automated freeze–evacuate–thaw cycles carried out as follows: The reaction mixture was cooled to −90 °C while applying vortex to the reaction block (200 rpm). Vacuum (∼5 millibar) was then applied to the reactor block while



Scheme 1 Representation of the automated parallel synthesis of high order (multi) quasi-block copolymer libraries in one pot *via* sequential RAFT polymerization utilizing a RAFT agent (top) and a bis-RAFT agent (bottom). Illustration of the two most complex cases: ABCD (top) and CBABC (bottom), where A, B, C and D represent monomers BMA, MMA, DEGMA and BzMA, respectively. The letters also indicate the order of monomer incorporation.

warming the reactors to −10 °C with vortex (600 rpm, 2 min). Thereafter, the reactors were sealed under nitrogen and heated to the reaction temperature (85 °C) while applying vortex to the reaction block (typically 300 rpm); the temperature of the reflux condensers was set at 7 °C. The onset of the polymerizations was considered the point in which the reaction temperature in the apparatus reached the set point. At the pre-established reaction time of 11 h for all cases except for the BAB and CBABC cases (12 h), an aliquot of 200 μL was withdrawn with the automated liquid handling system from each reaction mixture and transferred to nuclear magnetic resonance (NMR) tubes and size exclusion chromatography (SEC) vials (75 μL each) to determine monomer conversion, molar mass and dispersities ($Đ$) of the formed polymer, respectively.

SEC and NMR samples for analysis were prepared with the automated liquid handling system of the synthesizer at the end of each sampling sequence by adding the corresponding SEC and NMR solvents. Once the pre-established reaction time elapsed, the polymerization mixture was cooled to 20 °C.

Synthesis of the BAB quasi-triblock copolymer libraries of poly(methyl methacrylate-quasi-*block*-butyl methacrylate-quasi-*block*-methyl methacrylate) (PMMA-*qb*-PBMA-*qb*-PMMA). After the synthesis of the PBMA bis-macro-RAFT agent described above, 1 mL of MMA (9.39×10^{-3} mol of MMA) was added to the reactor, followed by 1.5 mL DMF to improve the homogeneity of the new reaction mixture. The total reaction volume of this second polymerization was 4.05 mL. Thereafter this new reaction mixture was degassed through three automated freeze–evacuate–thaw cycles. The reactor was heated at 105 °C for 11 h to carry out the chain extension reaction and to obtain different BAB quasi-triblock copolymers. During this step, aliquots (200 μL) were automatically withdrawn from the reactors at different time intervals for NMR and SEC analysis (75 μL each).

Synthesis of the CBABC quasi-pentablock copolymer libraries of poly(di(ethylene glycol) methyl ether methacrylate-quasi-*block*-methyl methacrylate-quasi-*block*-butyl methacrylate-quasi-*block*-methyl methacrylate-quasi-*block*-di(ethylene glycol) methyl ether methacrylate) (PDEGMA-*qb*-PMMA-*qb*-PBMA-*qb*-PMMA-*qb*-PDEGMA). Following a similar procedure to the synthetic case of the BAB quasi-triblock copolymer materials, BAB bis-macro-RAFT agents were synthesized at 105 °C with a reaction time of 10 h. After this period, an aliquot of 200 μL was automatically withdrawn from each reaction mixture for NMR and SEC analysis (75 μL each), and the remaining polymerization mixtures were cooled to 20 °C. Thereafter, 1 mL of DEGMA (5.419×10^{-3} mol of DEGMA) and 0.25 mL of ACHN stock solution (4.215×10^{-6} mol of initiator) were added to the reactor. 1.5 mL of DMF (in total) was also added to the reactor to improve the homogeneity of the new reaction mixture. The total reaction volume of this second polymerization was 6.35 mL. This new reaction mixture was degassed through three automated freeze–evacuate–thaw cycles. The reactor was heated at 85 °C for 8 h to carry out the second chain extension reaction and to obtain different CBABC quasi-pentablock copolymers. During this step, aliquots (200 μL) were automatically withdrawn from the reactors at different time intervals for NMR and SEC analysis (75 μL each).

Synthesis of the ABC quasi-triblock copolymer libraries of poly(butyl methacrylate-quasi-*block*-methyl methacrylate-quasi-*block*-di(ethylene glycol) methyl ether methacrylate) (PBMA-*qb*-PMMA-*qb*-PDEGMA). Following similar procedures to the synthetic cases of the BAB quasi-triblock and CBABC quasi-pentablock copolymer materials explained above, AB macro RAFT agents were synthesized at 105 °C with a reaction time of 10 h. After this period, an aliquot of 200 μL was automatically withdrawn from each reaction mixture for NMR and SEC analysis (75 μL each), and the remaining polymerization mixtures were cooled to 20 °C. Thereafter, 1 mL of DEGMA (5.419×10^{-3} mol of DEGMA) and 0.25 mL of ACHN stock solution (4.215×10^{-6} mol of initiator) were added to the reactor. 1.5 mL of DMF (in total) was also added to the reactor to improve the homogeneity of the new reaction mixture. The total reaction volume of this second polymerization was 6.35 mL. Next, this new reaction mixture was additionally degassed through three automated freeze–evacuate–thaw cycles as explained above. The reactor was heated at 85 °C for 8 h to carry out the second chain extension reaction and to obtain different ABC quasi-triblock copolymers. During this step, aliquots (200 μL) were automatically withdrawn from the reactors at different time intervals for NMR and SEC analysis (75 μL each).

