Concurrent control over sequence and dispersity in multiblock copolymers

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Abstract

Controlling monomer sequence in synthetic macromolecules is a major challenge in polymer science and the order of building blocks has already been demonstrated to determine macromolecular folding, self-assembly and fundamental polymer properties. Dispersity is another key parameter in material design, with both low and high dispersity polymers displaying complementary properties and functions. However, synthetic approaches that can simultaneously control both sequence and dispersity remain experimentally unattainable. Here we report a simple, one pot, and rapid synthesis of sequence-controlled multiblocks with on demand control over dispersity while maintaining high livingness, excellent agreement between theoretical and experimental molecular weights and quantitative yields. Key to our approach is the regulation in chain transfer agent activity during controlled radical polymerization that enables the preparation of multiblocks with gradually ascending ($Đ$=1.16 →1.60), descending ($Đ$=1.66 →1.22), alternating low and high dispersity values ($Đ$=1.17 →1.61 →1.24 →1.70 →1.26) or any combination thereof. The enormous potential of our methodology was further demonstrated through the impressive synthesis of highly ordered pentablock, octablock and decablock copolymers yielding the first generation of multiblocks with concurrent control over both sequence and dispersity.

Introduction

The preparation of synthetic macromolecules with ordered monomer sequences has been a long-standing challenge in polymer chemistry.[1-6] Although natural polymers such as DNA and proteins are precisely constructed at the cellular level with perfect monomer sequence, synthetically this level of precision remains largely unaccomplished. Undoubtedly, solid-state peptide synthesis (Merrifield synthesis) has been a significant breakthrough.[7] However, the inherent limitations of this method (e.g. time-consuming, high cost, low yields, limited scalability, access only to lower molecular weight materials) have urged polymer chemists to seek alternatives in a homogeneous liquid phase. As such, a range of chemical approaches have emerged that can access sequence-controlled or sequence-defined materials at a larger scale including single monomer insertion,[8] segregating templating,[9,10] kinetic control,[11] tandem monomer addition and modification[12] and solution polymerization.[13,14]

Controlled radical polymerization has also made a significant step towards this goal through the synthesis of sequence-controlled multiblock copolymers yielding complex structures with unlimited variations in chain length, composition and encoded information.[3,15] Importantly, the synthesis of sequence-controlled multiblocks is scalable, applicable to higher molecular weight polymers and amenable to non-experts, in particular when combined with simple and one pot processes that do not necessitate the use of any specialized equipment.[3] Such materials have already shown great promise in a range of applications where sequence has been demonstrated to determine fundamental polymer properties and applications (e.g. macromolecular folding, phase separation, antimicrobial materials, etc.).[16-23] Owing to these advantages, the groups of Hawker, Matyjaszewski, Boyer, Whittaker, Haddleton, Junkers and Perrier have reported the remarkable synthesis of sequence-controlled multiblocks.[20,24-38] For instance, Whittaker and co-workers first reported the synthesis of high-order multiblocks via iterative Cu(0)-mediated radical polymerization while omitting the need for purification between the iterative block formation steps.[27] Junkers showed that photo-ATRP (atom transfer radical polymerization) could also enable the synthesis of well-defined multiblocks in the absence of dye sensitizers or photoinitiators.[33] Perrier and co-workers revolutionized RAFT (reversible addition-fragmentation chain-transfer) polymerization by demonstrating that a large number of multifunctional multiblocks could be possible if high livingness could be ensured during each block addition.[36,39] However, a significant limitation of all previous strategies is that they are incapable of simultaneously controlling both polymer sequence and dispersity. This is due to inherent limitations of controlled radical polymerization which enforce the synthesis of multiblock copolymers with gradually increasing dispersities as a result of the accumulation of dead chains and loss of the end-group fidelity. Indeed, in both ATRP and RAFT methodologies, although the first block can be synthesized with a low dispersity value, a gradual low and high molecular weight tailing/shoulder appears during the subsequent monomer additions, thus yielding multiblocks with much higher dispersity values and loss of control over both dispersity and livingness.[29,33] This phenomenon is further accentuated during the synthesis of higher molecular weight multiblocks (DP ~100 per block) which are accompanied by an even greater loss of control over dispersity and end-groups.[39,40] Therefore, on demand tuning dispersity of sequence-controlled multiblock copolymers remains unattainable.

However, dispersity is a key parameter in polymer design and can significantly influence material properties (e.g. bulk and solution self-assembly, mechanical and rheological behaviour, etc.).[41-43] In fact, both high and low dispersity polymers exhibit complementary properties and functions and this encouraged many groups to pioneer a number of strategies whereby precise control over the dispersity could be achieved.[44,45] For instance, the Fors group elegantly exploited a modular strategy which controls the temporal regulation of initiation during chain growth polymerization while Matyjaszewski and co-workers leveraged the catalyst concentration to govern the molecular weight distributions.[46-51] Despite the tremendous importance of dispersity in polymer science, the synthesis of sequence-controlled multiblocks with tuneable dispersity remains a formidable challenge and is far from being realised. This is because high dispersity polymers are often associated with increased terminations and side reactions which prevent the successful addition of subsequent blocks. A few recent breakthroughs allowed for the synthesis of high dispersity polymers with minimal termination, thus promoting the preparation of diblock copolymers.[44,45] However, full control over the dispersity even in diblock copolymers remains severely restricted due to inherent limitations of the reported synthesis approaches. For instance, the use of mixtures of RAFT agents can accurately control the dispersity of homopolymers but this level of control cannot be extended to diblock copolymers.[52] In a similar vein, using low deactivator concentrations enabled the synthesis of polymers with variable dispersities, but even a low to high dispersity diblock is currently unattainable.[53,54] Collectively, these constraints hinder the development of sequence-controlled multiblock copolymers with on demand control over dispersity.

