nature chemistry

ARTICLES

PUBLISHED ONLINE: XX XX 2016 | DOI: 10.1038/NCHEM.2634

Sequence-controlled methacrylic multiblock copolymers via sulfur-free RAFT emulsion polymerization

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Translating the precise monomer sequence control achieved in nature over macromolecular structure (for example, DNA) to whole synthetic systems has been limited due to the lack of efficient synthetic methodologies. So far, chemists have only been able to synthesize monomer sequence-controlled macromolecules by means of complex, time-consuming and iterative chemical strategies such as solid-state Merrifield-type approaches or molecularly dissolved solution-phase systems. Here, we report a rapid and quantitative synthesis of sequence-controlled multiblock polymers in discrete stable nanoscale compartments via an emulsion polymerization approach in which a vinyl-terminated macromolecule is used as an efficient chain transfer agent. This approach is environmentally friendly, fully translatable to industry and thus represents a significant advance in the development of complex macromolecule synthesis, where a high level of molecular precision or monomer sequence control confers potential for molecular targeting, recognition and biocatalysis, as well as molecular information storage.

The timeline of evolution has given rise to diversity at all levels of biological organization, enabling the synthesis of complex, diverse and functional sequence-ordered macromolecules such as DNA and proteins in discrete compartments (for example, cells, nuclei, cytoplasm and mitochondria). These sequence-controlled biomacromolecules play a vital role in the development, functioning and reproduction of all living organisms. Therefore, the ability to translate molecular precision, as demonstrated in nature, to highly organized sequence-controlled synthetic analogues would be a significant breakthrough with potential applications in many fields, including nanomedicine and nanotechnology. Arguably, solid-state peptide synthesis (Merrifield synthesis) revolutionized the field, providing access to precisely controlled macromolecules[1]. However, the time-consuming and iterative attachment/deprotection of monomers in the solid state can be expensive, often results in poor yields, is difficult to scale up, and is often limited to the synthesis of relatively low-molecular-weight oligomers.

Synthetic chemical approaches in the homogeneous liquid phase have also been exploited in the last decade to allow access to a wider range of chemical functionalities as well as the synthesis of polymer-based sequence-controlled materials on a larger scale (g or kg rather than mg)[2–5]. More recently, a range of methodologies have been investigated that aim to more precisely control the sequence of monomers, including single monomer insertion[6–8], tandem monomer addition and modification[9,10], kinetic control[11,12], solution[1,13–15], segregating templating[16], selected reactivities and sequential growth on soluble polymer supports[5,17–19]. Importantly, the majority of these strategies remain limited to the synthesis of low-molecular-weight oligomers. In contrast, the synthesis of multiblock copolymers is more scalable and allows for the production of higher-molecular-weight polymers, while the incorporation of a wide range of functionalities along the polymer backbone with controlled physico-chemical properties can lead to the formation of highly ordered materials exhibiting unique functions and properties.

As such, improving control over the synthesis of multiblock copolymers dissolved in the solution phase has received considerable interest. Contributions by Whittaker, Haddleton, Junkers, Perrier and their co-workers have reported the impressive synthesis of acrylic and acrylamide multiblock copolymers[20–31]. However, because they made use of catalysts containing either transition metals (usually copper) or sulfur, multiple purification steps were required to isolate the final pure materials. In addition, the halide (as used in transition-metal-mediated approaches) and reversible addition fragmentation chain transfer (RAFT) agents are typically attached to the polymer backbone even after purification, and may be undesirable in certain applications. Further limitations of these approaches often include high dispersities (>1.70 for a decablock copolymer), non-quantitative final conversions (~80%)[21,32], extended reaction times per chain extension (up to 48 h)[21–23], and undesirable hydrolysis[24] of the chain ends leading to architectural heterogeneity. Importantly, these systems have so far proved either incompatible with monomers exhibiting relatively low rates of propagation, k_p, such as methacrylates, or exhibit undesirable termination or chain transfer events[21,32]. This limitation has a detrimental effect on a wide range of applications that require higher glass transition temperatures (T_g), as methacrylic polymers exhibit significantly higher values than their acrylic counterparts.

To address these limitations, we were inspired by the segregation strategy commonly used in nature to synthesize structurally 'pure' complex biomolecules. Indeed, the well-established 'emulsion polymerization' (used industrially to make many coatings, adhesives and personal care products) is a widely used efficient synthetic application of this approach, where monomers and catalysts are isolated in nanoscale micelles dispersed in a continuous aqueous

