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Pushing the Limit of the RAFT Process: Multiblock Copolymers by One-Pot Rapid Multiple Chain Extensions at Full Monomer Conversion

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Ⓢ *Supporting Information*

ABSTRACT: We describe an optimized method to prepare multiblock copolymers. The approach is based on our previously reported use of reversible addition−fragmentation chain transfer (RAFT) polymerization, which here has been optimized into a fast, versatile, efficient, and scalable process. The one-pot, multistep sequential polymerization proceeds in water, to quantitative yields (>99%) for each monomer addition, thus circumventing requirements for intermediate purification, in 2 h of polymerization per block. The optimization of the process is initially demonstrated via the synthesis of a model decablock homopolymer (10 blocks) of 4-acryloylmorpholine with an average degree of polymerization of 10 for each block ($Đ = 1.15$ and livingness >93% for the final polymer). Both the potential and the limitations of this approach are illustrated by the synthesis of more complex high-order multiblock copolymers: a dodecablock copolymer (12 blocks with 4 different acrylamide monomers) with an average degree of polymerization of 10 for each block and two higher molecular weight pentablock copolymers (5 blocks with 3 different acrylamide monomers) with an average degree of polymerization of 100 per block.
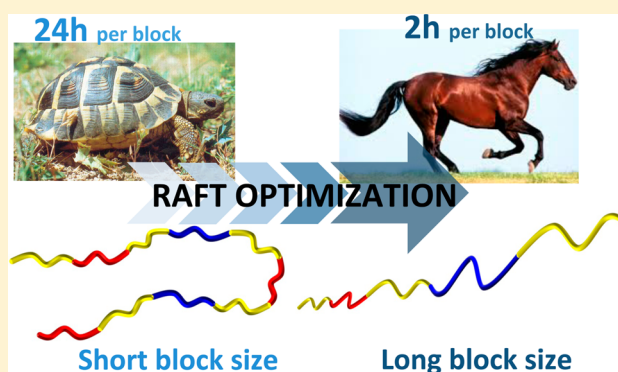
■ INTRODUCTION

Over the past 50 years, block copolymer synthesis has seen considerable progress with the introduction and development of living anionic polymerization and with the advances of "living" radical polymerization (LRP)[1−3] (defined by IUPAC as reversible deactivation radical polymerization, RDRP)[4] such as reversible addition−fragmentation chain transfer (RAFT) polymerization, nitroxide-mediated radical polymerization (NMP),[5−7] and atom transfer radical polymerization (ATRP).[8−10] Recently, more advanced block copolymer architectures, that is, multiblock copolymers, have become the subject of great attention as a step toward sequence control in synthetic polymers.[11−15] Alongside biopolymers such as proteins and poly(nucleic acids) that present a perfectly controlled primary structure (i.e., sequence regulation of repeat units or functionalities along the polymer backbone), multiblock copolymers are unique and original structures that also exhibit a type of primary structure. Despite a sequence control that is typically limited by the monomer distribution within each block, multiblock copolymers are very attractive synthetic sequence-defined macromolecules, as control over the block sequence is easier to access and more scalable than sequence regulation of individual monomer units.[16−34] Moreover, attempting to anticipate the relationship between a linear monomer sequence and its resulting structure and function is of extreme complexity.[35] Multiblock copolymers are therefore of great interest for the design of new soft materials,[36−41] including systems that are capable of self-assembly into ordered nanostructures.[42] Supramolecular folding can also be achieved by tuning the interactions between different blocks within a single polymer chain.[43−46]

Despite their great promises, the synthesis of high-order multiblock copolymers still remains a challenge and a time-consuming task, with only a few reports describing highly complex architectures.[47−57] This is mainly due to (1) the decrease in chain-end fidelity with increasing the number of blocks and (2) the necessity to remove any unreacted monomer before each new block extension.[58] To keep a high proportion of living end groups, polymerizations are normally stopped at moderate conversions.[59] Recently, the synthesis of multiblock copolymers has made considerable progress with optimized

strategies based on one-pot sequential addition of vinyl monomers. Polymerizations are now conducted to full conversion and no purification is needed between each block, which greatly simplifies the procedure and allows the production of polymers in quantitative yields. This approach has been successfully used for the first time with Cu(0)-mediated radical polymerization, leading to very well-defined hexablock copolymers ($Đ \approx 1.20$) in very high yield with an average degree of polymerization (DP) of two per block and comprising four different acrylate monomers.[60] However, Cu(0)-mediated radical polymerization has shown some limitations when a higher number of blocks of larger DP were targeted. For instance, in the synthesis of a hexablock homopolymer PMA-*b*-PMA-*b*-PMA-*b*-PMA-*b*-PMA-*b*-PMA with a DP of 100 per block,[61] full monomer conversions were not achieved (conversions between 92 and 100%, thus leading to the synthesis of quasi-block copolymers), and a large increase in the polymerization time per block was required (up to 5 days for the last block). However, in all cases, the control of the molecular weight appears excellent with a final dispersity as low as 1.10.

Very recently, our group has shown that the RAFT process is one of the best techniques so far to access multiblock copolymers with the first example of an icosablock (20 blocks) copolymer (average DP of 3 per block) with a remarkable final dispersity ($Đ$ < 1.4) and a very high theoretical livingness (∼94%).[62] This achievement is remarkable because degenerative transfer radical polymerization techniques such as RAFT are generally considered to have lower chain end retention than polymerization techniques based on deactivation by reversible termination due to the requirement of an external source of radicals (e.g., an azoinitiator).[63−65] However, a radical initiator can be used to our advantage, as described in our recent publication with the preparation of a very well-defined decablock homopoly(4-acryloylmorpholine) with a final dispersity of 1.15 and a theoretical number fraction of living chains of 97%.[66] However, a long polymerization time of 24 h per block was still required to reach complete monomer conversion. The aim of the present work was first to improve further the reaction to reduce polymerization times, then to employ the overall optimized conditions for the preparation of more complex (functional) microstructures, and finally to highlight the limitations of the RAFT process for the production of this type of materials.

■ MATERIALS AND METHODS

Materials. Tetrahydrofuran (THF, Ajax Finechem, 99%), *N,N*-dimethylformamide (DMF; Merck, HPLC-grade), and 2,2′-azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride (VA-044, Wako) were used without further purification. Milli-Q water was directly used as the solvent for polymerizations. 1,4-Dioxane (Sigma-Aldrich, ≥99%) was distilled under reduced pressure prior to use. *N,N*-Dimethylacrylamide (DMA, Sigma-Aldrich, 99%) was filtered through a basic aluminum oxide (activated, basic, Brockmann I, standard grade, ∼150 mesh, 58A) column before use to remove the radical inhibitor. *N*-Isopropylacrylamide (NIPAM; Sigma-Aldrich, 97%) was used after purification by recrystallization in *n*-hexane. *N*-Hydroxyethylacrylamide (HEAm; Sigma-Aldrich, 97%) was used without further purification. 4-Acryloylmorpholine (NAM, Sigma-Aldrich, 97%) and *N,N*-diethylacrylamide (DEA) were purified by vacuum distillation. All polymerizations were carried out under an argon atmosphere. The RAFT agent, (propanoic acid)yl butyl trithiocarbonate (PABTC), was obtained from Dulux Group Australia and used as received.

Methods. *Nuclear Magnetic Resonance (NMR) spectroscopy.* ^{1}H NMR spectra were recorded on a Bruker Avance 300 spectrometer (300 MHz) at 27 °C in deuterium oxide (D$_2$O). For ^{1}H NMR, the delay time

(d1) was 2 s. Chemical shift values (δ) are reported in ppm. The residual proton signal of the solvent was used as internal standard (δH 4.79).