Results and Discussion

To address these limitations, we envisioned that the use of a single RAFT agent that can on-demand switch its activity (e.g. from low to high and vice versa) would enable the synthesis of sequence-controlled multiblocks where the dispersity can be controlled throughout the addition of each building block. Switchable RAFT agents have been previously developed as universal RAFT agents to provide access to low dispersity materials from either activated or less activated monomers.[55-57] In contrast, to realize our concept, we hypothesized that, for a certain monomer class, switchable RAFT agents can transition “in-situ” from a low to a high activity RAFT agent (or vice versa) by simply adjusting the amount of added acid (or base), thus enabling full control over the dispersity in highly ordered sequence-controlled multiblock copolymers (Figure 1 & Supplementary Scheme 1).

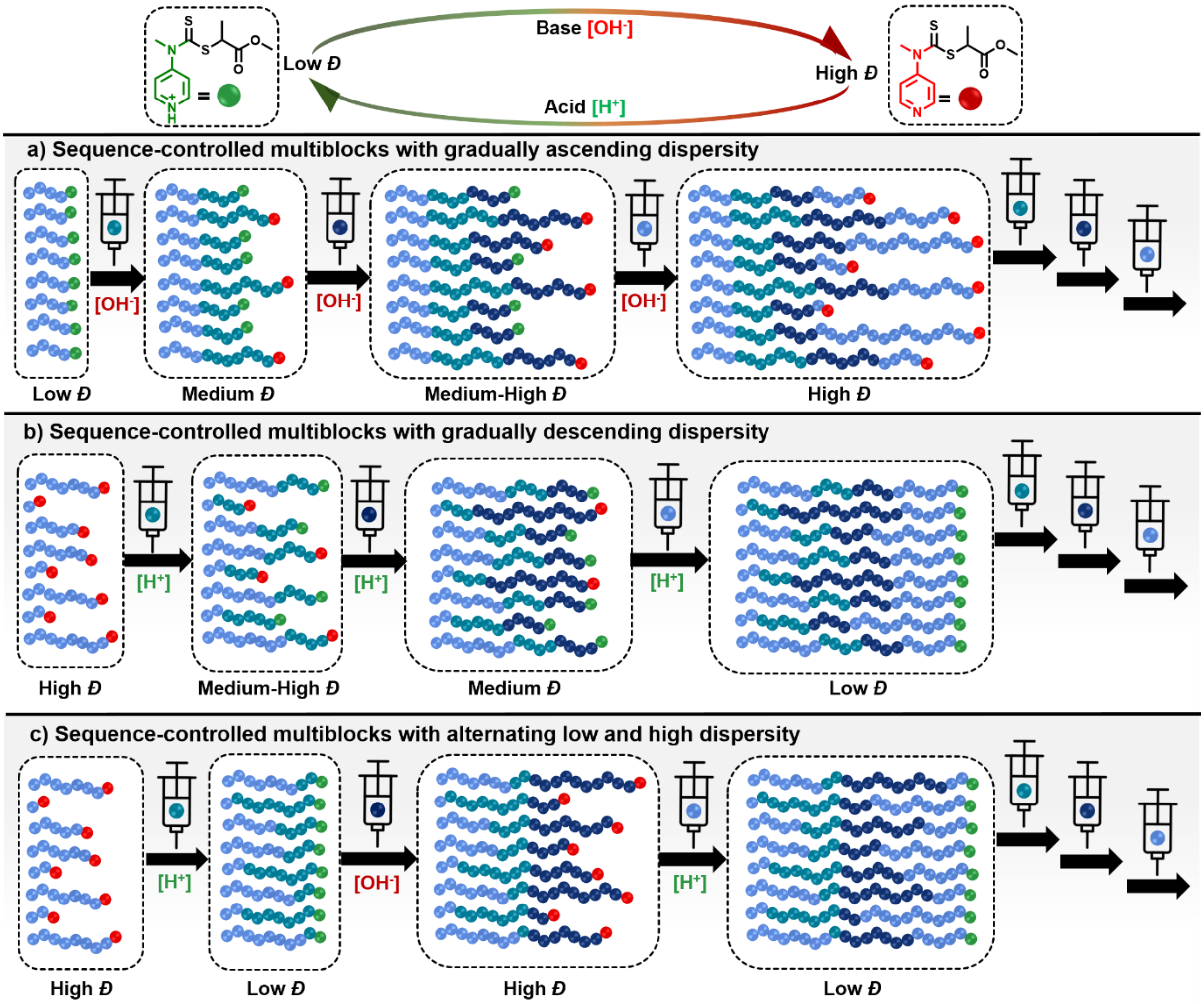

Figure 1. Schematic representation of our proposed approach for the preparation of multiblocks with tuneable dispersity. In **a,** the addition of base results in gradual deprotonation of the chain transfer agent yielding multiblock copolymers with incremental increases in dispersity. In **b,** the addition of acid results in a gradual protonation of the CTA yielding multiblock copolymers with incremental decreases in dispersity. In **c**, the addition of acid and base yields multiblock copolymers with alternating high and low dispersity blocks, respectively.

To first demonstrate this concept, we utilized dimethyl acrylamide (DMA) as the model monomer, methyl 2-[methyl(4-pyridinyl)carbamothioylthio]propionate as the switchable RAFT agent, and 2,2'-azobis(2-methylpropionitrile) (AIBN) as the free radical initiator (0.1 equivalents with respect to the RAFT agent) in DMF. In the absence of added acid (i.e. fully deprotonated RAFT agent), a broad, yet monomodal, molecular weight distribution (M_n=17500, $Đ$=1.67) could be obtained when targeting DP=200 (Supplementary Table 1 Entry 1 & Supplementary Figure 1). Importantly, and despite the high dispersity, nearly perfect agreement between the theoretical and experimental molecular weights was observed at high conversions, as measured by nuclear magnetic resonance (^{1}H NMR, Supplementary Figure 2).

