Concurrent control over sequence and dispersity in multiblock copolymers

Maria-Nefeli Antonopoulou,[a] Richard Whitfield,[a] Nghia P. Truong,[a, b] Dries Wyers,[c] Simon Harrisson,[d] Tanja Junkers,[c] Athina Anastasaki*[a]

a - *Laboratory of Polymeric Materials, Department of Materials, ETH Zürich, Vladimir-Prelog-Weg 5, 8093 Zürich, Switzerland.*

b - *Monash Institute of Pharmaceutical Sciences, Monash University, 399 Royal Parade, Parkville, VIC 3152, Australia.*

c - *Polymer Reaction Design Group, School of Chemistry, Monash University, 19 Rainforest Walk, Clayton, VIC 3800, Australia.*

d - *Laboratoire de Chimie des Polymères Organiques, University of Bordeaux/ENSCBP/CNRS UMR5629, 33607, Pessac, France.*

Abstract

Controlling monomer sequence and dispersity in synthetic macromolecules is a major challenge in polymer science with both parameters determining materials' 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, good 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.[1-7] 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. While solid-state peptide synthesis (Merrifield synthesis) has been a significant breakthrough,[8] the limitations of this method (e.g. time-consuming, high cost, low yields, limited scalability, access only to lower molecular weight materials) have forced 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,[9] segregating templating,[10,11] kinetic control,[12] tandem monomer addition and modification[13] and solution polymerization.[14,15]

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.[4,16] 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.[4] 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.).[17-25] Owing to these advantages, the groups of Hawker, Matyjaszewski, Boyer, Whittaker, Haddleton, Junkers and Perrier have reported the

remarkable synthesis of sequence-controlled multiblocks.[21,26-40] 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.[29] The Junkers group 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.[35] 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.[38,41] 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 gradually increasing dispersities in multiblock copolymer synthesis 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 low dispersity, low and high molecular weight tailing/shoulders gradually appear during subsequent monomer additions, thus yielding multiblocks with much higher dispersity values and loss of control over both dispersity and livingness.[31,35] 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.[41,42] 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.).[43-45] In fact, high and low dispersity polymers exhibit unique properties and functions, which has encouraged many groups to develop strategies that can precisely control dispersity.[46,47] For instance, the Fors group elegantly exploited a modular strategy which controls the temporal regulation of initiation during chain growth polymerization,[48-51] while

Matyjaszewski and co-workers leveraged the catalyst concentration to govern the molecular weight distributions.[52,53] 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 realized. This is because high dispersity polymers are often associated with increased terminations and side reactions which prevent the efficient addition of subsequent blocks. A few recent breakthroughs have allowed the synthesis of high dispersity polymers with minimal termination, thus promoting the preparation of diblock copolymers.[46,47] However, full control over the dispersity even in diblock copolymers remains severely restricted due to inherent limitations of the reported synthesis approaches. For example, 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.[54,55] In a similar vein, using low deactivator concentrations in ATRP enabled the synthesis of polymers with variable dispersities, but even a low to high dispersity diblock is currently unattainable.[56,57] Collectively, these constraints hinder the development of sequence-controlled multiblock copolymers with on demand control over dispersity.