Synthesis of the ABCD quasi-tetrablock copolymer libraries of poly(butyl methacrylate-quasi-*block*-methyl methacrylate-quasi-*block*-di(ethylene glycol) methyl ether methacrylate-quasi-*block*-benzyl methacrylate) (PBMA-*qb*-PMMA-*qb*-PDEGMA-*qb*-PBzMA). Following a similar procedure to the synthetic case of the ABC quasi-triblock copolymer materials explained above, ABC macro-RAFT agents were synthesized at 85 °C with a reaction time of 12 h. At the onset of the respective second chain extension reaction and after 12 h, aliquots of 200 μL were automatically withdrawn from each reaction mixture for NMR and SEC analysis (75 μL each). Thereafter, the remaining polymerization mixtures were cooled to 20 °C. Subsequently, 1 mL of BzMA (5.902×10^{-3} mol of BzMA) and 0.25 mL of ACHN stock solution (4.215×10^{-6} mol of initiator) were added to the reactor. 1.5 mL of DMF (in total) was also added to the reactor to improve the homogeneity of the new reaction mixture. The total reaction volume of this second polymerization was 8.45 mL. This new reaction mixture was additionally degassed through three automated freeze–

Table 1 Characteristics of PMMA-*qb*-PBMA-*qb*-PMMA materials obtained from the chain extension of three different bis-macro-RAFT agents in the automated parallel synthesizer[a]

ID	Reaction time (h)	M_n (g mol^{-1})	$Đ$	$M_{n(\text{theory})}$ (g mol^{-1})	MMA conversion (%)
1. A bis-macro-RAFT agent (M_n = 5400 g mol^{-1}, $Đ$ = 1.14)					
1A	1	11 300	1.12	10 632	29
1B	2	14 900	1.14	13 708	51
1C	3	17 100	1.15	15 428	64
1D	4	18 700	1.16	16 370	71
1E	5	19 700	1.17	17 358	78
1F	6	20 900	1.14	18 040	83
1G	8	21 700	1.18	18 860	89
1H	11	22 400	1.19	19 463	93
2. A bis-macro-RAFT agent (M_n = 7800 g mol^{-1}, $Đ$ = 1.13)					
2A	1	15 800	1.14	16 279	31
2B	2	19 900	1.16	20 478	52
2C	3	22 600	1.17	22 669	63
2D	4	24 400	1.18	24 512	72
2E	5	25 500	1.19	25 641	78
2F	7	27 000	1.20	26 971	84
2G	9	27 700	1.21	27 918	89
2H	11	28 000	1.20	28 493	92
3. A bis-macro-RAFT agent (M_n = 10 600 g mol^{-1}, $Đ$ = 1.13)					
3A	1	20 900	1.17	21 408	31
3B	2	26 200	1.19	26 574	50
3C	3	28 900	1.20	28 926	59
3D	4	31 100	1.21	30 588	65
3E	5	32 100	1.23	32 256	72
3F	6	33 500	1.25	34 264	79
3G	8	34 300	1.26	35 558	84
3H	11	34 900	1.26	36 560	87

[a] Number average molar mass (M_n) and dispersity ($Đ = M_w/M_n$) were estimated by SEC and are reported as PMMA equivalents. The monomer to polymer conversion was determined by ^{1}H-NMR. $M_{n(\text{theory})}$ was estimated using the formula: $M_{n(\text{theory})} = ([M_{\text{BMA}}]_o \times M_{\text{BMA}} \times \%\ \text{conversion}_{\text{BMA}} + [M_{\text{MMA}}]_o \times M_{\text{MMA}} \times \%\ \text{conversion}_{\text{MMA}})/[\text{bis-RAFT}]_o + M_{\text{bis-RAFT.}}$ M_{BMA}, M_{MMA} and $M_{\text{bis-RAFT}}$ are the molar masses of BMA, MMA and bis-RAFT agent, respectively. $[M_{\text{BMA}}]_o$, $[M_{\text{BMA}}]_o$ and $[\text{bis-RAFT}]_o$ are the initial concentrations of BMA, MMA and bis-RAFT agent, respectively. For the synthesis of the A bis-macro-RAFT agents, $[M_{\text{BMA}}]_o$ = 2.143 M, reaction temperature = 85 °C and reaction time = 12 h; [RAFT] : [Initiator] : $[M_{\text{BMA}}]$ ratios of 1 : 0.1 : 50, 1 : 0.15 : 75 and 1 : 0.2 : 100 were utilized for the cases of bis-macro-RAFT agents 1, 2 and 3, respectively. For the chain extension reaction of the respective bis-macro-RAFT agents, $[M_{\text{MMA}}]_o$ = 2.318 M, reaction temperature = 105 °C and reaction time = 11 h.