This is in contrast to previous methodologies, where higher $Đ$ polymers were accompanied by very low conversions (~20%) and a significant deviation between theoretical and experimental values, as a result of slow initiation.[54] By repeating the experiment, albeit in the presence of a small amount of sulphuric acid (SA, 1 μL, 18M), the $Đ$ was decreased to 1.50 while maintaining a unimodal shape (Supplementary Table 1 Entry 2 & Supplementary Figure 1). Further increase in the amount of added SA (2 μL, 3.5 μL and 8 μL, 18M), led to significantly lower $Đ$s yielding PDMA with a $Đ$ of 1.42, 1.29 and 1.18 respectively (Supplementary Table 1 Entries 3-5 & Supplementary Figure 1). As a result, a range of targeted monomodal molecular weight distributions (M_n ~17300-17500, $Đ$=1.18-1.67) at very high monomer conversions could be successfully obtained while also possessing identical end-groups (either in the protonated or deprotonated form). This is a significant improvement over previous strategies where employing RAFT agent's mixtures led to vastly different end-groups or the addition of comonomers and termination agents led to adulterated polymer chains and chains without functional end-groups, respectively.[45,52,58] These results suggest that the activity of the RAFT agent used can be modulated by increasing or decreasing the electron withdrawing capacity of the pyridine group via protonation or deprotonation of the aromatic amine, respectively (Figure 1).

These initial data encouraged us to demonstrate the concept of tailoring polymer dispersity in sequence-controlled multiblocks by modulating the activity of the RAFT agent in each iterative block formation step. The first target was a sequence-controlled pentablock copolymer with gradually descending $Đ$s via sequential additions of individual aliquots from a palette of three different acrylamide-based monomers. The initial ratio of [RAFT Agent]:[VA-044 (2,2'-Azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride)] was optimized at 1:0.034 and experiments were performed at 70 ℃ in aqueous solutions with the addition of organic solvent (DMF, 20% v/v) to allow for the complete solubility of the RAFT agent. Under these conditions, the first poly(4-acryloylmorpholine) (PNAM) block was obtained at near quantitative conversion (98%) as characterized by ^{1}H NMR yielding a homopolymer with a broad molecular weight distribution (M_n=12000, $Đ$=1.66) and good agreement between experimental and theoretical molecular weight (Figures 2a-c & Supplementary Table 2 Entry 1). Upon addition of the second monomer (DMA) together with a small amount of SA (0.65 µL, 18M), a gradual decrease in the $Đ$ of the diblock (M_n=22200, $Đ$=1.50) was evident. This was accompanied with a clear shift to higher molecular weights, without any visible trace of high or low molecular weight shouldering, which would indicate potential termination events (Figure 2a-c & Supplementary Table 2 Entry 2). The decrease in the $Đ$ was attributed to the addition of the acid and the partial protonation of the RAFT agent, as in the absence of acid an equally high $Đ$ could be maintained for a diblock or even a pentablock (Supplementary Table 3 & Supplementary Figures 3-5). When full conversion was reached, another aliquot of acid (1.5 µL) was subsequently injected together with the third monomer diethyl acrylamide (DEA) yielding a triblock with a further decrease in the dispersity (M_n=33600, $Đ$=1.41, Supplementary Table 2 Entry 3). This process was repeated two more times while gradually increasing the amount of the added acid alongside the sequential monomer additions, yielding a tetrablock (2.0 µL SA, M_n=45600) and a pentablock (3.8 µL SA, M_n=65300) copolymer with $Đ$=1.34 and $Đ$=1.22 respectively (Figures 2a-c, Supplementary Table 2 Entries 4-5 & Supplementary Scheme 2a). Importantly, this is the first example of sequence-controlled multiblock copolymers with gradually descending $Đ$s and contrasts all previously reported examples where a gradual increase in the dispersity could only be achieved as a result of the gradual accumulation of dead polymer chains often resulting in the loss of the unimodal shape.[29,30,33,39] However, in our system very little tailing can be observed showing minimized termination events while we can also maintain monomodal distributions.