Results and Discussion

Tailoring Polymer Dispersity in Homopolymers using a Switchable RAFT Agent

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 block. Switchable RAFT agents were developed as universal RAFT agents to provide access to low dispersity materials from either more or less activated monomers.[58-61] 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).
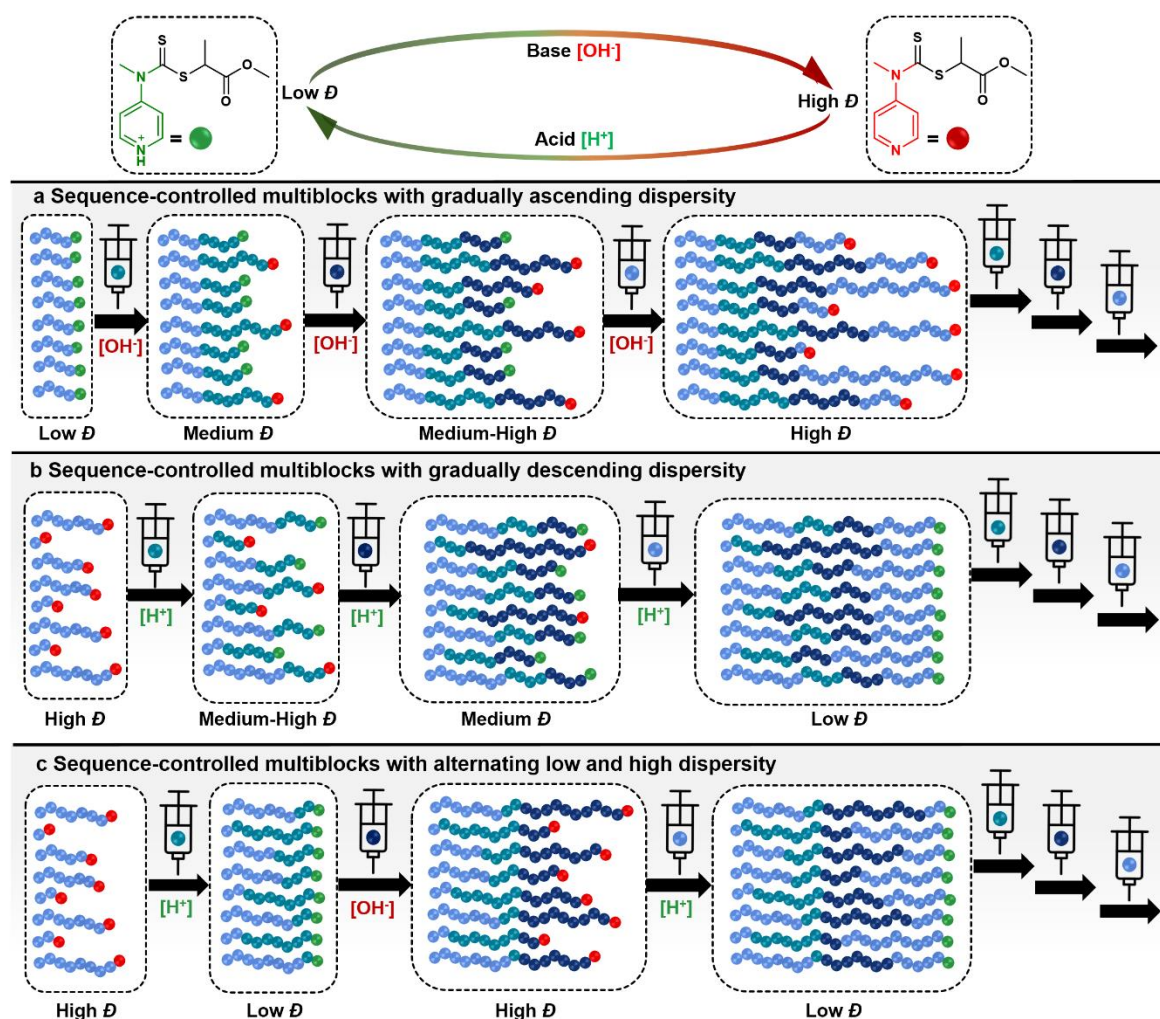

Figure 1. Schematic representation of our proposed approach for the preparation of multiblocks with tuneable dispersity. In **a,** the addition of base results in gradual deprotonation of the chain transfer agent yielding multiblock copolymers with incremental increases in dispersity. In **b,** the addition 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 dispersities .

To demonstrate this concept, we used dimethyl acrylamide (DMA) as a 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) was obtained when targeting DP=200 (Supplementary Table 1 Entry 1 & Supplementary Figure 1).

Importantly, and despite the high dispersity, good agreement between the theoretical and experimental molecular weights was observed at high conversions (Supplementary Figure 2, NMR was used in calculating theoretical M_n, depicted as $M_{n(Theo)}$, and SEC was employed to determine the experimental M_n, depicted as $M_{n\,(SEC)}$). 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 molecular weight values, as a result of slow initiation.[57] By repeating the experiment, albeit in the presence of a small amount of sulphuric acid (H_2SO_4, 1 µL, 18M, 0.5 equiv.), 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 H_2SO_4 (2 µL (1 equiv.), 3.5 µL (1.74 equiv.) and 8 µL (4 equiv.), 18M), led to significantly lower Đs 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 ~17200-17500, Đ=1.18-1.67) at very high monomer conversions could be obtained. An important feature of this technique is that the polymers possess identical end-groups (either in the protonated or deprotonated form), regardless of their dispersity. We noted that to achieve the lowest possible Đ, higher than stoichiometric amounts of acid were required. This is because the RAFT agent is a weak base in very dilute solution and the presence of the organic solvent and monomer can also reduce the polarity of the solution, thus lowering the protonation of the RAFT agent. [62,63] Therefore, even more acid was added to drive the equilibrium to the protonated form. This is confirmed when the target DP of the polymerization or the reaction medium are changed, whereby different equivalents of acid are required so to obtain the lowest possible dispersity (Supplementary Tables 2-3 & Supplementary Figures 3-4). Next, we reversed the phenomenon (i.e. the control increase of Đ in homopolymers) by starting with a polymer of low Đ (through the addition of acid) and subsequently repeated the polymerization in the presence of gradually