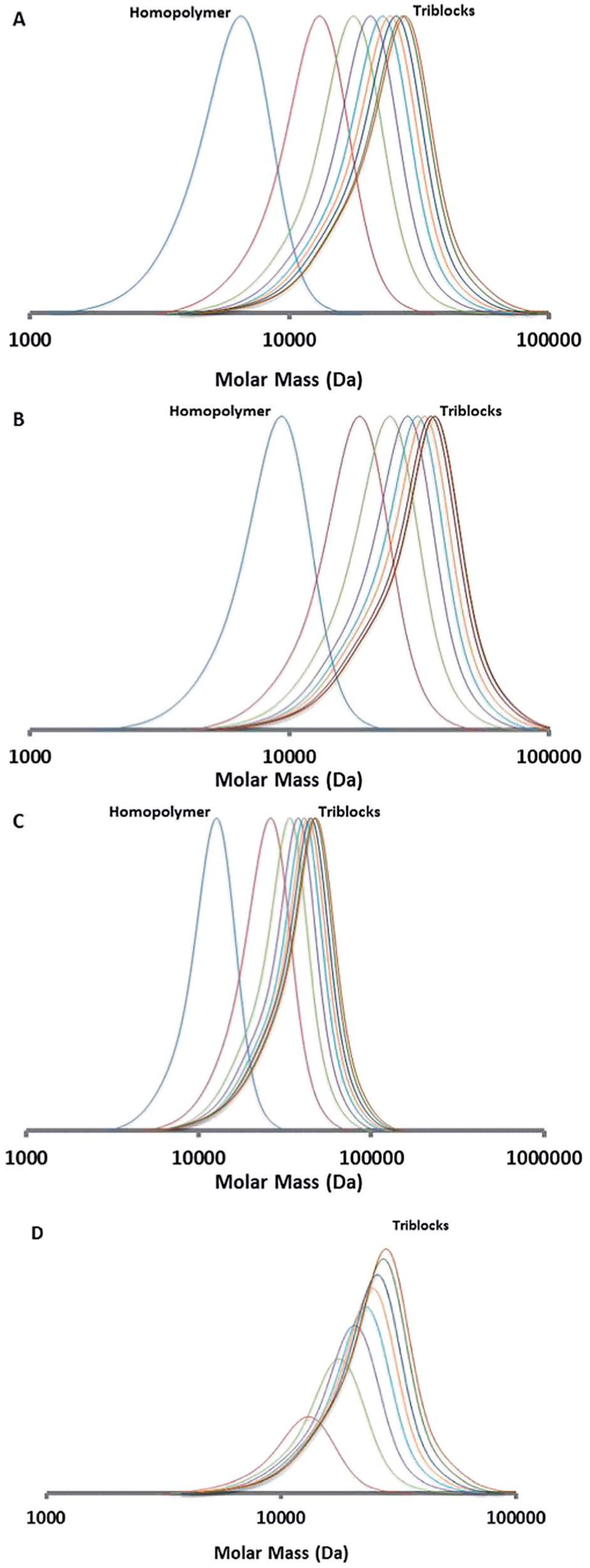


Fig. 1 SEC traces of the chain extension bis-macro-RAFT polymerization (Table 1) of the synthesized PMMA-*qb*-PBMA-*qb*-PMMA quasi-triblock copolymer materials derived from bis-macro-RAFT (A) precursor agent 1, (B) precursor agent 2, (C) precursor agent 3 and (D) precursor agent 1 scaled against conversion of MMA.

evacuate–thaw cycles. The reactor was heated at 85 °C for 10 h to carry out the third chain extension reaction and to obtain different ABCD quasi-triblock copolymers. During this step, aliquots (200 μL) were automatically withdrawn from the reactors at different time intervals for NMR and SEC analysis (75 μL each).

Results and discussion

Within this investigation the simplest library synthesis corresponds to the BAB block copolymer case, which utilizes a similar procedure to that described in our previous contribution for quasi-diblock copolymer libraries.[4b] For this a series of one pot (two step) sequential polymerizations were performed in the automated synthesizer using a bis-macro-RAFT agent to yield a library of 24 PMMA-*qb*-PBMA-*qb*-PMMA quasi-triblock copolymers derived from three different bis-macro-RAFT agents. Table 1 summarizes the synthetic results and the reaction conditions utilized (see Table 1 footnote a) of this library and shows that all materials have *Đ* values below 1.27. Fig. 1 displays representative SEC traces demonstrating an efficient chain extension process for each specific case. The same data is presented with the SEC traces scaled against monomer conversion (MMA) during the chain extension reaction of bis-RAFT agent precursor 1 in Fig. 1D.

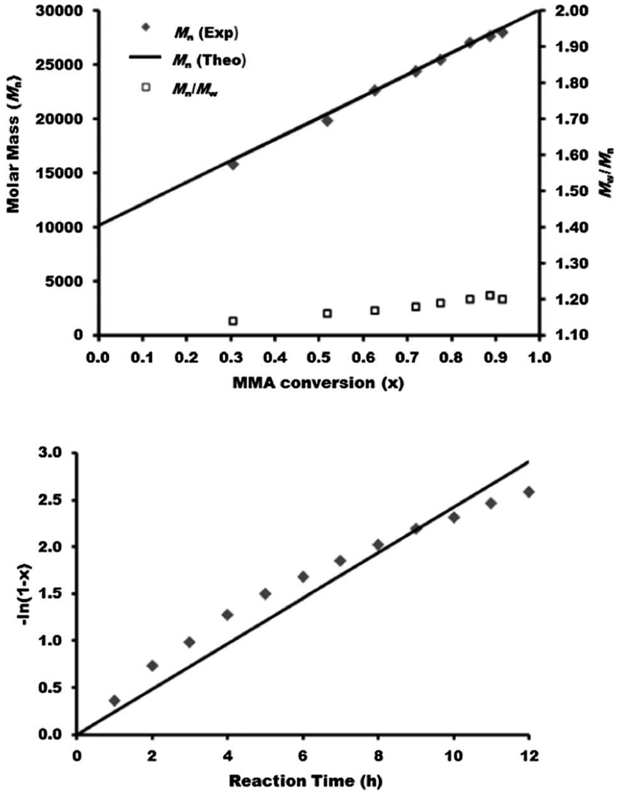


Fig. 2 Kinetic data of the synthesized PMMA-*qb*-PBMA-*qb*-PMMA quasi-triblock copolymer materials derived from bis-macro-RAFT agent 2 (Table 1). M_n and $Đ = M_w / M_n$ as a function of the MMA conversion (top) and MMA conversion as a function of reaction time (bottom).

Table 2 Characteristics of PDEGMA-*qb*-PMMA-*qb*-PBMA-*qb*-PMMA-*qb*-PDEGMA materials obtained from the chain extension of three different bis-macro RAFT agents in the automated parallel synthesizer[a]

ID	Reaction time (h)	M_n (g mol^{-1})	Đ	$M_{n(theory)}$ (g mol^{-1})	DEGMA conversion (%)
4. BAB bis-macro-RAFT agent (M_n = 18 900 g mol^{-1}, Đ = 1.15)					
4A	1	23 500	1.18	22 594	25
4B	2	26 100	1.19	24 471	37
4C	3	27 800	1.20	26 560	48
4D	4	27 900	1.22	27 554	55
4E	6	28 900	1.25	29 150	64
4F	8	30 000	1.25	29 869	68
4G	10	31 600	1.26	30 855	74
4H	12	32 300	1.27	31 538	78
5. BAB bis-macro-RAFT agent (M_n = 23 800 g mol^{-1}, Đ = 1.18)					
5A	1	29 200	1.20	34 428	25
5B	2	31 400	1.24	37 357	37
5C	3	33 800	1.24	39 536	47
5D	4	33 400	1.26	41 033	53
5E	6	35 400	1.28	43 676	63
5F	8	36 900	1.29	45 126	69
5G	10	38 400	1.30	46 421	75
5H	12	39 600	1.30	47 569	80
6. BAB bis-macro-RAFT agent (M_n = 32 600 g mol^{-1}, Đ = 1.22)					
6A	1	38 900	1.27	44 392	25
6B	2	41 000	1.30	47 515	34
6C	3	42 900	1.31	50 151	42
6D	4	42 200	1.34	52 138	48
6E	6	44 000	1.34	55 626	58
6F	8	47 000	1.33	57 084	63
6G	10	48 800	1.34	59 149	69
6H	12	49 700	1.37	60 427	73