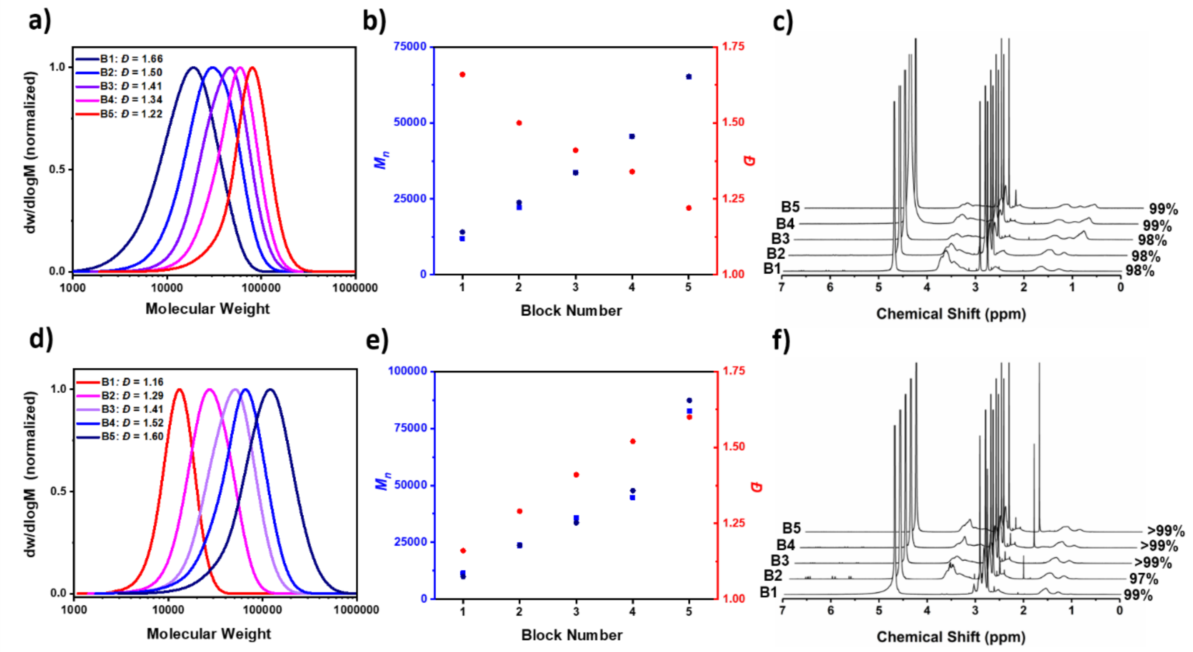

Figure 2. Pentablock copolymers with gradually evolving dispersity. a, SEC traces illustrating the molecular weight distributions for consecutive cycles during the synthesis of a descending dispersity pentablock copolymer. **b** Evolution of dispersity (red) and the measured molecular weight (light blue) compared to theoretical (dark blue) during this multiblock synthesis. **c**, ^{1}H NMR spectra for each cycle, illustrating the monomer conversion for each block (≥ 96% in all cases). **d**, SEC traces illustrating the molecular weight distributions for consecutive cycles during the synthesis of an ascending dispersity pentablock copolymer. **e**, Evolution of dispersity (red) and the measured molecular weight (light blue) compared to theoretical (dark blue) during this multiblock synthesis. **f**, ^{1}H NMR spectra for each cycle, illustrating the monomer conversion for each block (≥ 96% in all cases).

The reverse scenario was then attempted aiming at a sequence-controlled multiblock with gradually ascending *Đ*s. For this purpose, PDMA with a narrow molecular weight distribution was first prepared (M_n=11500, *Đ*=1.16, Figures 2d-f & Supplementary Table 4 Entry 1) by employing an excess of sulphuric acid. To incrementally increase the *Đ*, four subsequent monomer additions were performed where the amount of added base (sodium hydroxide) was slowly increased. ^{1}H NMR spectroscopy confirmed high monomer conversions in all steps yielding higher ordered multiblocks with continuously increased *Đ*s (*Đ*$_{\mathrm{Homopolymer}}$=1.16, *Đ*$_{\mathrm{Diblock}}$=1.29, *Đ*$_{\mathrm{Triblock}}$=1.41, *Đ*$_{\mathrm{Tetrablock}}$=1.52 and *Đ*$_{\mathrm{Pentablock}}$=1.60, Figures 2d-f, Supplementary Table 4 Entries 2-5 & Supplementary Scheme 2b). Importantly, the pentablock copolymer retained a monomodal shape indicating negligible termination as opposed to previous work where the increase in *Đ* was only possible through consecutive termination events, as evident by the large extent of low and high molecular weight shoulders.

The next challenging step towards the synthesis of sequence-controlled multiblocks with tailored *Đ*s was to achieve full control over the *Đ* in multiblock copolymers where any *Đ* combination could be feasible. To achieve this ambitious target, we first aimed to synthesize three diblock extremes with; (i) high *Đ* for both the homopolymer and the diblock, (ii) high *Đ* for the homopolymer and low *Đ* for the diblock and (iii), low *Đ* for the homopolymer and high *Đ* for the diblock with the later one being particularly challenging for any reported methodology (Figure 3a).[42] For all the diblock experiments, DMA and NAM were used as the monomers. A crucial factor was to ensure very high monomer conversions (99%) for the first block in order to assess the suitability of our system to afford the synthesis of "*in-situ*" diblocks. PNAM with *Đ*=1.60 was initially synthesized as previously stated through the use of the deprotonated RAFT agent (no acid was added, Figure 3b & Supplementary Table 5 Entry 1). Upon driving the polymerization to completion (>99%), DMA was subsequently added yielding a well-defined diblock copolymer with a comparably high dispersity (M_n=12000 *Đ*=1.66, Figure 3b & Supplementary Table 5 Entry 2). This data strongly suggests that despite the high *Đ* of the first block (resembling values typically acquired in free radical polymerization), it can however maintain high livingness and high dispersity allowing for *in-situ* formation of block copolymers. Moreover, when the second monomer was added together with an excess of SA to ensure full protonation of the RAFT agent, the final diblock copolymer presented a much lower *Đ*=1.19 while fully shifting to higher molecular weights, thus further highlighting the high livingness maintained in our system (Figure 3c & Supplementary Table 5 Entries 3-4). Last but not least, PDMA with low *Đ*=1.16 was also synthesized by complete protonation of the RAFT agent. This time, together with the second monomer an excess of a base (sodium hydroxide) was also injected yielding P(DMA-*b*-NAM) with *Đ*=1.58 (Figure 3d & Supplementary Table 5 Entries 5-6). It should be highlighted that the later example has never been synthesized by any controlled radical polymerization methodology and would be fundamentally incompatible with already developed strategies such as the use of a mixture of RAFT agents or when employing ppm concentrations of copper.[52,54] It is also noted that all the chain extensions were performed *in-situ* at near-quantitative conversion, in contrast to previous methods where the isolation of the macroinitiator was essential.[46,54] Altogether, our proposed approach allows full control over dispersity of both homopolymers and diblock copolymers.