increased sodium hydroxide (NaOH) concentrations (Supplementary Table 4 & Supplementary Figure 5). It should be highlighted that even higher amounts of NaOH (i.e. 6 equivalents or higher) must be avoided as this would lead to the degradation of the RAFT agent and an uncontrolled polymerization, while under the conditions utilized (i.e. 4-5 equivalents) no RAFT agent degradation is observed even after 10 hours (Supplementary Table 5 & Supplementary Figure 6-9). This is a significant improvement over previous strategies where employing RAFT agent mixtures led to vastly different end-groups or the addition of co-monomers and termination agents led to adulterated polymer chains and chains without functional end-groups, respectively.[47,54,55,64] These results confirm 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 & Supplementary Scheme 1).

Tailoring Polymer Dispersity in Pentablock Copolymers

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. For subsequent polymerizations a target of DP=100 per block was selected to minimize the number of defective chains, i.e. chains where one or more block is not incorporated. Previously, Harrisson and co-workers illustrated that for low dispersity multiblock copolymers DP=6 was required per block to avoid defective chains, but for the synthesis of high dispersity materials, there is a higher chance of defects, so higher DP blocks must be prepared.[65,66] By targeting DP=100 we minimize the number of defective chains, with target dispersities of 1.1 and 1.7, giving ~0% and ~0.2% of defective chains respectively. The percentage of defective chains for each dispersity value can be found in Supplementary Table 6 & Supplementary Figures 10-11). We optimized an initial ratio of [RAFT Agent]:[VA-044 (2,2'-Azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride)] 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. It is noted that an increased water content in the solvent composition was selected to accelerate the polymerization rate, so lower amounts of free radical initiator are required and the number of terminated chains reduced. To investigate end-group fidelity, two low molecular weight PDMA polymers were synthesized; the first one in the absence of added acid (yielding higher Đ) and the second one using an excess of acid (yielding lower Đ). The two polymers (without further purification) were then characterized by electrospray ionization mass-spectrometry (ESI-MS). The generated ESI data with full peak assignments can be found in the SI (Supplementary Tables 7-8 & Supplementary Figures 12-16). Pleasingly, even in the absence of acid, the major polymer peak distributions correspond to the expected PDMA with the RAFT end-group attached. Importantly, negligible termination, if any, could be detected which confirms that our selected conditions yield high end-group fidelity polymers. Matrix assisted desorption ionization time-of-flight mass-spectrometry (MALDI-ToF-MS) was also conducted for both a low and a high dispersity polymer and further supported the high livingness observed in our system (Supplementary Figures 17-18). Another note is that we use poly(methyl methacrylate) standards in our SEC so to confirm the good agreement between theoretical and experimental molecular weight we have also calculated the experimental molecular weight for both low and high dispersity polymers via ^{1}H NMR (by comparing the protons from the RAFT agent to the protons of the repeat unit for both the purified and the unpurified polymers) and found a very good agreement (Supplementary Figures 19-24). The water solubility of the RAFT agent was also considered (Supplementary Figure 24b).