Size Exclusion Chromatography. Molar mass distributions were measured using size exclusion chromatography (SEC) either on a Shimadzu LC-20AD or on an Agilent GPC50 liquid chromatography system:

The Shimadzu LC-20AD liquid chromatography system used a Jordi Gel DVB 500 Å guard column (50 × 7.8 mm) followed by two PL gel, 5 μm, MIXED-C columns (300 × 7.5 mm). THF was used as eluent at 1.0 mL·min^{-1} at 40 °C and with 0.5 vol % toluene (flow rate marker). Polystyrene standards were used to calibrate the SEC system. Analyte samples contained toluene (0.5 vol %) as the flow rate marker and were filtered through a polytetrafluoroethylene (PTFE) membrane with 0.2 μm pore before injection (100 μL). Respectively, experimental molar mass ($M_{n,SEC}$) and dispersity ($Đ$) values of synthesized polymers were determined by conventional calibration using ASTRA for Windows software (version 6.90.08).

The Agilent GPC50 liquid chromatography system used a Polar Gel-M guard column (50 × 7.5 mm) and two Polar Gel-M columns (300 × 7.5 mm). DMF + 0.1% LiBr was used as eluent at 0.7 mL·min^{-1} at 50 °C. Poly(methyl methacrylate) standards were used to calibrate the SEC system. Analyte samples contained water (0.5 vol %) as the flow rate marker and were filtered through a PTFE membrane with 0.2 μm pore before injection (100 μL). Respectively, $M_{n,SEC}$ and $Đ$ values were determined by conventional calibration using Cirrus software.

Multiblock Copolymer Preparation by Iterative RAFT Polymerization. *Multiblock Copolymer Preparation by RAFT Polymerization.* A typical synthesis of the first block is as follows: chain transfer agent (CTA), monomer, initiator, and solvent are introduced in a flask equipped with a magnetic stirrer and sealed with a rubber septum (Tables S1, S3, S5, S8, and S10 in the Supporting Information for the quantity of reagents needed for the five multiblock copolymers). The mixture is degassed by bubbling argon for ca. 15 min; then, polymerization is performed in a thermostated oil bath at the desired temperature (70 °C). After 2 h, a sample is withdrawn from the polymerization medium using a degassed syringe for ^{1}H NMR and SEC analysis.

Typical Synthesis of Subsequent Blocks. For iterative block extensions, a further mixture of degassed monomer, initiator, and solvent is added to the polymerization medium via gastight syringe, and the mixture is stirred at 70 °C for 2 h (Tables S1, S3, S5, S8, and S10 in the Supporting Information for the quantity of reagents needed for the five multiblock copolymers). Before each new addition, a sample is withdrawn from the polymerization medium using a degassed syringe for ^{1}H NMR and SEC analysis. This step is performed as many times as needed depending on the desired number of blocks. At any time before a new iterative chain extension, the polymerization can be interrupted by storing the flask in the fridge until further chain extension.

Determination of Monomer Conversions. Monomer conversions (p) were calculated from ^{1}H NMR data using the following equation: $p = 1 - (\int I_{5.5-6.75ppm} / \int I_a / DP_{targeted})$, where $\int I_{5.5-6.75ppm}$ is the integral of the three vinyl protons from the monomer, $\int I_a$ is the integral of the three methyl protons belonging to the Z group of the RAFT agent ($-CH_2-CH_3$), and $DP_{targeted}$ is the average degree of polymerization targeted.

Calculation of $M_{n,th}$. The theoretical number-average molecular weight ($M_{n,th}$) is calculated using eq 1.

$$M_{n,th} = \frac{[M]_0 p M_M}{[CTA]_0 + 2f[I]_0\left(1 - e^{-k_d t}\right)\left(1 - \frac{f_c}{2}\right)} + M_{CTA} \tag{1}$$

where $[M]_0$, $[CTA]_0$, $[I]_0$ are the initial concentrations (in mol L^{-1}) of the monomer, the chain transfer agent, and the initiator, respectively; p is the monomer conversion, as determined by ^{1}H NMR; M_M and M_{CTA} are the molar masses (in g mol^{-1}) of the monomer and the chain transfer agent, respectively; k_d is the decomposition rate constant (in s^{-1}) of the azoinitiator; and t represents the polymerization time (in seconds). The factor "2" accounts for the fact that one molecule of azoinitiator yields two primary radicals with the efficiency f (assumed to be equal to 0.5 in this study). The decomposition rate constant for VA-044 at the

Scheme 1. Strategy Employed for the Preparation of Multiblock Copolymers by RAFT via One-Pot Sequential Addition of Vinyl Monomers[a]
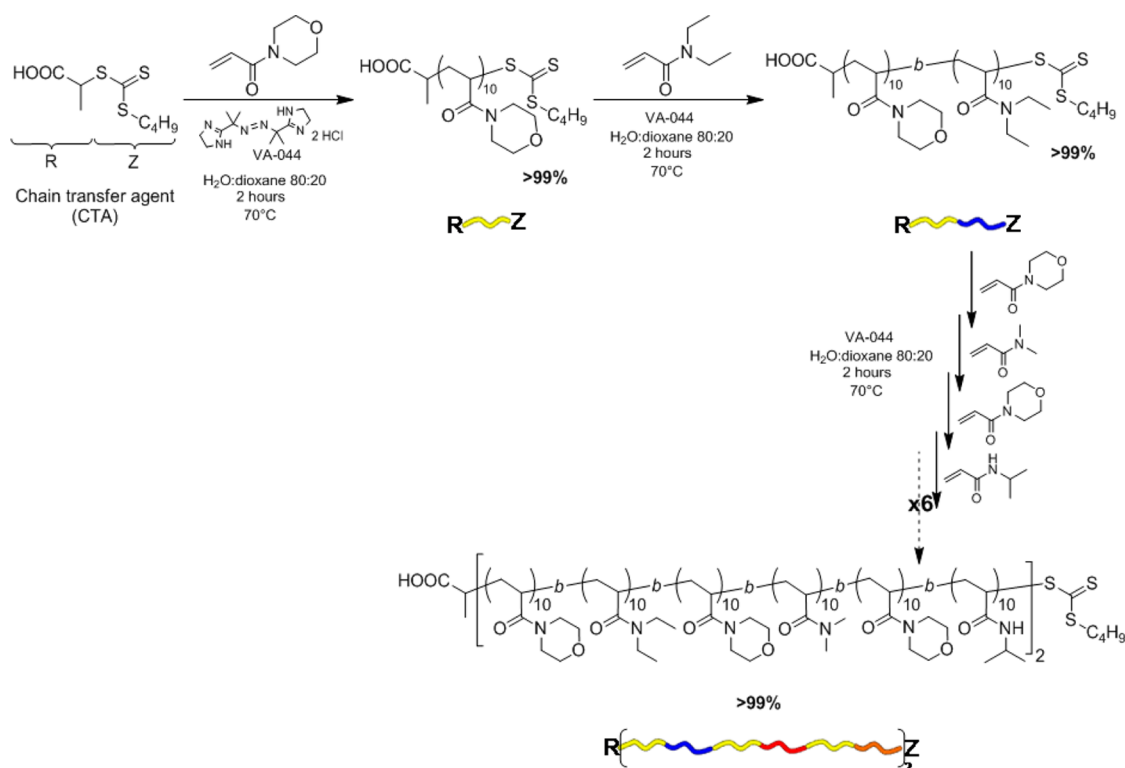
[a]Synthesis of the dodecablock copolymer (Scheme 3b) is used as an example.