[a] Number average molar mass (M_n) and dispersity (Đ = M_w/M_n) were estimated by SEC and are reported as PMMA equivalents. The monomer to polymer conversion was determined by ^{1}H-NMR. $M_{n(theory)}$ was estimated using the formula: $M_{n(theory)}$ = ([M_{BMA}]$_o$ × M_{BMA} × % conversion$_{BMA}$ + [M_{MMA}]$_o$ × M_{MMA} × % conversion$_{MMA}$ + [M_{DEGMA}]$_o$ × M_{DEGMA} × % conversion$_{DEGMA}$)/[bis-RAFT]$_o$ + $M_{bis\text{-}RAFT.}$ M_{BMA}, M_{MMA}, M_{DEGMA} and $M_{bis\text{-}RAFT}$ are the molar masses of BMA, MMA, DEGMA and bis-RAFT agent, respectively. [M_{BMA}]$_o$, [M_{BMA}]$_o$, [M_{DEGMA}]$_o$ and [bis-RAFT]$_o$ are the initial concentrations of BMA, MMA, DEGMA and bis-RAFT agent, respectively. For the synthesis of the A bis-macro-RAFT agents, [M_{BMA}]$_o$ = 2.143 M, reaction temperature = 85 °C and reaction time = 12 h; [RAFT] : [Initiator] : [M_{BMA}] ratios of 1 : 0.1 : 50, 1 : 0.15 : 75 and 1 : 0.2 : 100 were utilized for the cases of bis-macro-RAFT agents 4, 5 and 6, respectively. For the synthesis of the BAB bis-macro-RAFT agents, [M_{MMA}]$_o$ = 2.318 M, reaction temperature = 105 °C and reaction time = 10 h. For the chain extension reaction of the respective BAB bis-macro-RAFT agents with DEGMA, [M_{DEGMA}]$_o$ = 0.853 M, additional [Initiator]$_o$ = 6.638 × 10^{-4} M, reaction temperature = 85 °C and reaction time = 12 h.

Fig. 2 displays kinetic plots of the chain extension reaction of one of the investigated cases (bis-macro-RAFT agent 2 in Table 1) where a linear relationship can be observed between the number average molar mass (M_n) *vs.* conversion (x). and the $-\ln(1 - x)$ *vs.* reaction time indicating good control over the consecutive polymerizations. Additional kinetic plots for the cases of the bis-macro-RAFT agents 1 and 3 (Table 1) can be found in Fig. S2† in the ESI. As full conversion was not achieved during the first polymerization the residual BMA is incorporated within the PMMA blocks of the PMMA-*qb*-PBMA-*qb*-PMMA quasi-triblock copolymers. The monomer conversions for the three different bis-macro-RAFT agents of Table 1 were 86, 91 and 89% for 1, 2 and 3, respectively. Based on these measurements and using a similar ^{1}H-NMR analysis as reported elsewhere,[4] the amount of BMA incorporated into the PMMA blocks during the second polymerization step can be estimated. In all cases of Table 1 was found that the PMMA-*qb*-PBMA-*qb*-PMMA quasi-triblock copolymers have BMA units within the PMMA blocks below or at a value of 4 mol%.

Next, we consider the synthesis of a PDEGMA-*qb*-PMMA-*qb*-PBMA-*qb*-PMMA-*qb*-PDEGMA quasi-pentablock copolymer library (CBABC case). For this CBABC case, three similar bis-macro-RAFT agents to those reported in Table 1 were sequentially chain extended with MMA to obtain the respective BAB bis-macro-RAFT agents of the type PMMA-*qb*-PBMA-*qb*-PMMA quasi-triblock copolymers. Thereafter, a second chain extension polymerization step with DEGMA to the three BAB bis-macro-RAFT agents was sequentially undertaken to yield a library of 24 PDEGMA-*qb*-PMMA-*qb*-PBMA-*qb*-PMMA-*qb*-PDEGMA quasi-pentablock copolymers. Table 2 summarizes the synthetic results and the reaction conditions utilized (see Table 2 footnote a) of this library and shows that all the materials had Đ values below or at 1.37, whereas Fig. 3 displays representative SEC traces demonstrating an efficient second chain extension process for each specific case. Fig. 4 displays kinetic plots of the chain extension reaction of one of the investigated cases (BAB bis-macro-RAFT agent 4 in Table 2) where a linear relationship can be observed between M_n *vs.* conversion (x) and the

$-\ln(1-x)$ *vs.* reaction time indicating good control over the consecutive polymerization. Additional kinetic plots for the cases of the BAB bis-macro-RAFT agents 5 and 6 (Table 2) can be found in Fig. S3† in the ESI.

Similar to the previous analysis, full conversion was also not reached during the second polymerization step. Thus, the residual MMA was incorporated within the PDEGMA blocks of the PDEGMA-*qb*-PMMA-*qb*-PBMA-*qb*-PMMA-*qb*-PDEGMA quasi-pentablock copolymers. The MMA monomer conversions for the three different BAB bis-macro-RAFT agents of Table 2 were 82, 86 and 82% for 4, 5 and 6, respectively. Based on these measurements and using the ^{1}H-NMR analysis described in the experimental section, the amount of MMA incorporated into the PDEGMA blocks during the third polymerization step can be estimated. It was found that the PDEGMA-*qb*-PMMA-*qb*-PBMA-*qb*-PMMA-*qb*-PDEGMA quasi-pentablock copolymers have MMA units within the PDEGMA blocks in the range of 18 to 25 mol%. The relative high impurity found in the PDEGMA block can be ascribed to the lower MMA monomer conversion obtained during the second polymerization as well as to the low concentration of DEGMA monomer utilized for the third polymerization step. It was found that, within the investigated reaction conditions, higher conversions during the second polymerization, higher concentration of third monomer values in the materials or dead polymer in the third sequential polymerization led to higher dispersity chains. This aspect is analysed in more detail below for the ABC quasi-triblock copolymer library case. Nevertheless, further optimization to reduce these defects or impurities in the sequentially formed blocks could be easily achieved.