After all these considerations, our initial target was a sequence-controlled pentablock copolymer with gradually descending Đs via sequential additions of individual aliquots from a palette of three different acrylamide-based monomers. First, a 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 9 Entry 1). Upon addition of the second monomer (DMA) together with a small amount of H_2SO_4 (0.65 µL, 18M, 0.41 equiv.), a gradual decrease in the $Đ$ of the diblock (M_n=22200, $Đ$=1.50) was evident. This was accompanied by a clear shift to higher molecular weights. (Figure 2a-c & Supplementary Table 9 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 10 & Supplementary Figures 25-27). When full conversion was reached, another aliquot of acid (1.5 µL, 0.95 equiv.) was subsequently injected together with the third monomer diethylacrylamide (DEA) yielding a triblock with a further decrease in the dispersity (M_n=33600, $Đ$=1.41, Supplementary Table 9 Entry 3). This process was repeated two more times while gradually increasing the amount of the added acid alongside the sequential monomer additions, yielding tetrablock (2.0 µL H_2SO_4, 1.26 equiv. M_n=45600) and pentablock (3.8 µL H_2SO_4, 3.75 equiv., M_n=65300) copolymers with $Đ$=1.34 and $Đ$=1.22, respectively (Figures 2a-c, Supplementary Table 9 Entries 4-5 & Supplementary Scheme 2a). 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.[31,32,35,41] However, in our system very little termination is observed, and we also maintain monomodal distributions. In particular, a high livingness of the final pentablock was obtained (92.5%) as expected from theory (see SI for RAFT livingness equation). Importantly, due to the high DP of each block, defective chains are minimized.
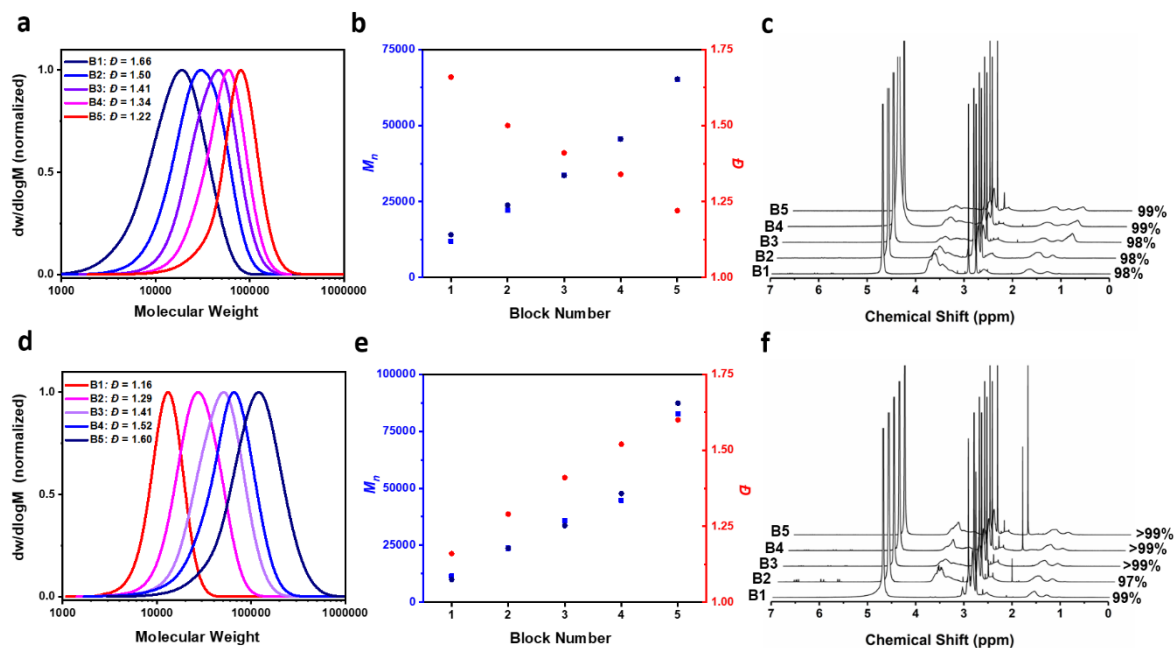
Figure 2. Pentablock copolymers with gradually evolving dispersity. a, SEC traces illustrating the molecular weight distributions for consecutive cycles during the synthesis of a descending dispersity pentablock copolymer. **b** Evolution of dispersity (red) and the measured molecular weight (light blue) 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 11 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 (NaOH) was slowly increased. ^{1}H NMR spectroscopy confirmed high monomer conversions in all steps yielding higher ordered multiblocks with continuously increased $Đ$s ($Đ_{Homopolymer}$=1.16, $Đ_{Diblock}$=1.29, $Đ_{Triblock}$=1.41, $Đ_{Tetrablock}$=1.52 and $Đ_{Pentablock}$=1.60, Figures 2d-f, Supplementary Table 11 Entries 2-5 & Supplementary Scheme 2b). Importantly, the pentablock copolymer retained a monomodal shape in contrast to previous work where the increase in $Đ$ was accompanied by 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 latter one being particularly challenging for any reported methodology (Figure 3a).[44] 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 12 Entry 1). Once >99% polymerization conversion had been reached, DMA was added yielding a well-defined diblock copolymer with a comparably high dispersity ($M_n=12000$ $Đ=1.66$, Figure 3b & Supplementary Table 12 Entry 2). This data indicates that despite the high $Đ$ of the first block (resembling values typically acquired in free radical polymerization), high end-group fidelity is maintained allowing for the *in-situ* formation of block copolymers. Moreover, when the second monomer was added together with an excess of H_2SO_4 (to ensure full protonation of the RAFT agent), the final diblock copolymer presented a much lower $Đ$ of 1.19 while fully shifting to higher molecular weights, further emphasizing the high chain end fidelity maintained in our system (Figure 3c & Supplementary Table 12 Entries 3-4). Finally, PDMA with low dispersity ($Đ=1.16$) was also synthesized by complete protonation of the RAFT agent. This time, an excess of base (NaOH) was injected together with the second monomer, yielding P(DMA-*b*-NAM) with $Đ=1.58$ (Figure 3d & Supplementary Table 12 Entries 5-6). It should be highlighted that such a low-to-high dispersity diblock has never been synthesized by any controlled radical polymerization methodology and would be fundamentally incompatible with