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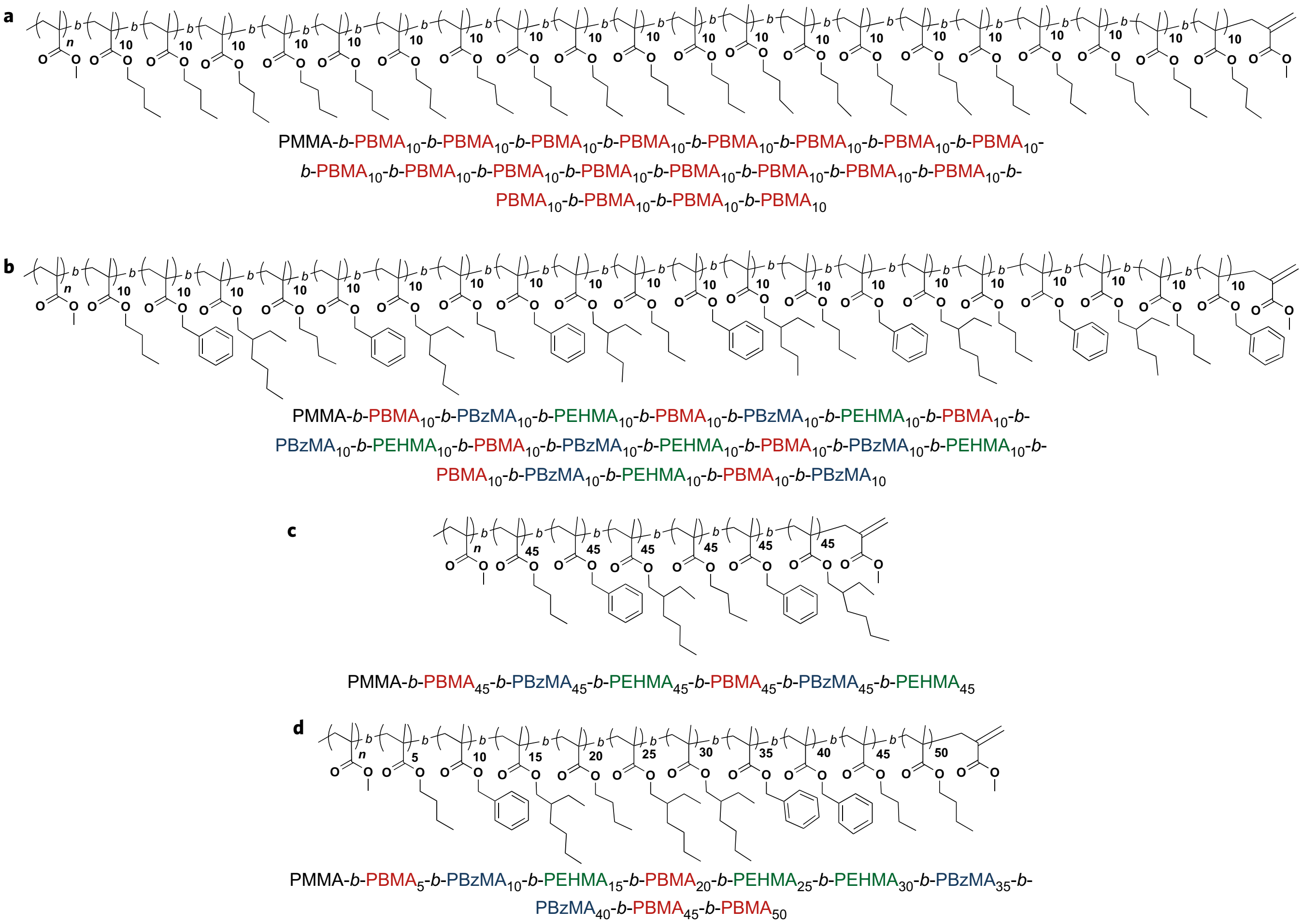

Figure 1 | Structure of multiblock copolymers synthesized in this work by a combination of catalytic chain transfer polymerization (macromonomer synthesis) followed by sulfur-free RAFT emulsion polymerization. All multiblock copolymers were prepared at 85 °C (in a 0.5 l reactor under monomer-starved conditions) via the segregation approach of emulsion polymerization using KPS as initiator and PMMA (~2,000 g mol^{-1}) as the initial CTA. **a**, Structure of the heneicosablock homopolymer using BMA as the model monomer (DP_n = 10 per block, on average 2 h per block). **b**, Structure of the heneicasoblock multiblock copolymer consisting of BMA, BzMA, EHMA and MMA (DP_n = 10 per block, on average 2 h per block). **c**, Structure of higher-molecular-weight heptablock multiblock copolymer consisting of BMA, BzMA, EHMA and MMA (DP_n = 45 per block). **d**, Structure of the undecablock multiblock copolymer, altering the monomer sequence and composition throughout the polymerization ($DP = \sum_{i=1}^{10}(5i)$ per block).

phase[33,34]. This isolation provides spatial separation to individual growing macromolecules and can significantly reduce unwanted side reactions such as termination (seen in radical polymerizations), and can control chemistry via a kinetic approach. In this Article, we demonstrate for the first time that well-defined, sequence-controlled multiblock copolymers can be synthesized in a facile, rapid, quantitative and scalable manner by developing a novel 'transition metal' and 'sulfur' free polymerization approach combined with an emulsion biomimetic segregation strategy. Catalytic chain transfer polymerization (CCTP), carried out in emulsion, was exploited in the first stage to synthesize a vinyl-terminated poly(methyl methacrylate) (PMMA) macromolecule that was subsequently used *in situ* (Q6) as a chain transfer agent for the reversible addition-fragmentation chain transfer polymerization of various methacrylic monomers.

Results and discussion

Butyl methacrylate (BMA) was first selected as the building block of the sequence-controlled macromolecules to test whether the segregation approach of emulsion polymerization is suitable for the synthesis of well-defined multiblock polymers via multi-sequential monomer addition. We decided to focus this study on members of the methacrylate monomer family, which have proved challenging as they exhibit significantly higher rates of termination relative to chain propagation due to their relatively low values of k_p, and most previous investigations have been directed towards the polymerization of monomers with higher k_p (such as acrylamides and acrylates). A PMMA oligomer with a number-averaged molecular weight (M_n) of ~2,000 g mol^{-1} ($Đ$ ~ 1.7) was (Q7) synthesized in a 0.5 l double-jacketed reactor via CCTP emulsion polymerization[35–38], and the presence of the terminal vinyl protons was confirmed by both ^{1}H NMR and matrix-assisted laser desorption ionization time of flight mass spectrometry ~~MALDI-TOF-MS~~ (Q8) (Supplementary Figs 1 and 2). The mechanism of CCTP is depicted in Supplementary Fig. 3 and uses appropriate low-spin d^6 Co(II) complexes (cobaloximes), abstracting a hydrogen from a propagating methacrylic radical to yield a Co(III)–H intermediate and an oligomer with a terminal vinyl group[39,40]. These unsaturated macromolecules have been found to exhibit chain transfer activity in the radical polymerization of methacrylates[41]. The chain transfer mechanism proceeds via chain transfer followed by fragmentation to give a macroradical that is able to initiate ~~monomer B~~, ultimately leading to block copolymers. Fragmentation is favoured over chain growth as the rate of chain growth from the sterically hindered macroradical is greatly reduced relative to a normal methacrylic radical, while the rate of unimolecular fragmentation is unaffected by the increased steric constraints. The new chain propagates via