For the PBMA-*qb*-PMMA-*qb*-PDEGMA ABC case, two macro-RAFT agents were sequentially chain extended with MMA monomer utilizing the reaction conditions described in the Experimental section to obtain the respective AB macro-RAFT

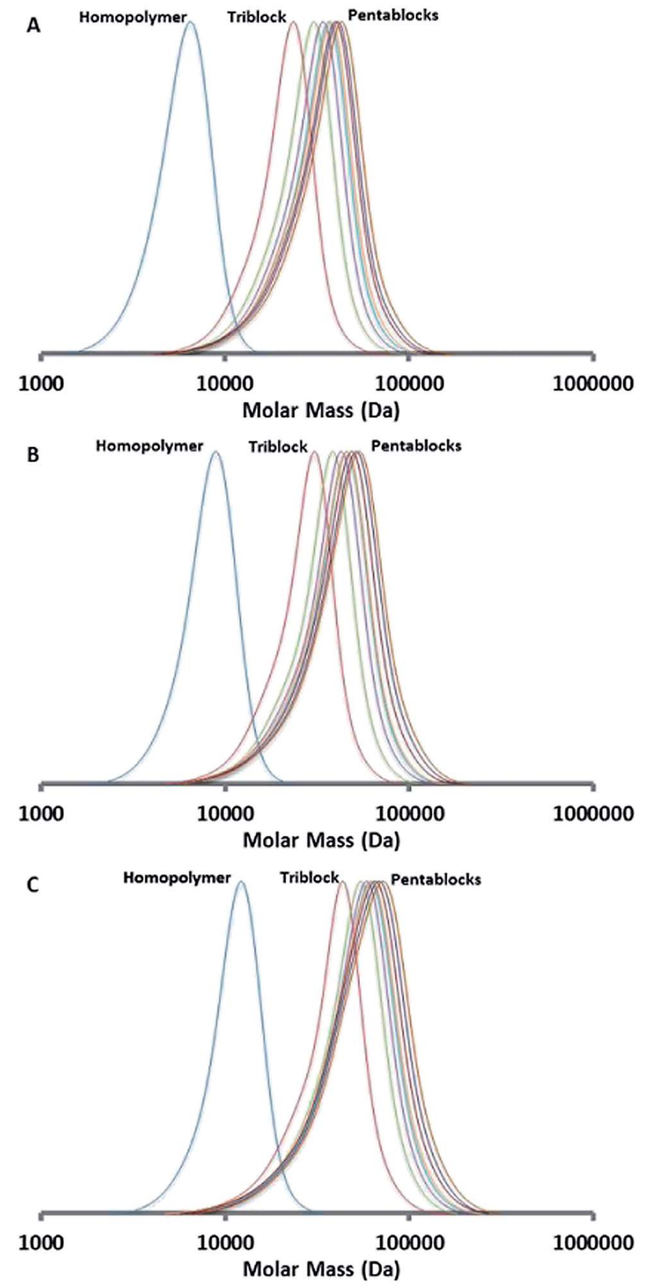


Fig. 3 SEC traces of the chain extension bis-macro-RAFT polymerization (Table 2) of the synthesized PDEGMA-*qb*-PMMA-*qb*-PBMA-*qb*-PMMA-*qb*-PDEGMA quasi-pentablock copolymer materials derived from bis-macro-RAFT (A) precursor agent 4 (B) precursor agent 5 and (C) precursor agent 6.

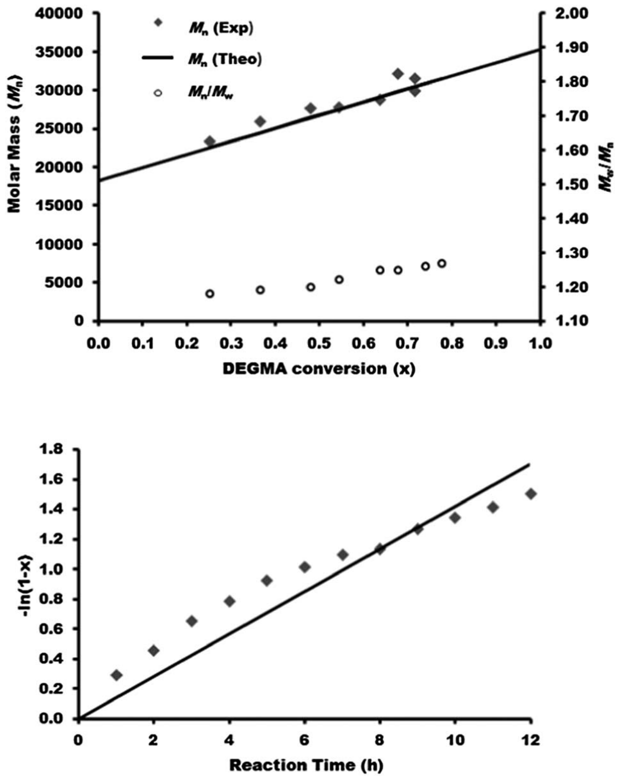


Fig. 4 Kinetic data of the synthesized PDEGMA-*qb*-PMMA-*qb*-PBMA-*qb*-PMMA-*qb*-PDEGMA quasi-pentablock copolymer materials derived from BAB bis-macro-RAFT agent 4 (Table 2). M_n and $Đ = M_w/M_n$ of as a function of the DEGMA conversion (top) and DEGMA conversion as a function of reaction time (bottom).