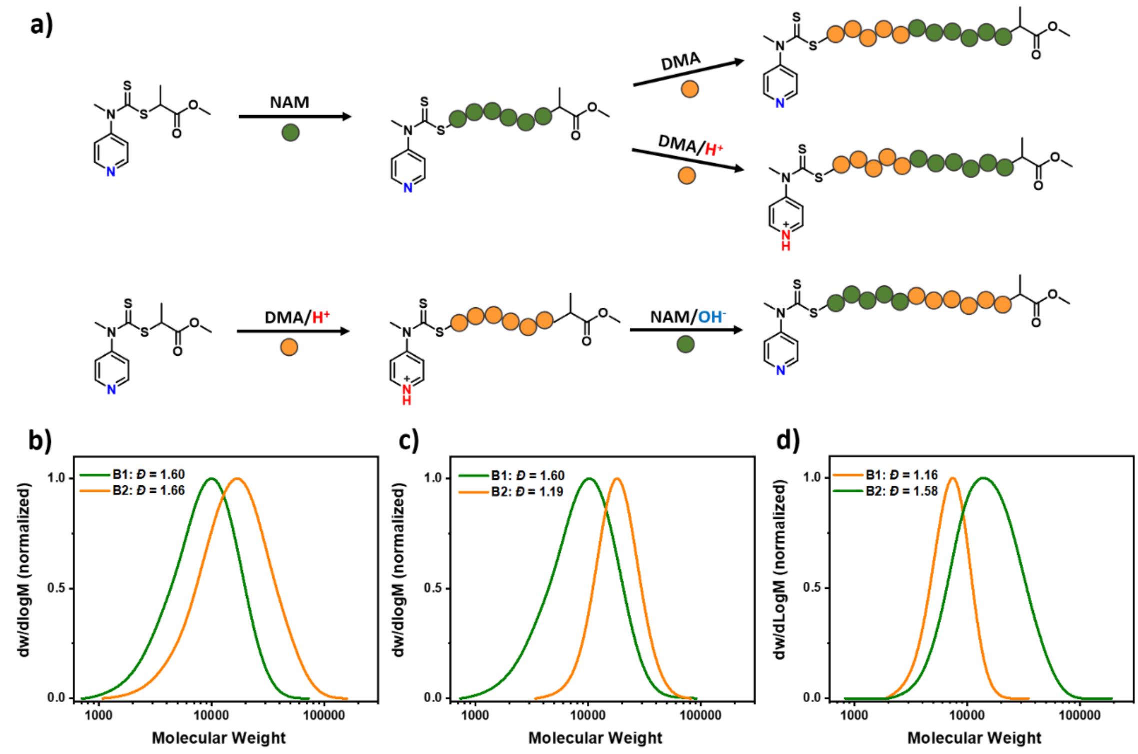

Figure 3. Diblock copolymers synthesised with dispersity value extremes by switching the activity of the RAFT agent. a, scheme illustrating the preparation of high to high dispersity, high to low dispersity and low to high dispersity diblocks directly corresponding to the SEC traces in **b**, **c** and **d**.

To demonstrate the versatility of our approach and achieve the ambitious goal of on-demand control over the dispersity of multiblocks, a considerably challenging multiblock copolymer was designed. In particular, an "extreme" pentablock copolymer was set as the goal, where low and high *Đ* values would alternate throughout the iterative monomer additions. In the presence of an excess of sulphuric acid, a low *Đ* PDMA homopolymer was prepared (M_{n}=5200, *Đ*=1.17, Figures 4a-c & Supplementary Table 6 Entry 1). When near-quantitative conversion was ensured (>96%), the second monomer and an excess of sodium hydroxide were subsequently injected in order to obtain a much higher *Đ* for the diblock (M_{n}=11500, *Đ*=1.61, Figures 4a-c

& Supplementary Table 6 Entry 2). The inclusion of the third monomer in the reaction mixture was accompanied with a high dosage of acid and as a result the triblock copolymer reached a low dispersity value (M_n=25900, $Đ$=1.24, Figures 4a-c & Supplementary Table 6 Entry 3). By alternating the addition of base and acid together with the subsequent monomer injections, tetrablock and pentablock copolymers could be prepared in a facile manner with $Đ$=1.70 (M_n=45400) and $Đ$=1.26, (M_n=88400) respectively (Figures 4a-c, Supplementary Table 6 Entries 4-5 & Supplementary Scheme 2c). The reverse multiblock copolymer was also possible by switching between fully basic and fully acidic conditions throughout the monomer additions ($Đ_{\mathrm{Homopolymer}}$=1.52, $Đ_{\mathrm{Diblock}}$=1.21, $Đ_{\mathrm{Triblock}}$=1.52 and $Đ_{\mathrm{Tetrablock}}$=1.25) and the final pentablock copolymer presented a dispersity of 1.52 (M_n=74600) and a fairly unimodal shape (Figures 4d-f, Supplementary Table 7 Entries 1-5 & Supplementary Scheme 2d). Our experiments confirm that we can achieve on demand control over the dispersity in sequence-controlled multiblock copolymers. Another important highlight of our work is that we can prepare such complex materials while at the same time reaching relatively high molecular weights. It is widely accepted within the polymer community that the higher the molecular weight of the final multiblock copolymer, the harder it is to control the dispersity while maintaining a monomodal molecular weight distribution; yet our system presents fairly small amounts of termination and maintains monomodality.