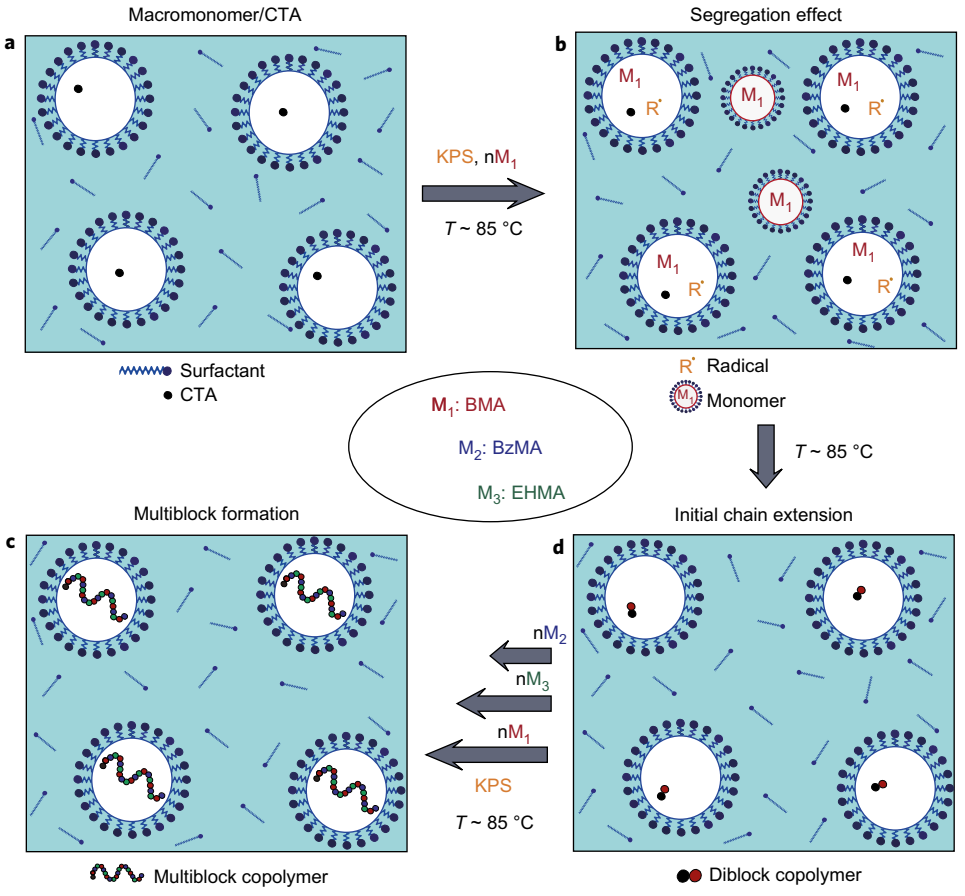

Figure 2 | Conceptual scheme for the synthesis of multiblock copolymers via sulfur-free RAFT emulsion polymerization. a, Macromonomer formation via catalytic chain transfer polymerization in emulsion. **b**, Segregation effect during particle formation. **c**, Diblock copolymer obtained after initial chain extension. **d**, Multiblock formation after 20 consecutive chain extensions.

repeated addition of monomer ~~B~~. The propagating block copolymer chain can again react with the macromonomer, resulting in an addition fragmentation process not unlike RAFT, mediated by sulfur-containing chain transfer agents. The PMMA 'macromonomer' is subsequently used as a chain transfer agent (CTA; without purification) to facilitate the synthesis of multiblock copolymers with an initial ratio of [CTA]:[monomer]:[initiator] = 1:10:0.03 via reversible addition fragmentation chain transfer emulsion polymerization. This approach is summarized in Fig. ~~1~~ 2. BMA was used as the second monomer and each block was designed to be $DP_n = 10$ (Fig. ~~2a~~ 2). Note that a targeted DP of 10 for each chain extension was selected to minimize the proportion of missing blocks (percent of defective chains) in the final multiblock material, which will be minimal according to a recently published paper by Harrisson and co-workers[42]. Under the aforementioned conditions, degassed mixtures of (1) monomer and (2) initiator in water were fed into the reactor via a syringe pump (see Supplementary Fig. 4 for the synthesis setup). It should be noted that an oxygen centred radical initiator (potassium persulfate) is used at this step to deactivate, *in situ*, the CoBF catalyst (used in the first step for the formation of the macromonomer) via radical addition to the unsaturated groups with ligand 'bleaching', thus precluding the need for purification of the CTA before subsequent block formation[43]. This second stage of polymerization resembles a typical RAFT polymerization. The following components were included: (1) a free radical initiator (potassium persulfate in this case) to generate the radical source and at the same time deactivate CoBF, (2) a CTA (vinyl-terminated PMMA in this case) and (3) a monomer (BMA in this case). On completion of the addition, the reaction was allowed to proceed for 1 h (giving a total of two and a half hours, including the feeding time), after which a sample was taken for further analysis. ^{1}H NMR spectroscopy confirmed high monomer conversion (>99%) while SEC showed the molecular weight distributions (MWDs) shifting to higher molecular weights, with an observed decrease in dispersity ($Đ \sim 1.3$) and excellent agreement between the theoretical and experimental molecular weights (Fig. 3). This confirmed the potential of this technique to support the synthesis of low-dispersity multiblock copolymers from methacrylates. When a second aliquot of BMA was subsequently added, a further reduction in dispersity was evident ($Đ \sim 1.25$), which decreased further upon addition of each subsequent monomer aliquot, reaching a quasi hexablock multiblock copolymer with $M_n \sim 10{,}400$ g mol^{-1} and a final dispersity of 1.10 (see Supplementary Tables 1 and 2 for details of synthesis). This sequential addition was performed with success 20 times, resulting in a heneicosa (21) quasi multiblock copolymer (including the CTA, as the CTA itself is also a polymer with $M_n = 2{,}000$ g mol^{-1}) with a relatively narrow molecular weight distribution ($Đ \sim 1.20$) and high degree of control, as demonstrated both by the good control over the MWDs and the satisfactory correlation between theoretical and experimental values, despite 20 cycles of sequential monomer addition. Throughout all the monomer additions, SEC showed monomodal distributions that shifted to higher molecular weights, while ^{1}H NMR confirmed >99% monomer conversion in each step (Fig. 3a,b and Table 1, entry 1). Following additional chain extensions, no compromise over control of the molecular weight distributions was observed, and the dispersity of the resultant tetracosa (24) multiblock remained as low as 1.21 (Supplementary Figs 5