Scheme 2. Structures of the Chain Transfer Agent, The Vinyl Monomers and the Azoinitiators Used
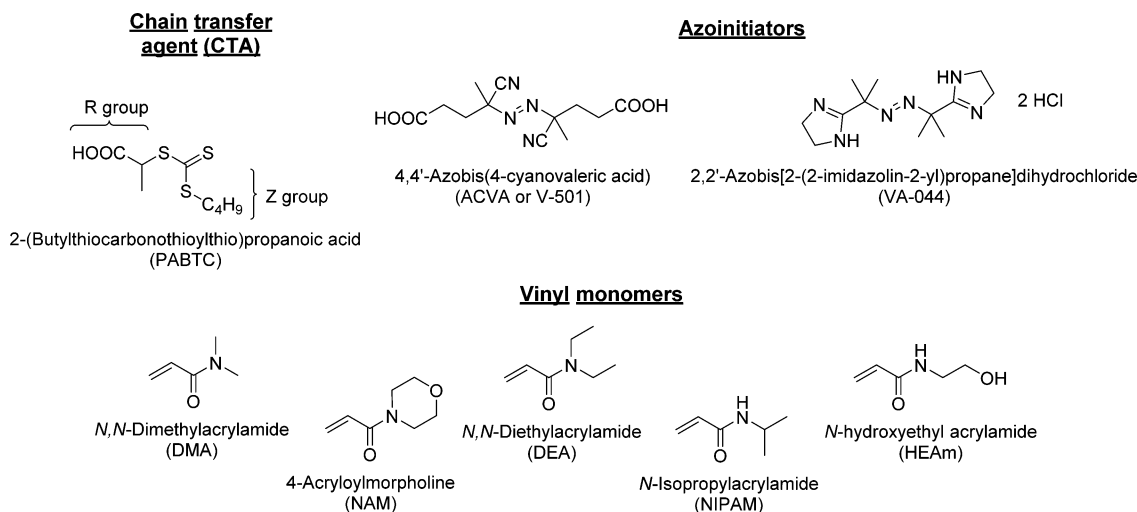
temperature T ($k_{d,VA\text{-}044(T)}$) was determined from the values obtained from Wako ($k_{d,VA\text{-}044(44\,°C)} = 1.92 \times 10^{-5}$ s^{-1} and $E_a = 108\,000$ J·mol^{-1}) using the Arrhenius equation ($k_{d,VA\text{-}044(70\,°C)} = 4.30 \times 10^{-4}$ s^{-1}). The term $1 - (f_c/2)$ represents the number of chains produced in a radical–radical termination event with f_c representing the coupling factor. An f_c value of 1 means that all bimolecular terminations occur by combination, whereas a value of 0 indicates that 100% of bimolecular terminations result from disproportionation. In this study, 100% terminations by disproportionation are assumed ($f_c = 0$).

Calculation of the Theoretical Number Fraction of Living Chains (L). The number fraction of living chains is calculated using eq 2.

$$L = \frac{[\text{CTA}]_0}{[\text{CTA}]_0 + 2f[\text{I}]_0\left(1 - e^{-k_d t}\right)\left(1 - \frac{f_c}{2}\right)} \qquad (2)$$

■ **RESULTS AND DISCUSSION**

Our approach for the synthesis of multiblock copolymers is depicted in Scheme 1, and the structures of reactants are shown in Scheme 2. This study aims at showing that (i) the reaction time in RAFT polymerization can be greatly reduced (e.g., from 24 to 2 h per block) without a concomitant loss of livingness, (ii) the one-pot sequential addition of monomers can also be used for

Scheme 3. Microstructures of the Multiblock Copolymers Prepared in This Work

a) Decablock homopolymer:
$PNAM_{10}$-b-$PNAM_{10}$-b-$PNAM_{10}$-b-$PNAM_{10}$-b-$PNAM_{10}$-b-$PNAM_{10}$-b-$PNAM_{10}$-b-$PNAM_{10}$-b-$PNAM_{10}$-b-$PNAM_{10}$

b) Dodecablock copolymer:
$PNAM_{10}$-b-$PDEA_{10}$-b-$PNAM_{10}$-b-$PDMA_{10}$-b-$PNAM_{10}$-b-$PNIPAM_{10}$-b-$PNAM_{10}$-b-$PDEA_{10}$-b-$PNAM_{10}$-b-$PDMA_{10}$-b-$PNAM_{10}$-b-$PNIPAM_{10}$

c) Octablock homopolymer:
$PNAM_{40}$-b-$PNAM_{40}$-b-$PNAM_{40}$-b-$PNAM_{40}$-b-$PNAM_{40}$-b-$PNAM_{40}$-b-$PNAM_{40}$-b-$PNAM_{40}$

d) Pentablock copolymer:
$PNAM_{100}$-b-$PDMA_{100}$-b-$PNAM_{100}$-b-$PDEA_{100}$-b-$PNAM_{100}$

e) Pentablock copolymer:
$PNAM_{100}$-b-$PDMA_{100}$-b-$PNAM_{100}$-b-$PHEAm_{100}$-b-$PNAM_{100}$

the production of larger multiblock copolymers (e.g., going from a DP 10 per block to a DP 100).

Optimization of Polymerization Time. In our previous work,[66] each block required 24 h to reach full monomer conversion. Such a long polymerization time makes large-scale production of multiblock copolymers unrealistic. Our first goal was then to tune the polymerization conditions to reach full monomer conversion in only a few hours while keeping a similar MW control and a similar fraction of living chains. This objective is challenging, as it is often suggested in the literature that an increase in the rate of polymerization (i.e., increase in propagating radicals concentration, $[P\cdot]$) leads to an increase in the termination rate (i.e., proportional to $[P\cdot]^2$) and hence a decrease in livingness.[67] In a degenerative transfer system such as RAFT, because the number of dead chains is only governed by the number of radicals generated throughout the polymerization, the rate at which these radicals are generated does not influence the livingness but only the rate at which those radicals terminate (i.e., decreasing the final monomer conversion over the same time). It follows that an increase in the rate of radical generation by using an initiator possessing a high decomposition rate coefficient (k_d) should allow one to speed up the polymerization without affecting the livingness.

This concept was illustrated by mimicking our previous work based on the RAFT polymerization of the monomer NAM in the presence of initiator ACVA at 70 °C[66] and replacing ACVA by VA-044 (Scheme 2, half-life time of 10 h at 44 °C). At this temperature, VA-044 undergoes ~95% decomposition in 2 h compared with 85% for ACVA in 24 h (Figure S1 in the Supporting Information). A model decablock poly(4-acryloyl-morpholine) (Scheme 3a) was prepared under new conditions (i.e., H_2O/dioxane/VA-044/70 °C/2 h per block) and compared with our previous system (H_2O/ACVA/70 °C/24 h per block).[66] As previously observed, the synthesis of the first block requires a slightly higher concentration in initiator due to the induction period caused by the slow consumption of the initial CTA.[68−70]

An initial monomer concentration ($[NAM]_0$) of 3 M (giving a workable solution viscosity) in a 20% dioxane aqueous solution (to facilitate solubilization of the CTA) and initiator concentration ($[VA-044]_0$) of 7.50×10^{-4} M (Table S1 in the Supporting Information) led to full monomer conversion in 2 h (Figure S2 in the Supporting Information). This low initiator concentration represents an initial ratio $[CTA]_0/[VA-044]_0$ of 400, which theoretically leads to a very high fraction of living chains at the end of the first block ($L \approx 99.8\%$). The subsequent block extensions did not require dioxane because the macroCTA is fully water-soluble. It was interesting to note that a much lower initiator concentration achieved full monomer conversion ($[VA-044]_0 = 2.17 \times 10^{-4}$ M, Figure S3 in the Supporting Information)