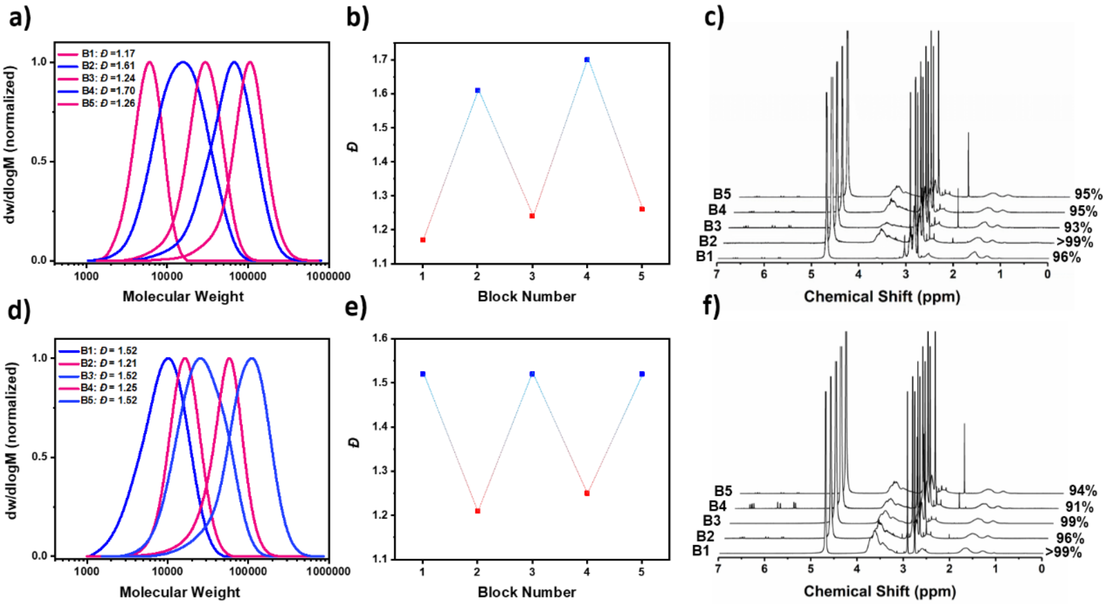

Figure 4. Pentablock copolymers synthesised with dispersity extremes. a, SEC traces illustrating the molecular weight distributions for consecutive cycles during the synthesis of an alternating high and low dispersity pentablock copolymer. **b,** Dispersity evolution during this multiblock synthesis. **c,** SEC traces illustrating the molecular weight distributions for consecutive cycles during the synthesis of an alternating low and high dispersity pentablock copolymer. **d,** Dispersity evolution during this multiblock synthesis.

Excited by this data, we then targeted even higher-ordered multiblock copolymers consisting of further variations in dispersity and also a larger number of blocks. First, we targeted a decablock copolymer. Under acidic conditions, the first block was synthesized with a low initial Đ value (Đ=1.15, Figures 5a-c & Supplementary Table 8 Entry 1). By switching to basic conditions together with the next monomer addition (deprotonated RAFT agent), the chain extension yielded a diblock copolymer with a clear shift to higher molecular weights and a much higher value (Đ=1.62, Figures 5a-c & Supplementary Table 8 Entry 2). For the next three monomer additions, a small amount of acid was injected thus leading to the preparation of triblock, tetrablock and pentablock copolymers with lower dispersities (Đ$_{\text{Triblock}}$=1.49, Đ$_{\text{Tetablock}}$=1.40 and Đ$_{\text{Pentarablock}}$=1.35, respectively, Figures 5a-c & Supplementary Table 8 Entries 3-5). We then aimed to hold the dispersity at ~1.35 and to do so, no additional acid or base was added for the next four blocks. Indeed, the hexablock, heptablock, octablock and nonablock copolymers presented a value at around ~1.35 (Đ$_{\text{Hexablock}}$=1.35, Đ$_{\text{Heptablock}}$=1.33, Đ$_{\text{Octablock}}$=1.35 and Đ$_{\text{Nonablock}}$=1.37 respectively, Figures 5a-c & Supplementary Table 8 Entries

6-9). For the last block, a protonation of the RAFT agent was attempted leading to a decablock copolymer with a final dispersity of 1.27 (Figures 5a-c, Supplementary Table 8, Entry 10 & Supplementary Scheme 2g). Similarly, an octablock copolymer could be prepared where high dispersity was maintained for the last seven blocks ($Đ_{\mathrm{Homopolymer}}$=1.15, $Đ_{\mathrm{Diblock}}$=1.57, $Đ_{\mathrm{Triblock}}$=1.54, $Đ_{\mathrm{Tetrablock}}$=1.53, $Đ_{\mathrm{Pentablock}}$=1.57, $Đ_{\mathrm{Hexablock}}$=1.53, $Đ_{\mathrm{Heptablock}}$=1.53 and $Đ_{\mathrm{Octablock}}$=1.52), further illustrating the versatility of our system (Supplementary Figure 6, Supplementary Table 9 & Supplementary Scheme 2e). Aside from the good control over the dispersity accomplished, all additions were accompanied by a satisfactory shift to higher molecular weights (confirmed by SEC) and near-quantitative conversions (>95%). It is also noted that for all syntheses the minimum targeted DP per block was set at 15 in order to substantially minimize the defective chains in the final multiblock copolymer, as elegantly demonstrated by Harrisson and co-workers.[59] A second high-order multiblock copolymer was also targeted. This time, the first block was designed to possess high dispersity and this could be achieved in the absence of acid ($Đ$=1.61, Figures 5d-f & Supplementary Table 10 Entry 1). The subsequent five blocks were designed to have gradually descending dispersities. To achieve this, an increase amount of acid was injected together with the subsequent monomer addition thus eventually producing a hexablock copolymer with $Đ$=1.24 (Full dispersity evolution: $Đ_{\mathrm{Homopolymer}}$=1.61, $Đ_{\mathrm{Diblock}}$=1.52, $Đ_{\mathrm{Triblock}}$=1.43, $Đ_{\mathrm{Tetrablock}}$=1.37, $Đ_{\mathrm{Pentablock}}$=1.32 and $Đ_{\mathrm{Hexablock}}$=1.24, Figures 5d-f & Supplementary Table 10 Entries 2-6). Low dispersity could be maintained for subsequent blocks by neither addition of acid nor base (Supplementary Figure 7, Supplementary Table 11 & Supplementary Scheme 2f) but our goal was to gradually increase the dispersity for the next three blocks. By adding a gradually increasing amount of base along with the monomer injections, heptablock, octablock and nonablock copolymers with gradually increasing dispersities could be prepared ($Đ_{\mathrm{Heptablock}}$=1.29, $Đ_{\mathrm{Octablock}}$=1.38 and $Đ_{\mathrm{Nonablock}}$=1.52, Figures 5d-f & Supplementary Table 10 Entries 7-9). As a final goal, we applied acidic conditions when the final batch of monomer was added, in order to again decrease the dispersity to 1.26 for the decablock copolymer (Figures 5d-f, Supplementary Table 10 Entry 10 & Supplementary Scheme 2h). Taken all together, complex decablock copolymers can be rigorously synthesized with control over the dispersity achieved in all addition steps. Again, high monomer conversions were maintained throughout the synthesis. By carefully adjusting the amount of acid and base, the dispersity of every block can be targeted on demand, thus significantly increasing accessible multiblock copolymers.