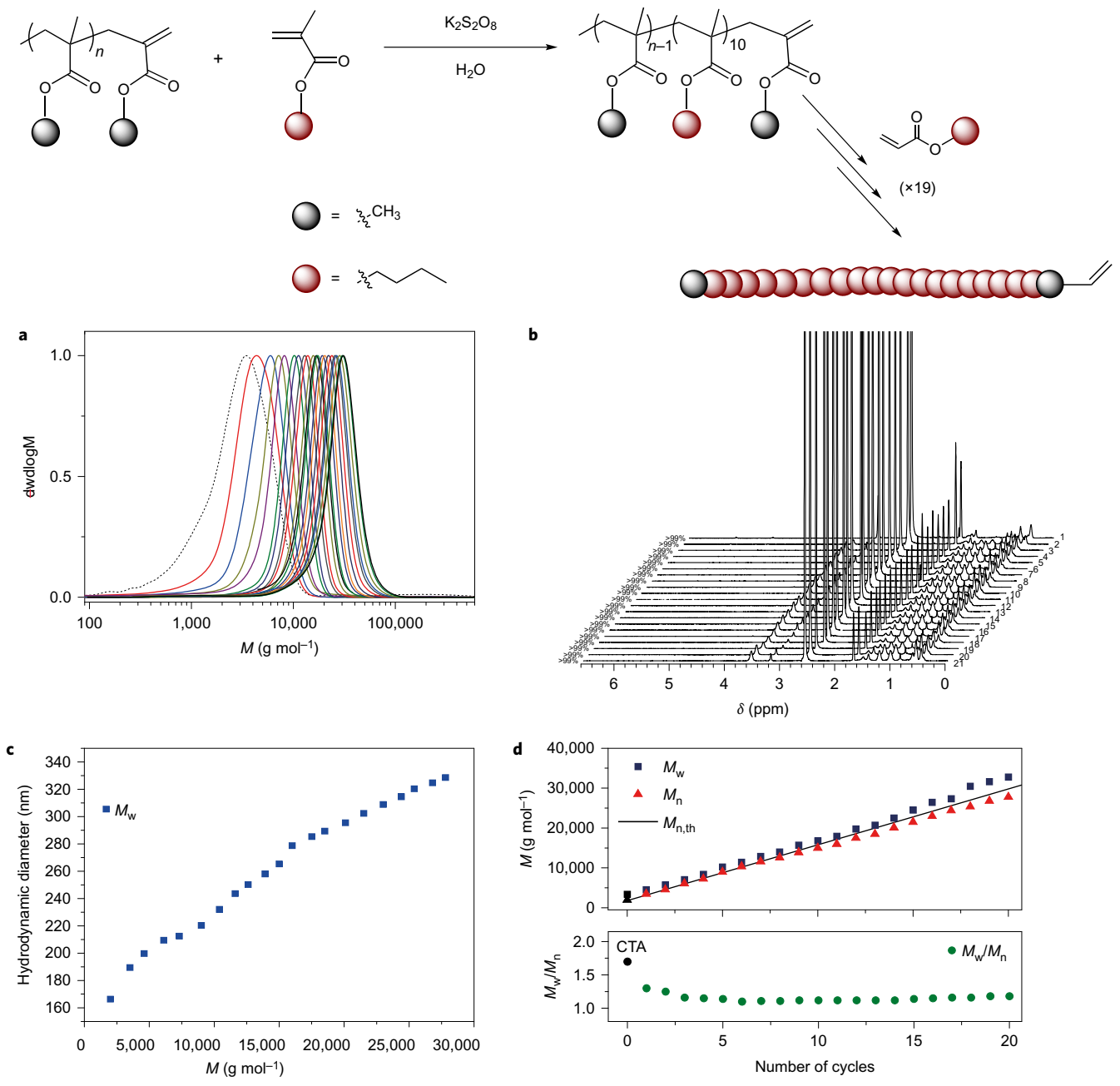

Figure 3 | Synthesis and characterization of model heneicasoblock BMA homopolymer via sulfur-free RAFT emulsion polymerization. a, SEC traces of molecular weight distributions for consecutive cycles during synthesis of the heneicasoblock homopolymer. **b**, ^{1}H NMR spectra for consecutive cycles. **c**, Hydrodynamic diameter evolution of the heneicasoblock homopolymer, as obtained by *Z*-average measurements versus M_n as measured by DLS. **d**, Evolution of theoretical (black straight line) and experimental molecular weight M_n (red triangles) and M_w (blue squares) determined by SEC and M_w/M_n (green circles) versus the number of cycles during synthesis of the heneicosablock homopolymer.

to 8). These data confirm the capacity of the segregation approach of emulsion polymerization to successfully synthesize well-defined sequence-controlled multiblock copolymers from the challenging methacrylic monomers.