for subsequent block extensions, consistent with the existence of a strong induction period during the synthesis of the first block. (Chain-length-dependent k_p and k_t would also be expected to influence the rate of polymerization to a lesser extent.[71]) This low initiator concentration results in a very high initial ratio $[CTA]_0/[VA\text{-}044]_0$, ranging from 400 to 160 throughout the whole process, a range that is very similar to the ratio $[CTA]_0/[ACVA]_0$ for a polymerizations 12 times slower for each block (24 h).[66] Such a high ratio should lead in theory to a very low fraction of dead chains initiated either by the CTA (∼3.4% in number) or by VA-044 (∼0.1% in number),[66] even after nine successful reinitiations. Figure 1b shows the MWDs shifting perfectly to higher molecular weights for each new block, confirming experimentally the high livingness of the final polymer as expected from theory ($L \approx 97\%$, run 1 in Table 1). In addition, the plot of the experimental number-average molecular weight versus the number of blocks (Figure 1c) shows a perfect linear increase, which confirms the negligible fraction of initiator-derived chains still living (3.4% in number) or dead (0.1% in number). The discrepancy observed between the $M_{n,SEC}$ and the $M_{n,th.}$ is due to the difference of hydrodynamic volume between PNAM and PSty used as molecular weight standards. The final decablock $[PNAM_{10}]_{10}$ has a theoretical number percentage of α,ω-functional polymer chains as high as 93% (run 1 in Table 1 and Table S2 in the Supporting Information). Finally, an overlay of the MWDs of the two same decablock poly(4-acryloylmorpholine) synthesized in $10 \times 24\,h$ = 240 h (our previous work)[66] and $10 \times 2\,h$ = 20 h (Figure 2), respectively, shows that the control of the MWD is the same even after nine reinitiations ($Đ = 1.15$ for both). The perfect alignment of the two final MWDs is remarkable and demonstrates the successful optimization of increasing the polymerization rate by a factor 12 by simply changing the nature of the azoinitiator while also highlighting the high hydrolytic stability of the CTA in water.

Preparation of Highly Complex Multiblock Copolymer. To demonstrate the level of structural complexity that can be easily achieved via our approach, a more complex multiblock copolymer was attempted comprising four different acrylamide monomers (*N,N*-dimethyl acrylamide, DMA; *N,N*-diethyl acrylamide, DEA; *N*-isopropylacrylamide, NIPAM; and NAM; Scheme 2). Our target was a dodecablock copolymer comprising two similar sequences of six blocks each (PNAM-*b*-PDEA-*b*-PNAM-*b*-PDMA-*b*-PNAM-*b*-PNIPAM) and with an average DP of 10 per block (Scheme 3b). The optimized conditions (H_2O/VA-044/70 °C/2 h per block) previously determined with the model decablock $[PNAM_{10}]_{10}$ were used (Table S3 in the Supporting Information) with a ratio H_2O/dioxane of 80/20 kept constant over the course of the polymerizations to avoid possible precipitation of the water thermoresponsive PDEA and PNIPAM. Indeed, attempts to perform the polymerization in <20% dioxane led to low polymer solubility and a loss of molecular weight control. Several initial tests were required to determine the amount of VA-044 necessary to reach full conversion because the k_p values differ between each monomer.

Full overall monomer conversions for each block (>99%) were confirmed by ^1H NMR spectroscopy (Figure 3a, Table S4 in the Supporting Information). Analysis of the MWDs revealed monomodal distributions with a clear shift to higher molecular weights after each monomer addition (Figure 3b). Some low-molecular-weight tailing was observed after each block extension, ascribed to the accumulation of initiator-derived chains (initiator moiety at α-end; ∼8% in number after 12 blocks, comprising
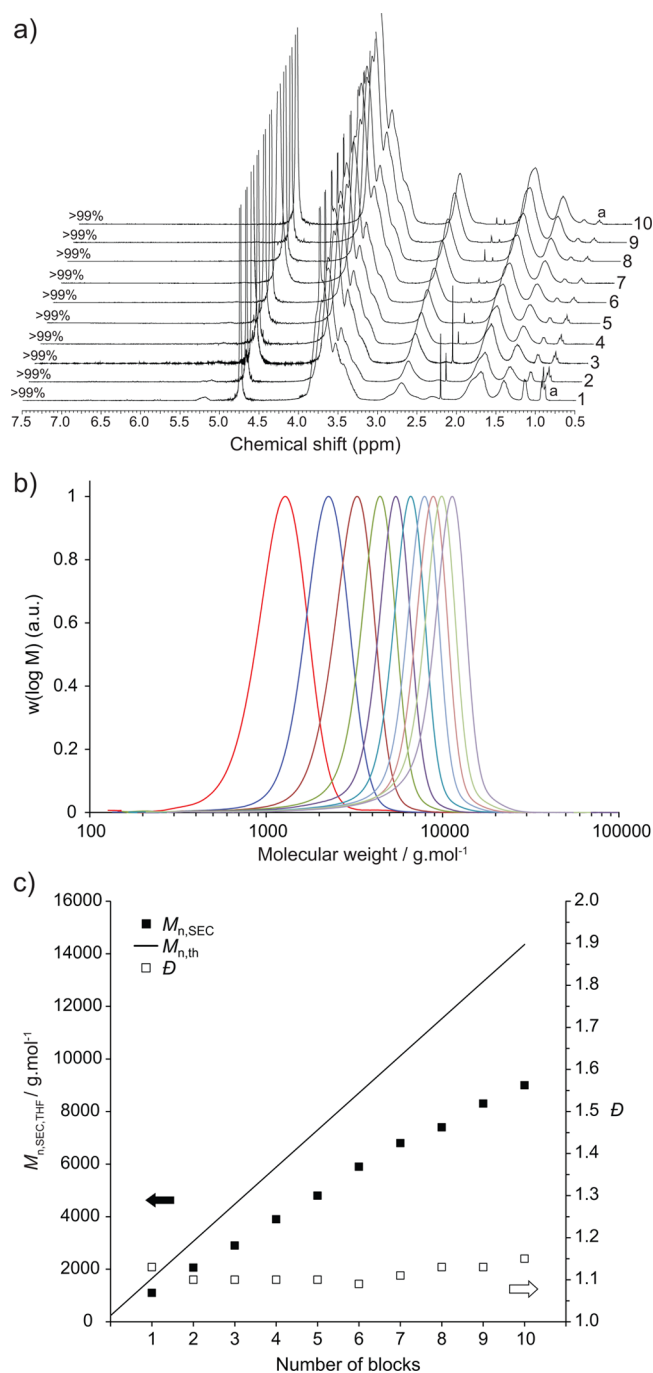
Figure 1. (a) ^1H NMR spectra (D_2O, 300 MHz) showing the conversion of 4-acryloylmorpholine for each new block after 2 h of iterative RAFT polymerizations. (b) MWDs for successive chain extension of the decablock poly(4-acryloylmorpholine) ($[PNAM_{10}]_{10}$) (Scheme 3a) in H_2O at 70 °C with VA-044 as initiator (2 h per block). (c) Evolution of number-average molecular weights and dispersities with the number of blocks for the preparation of the decablock $[PNAM_{10}]_{10}$. The black line represents the theoretical molecular weight calculated from eq 1. Full squares represent the experimental molecular weight from SEC. Empty squares represent the dispersity values from SEC.

7.6% living and 0.4% dead chains), and dead polymer chains initiated by the CTA (∼7% in number after 12 blocks), leading to the dispersity continuously increasing from 1.2 to 1.4 (Figure 3c, Table S4 in the Supporting Information). This higher increase in dispersity in comparison with the previous decablock

Table 1. Summary of the Characteristics of the Multiblock Copolymers Synthesized in This Study

run	final multiblock copolymer	$M_{n,th}$ (g mol^{-1})^a	$M_{n,SEC}$ (g mol^{-1})	$Đ^b$	% L^c	% α,ω functional chains^d
1	**decablock homopolymer a** PNAM$_{10}$-b-PNAM$_{10}$-b-PNAM$_{10}$-b-PNAM$_{10}$-b-PNAM$_{10}$-b-PNAM$_{10}$-b-PNAM$_{10}$-b-PNAM$_{10}$-b-PNAM$_{10}$-b-PNAM$_{10}$	14 300	9000^e	1.15	96.6	93.1
2	**dodecablock copolymer b** PNAM$_{10}$-b-PDEA$_{10}$-b-PNAM$_{10}$-b-PDMA$_{10}$-b-PNAM$_{10}$-b-PNIPAM$_{10}$-b-PNAM$_{10}$-b-PDEA$_{10}$-b-PNAM$_{10}$-b-PDMA$_{10}$-b-PNAM$_{10}$-b-PNIPAM$_{10}$	15 300	11700^f	1.41^g	92.3	84.7
3	**octablock homopolymer c** PNAM$_{40}$-b-PNAM$_{40}$-b-PNAM$_{40}$-b-PNAM$_{40}$-b-PNAM$_{40}$-b-PNAM$_{40}$-b-PNAM$_{40}$-b-PNAM$_{40}$	44 700	22600^e	1.33	91.9	84.0
4	**pentablock copolymer d** PNAM$_{100}$-b-PDMA$_{100}$-b-PNAM$_{100}$-b-PDEA$_{100}$-b-PNAM$_{100}$	63 500	39200^f	1.47	93.5	87.3
5	**pentablock copolymer e** PNAM$_{100}$-b-PDMA$_{100}$-b-PNAM$_{100}$-b-PHEAm$_{100}$-b-PNAM$_{100}$	63 300	52900^h	1.27^h	93.3	87.0