agents of the type PBMA-*qb*-PMMA quasi-diblock copolymers. Thereafter, a second chain extension with DEGMA monomer to the two AB macro-RAFT agents was sequentially undertaken to yield a library of 16 PBMA-*qb*-PMMA-*qb*-PDEGMA quasi-triblock copolymers. Table 3 summarizes the synthetic results and the utilized reaction conditions (see Table 3 footnote a) of this library and shows that all the materials have *Đ* values below or at 1.34, whereas Fig. 5 displays representative SEC traces demonstrating an efficient second chain extension process for each specific case. Fig. 6 displays kinetic plots of the chain extension reaction of one of the investigated cases (AB macro RAFT agent 7 in Table 3) where a linear relationship can be observed between the M_n *vs.* conversion (x) and the $-\ln(1-x)$ *vs.* reaction time indicating all in all a good control over the consecutive polymerization. Kinetic plots for the additional case of the AB macro-RAFT agent 8 (Table 3) can be found in Fig. S4† in the ESI. Similar to the previous analysis, full conversion was also not reached during the second polymerization step (synthesis of the AB macro-RAFT agents). Thus, the residual MMA was incorporated within the PDEGMA blocks of the PBMA-*qb*-PMMA-*qb*-PDEGMA quasi-triblock copolymers. The MMA monomer conversions for the two different AB macro-RAFT agents of Table 3 were 80% for both cases (7 and 8). Attempts for bringing to higher conversions (>80%) these polymerization reactions led to the appearance of a considerable amount of dead polymer chains as revealed by SEC traces (appearance of shoulders and tails in the low molar mass range during the second chain extension reaction; see Fig. S5† in the ESI for an example where a reaction time of 12 h was utilized instead of 11 h). Similar to our optimization of the reaction time, to provide a reasonable balance between high monomer conversion and minimal dead polymer chains, optimization experiments could be performed using our high-throughput methodology to establish the minimum amount of initiator required to reach a desired conversion and level of end group fidelity.[5,10] This optimal initiator level might also be estimated by simulations[11,16] for systems where kinetic parameters are available.[2b] As a direct consequence of the relatively low conversion in the first chain extension reaction (polymerization of MMA), higher amounts of MMA monomer will be incorporated into the PDEGMA block as "impurity" during the second chain extension reaction. Based on this and using the ^{1}H-NMR analysis, the amount of MMA incorporated into the PDEGMA blocks during the third polymerization step was estimated to be in the range of 18 to 27 mol%. Similar to the previous discussed case, the relatively high impurity found in the PDEGMA block can be ascribed to the low MMA monomer conversion during the second polymerization and the relatively low concentration of DEGMA monomer utilized for the third polymerization step.

For the PBMA-*qb*-PMMA-*qb*-PDEGMA-*qb*-PBzMA ABCD case, the ABC macro-RAFT agent was sequentially chain extended with BzMA monomer in a third polymerization step. This

Table 3 Characteristics PBMA-*qb*-PMMA-*qb*-PDEGMA materials obtained from the chain extension of two different macro RAFT agents in the automated parallel synthesizer[a]

ID	Reaction time (h)	M_n (g mol^{-1})	*Đ*	$M_{n(\text{theory})}$ (g mol^{-1})	DEGMA conversion (%)
7. AB macro-RAFT agent (M_n = 24 400 g mol^{-1}, *Đ* = 1.16)					
7A	1	28 200	1.19	30 338	17
7B	2	30 800	1.22	33 601	31
7C	3	32 900	1.23	35 932	41
7D	4	34 300	1.24	37 709	48
7E	6	35 900	1.26	40 071	58
7F	8	37 400	1.27	41 694	65
7G	10	38 100	1.29	43 161	71
7H	12	39 100	1.30	44 341	76
8. AB macro-RAFT agent (M_n = 29 800 g mol^{-1}, *Đ* = 1.21)					
8A	1	34 800	1.22	39 921	17
8B	2	37 600	1.25	45 265	32
8C	3	39 400	1.27	47 688	39
8D	4	41 400	1.27	49 938	46
8E	5	42 600	1.25	51 583	52
8F	7	44 100	1.31	54 310	60
8G	10	46 100	1.33	57 458	70
8H	12	47 100	1.34	59 052	75

[a] Number average molar mass (M_n) and dispersity ($Đ = M_w/M_n$) were estimated by SEC and are reported as PMMA equivalents. The monomer to polymer conversion was determined by ^{1}H-NMR. $M_{n(\text{theory})}$ was estimated using the formula: $M_{n(\text{theory})} = ([M_{\text{BMA}}]_o \times M_{\text{BMA}} \times \%\ \text{conversion}_{\text{BMA}} + [M_{\text{MMA}}]_o \times M_{\text{MMA}} \times \%\ \text{conversion}_{\text{MMA}} + [M_{\text{DEGMA}}]_o \times M_{\text{DEGMA}} \times \%\ \text{conversion}_{\text{DEGMA}})/[\text{RAFT}]_o + M_{\text{RAFT.}}$ M_{BMA}, M_{MMA}, M_{DEGMA} and M_{RAFT} are the molar masses of BMA, MMA, DEGMA and RAFT agent, respectively. $[M_{\text{BMA}}]_o$, $[M_{\text{BMA}}]_o$, $[M_{\text{DEGMA}}]_o$ and $[\text{RAFT}]_o$ are the initial concentrations of BMA, MMA, DEGMA and RAFT agent, respectively. For the synthesis of the A macro RAFT agents, $[M_{\text{BMA}}]_o$ = 2.143 M, reaction temperature = 85 °C and reaction time = 11 h; $[\text{RAFT}]:[\text{Initiator}]:[M_{\text{BMA}}]$ ratios of 1 : 0.15 : 75 and 1 : 0.2 : 100 were utilized for the cases of macro RAFT agents 7 and 8, respectively. For the synthesis of the AB macro RAFT agents, $[M_{\text{MMA}}]_o$ = 2.318 M, reaction temperature = 105 °C and reaction time = 10 h. For the chain extension reaction of the respective AB macro RAFT agents with DEGMA, $[M_{\text{DEGMA}}]_o$ = 0.853 M, additional $[\text{Initiator}]_o = 6.638 \times 10^{-4}$ M, reaction temperature = 85 °C and reaction time = 12 h.