It is noted that in the ^{1}H NMR results, the remaining vinyl peaks observed between 5.5 and 6.6 ppm correspond to the terminal double bond from the CTA, as the monomer vinyl peaks appear at a slightly different chemical shift (see Supplementary Fig. 9 for further details). This allows for calculation of the monomer conversion and also shows that the residual vinyl peaks in the spectrum of the final product correspond to the CTA rather than any remaining unreacted monomer. An important consideration for successful synthesis of this quasi multiblock copolymer is to maintain the solid content of the emulsion in relatively low/moderate levels to stabilize it and avoid coagulation, which would limit the final yield and increase the structural heterogeneity of the final product. To circumvent this, the system was further diluted before the addition of each monomer batch (Supplementary Table 1). It is remarkable that when comparing the first ten methacrylate block homopolymers ($Đ \sim 1.12$) with the fully optimized acrylamide deca-block homopolymer reported in the literature ($Đ \sim 1.15$), not only do they exhibit a similar level of control ($Đ \sim 1.12$ versus 1.15), but the overall polymerization rates are also similar (~2 h per block), despite the methacrylates having such a low k_p (between 1,000 and 1,500 ~~l mol^{-1} dm^{-3}~~; acrylates: 40,000–60,000 ~~l mol^{-1} dm^{-3}~~)[28,44–46]. Of course, this is only possible due to the compartmentalization

Table 1 | Summary of the analysis of the multiblock copolymers obtained in this study including final conversions, molecular weights and dispersities.

Block composition	No of blocks	Conversion* (%)	$M_{n,th}$† (g mol^{-1})	$M_{n,SEC}$‡ (g mol^{-1})	$Đ_{SEC}$§	Diameter‖ (nm)	PSD¶
$DP_n = 10$	21	>99	29,800	27,800	1.20	330	0.117
$DP_n = 10$	21	>99	36,400	29,500	1.35	360	0.112
$DP_n = 45$	7	98	48,200	41,300	1.24	400	0.125
$DP_n = \sum_{i=1}^{10} (5i)$	11	>99	44,100	42,000	1.25	450	0.250

*Overall monomer conversion for all additions characterized by ^{1}H NMR. $CDCl_3$:acetone-d_6 (3:2 vol/vol). Conversions for each iteration are tabulated in the Supplementary Information; †$M_{n,th} = [M]_0 \times p \times M_M / [CTA]_0 + M_{CTA}$; ‡Number-averaged molecular weight as measured by SEC ($M_{n,SEC}$); §Dispersity of molecular weight as measured by SEC ($Đ_{SEC}$); ‖Diameter of polymer particles as measured by DLS; ¶Polydispersity of particle diameters as measured by DLS (PSD). Each coloured sphere represents one block, with the black sphere representing the CTA, and red, blue and green representing BMA, BzMA and EHMA blocks, respectively. Q23 Q24

effects of emulsion polymerization, which result in an acceleration of the polymerization rate while maintaining low termination levels due to the low concentrations of the ~~radical~~[47,48]. Further evidence for the high control of the system can be seen from the plot of the evolution of the number-averaged molecular weight with each monomer addition, where both M_n and weight-averaged molecular weight (M_w) increase linearly with time, with very little deviation from theoretical values (Fig. 3d). In addition, dynamic light scattering (DLS) was used to characterize this multiblock homopolymer, demonstrating an increase in the hydrodynamic diameter with increasing M_n, which supports the gradual growth of the material (Fig. 3c)[47].

Having optimized the conditions for the synthesis of a quasi multiblock homopolymer, we were interested in applying them for the fabrication of more complex multiblock materials with the inclusion of different monomers to impart a wide range of Q14 physico-chemical properties to the final materials. Apart from the PMMA macro CTA, which was used as the first (or the last) block, a family of three additional methacrylic monomers was used, including benzyl methacrylate (BzMA), 2-ethyl hexyl methacrylate (EHMA) and BMA. The inclusion of different monomers (see Supplementary Tables 3 and 4 for details) resulted in a heneicosablock (21) multiblock copolymer that exhibited relatively narrow molecular weight distributions ($Đ \sim 1.35$) for such a complex structure (Fig. ~~2b~~). Note that when an icosablock (20) multiblock copolymer was synthesized by Perrier and co-workers using a much more quickly propagating monomer family (acrylamides), a similar level of control was attained ($Đ \sim 1.35$ for both systems)[28]. SEC again confirmed complete shifts to higher molecular weight following each monomer addition (Fig. 4a), while DLS showed an increase in the hydrodynamic diameter of the particles with increasing M_n (Supplementary Fig. 10), and ^{1}H NMR revealed very high conversions (>99%) throughout the block copolymerization cycles (Supplementary Fig. 11), demonstrating the quantitative synthesis of highly ordered sequence-controlled multiblock copolymers. Additional chain extensions could also be achieved, although the dispersities increased further. Nevertheless, a tetracosa (24) multiblock copolymer could be attained (Supplementary Figs 10 to 13). The final product contained no contaminating halide or sulfur moieties, in contrast with both classical ~~ATRP~~ and RAFT polymerization Q15 where typical purification methods such as precipitation or dialysis cannot remove the covalently attached halogen or RAFT agent[49,50].