^{a}See eq 1 for $M_{n,th}$ calculation. ^{b}Dispersity $Đ = M_w/M_n$. ^{c}L = theoretical number fraction of living chain determined via eq 2. ^{d}Theoretical percentage of polymer chains having dual functionalities (R and Z group) at the end of the run if only bimolecular termination occurs (no side reactions).[66] ^{e}Determined by SEC/RI in THF with PSty used as molecular weight standards. ^{f}Determined by SEC/RI in DMF with PMMA used as molecular weight standards. ^{g}A final dispersity of 1.22 was found after analysis with a different SEC-DMF system. (See Figure S4 in the Supporting Information.) ^{h}Determined with a different SEC/RI instrument (see Methods in the Supporting Information); SEC-DMF with PMMA standards.

Figure 2. Comparison of final MWDs (tenth block) obtained for the decablock [PNAM$_{10}$]$_{10}$ synthesized in H$_2$O at 70 °C with the initiator ACVA (24 h per block)[66] and the same decablock [PNAM$_{10}$]$_{10}$ synthesized in H$_2$O at 70 °C with the initiator VA-044 (2 h per block).

[PNAM$_{10}$]$_{10}$ is attributed to three parameters: (1) the different nature of monomer used, (2) the higher number of blocks targeted, which required much higher initial initiator concentration to reach full monomer conversion, and (3) the multiblock copolymer analysis performed with a different SEC system (here in DMF, previously in THF; see the comparison in MWDs and $Đ$ obtained for the same dodecablock copolymer between two different SEC-DMF system in Figure S4 in the Supporting Information). The difference in dispersity observed for the first block PNAM$_{10}$ in the decablock and the dodecablock (i.e., 1.13 vs 1.24, respectively) is due again to the different SEC system used (SEC,DMF vs SEC,THF previously) and not to a lack of molecular weight control. As a result of the high number of blocks targeted, the ratio [CTA]$_0$/[ACVA]$_0$ significantly decreases from 400 to 79 for the final block. However, after 12 cycles, the theoretical number fraction of living chains is still high, ~92% (run 2 in Table 1) and is clearly illustrated experimentally by the good control over the MWDs (Figure 3b). Although the evolution of the experimental molecular weight ($M_{n,SEC}$) with the number of blocks (Figure 3c) cannot be plotted accurately because blocks of different nature considerably affect the hydrodynamic volume of the multiblock copolymer, a linear

evolution is still observed, confirming that the number of initiator-derived chains is negligible in comparison with the total number of CTA. The final dodecablock copolymer has a theoretical percentage of α,ω-functional polymer chains as high as 85% (run 2 in Table 1 and Table S4 in the Supporting Information).

Limitations of the Process. The livingness of a system is strongly correlated with the DP targeted; our next target was to assess if multiblock copolymers exhibiting longer blocks could be well-controlled using our conditions. We attempted the synthesis of a model multiblock homopolymer, which comprised eight blocks of NAM with a DP of 40 each (Scheme 3c). The first step was again to determine what minimum initiator concentration was necessary to reach full monomer conversion for the first two blocks. The initial monomer concentration [NAM]$_0$ was decreased to 2.5 M instead of 3 M previously to reduce the viscosity (higher molecular weight polymer would lead to higher viscosity). The ratio H$_2$O/dioxane was increased to 90/10 (instead of 80/20 when DP 10 was targeted) for the first block because targeting a higher DP requires less initial amount of CTA (i.e., less amount of dioxane needed for CTA solubilization) (Table S5 in the Supporting Information).

We observed that reaching full monomer conversion requires a much lower initiator concentration for the first block when targeting a DP of 40 ([VA-044]$_0$ = 2.50 × 10^{-4} M) than when targeting a DP of 10 ([VA-044]$_0$ = 7.5 × 10^{-4} M) (runs 1 and 2 in Table S6 in the Supporting Information). This result is in agreement with a reduction in the induction period and, to a lesser extent, in the retardation due to a lower initial CTA concentration. For the second block, the required initiator concentration was similar for DP 40 and DP 10 ([VA-044]$_0$ = 1.1 × 10^{-4} and 2.2 × 10^{-4} M, respectively) (runs 3 and 4 in Table S6 in the Supporting Information). This result is consistent with the low-molecular-weight CTA having been converted to macro-CTA. Finally, for the subsequent blocks, a constant initiator concentration of ~1 × 10^{-4} M was found suitable to obtain full monomer conversion (Figure 4a, Table S7 in the Supporting Information). Despite this low initiator concentration, the ratio [macroCTA]$_0$/[VA-044]$_0$ decreased dramatically from 250 to 48 after eight blocks due to the low initial amount of CTA (because of the high DP targeted).
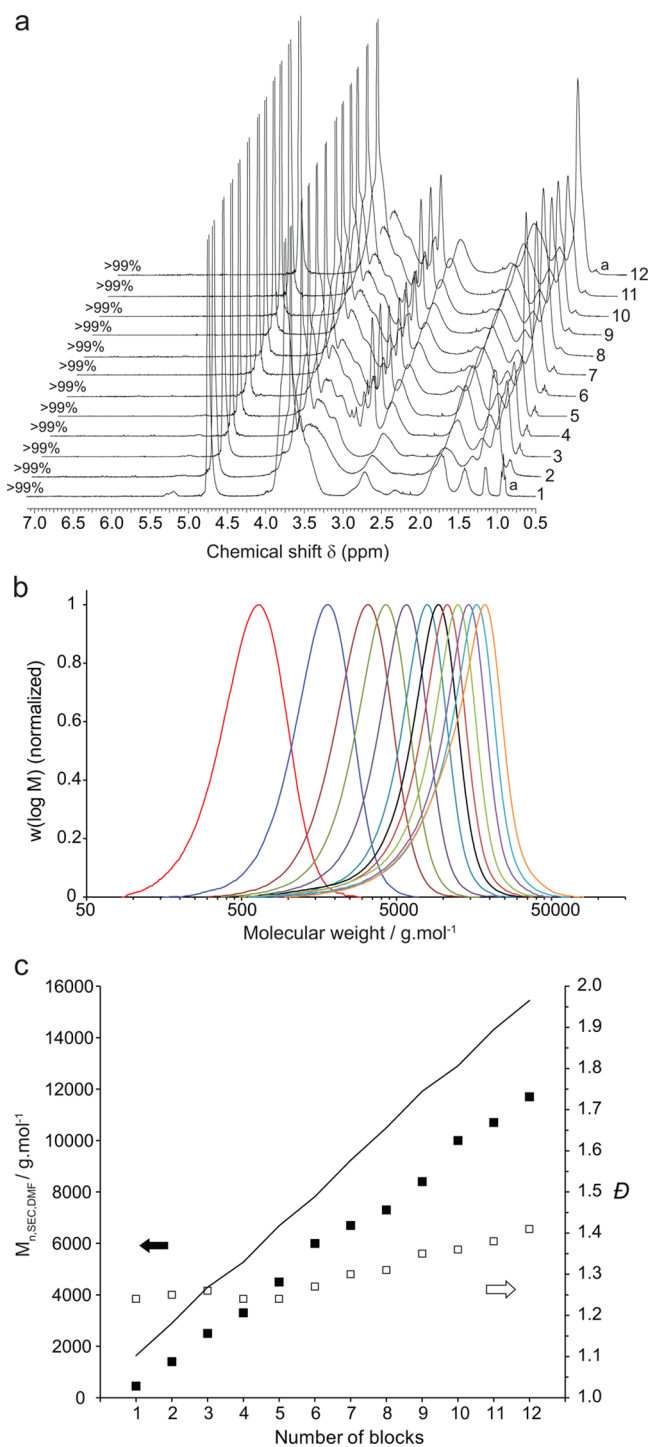
a