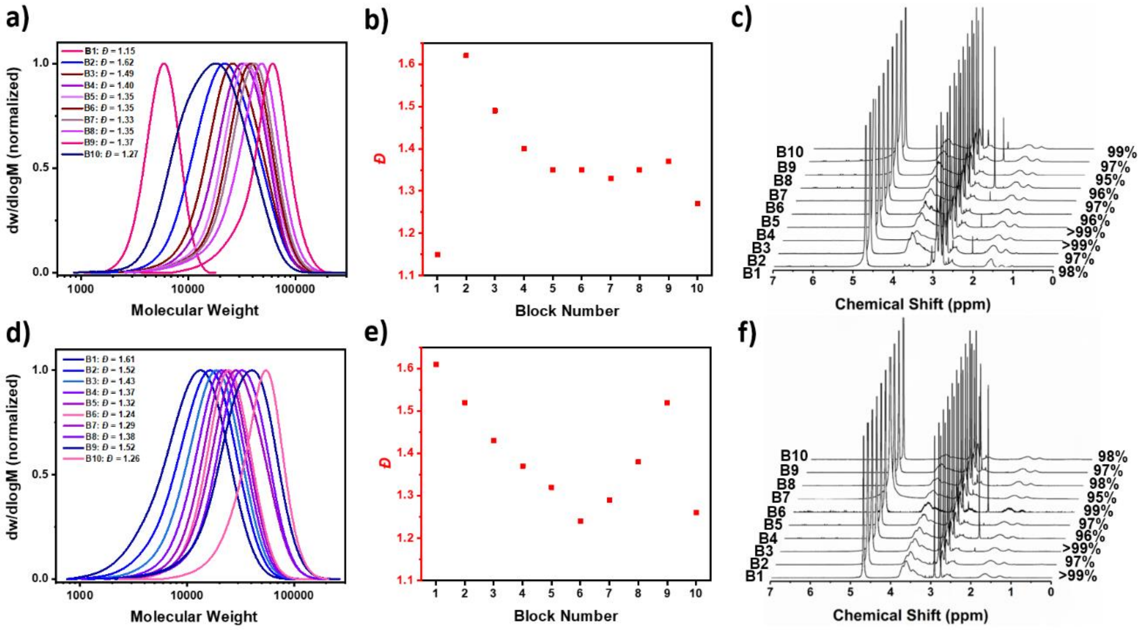

Figure 5. Decablock copolymers synthesised with tunable dispersity. a, SEC traces illustrating the molecular weight distributions for consecutive cycles during the synthesis of a decablock copolymer. In block 1, a high dispersity polymer is prepared, followed by targeted decreases and increases in the dispersity of subsequent blocks on addition of acid or base. **b**, The controlled evolution of dispersity during this multiblock synthesis. **c**, ^{1}H NMR spectra for each cycle, illustrating the monomer conversion for each block (≥95% in all cases). **d**, SEC traces illustrating the molecular weight distributions for consecutive cycles during the synthesis of a decablock copolymer. In block 1, a low dispersity polymer is prepared, followed by targeted increases and decreases in the dispersity of subsequent blocks on addition of acid or base. **e**, The controlled evolution of dispersity during this multiblock synthesis. **f**, ^{1}H NMR spectra for each cycle, illustrating the monomer conversion for each block (≥95% in all cases).

Conclusions

To summarize, we have reported a new generation of sequence-controlled multiblock copolymers with on demand control over dispersity. A number of multiblock copolymers could be efficiently synthesized with gradual increasing and gradual decreasing dispersities, alternating dispersities or any combination thereof. This breakthrough was achieved by regulating the chain transfer activity of a RAFT agent through the simple addition of acid or base together with the new monomer additions. Despite full control over the dispersity, very little termination could be observed in the SEC chromatographs while near-quantitative conversions could be achieved throughout the iterative block formations and near-perfect match between theorical and experiemental molecular weights was observed. We believe that this new concept will open the door for the synthesis of advanced sequence-controlled materials that can be then used in various applications including phase-separation, rheology, macromolecular folding and drug delivery.

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Methods

See supplementary information for detailed methods and protocols

Synthesis of a pentablock copolymer from a high *Đ* first block (descending in dispersity)

Into a 4 mL glass vial, 7.70 mg of methyl 2-[methyl(4-pyridinyl)carbamothioylthio]propionate (CTA, 28.5 μmol, 1 equiv.) were dissolved in 0.29 mL of DMF. A stock solution of VA-044 (6.2 mg) was prepared in 10 mL of water, and 500 μL of this solution (0.32 mg, 0.96 μmol, 0.034 equiv.) were transferred to the vial. Subsequently, 0.36 mL of N-acrylomorpholine (0.40 g, 2.85 mmol, 100 equiv., 20% solution v/v in 80:20 H_2O:DMF), 0.65 mL of distilled water and a stirrer bar were added. The vial was then sealed with a septum, prior to deoxygenation by nitrogen bubbling for 15 minutes. Polymerization was conducted in an oil bath at 70°C for 2 h with a 200-rpm stirring rate to reach a conversion of >95% by ^{1}H NMR. In a separate vial, 0.30 ml of DMA (0.29 g, 2.85 mmol, 100 equiv., 20% solution v/v in 80:20 H_2O:DMF), 0.65 µL of sulphuric acid (11.7 µmol, 18 M, 0.41 equiv.) and 175 µL of initiator solution (0.11 mg, 0.34 µmol, 0.0118 equiv.) were mixed and degassed together for 15 minutes prior to addition to the polymerization mixture via a nitrogen purged syringe. Polymerization was again conducted for 2 h, yielding a lower dispersity second block. This process was repeated for all subsequent block to gradually decrease the dispersity. In block 3, 1.5 µL (27.1 µmol, 18 M, 0.95 equiv.) of sulphuric acid solution was added along with 0.39 mL of DEA (0.36 g, 2.85 mmol, 100 equiv., 20% solution v/v in 80:20 H_2O:DMF) and 160 µL of initiator solution (0.10 mg, 0.31 µmol, 0.0108 equiv.). In block 4, 0.36 mL of NAM (0.40g, 2.85 mmol, 100 equiv., 20% solution v/v in 80:20 H_2O:DMF), 2 µL (35.9 µmol, 18 M, 1.26 equiv.) of sulphuric acid solution and 130 µL (0.08 mg, 0.25 µmol, 0.0088 equiv.) of initiator solution were added and for block 5, 0.6 mL of DMA (0.58 g, 5.7 mmol, 200 equiv., 20% solution v/v in 80:20 H_2O:DMF), 3.75 µL of sulphuric acid solution (67.8 µmol, 18 M, 2.37 equiv.) and 210 µL (0.13 mg, 0.40 µmol, 0.0141 equiv.) of initiator stock solution were added to the reaction. This procedure corresponds to the data in Figures 2a-2c and Supplementary Table 2.