existing strategies such as the use of a mixture of RAFT agents or when employing ppm concentrations of copper in ATRP.[54,57] We also note 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.[48,57] Altogether, our proposed approach allows full control over dispersity of both homopolymers and diblock copolymers.
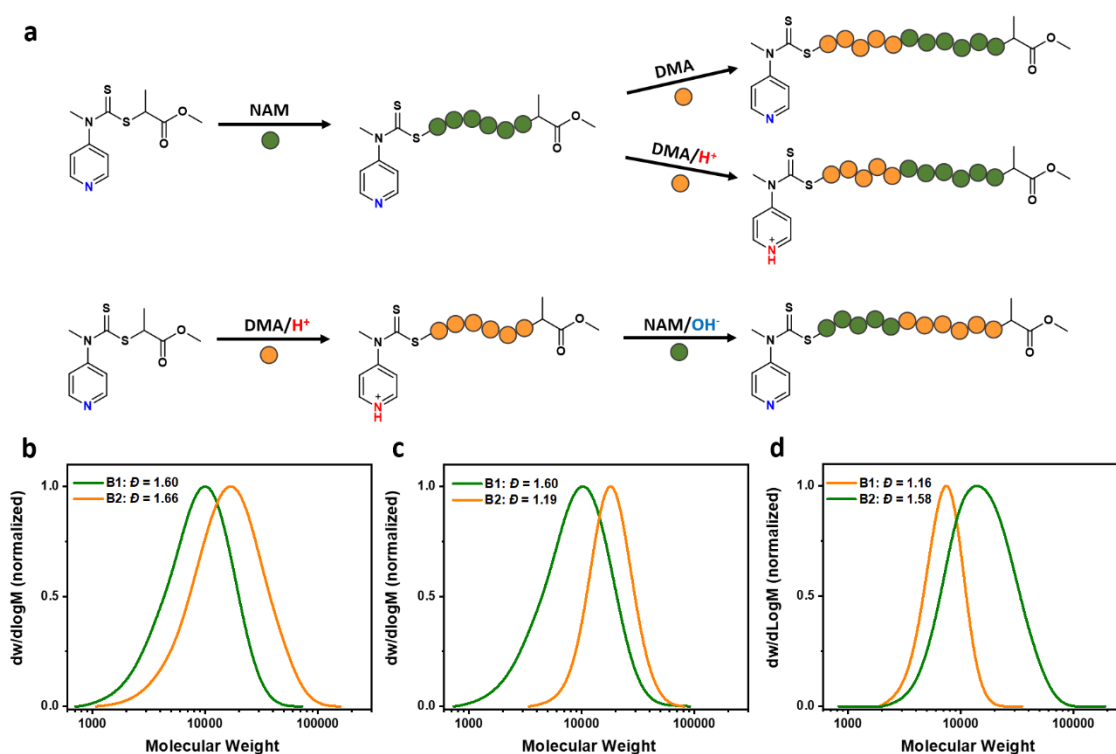

Figure 3. Diblock copolymers synthesized with dispersity value extremes by switching the activity of the RAFT agent. a, scheme illustrating the preparation of high to high dispersity, high to low dispersity and low to high dispersity diblocks directly corresponding to the SEC traces in **b**, **c** and **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 13 Entry 1). When near-quantitative conversion was achieved (>96%), the second monomer and an excess of NaOH were subsequently injected in

order to obtain a much higher $Đ$ diblock (M_n=11500, $Đ$=1.61, Figures 4a-c & Supplementary Table 13 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 13 Entry 3). By alternating the addition of base and acid together with the subsequent monomer injections, tetrablock and pentablock copolymers could easily be prepared with $Đ$=1.70 (M_n=45400) and $Đ$=1.26, (M_n=88400), respectively (Figures 4a-c, Supplementary Table 13 Entries 4-5 & Supplementary Scheme 2c). With these results, we next wanted to investigate further the reactivity switch of the RAFT agent upon addition of base and acid and thus performed Predici simulations. Modelling was performed by assuming typical parameters for a thermal acrylamide RAFT polymerization at 70°C, incorporating our experimental conditions (i.e. [CTA]:[VA-044] = 1:0.01 and a switch in the chain transfer coefficient of the CTA on the addition of either acid (C_{T1}=15) or base (C_{T2}=1) for each block (Supplementary Scheme 3). Pleasingly, the molecular weight distributions nicely switched from low dispersity to high dispersity (and vice versa) on each block addition with a variation in dispersity between roughly 1.2 and 1.6, replicating what was observed experimentally (Supplementary Figure 28). Furthermore, the simulation allowed the amount of terminated polymer compared to the full polymer sample to be analyzed throughout the chain extensions. Importantly, neither, the full variation in the value of the chain transfer constant or the switching of the reactivity of the chain transfer agent, by addition of acid or base, had any significant impact on the amount of termination. (This is in line with what one would expect from the RAFT livingness equation). It is also clearly visible that the amount of termination levels off prior to the addition of fresh monomer, indicating that full conversion is reached for each block. Termination data for a range of chain transfer constants is illustrated in Supplementary Figure 29, demonstrating a high retention of livingness in all cases, independent of what dispersity block is created during each chain extension.