b

c

Figure 3. (a) ^{1}H NMR spectra (D$_2$O, 300 MHz) showing the monomer conversion for each block after 2 h of iterative RAFT polymerization. (b) MWDs for successive block extensions of the dodecablock copolymer (Scheme 3b) in water/dioxane 80/20 at 70 °C with VA-044 as initiator (2 h per block). (c) evolution of number-average molecular weights and dispersity values with the number of blocks for the preparation of the dodecablock copolymer. The black line represents the theoretical molecular weight calculated from eq 1. Full squares represent the experimental molecular weight from SEC. Empty squares represent the dispersity values from SEC.

Analysis of the MWDs revealed monomodal distributions with a clear shift to higher molecular weights after each monomer addition (Figure 4b). However, some low-molecular-weight

a)

b)

c)
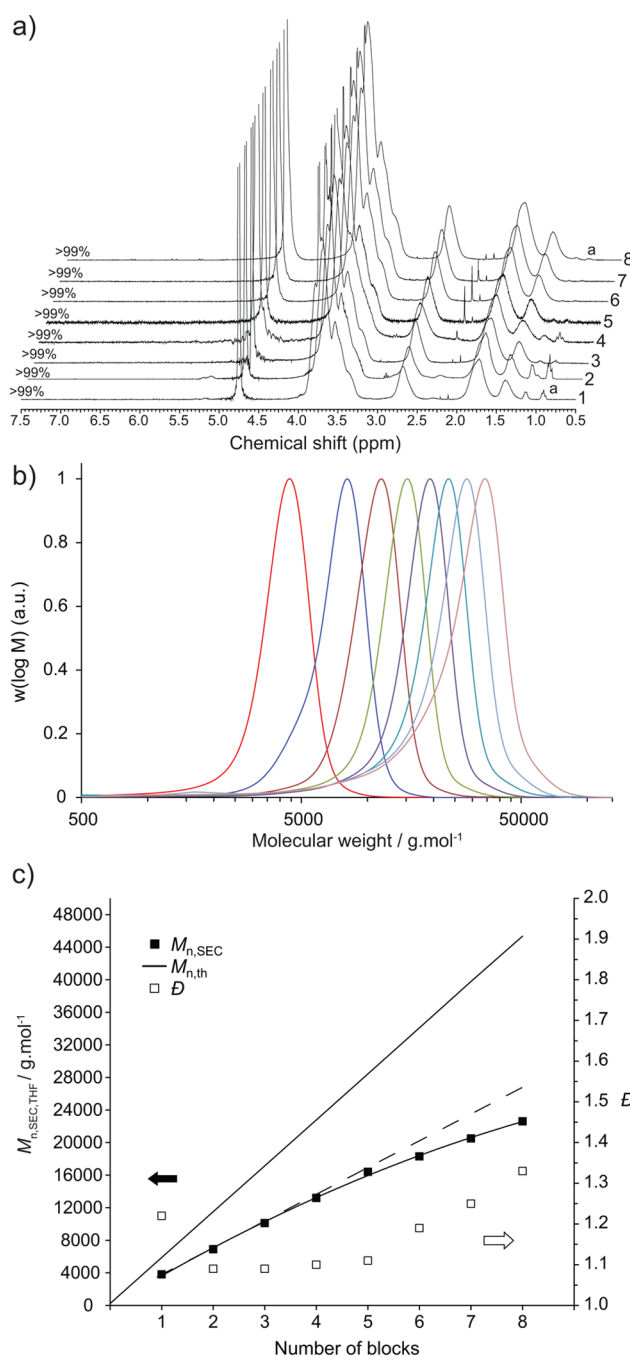
Figure 4. (a) ^{1}H NMR spectra (D$_2$O, 300 MHz) showing the conversion of 4-acryloylmorpholine for each new block after 2 h of iterative RAFT polymerizations. (b) MWDs for successive chain extension of the octablock poly(4-acryloylmorpholine) ([PNAM$_{40}$]$_8$) (Scheme 3c) in H$_2$O at 70 °C with VA-044 as initiator (2 h per block). (c) Evolution of number-average molecular weights and dispersity values with the number of blocks for the preparation of the octablock [PNAM$_{40}$]$_8$. The black line represents the theoretical molecular weight calculated from eq 1. Full squares represent the experimental molecular weight from SEC. Empty squares represent the dispersity values from SEC.

tailing is observed after each block extension, and the tailing becomes more pronounced after the fifth block, presumably due to the accumulation of initiator-derived chains (~4.9% in number, comprising 4.8% living and 0.1% dead chains) and dead polymer chains initiated by the CTA (~4.7% in number

after six blocks). An impact is observed on $M_{n,exp}$, which starts to deviate downward from linearity (Figure 4c). However, this negative deviation is not in agreement with theory: $M_{n,th}$ versus number of blocks remains linear throughout the process. A negative deviation of the $M_{n,SEC}$ could be explained by some chain-transfer reactions to monomer, to solvent, or to polymer followed by β-scission. However, evidence of such side reactions has not been observed for the previous multiblock PNAM. The consequence is an increase in the dispersity values after the fifth block from 1.10 to 1.33 (Figure 4c, Table S7 in the Supporting Information). Finally, after eight cycles, the theoretical number fraction of living chains is ~92% (run 3 in Table 1), compared with 97% for the decablock $[PNAM_{10}]_{10}$. This experiment confirms that raising the targeted DP per block causes a decrease in livingness and overall control over MWD.

Pushing the Limit of the Process. To demonstrate the level of complexity that can be achieved via one-pot sequential RAFT polymerization, we targeted two more complex multiblock copolymers (Scheme 3d,e). The first one, a pentablock copolymer possessing three different acrylamide monomers (DMA, DEA, and NAM) with a DP 100 for each block, is clearly challenging because extending a chain four times to full conversion at such high DP may strongly affect its livingness. The optimized conditions (H₂O/VA-044/70 °C/2 h per block) used for the previous multiblock copolymer syntheses were employed, although the presence of a PDEA, a thermoresponsive polymer with a LCST ~30 °C, as the fourth block significantly complicated the system. The ratio H₂O/dioxane was thus reduced to 70/30 in this stage, allowing better solubility of the multiblock copolymer during the whole process. For the synthesis of the first block, a very low initiator concentration ($[VA\text{-}044]_0 = 1.0 \times 10^{-4}$ M) was required to reach full conversion, as the initial amount of CTA was kept low by the high DP of 100 targeted (Figure 5a). For the subsequent blocks, optimized amounts of initiator were determined. For the second and the fourth blocks ($PDMA_{100}$ and $PDEA_{100}$), higher initiator concentrations were required (Table S8 in the Supporting Information). Consequently, the ratio $[macroCTA]_0/[VA\text{-}044]_0$ drops from 99 to 30 from the third to the fourth block but increases to 60 for the fifth block.