As high-molecular-weight block copolymers are of interest because of their ability to self-assemble and/or phase separate to form higher ordered structures in both solution and the solid state, we were interested in probing the potential of the technique for the synthesis of higher-molecular-weight multiblock copolymers. Under the previously optimized conditions, each block was designed to have $DP_n = 45$, resulting in a well-defined heptablock multiblock copolymer) consisting of MMA, BMA, BzMA and EHMA (Fig. ~~2c~~). Other important considerations when synthesizing complex materials such as sequence-controlled multiblock copolymers are potential issues associated with scaling up of the polymerization process. To bridge the gap between small-scale synthesis in research laboratories and commercialization, and explore the robustness of our technique, we synthesized the high-molecular-weight multiblock copolymers on a high multigram scale (~80 g) in a 0.5 l double-jacketed reactor (Fig. 4b). ~~This contrasts~~ with solid peptide syntheses or even with iterative exponential growth approaches, which are typically limited to milligrams of product[19]. Despite this process scale-up, quantitative or near-quantitative conversions (>99%) were achieved throughout the monomer addition cycles (Supplementary Fig. 14). DLS showed a gradual evolution of the hydrodynamic diameter, and the final polymer had a dispersity value of 1.24 ($M_n \sim 41{,}300$ g mol^{-1}, Table 1, entry 3). The ease of scale-up and maintenance of polymer architectural control highlights the versatility and robustness of this system in facilitating the synthesis of higher-molecular-weight materials (Fig. 4c; see Supplementary Figs 14 and 15 and Supplementary Tables 5 and 6 for further details). As such, the diblock and triblock copolymers that are typically used at this molecular weight ($M_n \sim 10{,}000$–$40{,}000$ g mol^{-1}) can be easily prepared quantitatively within a few hours. Post-synthesis, the multiblock was isolated via dialysis, yielding 80 g of a white solid material (Fig. 4d). It should be highlighted that, because the macromonomer has the dual role of simultaneously being the CTA and the last (or first) building block, the final material is a clear white solid, in contrast to copper- or sulfur-catalysed polymerizations, where brown/green and pink/

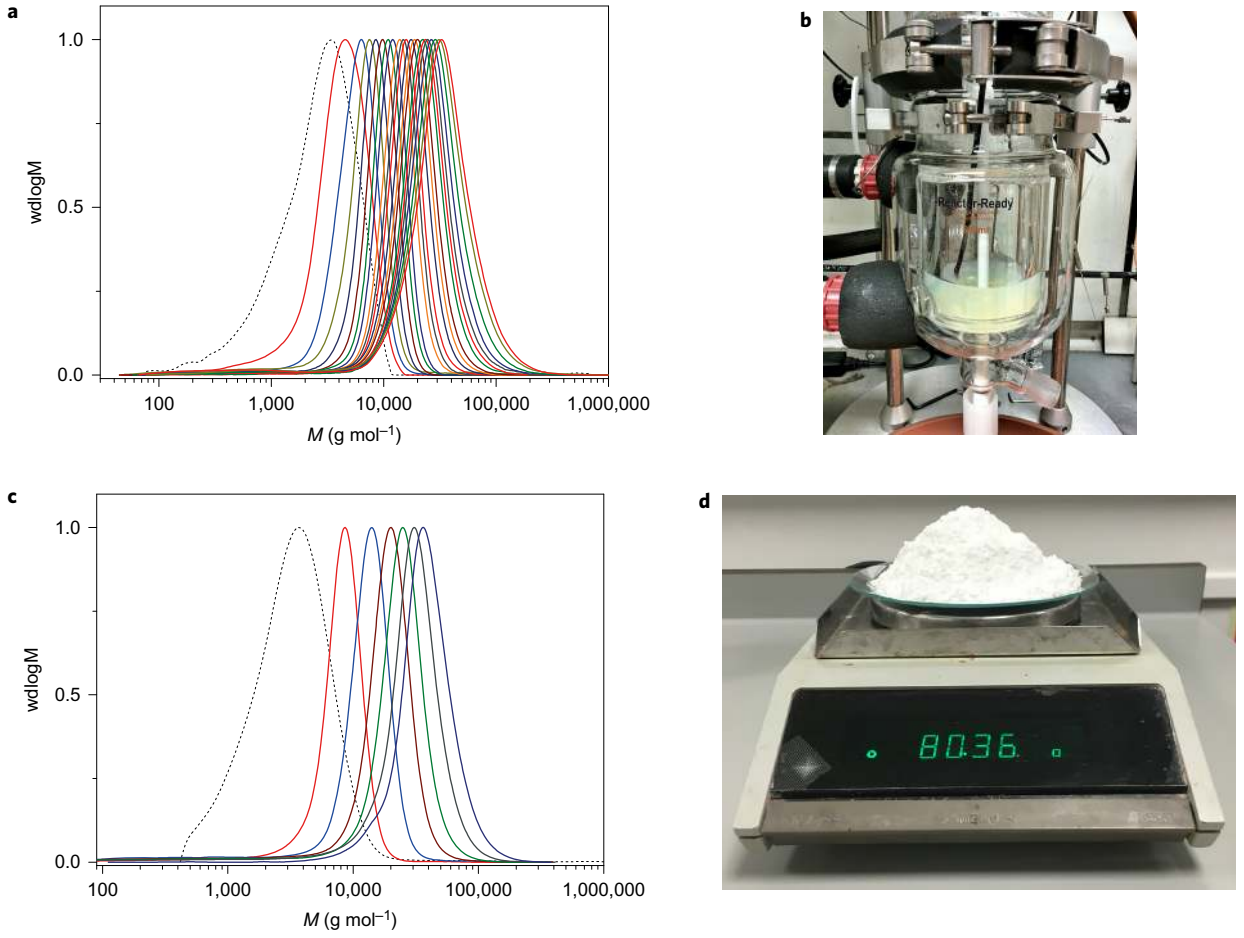

Figure 4 | Scalable synthesis of the high-molecular-weight hexablock copolymer. The copolymer consists of BMA, BzMA, EHMA and MMA at 85 °C (in a 0.5 l reactor with monomer-starved conditions) via a segregation approach of emulsion polymerization using KPS as initiator and PMMA (~2,000 g mol^{-1}) as the initial CTA. **a**, Molecular weight distributions of heneicosablock multiblock copolymer by SEC. **b**, Image of the double-jacketed 0.5 l reactor used for the high-scale synthesis. **c**, Molecular weight distributions of heptablock copolymer by SEC. **d**, Total amount of material/product obtained after six successive additions.

yellow products are typically obtained at the end of the polymerizations and, even after several purification processes (for example, dialysis, precipitation and so on), the RAFT agent and the halogen will still be present at the termini of the macromolecules.