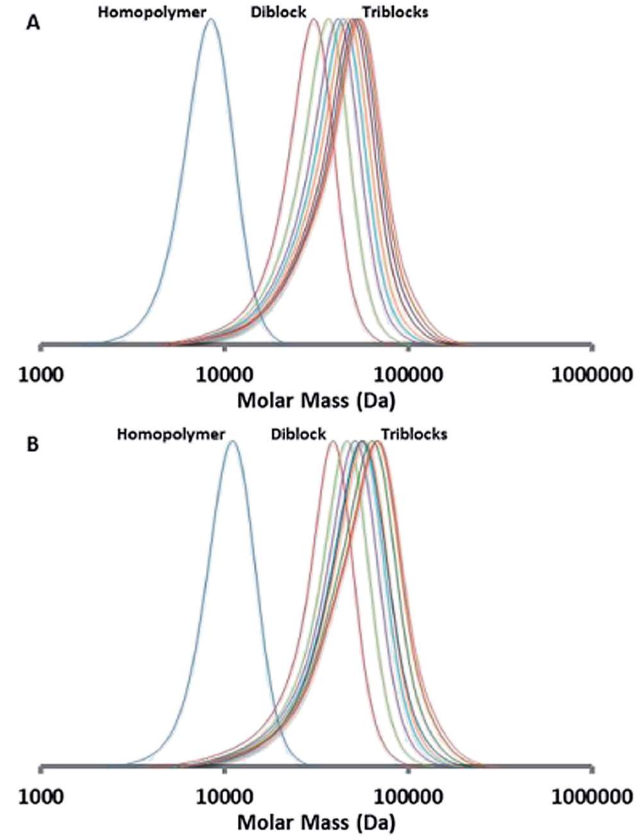


Fig. 5 SEC traces of the chain extension RAFT polymerization (Table 3) of the synthesized PBMA-*qb*-PMMA-*qb*-PDEGMA quasi-triblock copolymer materials derived from macro-RAFT (A) precursor agent 7 and (B) precursor agent 8.

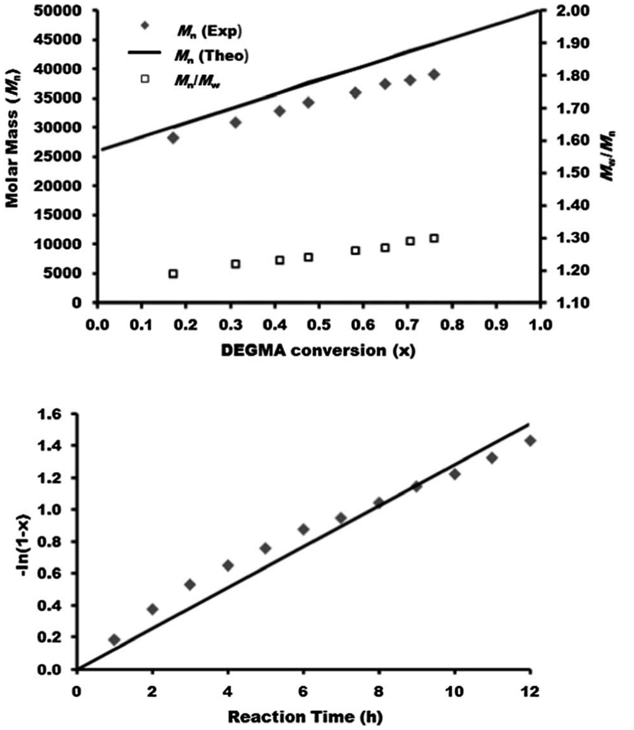


Fig. 6 Kinetic data of the synthesized PBMA-*qb*-PMMA-*qb*-PDEGMA quasi-triblock copolymer materials derived from AB macro RAFT agent 7 (Table 3). M_n and $Đ = M_w / M_n$ of as a function of the DEGMA conversion (top) and DEGMA conversion as a function of reaction time (bottom).

resulted in 8 PBMA-*qb*-PMMA-*qb*-PDEGMA-*qb*-PBzMA quasi-tetrablock copolymers. Table 4 summarizes the synthetic results and the reaction conditions utilized (see Table 4 footnote a) of this library and shows that all the materials had *Đ* values below or at 1.46, whereas Fig. 7 displays representative SEC traces demonstrating an efficient third chain extension process for this case. Fig. 8 displays kinetic plots of the chain extension reaction of these cases (ABC macro-RAFT agent 9 in Table 4) where a linear relationship can be observed between the M_n *vs.* conversion (x) and the $-\ln(1-x)$ *vs.* reaction time indicating good control over the consecutive polymerizations. However, after three consecutive polymerization reactions the *Đ* values of the materials become higher with tailing to low molar mass evident in the SEC traces due to the unavoidable contribution of initiator-derived dead chains from the necessary use of relatively high initiator concentrations.

Furthermore, similar to the previous analysis, full conversion was also not reached during the third polymerization step (synthesis of the ABC macro-RAFT agent). Thus, the residual DEGMA was incorporated within the PBzMA blocks of the PBMA-*qb*-PMMA-*qb*-PDEGMA-*qb*-PBzMA quasi-tetrablock copolymers. The DEGMA monomer conversion for ABC macro-RAFT agent of Table 4 was 70%. Attempts to obtain higher conversion (>70%) in these polymerization reactions led to the appearance of a considerable amount of dead chains evident through SEC traces (see Fig. S6† in the ESI for an example where a lower molar mass ABC macro-RAFT agent was obtained at the level of 74% conversion). As a direct consequence of the relatively low conversion in the second chain extension reaction (polymerization of DEGMA), higher amounts of DEGMA monomer will be incorporated to the PBzMA block as "impurity" during the third chain extension reaction. Based on these findings and using the ^{1}H-NMR analysis described in the experimental section, the amount of DEGMA incorporated into the PBzMA blocks during the fourth polymerization step was estimated. It was found that the PBMA-*qb*-PMMA-*qb*-PDEGMA-*qb*-PBzMA quasi-tetrablock copolymers have DEGMA units within the PBzMA blocks in the range of 22 to 35 mol%. Similar to the previous discussed case, the relatively high impurity found in the PBzMA block can be ascribed to the relative lower DEGMA monomer conversion obtained during the third polymerization as well as to the relative low concentration of BzMA monomer utilized for the fourth polymerization step.