The MWDs were monomodal with a clear shift to higher molecular weights after each monomer addition (Figure 5b). However, the final MWD appears quite broad with a final dispersity around 1.5, probably due to (1) the large accumulation of initiator-derived chains (~6.5%, comprising 6.2% living and 0.3% dead chains) and (2) dead polymer chains initiated by the CTA (~6.2% in number). However, it cannot be excluded that the thermoresponsiveness of the fourth block in water at 70 °C also affects the final block extension by imparting partial inhomogeneity in the multiblock copolymer. As a further proof of evidence of solubility issue, another similar pentablock copolymer was synthesized by replacing the PDEA block by a nonstimuli responsive one, poly(hydroxyethyl acrylamide) (PHEAm) (Scheme 3e and Table S10 in the Supporting Information). This final pentablock copolymer shows a better MW control with a final dispersity below 1.3. (See Figure S5 in the Supporting Information.) In both cases, the quality of the molecular weight control is remarkable for such challenging multiblocks structures, as demonstrated by the linear increase in the $M_{n,exp}$ with the number of blocks (Figure 5c and Figure S5c in the Supporting Information). The theoretical number fraction of living chains for both pentablock copolymers remains high at ~94% (runs 4 and 5 in Table 1 and Table S9 in the Supporting
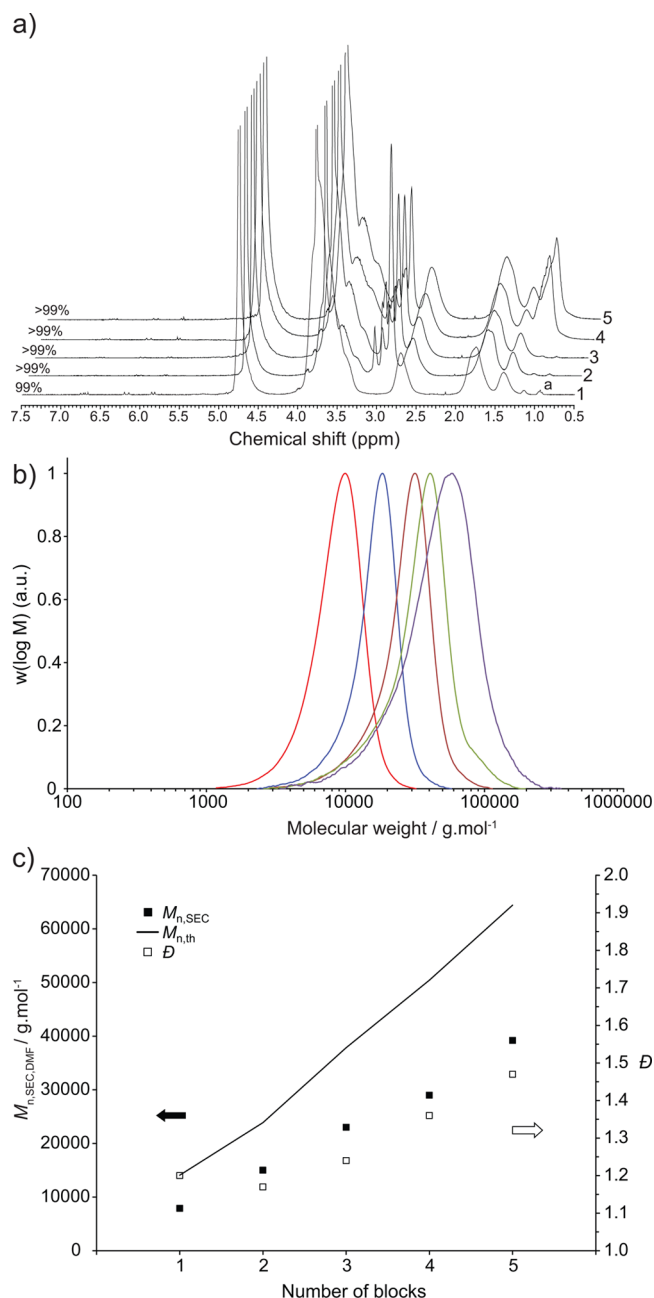

Figure 5. (a) ¹H NMR spectra (D₂O, 300 MHz) showing the monomer conversion for each block after 2 h of iterative RAFT polymerization. (b) MWDs for successive block extensions of the pentablock copolymer in water/dioxane 70/30 at 70 °C with VA-044 as initiator (2 h per block). (c) Evolution of number-average molecular weights and dispersity values with the number of blocks for the preparation of the pentablock copolymer d (Scheme 3). The black line represents the theoretical molecular weight calculated from eq 1. Full squares represent the experimental molecular weight from SEC. Empty squares represent the dispersity values from SEC.

Information). The successfully synthesis of such a demanding multiblock copolymers demonstrates well the high efficiency of the optimized RAFT conditions developed in this study.

■ CONCLUSIONS

A key feature of degenerative transfer radical polymerization techniques is the ability to tune *independently* the system in terms of polymerization rate and fraction of living chains through an

appropriate choice of initiator concentration and general polymerization conditions (temperature, solvent, etc.). In this work, we have exploited this feature and greatly optimized the RAFT system to enable the fast synthesis (2 h per block) of multiblock copolymer to full conversion, without requiring any intermittent purification steps. The key element of our approach is to replace the azoinitiator ACVA by the azoinitiator VA-044, which almost fully decomposes in only 2 h at 70 °C. This optimized approach has been successfully applied for the preparation of very-well-defined multiblock copolymers such as a model decablock homopolymer $[PNAM_{10}]_{10}$ ($Đ$ = 1.15) synthesized in only 20 h and with a very high theoretical number fraction of living chains of ∼97% after nine successive reinitiations. Remarkably, this decablock $[PNAM_{10}]_{10}$ exhibits the same level of control as the one synthesized in 240 h with the azoinitiator ACVA, demonstrating that we successfully reduced the time of polymerization by a factor 12 without a concomitant loss of livingness.

Our strategy was then successfully applied to the production of a more complex dodecablock copolymer, comprising four different acrylamide monomers distributed in two sequences of six blocks with a final dispersity of 1.4 and a theoretical number fraction of living chains ∼92% after 11 successive block extensions. Importantly, the ratio H_2O/dioxane has to be tuned to adapt the RAFT conditions to the nature of the monomer being polymerized. Finally, we have shown that these optimized conditions were also efficient for the production of multiblock copolymer with higher DP per block. Although it is much more demanding to target higher DP in terms of livingness, we successfully prepared an octablock $[PNAM_{40}]_8$ with a DP of 40 per block and two complex pentablock copolymers with a DP of 100 per block. The final dispersity below 1.3 to 1.5 and the theoretical fraction of living chains (92−94%) remains quite good for such complex macromolecules. These challenging multiblock copolymers also reveal the limitation of the RAFT process for the production of larger multiblock copolymers. The access to such a high level of complexity in polymer microstructure via such a manageable synthetic route (quantitative conversion for each block, no purification needed, no stringent reaction conditions, short 2 h polymerization times) offers new perspectives as a step toward sequence control in synthetic polymers.