The vast majority of the studies associated with multiblock copolymers maintain the same *DP* (or chain length) for each block. For example, the synthesis of a decablock with $DP_n \sim 10$ per block or a hexablock with $DP_n \sim 45$ per block does not necessarily mean that any combination of chain length can be incorporated into the same multiblock copolymer. At the same time, the multiblocks reported typically follow a specific pattern (for example, ABCDABCD) and thus a question arises about whether each monomer can equally support the propagation (for example, will ABCD work as well as ACBD and so on). To explore this, a gradually increasing *DP* undecablock gradient multiblock copolymer was targeted, poly(BMA$_5$-*b*-BzMA$_{10}$-*b*-EHMA$_{15}$-*b*-BMA$_{20}$-*b*-EHMA$_{25}$-*b*-EHMA$_{30}$-*b*-BzMA$_{35}$-*b*-BzMA$_{40}$-*b*-BMA$_{45}$-*b*-BMA$_{50}$-*b*-MMA$_{10}$), where the propagation of each monomer was investigated (Fig. 2d and Supplementary Tables 7 and 8). Indeed, all of the methacrylate monomers examined here were found to efficiently support the propagation, allowing the desired manipulation of the monomer sequence to yield a well-defined undecablock multiblock copolymer of $M_n \sim 42{,}000$ g mol^{-1}, with good agreement between theoretical and experimental molecular weights and narrow MWDs ($Đ \sim 1.25$, Fig. 5a,b and Supplementary Fig. 16). Note that relatively hydrophobic monomers have been used in these studies, as a certain degree of hydrophobicity is required to perform a successful emulsion polymerization; that is, an appropriate equilibrium of monomer is required in both the oil and water phases. However, for applications where hydrophilic monomers are required we envisage an inverse emulsion polymerization might alternatively be used, as well as a combination of protected and unprotected monomers for amphiphilic structures. Finally, we would like to acknowledge that although the targeted materials have been successfully obtained, as characterized by DLS, SEC and NMR, finding solid proof of the complex structure of these multiblock copolymers remains a challenge.

Conclusions

We have demonstrated that a segregation approach of emulsion polymerization is able to produce well-defined sequence-controlled macromolecules. Despite altering the sequence of the monomer composition, narrow molecular weight distributions were obtained while achieving a heneicosablock copolymer, with quantitative conversions attained throughout all the iterative monomer additions. Higher-molecular-weight multiblock copolymers could also be synthesized in a quantitative manner, which were subsequently scaled up to ~80 g, further highlighting the robustness of the technique. The absence of any transition metal or sulfur catalysts, the scalability of the process, the quantitative yields (>99%) and the high polymerization rates despite such a low activated monomer pave the way for the synthesis of a new class of macromolecular sequence-controlled materials for a wide range of applications including nanostructured

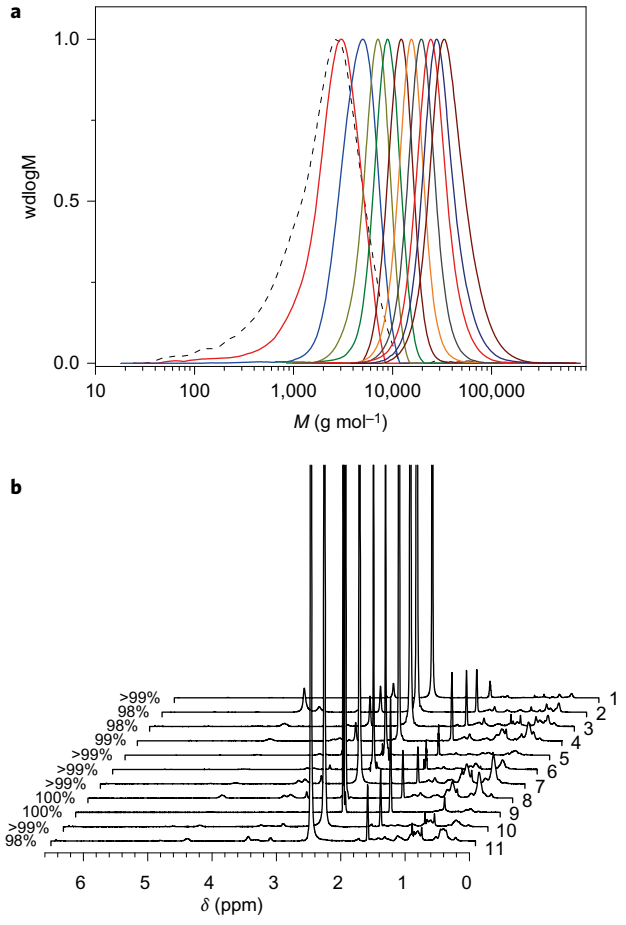

Figure 5 | Synthesis and characterization of the undecablock copolymer following various patterns obtained via consecutively switching between different monomers. a, SEC traces of the undecablock copolymer showing a clear shift towards higher molecular weights. **b**, ^{1}H NMR traces for synthesis of the undecablock copolymer following various patterns showing no remaining monomer throughout the sequential chain extensions. The copolymer consists of BMA, BzMA, EHMA and MMA at 85 °C (in a 0.5 l reactor with monomer-starved conditions) via a segregation approach of emulsion polymerization using KPS as initiator and PMMA (~2,000 g mol^{-1}) as the initial CTA.

materials, polymeric phase separation, single chain folding and drug delivery, among others.