Hadjiantoniou *et al.* synthesized a series of methacrylate based "pure" block copolymers in consecutive polymerization steps utilizing the RAFT technique.[10e] In specific, they synthesized di-, tri, tetra- and pentablock copolymers and obtained *Đ* values of 1.32, 1.48, 1.58 and 1.83, respectively. The results reported in this contribution clearly demonstrate that properly optimized one pot RAFT synthetic approaches can yield multiblock copolymers with lower *Đ* values as compared to other

Table 4 Characteristics PBMA-*qb*-PMMA-*qb*-PDEGMA-*qb*-BzMA materials obtained from the chain extension of a macro-RAFT agent in the automated parallel synthesizer[a]

ID	Reaction time (h)	M_n (g mol^{-1})	$Đ$	$M_{n(theory)}$ (g mol^{-1})	BzMA conversion (%)
9. ABC macro-RAFT agent (M_n = 39 600 g mol^{-1}, $Đ$ = 1.28)					
9A	1	42 900	1.34	50 411	15
9B	2	44 700	1.36	53 767	29
9C	3	46 100	1.37	55 615	36
9D	4	47 300	1.39	57 413	43
9E	6	48 200	1.43	60 183	54
9F	8	49 600	1.46	63 876	67
9G	10	52 000	1.45	64 955	70

[a] Number average molar mass (M_n) and dispersity ($Đ = M_w/M_n$) were estimated by SEC and are reported as PMMA equivalents. The monomer to polymer conversion was determined by ^{1}H-NMR. $M_{n(theory)}$ was estimated using the formula: $M_{n(theory)} = ([M_{BMA}]_o \times M_{BMA} \times \%\ \text{conversion}_{BMA} + [M_{MMA}]_o \times M_{MMA} \times \%\ \text{conversion}_{MMA} + [M_{DEGMA}]_o \times M_{DEGMA} \times \%\ \text{conversion}_{DEGMA} + [M_{BzMA}]_o \times M_{BzMA} \times \%\ \text{conversion}_{BzMA})/[\text{RAFT}]_o + M_{RAFT}$. M_{BMA}, M_{MMA}, M_{DEGMA}, M_{BzMA} and M_{RAFT} are the molar masses of BMA, MMA, DEGMA, BzMA and RAFT agent, respectively. $[M_{BMA}]_o$, $[M_{BMA}]_o$, $[M_{DEGMA}]_o$, $[M_{BzMA}]_o$ and $[\text{RAFT}]_o$ are the initial concentrations of BMA, MMA, DEGMA, BzMA and RAFT agent, respectively. The synthesis of the ABC macro RAFT agent was an extension of 7 in Table 3, $[M_{DEGMA}]_o$ = 0.853 M, additional $[\text{Initiator}]_o = 6.638 \times 10^{-4}$ M, reaction temperature = 85 °C and reaction time = 12 h. For the chain extension reaction of this ABC macro RAFT agent with BzMA, $[M_{BzMA}]_o$ = 0.682 M, additional $[\text{Initiator}]_o = 5.848 \times 10^{-4}$ M, reaction temperature = 85 °C and reaction time = 10 h.

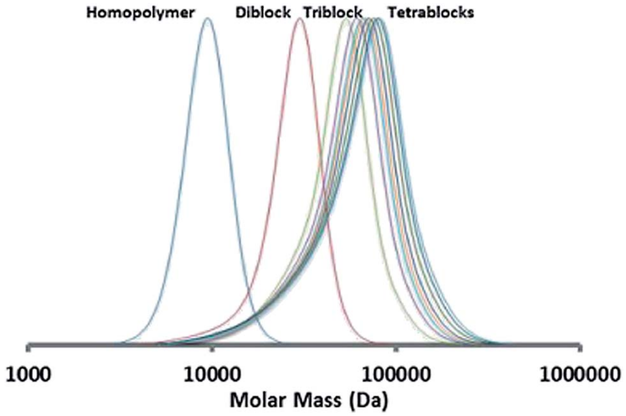


Fig. 7 SEC trace of the chain extension RAFT polymerization (Table 4) of the synthesized PBMA-*qb*-PMMA-*qb*-PDEGMA-*qb*-PBzMA quasi-tetrablock copolymer materials derived from macro-RAFT precursor agent 9.

more demanding methods where intermediate purification steps are applied for the synthesis of each block.

Conclusion

In this work, we have developed a convenient high-throughput approach for the one pot synthesis of quasi-block copolymer libraries of methacrylic monomers by RAFT polymerization. Utilizing this powerful technique, we could optimize reaction conditions and synthesize up to 71 different quasi-block copolymers, including diblocks, triblocks, tetrablocks and pentablocks, demonstrating that highly comprehensive and systematic polymer libraries can be obtained in a short period of time. Future efforts in this direction will include the synthesis of materials that utilize monomers of varying reactivity to further expand the range of materials that are easily accessible through process automation.

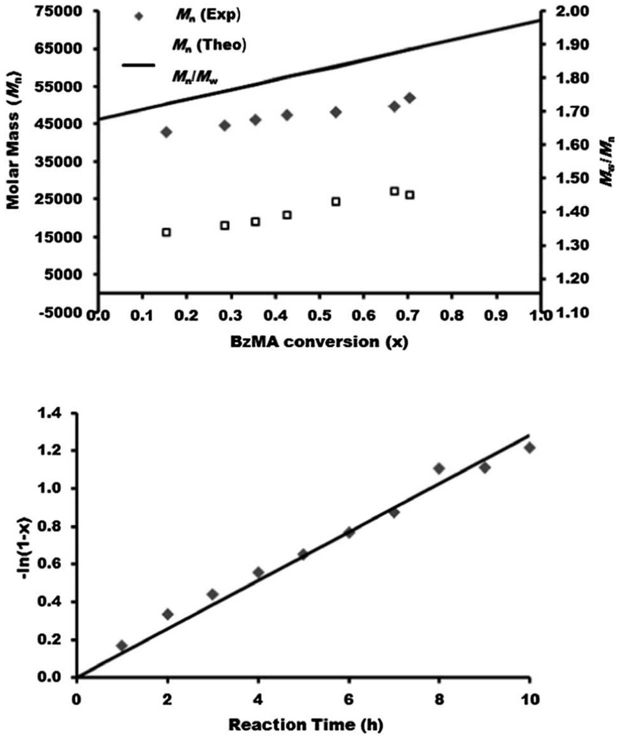


Fig. 8 Kinetic data of the synthesized PBMA-*qb*-PMMA-*qb*-PDEGMA-*qb*-BzMA quasi-tetrablock copolymer materials derived from ABC macro-RAFT agent 9 (Table 4). M_n and $Đ = M_w / M_n$ of as a function of the BzMA conversion (top) and BzMA conversion as a function of reaction time (bottom).

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