We next prepared the reverse multiblock copolymer by switching between fully basic and fully acidic conditions throughout the monomer additions ($Đ_{\text{Homopolymer}}$=1.52, $Đ_{\text{Diblock}}$=1.21, $Đ_{\text{Triblock}}$=1.52 and $Đ_{\text{Tetrablock}}$=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 14 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.
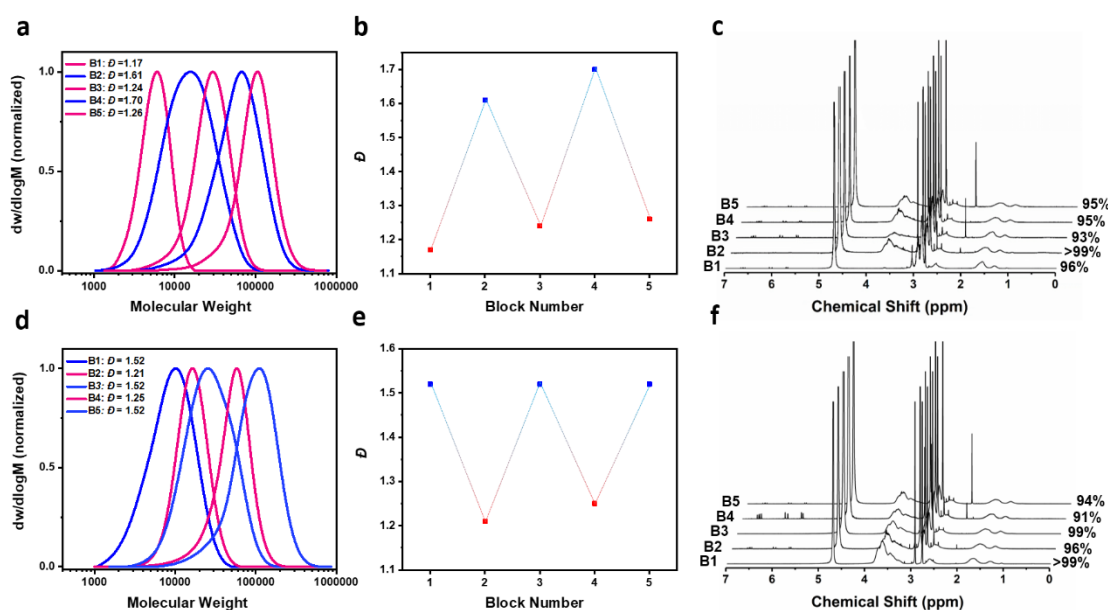

Figure 4. Pentablock copolymers synthesized with dispersity extremes. a, SEC traces illustrating the molecular weight distributions for consecutive cycles during the synthesis of an alternating high and low dispersity pentablock copolymer. **b,** Dispersity evolution during this multiblock synthesis.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