Synthesis of a decablock copolymer from a low *Đ* first block

Into a 10 mL glass vial, 7.70 mg of methyl 2-[methyl(4-pyridinyl)carbamothioylthio]propionate (CTA, 28.5 μmol, 1 equiv.) were dissolved in 0.15 mL of DMF. A stock solution of VA-044 (6.2 mg) was prepared in 10 mL of water, and 0.15 mL of this solution (0.093 mg, 0.288 μmol, 0.0102 equiv.) was transferred to the vial. Subsequently, 0.15 mL (0.14 g, 1.43 mmol, 50 equiv.) of DMA, 2.5 µL (46 µmol, 18 M, 1.60 equiv.) of sulphuric acid, 0.4 mL of distilled water and a stirrer bar were added. The vial was then sealed with a septum, prior to deoxygenation by nitrogen bubbling for 15 minutes. Polymerization was conducted in an oil bath at 70°C for 1.5 h with a 200-rpm stirring rate to reach a conversion >95% measured by ^{1}H NMR (*Đ* = 1.15). In a separate vial, 0.18 mL of NAM (0.20 g, 1.43 mmol, 50 equiv., 20% solution v/v in 80:20 H_2O:DMF), 163 µL (0.101 mg, 0.31 µmol, 0.0110 equiv.) of initiator solution and 32.5 µL of sodium hydroxide (55.3 µmol, 1.7 M, 1.94 equiv.) were mixed and degassed together for 15 minutes prior to addition to the polymerization mixture via a nitrogen purged syringe. Polymerization was again conducted for 1.5 h, yielding a high dispersity second block (*Đ* = 1.62). This process was repeated for all subsequent block additions. First the dispersity was incrementally lowered between blocks 3 and 5. In block 3, 1.5 µL (27.1 µmol, 18M, 0.95 equiv.) of sulphuric acid, 62.5 µL (0.039 mg, 0.12 µmol, 0.0042 equiv.) of initiator solution and 90 µL of DMA (0.087 g, 0.86 mmol, 30 equiv., 20% solution v/v in 80:20 H_2O:DMF) were added. In block 4, 1.0 µL (18.0 µmol, 18M, 0.63 equiv.) of sulphuric acid, 37.5 µL (0.023 mg, 0.072 µmol, 0.0025 equiv.) of initiator solution and 90 µL of NAM (0.1 g, 0.72 mmol, 25 equiv., 20% solution v/v in 80:20 H_2O:DMF) were added. In block 5, 0.5 µL (9.1 µmol, 18M, 0.32 equiv.) of sulphuric acid, 50 µL (0.031 mg, 0.096 µmol, 0.0034 equiv.) of initiator solution and 60 µL of DMA (0.058 g, 0.57 mmol, 20 equiv., 20% solution v/v in 80:20 H_2O:DMF) were added. This yielded dispersity values of 1.49, 1.40, and 1.35, respectively. Next, in the following four blocks neither acid nor base was added so to keep dispersity constant. In block 6, 25 µL (0.016 mg, 0.048 µmol, 0.0017 equiv.) of initiator solution and 54 µL of NAM (0.060 g, 0.43 mmol, 15 equiv., 20% solution v/v in 80:20 H_2O:DMF) were added. In block 7, 50 µL (0.031 mg, 0.096 µmol, 0.0034 equiv.) of initiator solution and 44 µL of DMA (0.042 g, 0.43 mmol, 15 equiv., 20% solution v/v in 80:20 H_2O:DMF) were added. In block 8, 25 µL (0.016 mg, 0.048 µmol, 0.0017 equiv.) of initiator solution and 54 µL of NAM (0.060 g, 0.43 mmol, 15 equiv., 20% solution v/v in 80:20 H_2O:DMF) of NAM were added. In block 9, 22 µL (0.014 mg, 0.043 µmol, 0.0015 equiv.) of initiator solution and 88 µL of DMA (0.084 g, 0.86 mmol, 30 equiv., 20% solution v/v in 80:20 H_2O:DMF) were added. This yielded dispersity values of 1.35, 1.33, 1.35 and 1.37, respectively. In the final block, 5.0 µl of sulphuric acid (90.1 µmol, 18 M, 3.16 equiv.), 0.25 mL (0.155 mg, 0.48 µmol, 0.0168 equiv.) of initiator solution and 0.32 mL (0.36 g, 2.16 mmol, 90 equiv., 20% solution v/v in 80:20 H_2O:DMF) of NAM were added, yielding a decablock copolymer with a final dispersity of 1.27. This procedure corresponds to the data in Figures 5a-5c and Supplementary Table 8.

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Author Contributions

A.A. conceived the initial idea and managed the overall project; M.N.A., N.P.T and A.A. designed the experiments; M.N.A performed the vast majority of experiments and analysed the data with input from A.A, N.P.T and R.W..; M.N.A. and A.A co-wrote the manuscript with input from N.P.T and R.W.. All authors discussed the results and commented on the manuscript.

Competing Interests

The authors declare no competing interests

Additional Information

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