Methods

Process for the synthesis of a PMMA macromonomer by CCTP in emulsion. In a typical CCTP in emulsion process, CoBF (7.5 mg) was placed in a 100 ml round-bottomed flask together with a stirring bar. The flask was purged with nitrogen for at least 1 h. Subsequently, MMA (20 ml, 18.72 g, 186.98 mmol), previously degassed for 30 min, was added to the flask via a degassed syringe. The mixture was vigorously stirred under an inert atmosphere until total dissolution of the catalyst. Meanwhile, 4,4′-azobis(4-cyanovaleric acid) (CVA) (0.5 g, 1.78 mmol), SDS (0.3 g, 1.04 mmol) and 130 ml water were charged into a three-neck, 500 ml double-jacketed reactor, equipped with an RTD temperature probe and an overhead stirrer. The mixture was purged with nitrogen and stirred at 325 r.p.m. for at least 30 min. Subsequently, the mixture was heated under an inert atmosphere. When the temperature in the reactor reached 70 °C, the MMA–CoBF solution was added using a degassed syringe and a syringe pump (feeding rate = 0.666 ml min^{-1}, feeding time = 30 min). When this addition was over, stirring continued for another 30 min under the same conditions. Subsequently, the heat pump settings were adjusted to 107 °C to maintain the reaction temperature at 80–82 °C and stirring continued for 60 min. M_n of the macromonomer was calculated from ^{1}H NMR spectra.

General process for the synthesis of multiblock copolymers by free-radical polymerization in emulsion. The amount of monomer to be added to the PMMA macromonomer latex was calculated according to the desired *DP*. For each addition, the volume of aqueous potassium persulfate (KPS) solution added was equal to the monomer volume. The additions were stopped and dilutions were made with water when the solid content reached values above which coagulation was very likely to occur. After every dilution, the solid content of the latex was measured (in g ml^{-1}) and the value was taken into account to calculate the amounts of reagents for the next addition cycle.

Process for chain extension of the PMMA macromonomer with BMA (DP_n = 10) by free-radical polymerization in emulsion. PMMA macromonomer latex (125 ml; 0.129 g ml^{-1}) was diluted by adding 37 ml of water to achieve 10% solid content. The resulting latex was charged in the reactor and purged with nitrogen for 30 min while stirring. The emulsion was then heated. When the temperature in the reactor reached 85–86 °C and was stable, BMA (15.9 ml, 14.22 g, 0.1 mol) and potassium persulfate aqueous solution (79.5 mg potassium persulfate in 15.9 ml of water) were added simultaneously (both having been degassed previously for 30 min) using degassed syringes and a syringe pump (feeding rate = 0.16 ml min^{-1}, feeding time = 100 min). When the addition was over, stirring was continued for another 60 min under the same conditions.

SEC. SEC analyses were performed on an Agilent 1260 SEC-MDS fitted with differential refractive index (DRI), light scattering (LS) and viscometry (VS) detectors equipped with 2 × PLgel 5 mm mixed-D columns (300 × 7.5 mm), 1 × PLgel 5 mm guard column (50 × 7.5 mm) and autosampler. Narrow linear PMMA standards in the range of 200 to 1.0 × 10^6 g mol^{-1} were used to calibrate the system. All samples were passed through a 0.45 µm PTFE filter before analysis. The mobile phase was chloroform with 2% triethylamine (flow rate of 1.0 ml min^{-1}). SEC data were analysed using Cirrus v3.3.

MALDI–TOF–MS. MALDI–TOF–MS was conducted using a Bruker Daltonics Ultra flex II MALDI–TOF–MS mass spectrometer, equipped with a nitrogen laser delivering 2 ns laser pulses at 337 nm with positive-ion TOF detection performed using an accelerating voltage of 25 kV. Solutions in tetrahydrofuran (50 µl) of 2,5-dihydroxybenzoic acid (DHB) as matrix (saturated solution), sodium iodide as cationization agent (1.0 mg ml^{-1}) and sample (1.0 mg ml^{-1}) were mixed and 0.7 µl of the mixture was applied to the target plate. Spectra were recorded in reflector mode calibrating PEG-Me 1,100 kDa.

^{1}H NMR. ^{1}H NMR spectra were recorded on a Bruker DPX-300 and HD-400 spectrometers using a mixture of deuterated chloroform and deuterated acetone (vol/vol = 3/2), both obtained from Aldrich. Chemical shifts are given in ppm downfield from the internal standard tetramethylsilane.

DLS. DLS measurements were performed on a Malvern Instruments Zetasizer Nano Series instrument with a detection angle of 173°, and the *Z*-average mean hydrodynamic diameter and the width of the particle size distribution (PSD) were obtained from analysis of the autocorrelation function. Latex (1 µl) was diluted with 1 ml of deionized water that had been filtered previously with a 0.20 µm membrane to ensure the minimization of dust and other particulates. At least three measurements were made at 25 °C for each sample, with an equilibrium time of 2 min before starting measurements.

Received 22 February 2016; accepted 2 September 2016; published online XX XX 2016

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Acknowledgements

The authors acknowledge financial support from the University of Warwick, the Australian Research Council (ARC) Centre of Excellence in Convergent Bio-Nano Science and Technology (CE140100036) and Lubrizol (to N.G.E.). D.M.H. is a Wolfson/Royal Society Research Fellow. The authors acknowledge the facilities and personnel (A.A., M.R.W., T.P.D. and D.M.H.) enabled by the Monash–Warwick Alliance.

Author contributions

A.A., D.M.H. and T.P.D. conceived and designed the experiments. N.G.E. and A.A. performed the experiments. N.G.E., A.A. and V.N. analysed the data. A.A. and N.G.E. co-wrote the paper. All authors discussed the results and commented on the manuscript. A.A. and N.G.E. contributed equally to this work. Q21

Additional information

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Competing financial interests

The authors declare no competing financial interests.

nchem.2634 Table of Contents summary

Achieving sequence control in a synthetic polymer is more challenging and time consuming than it is for biopolymers. Now, it has been shown that the synthesis of sequence-controlled multiblock copolymers can be carried out via emulsion polymerization. This approach is environmentally friendly and yields complex multiblock materials with low dispersity and high yields.