Tailoring Polymer Dispersity in Higher-Order Multiblock Copolymers

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 15 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 weight and a much higher dispersity value ($Đ$=1.62, Figures 5a-c & Supplementary Table 15 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 ($Đ_{Triblock}$=1.49, $Đ_{Tetablock}$=1.40 and $Đ_{Pentarablock}$=1.35, respectively, Figures 5a-c & Supplementary Table 15 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 ($Đ_{Hexablock}$=1.35, $Đ_{Heptablock}$=1.33, $Đ_{Octablock}$=1.35 and $Đ_{Nonablock}$=1.37 respectively, Figures 5a-c & Supplementary Table 15 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 15, Entry 10 & Supplementary Scheme 2g). Similarly, an octablock copolymer could be prepared where high dispersity was maintained for the last seven blocks ($Đ_{Homopolymer}$=1.15, $Đ_{Diblock}$=1.57, $Đ_{Triblock}$=1.54, $Đ_{Tetrablock}$=1.53, $Đ_{Pentablock}$=1.57, $Đ_{Hexablock}$=1.53, $Đ_{Heptablock}$=1.53 and $Đ_{Octablock}$=1.52), further illustrating the versatility of our system (Supplementary Table 16, Supplementary Figure 30, & 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%). 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 17 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: $Đ_{Homopolymer}$=1.61, $Đ_{Diblock}$=1.52, $Đ_{Triblock}$=1.43, $Đ_{Tetrablock}$=1.37, $Đ_{Pentablock}$=1.32 and $Đ_{Hexablock}$=1.24, Figures 5d-f & Supplementary Table 17 Entries 2-6). Low dispersity could be maintained for subsequent blocks by neither addition of acid nor base (Supplementary Table 18, Supplementary Figure 31 & 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 ($Đ_{Heptablock}$=1.29, $Đ_{Octablock}$=1.38 and $Đ_{Nonablock}$=1.52, Figures 5d-f & Supplementary Table 17 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 17 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 syntheses. By carefully adjusting the amount of acid and base, the dispersity of every block can be targeted on demand, thus significantly increasing the range of accessible multiblock copolymers. Impressively, the calculated livingness found for our decablock copolymers was very high (94.5% and 95.2%) as such small amounts of free radical initiator were employed.
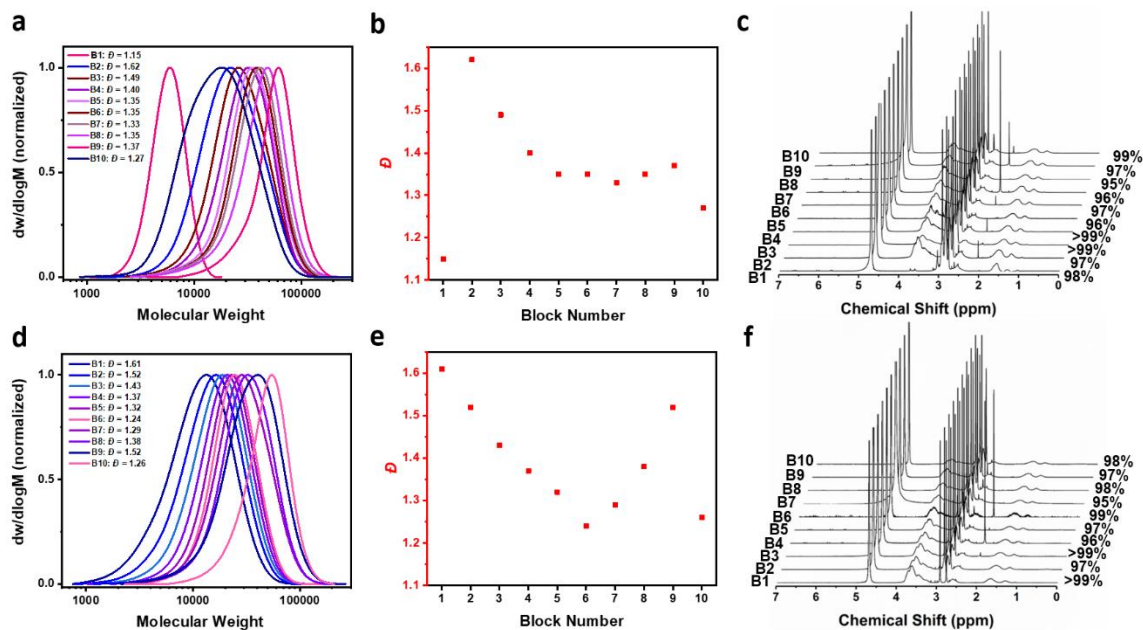
Figure 5. Decablock copolymers synthesized with tunable dispersity. a, SEC traces illustrating the molecular weight distributions for consecutive cycles during the synthesis of a decablock copolymer. In block 1, a high dispersity polymer is prepared, followed by targeted decreases and increases in the 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).

Expanding the Monomer Scope

We finally sought to demonstrate the compatibility of our methodology with another polymer class (i.e. polyacrylates by efficiently controlling the Đ in homopolymers, diblock, triblock and tetrablock copolymers. We first used methyl acrylate (MA) as a model monomer and conducted the polymerization in pure organic media (DMF). In the absence of acid, a high Đ PMA was observed (Đ=1.70) while the addition of a small amount of acid (0.30 equivalents with respect to the RAFT agent) led to a lower Đ (Đ=1.62) (Supplementary Figure 32 & Supplementary Table 19 Entries 1-2). Upon continuing to increase the acid concentration, the dispersity was gradually decreased to 1.41, 1.33 and 1.16 (Supplementary Figure 32 & Supplementary Table 19 Entries 3-5). Monomodal molecular weight distributions were observed in all cases with good agreement between experimental and theoretical molecular

weights. As a next step, we were interested in tailoring polymer dispersity in diblock copolymers. MA and ethyl acrylate (EA) were used as the two acrylic monomers and two extreme diblock copolymers were attempted. The first target was a diblock with a high $Đ$ homopolymer and a low $Đ$ final diblock copolymer. The high $Đ$ block one was first synthesized in the absence of any added acid, leading to a $Đ$ of 1.55. Upon addition of the second monomer and base, the $Đ$ could be reduced effectively to 1.19 (Supplementary Figure 33a & Supplementary Table 20 Entries 1-2). To illustrate the reverse scenario, we started from a low $Đ$ homopolymer ($Đ$=1.14) which was achieved by protonating the RAFT agent. The inclusion of the second monomer together with base subsequently led to a higher $Đ$ diblock copolymer ($Đ$=1.54, Supplementary Figure 33b & Supplementary Table 20 Entries 3-4). In a similar vein, $Đ$ could also be effectively tuned in sequence-controlled triblock and tetrablock copolymer (Supplementary Figures 34-35 & Supplementary Table 21-22). These experiments highlight the versatility of our approach to operate not only with another polymer class but also in organic media. We finally wanted to demonstrate the applicability of our method with low k_p monomers such as styrene. To do so, we attempted to *in-situ* chain extend a PEA macroinitiator ($Đ \sim 1.58$) with styrene while adding various amounts of acid thus targeting P(EA-*b*-S) diblock copolymers with tailored dispersity. In the first diblock copolymer, when PEA reached high monomer conversion (~97%), styrene together with 5% of acid with respect to the RAFT agent were added leading to a diblock copolymer with a dispersity of 1.68 (Supplementary Figure 36a & Supplementary Table 23). In a second diblock, PEA was chain extended with styrene along with a higher amount of acid (20% with respect to the RAFT agent) yielding a diblock copolymer with a dispersity of 1.44 (Supplementary Figure 36b & Supplementary Table 23). In a final diblock copolymer, PEA was chain extended with styrene using an excess of acid, yielding a well-defined diblock copolymer with a dispersity of 1.26 (Supplementary Figure 36c & Supplementary Table 23). We also attempted to control the dispersity during the

polymerization of unconjugated monomers (i.e. low activated monomers) but this was not possible either due to unavoidable side reactions in the presence of acid that degrade the monomers (e.g. N-vinyl carbazole, NVK, degrades to carbazole and N-vinyl pyrrolidone degrades to pyrrolidone, with acetaldehyde among other degradation products produced in both cases) or due to the lack of fragmentation in the case of the protonated RAFT agent (i.e. the protonated RAFT agent yields a more stable intermediate radical thereby preventing fragmentation and resulting in lack of polymerization (Suppplementary Tables 24-25 & Supplementary Figures 37).[61,67-69] Nevertheless, we were able to further expand the scope of our methodology by producing diblock copolymers consisting of a conjugated block (i.e. acrylate) where the dispersity could be tailored (i.e. $Đ$=1.67 or 1.42, (Suppplementary Table 26 & Supplementary Figures 38) and a second unconjugated block (i.e. vinyl carbazole or vinyl acetate, VAc) of lower dispersity ($Đ_{P(EA-b-NVK)}$~1.20 & $Đ_{P(EA-b-VAc)}$ ~1.28, Suppplementary Tables 26-27 & Supplementary Figures 38-39). We could also synthesize triblock copolymers with the dispersity of the first two blocks composed of acrylates and acrylamides could be fully controlled, followed by a third unconjugated block ($Đ_{PEA}$=1.18, $Đ_{P(EA-b-NAM)}$=1.55 and $Đ_{P(EA-b-NAM-b-NVK)}$=1.37, Suppplementary Table 28 & Supplementary Figures 40). Taken all together, our method can operate for both low and high k_p monomers and unconjugated moieties can also be incorporated even though their dispersity cannot be fully controlled.

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 along with a near-perfect match between theoretical and experimental molecular weights was observed. The experimental method can be applied to a number of different monomer classes and is fully supported by Predici simulations. We believe that this new concept will open the door for the synthesis of advanced sequence-controlled materials that can enable structure-property relationship studies and be used in various applications and fields including phase-separation, solution self-assembly, rheology, macromolecular folding and drug delivery.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/xxxx

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Methods

See supplementary information for detailed methods and protocols

Synthesis of a pentablock copolymer from a high Ð 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 9.

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 15.

Acknowledgements

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.. During the revisions, S.H, T.J. and D.W. were added as co-authors. D.W. and T.J performed the ESI-MS measurements and the Predici

simulations while S.H conducted the calculations for the percentage of defective chains. All authors discussed the results and commented on the manuscript.

Competing Interests

The authors declare no competing interests

Additional Information

Supplementary information is available for this paper at https://doi.org/xxx.

Correspondence and requests for materials should be addressed to A.A (athina.anastasaki@mat.ethz.ch).

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