ASSOCIATED CONTENT

⑤ Supporting Information

Details of methods and results. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Goto, A.; Fukuda, T. *Prog. Polym. Sci.* **2004**, *29*, 329−385.
(2) Braunecker, W. A.; Matyjaszewski, K. *Prog. Polym. Sci.* **2007**, *32*, 93−146.
(3) Zetterlund, P. B.; Kagawa, Y.; Okubo, M. *Chem. Rev.* **2008**, *108*, 3747−3794.
(4) Jenkins, A. D.; Jones, R. G.; Moad, G. *Pure Appl. Chem.* **2010**, *82*, 483−491.
(5) Moad, G.; Rizzardo, E. *Macromolecules* **1995**, *28*, 8722−8728.
(6) Hawker, C. J.; Bosman, A. W.; Harth, E. *Chem. Rev.* **2001**, *101*, 3661−3688.
(7) Nicolas, J.; Guillaneuf, Y.; Lefay, C.; Bertin, D.; Gigmes, D.; Charleux, B. *Prog. Polym. Sci.* **2013**, *38*, 63−235.
(8) Kamigaito, M.; Ando, T.; Sawamoto, M. *Chem. Rev.* **2001**, *101*, 3689−3745.
(9) Matyjaszewski, K.; Xia, J. H. *Chem. Rev.* **2001**, *101*, 2921−2990.
(10) Matyjaszewski, K. *Macromolecules* **2012**, *45*, 4015−4039.
(11) Lutz, J. F. *Polym. Chem.* **2010**, *1*, 55−62.
(12) Barner-Kowollik, C.; Lutz, J.-F.; Perrier, S. *Polym. Chem.* **2012**, *3*, 1677−1679.
(13) Badi, N.; Chan-Seng, D.; Lutz, J.-F. *Macromol. Chem. Phys.* **2013**, *214*, 135−142.
(14) Lutz, J. F.; Ouchi, M.; Liu, D. R.; Sawamoto, M. *Science* **2013**, *341*, 628−636.
(15) Schmidt, B.; Barner-Kowollik, C. *Nat. Chem.* **2013**, *5*, 990−992.
(16) Benoit, D.; Hawker, C. J.; Huang, E. E.; Lin, Z.; Russell, T. P. *Macromolecules* **2000**, *33*, 1505−1507.
(17) Pfeifer, S.; Lutz, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 9542−9543.
(18) Badi, N.; Lutz, J.-F. *Chem. Soc. Rev.* **2009**, *38*, 3383−3390.
(19) Satoh, K.; Ozawa, S.; Mizutani, M.; Nagai, K.; Kamigaito, M. *Nat. Commun.* **2010**, *1*, 6.
(20) Lutz, J.-F. *Nat. Chem.* **2010**, *2*, 84−85.
(21) Tong, X.; Guo, B.-h.; Huang, Y. *Chem. Commun.* **2011**, *47*, 1455−1457.
(22) Ouchi, M.; Badi, N.; Lutz, J. F.; Sawamoto, M. *Nat. Chem.* **2011**, *3*, 917−924.
(23) Schmidt, B.; Fechler, N.; Falkenhagen, J.; Lutz, J. F. *Nat. Chem.* **2011**, *3*, 234−238.
(24) Zamfir, M.; Theato, P.; Lutz, J.-F. *Polym. Chem.* **2012**, *3*, 1796−1802.
(25) Altintas, O.; Barner-Kowollik, C. *Macromol. Rapid Commun.* **2012**, *33*, 958−971.
(26) Chan-Seng, D.; Zamfir, M.; Lutz, J.-F. *Angew. Chem., Int. Ed.* **2012**, *51*, 12254−12257.
(27) Houshyar, S.; Keddie, D. J.; Moad, G.; Mulder, R. J.; Saubern, S.; Tsanaktsidis, J. *Polym. Chem.* **2012**, *3*, 1879−1889.
(28) Kakuchi, R.; Zamfir, M.; Lutz, J.-F.; Theato, P. *Macromol. Rapid Commun.* **2012**, *33*, 54−60.
(29) Hisano, M.; Takeda, K.; Takashima, T.; Jin, Z.; Shiibashi, A.; Matsumoto, A. *Macromolecules* **2013**, *46*, 3314−3323.
(30) Lutz, J.-F. *Acc. Chem. Res.* **2013**, *46*, 2696−2705.
(31) Vandenbergh, J.; Reekmans, G.; Adriaensens, P.; Junkers, T. *Chem. Commun.* **2013**, *49*, 10358−10360.
(32) Hisano, M.; Takeda, K.; Takashima, T.; Jin, Z.; Shiibashi, A.; Matsumoto, A. *Macromolecules* **2013**, *46*, 3314−3323.
(33) Solleder, S. C.; Meier, M. A. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 711−714.
(34) Espeel, P.; Carrette, L. L. G.; Bury, K.; Capenberghs, S.; Martins, J. C.; Du Prez, F. E.; Madder, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 13261−13264.
(35) Borner, H. G. *Macromol. Rapid Commun.* **2011**, *32*, 115−126.
(36) Eastwood, E. A.; Dadmun, M. D. *Macromolecules* **2002**, *35*, 5069−5077.
(37) Ruzette, A. V.; Leibler, L. *Nat. Mater.* **2005**, *4*, 19−31.
(38) Jones, R. *Nat. Nanotechnol.* **2008**, *3*, 699−700.
(39) Bates, F. S.; Hillmyer, M. A.; Lodge, T. P.; Bates, C. M.; Delaney, K. T.; Fredrickson, G. H. *Science* **2012**, *336*, 434−440.
(40) Schacher, F. H.; Rupar, P. A.; Manners, I. *Angew. Chem., Int. Ed.* **2012**, *51*, 7898−7921.

(41) Zhang, Q.; Collins, J.; Anastasaki, A.; Wallis, R.; Mitchell, D. A.; Becer, C. R.; Haddleton, D. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4435−4439.

(42) Hadjiantoniou, N. A.; Triftaridou, A. I.; Kafouris, D.; Gradzielski, M.; Patrickios, C. S. *Macromolecules* **2009**, *42*, 5492−5498.

(43) Darling, S. B. *Prog. Polym. Sci.* **2007**, *32*, 1152−1204.

(44) Hosono, N.; Gillissen, M. A. J.; Li, Y.; Sheiko, S. S.; Palmans, A. R. A.; Meijer, E. W. *J. Am. Chem. Soc.* **2012**, *135*, 501−510.

(45) Mai, Y.; Eisenberg, A. *Chem. Soc. Rev.* **2012**, *41*, 5969−5985.

(46) Zhang, J.; Lu, Z.-Y.; Sun, Z.-Y. *Soft Matter* **2013**, *9*, 1947−1954.

(47) Minoda, M.; Sawamoto, M.; Higashimura, T. *Macromolecules* **1990**, *23*, 4889−4895.

(48) You, Y. Z.; Hong, C. Y.; Pan, C. Y. *Chem. Commun.* **2002**, 2800−2801.

(49) Gemici, H.; Legge, T. M.; Whittaker, M.; Monteiro, M. J.; Perrier, S. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 2334−2340.

(50) Boyer, C.; Soeriyadi, A. H.; Zetterlund, P. B.; Whittaker, M. R. *Macromolecules* **2011**, *44*, 8028−8033.

(51) Zhao, G.; Zhang, P.; Zhang, C.; Zhao, Y. *Polym. Chem.* **2012**, *3*, 1803−1812.

(52) Boyer, C.; Derveaux, A.; Zetterlund, P. B.; Whittaker, M. R. *Polym. Chem.* **2012**, *3*, 117−123.

(53) Fetsch, C.; Luxenhofer, R. *Macromol. Rapid Commun.* **2012**, *33*, 1708−1713.

(54) Nakatani, K.; Ogura, Y.; Koda, Y.; Terashima, T.; Sawamoto, M. *J. Am. Chem. Soc.* **2012**, *134*, 4373−4383.

(55) Zhang, Q.; Wilson, P.; Li, Z. D.; McHale, R.; Godfrey, J.; Anastasaki, A.; Waldron, C.; Haddleton, D. M. *J. Am. Chem. Soc.* **2013**, *135*, 7355−7363.

(56) Lv, A.; Deng, X.-X.; Li, L.; Li, Z.-L.; Wang, Y.-Z.; Du, F.-S.; Li, Z.-C. *Polym. Chem.* **2013**, *4*, 3659−3662.

(57) Debuigne, A.; Detrembleur, C.; Jérôme, C.; Junkers, T. *Macromolecules* **2013**, *46*, 8922−8931.

(58) Hadjiantoniou, N. A.; Krasia-Christoforou, T.; Loizou, E.; Porcar, L.; Patrickios, C. S. *Macromolecules* **2010**, *43*, 2713−2720.

(59) Vandenbergh, J.; Ogawa, T. D.; Junkers, T. *J. Polym. Sci., Part A: Polym. Chem.* **2013**, *51*, 2366−2374.

(60) Soeriyadi, A. H.; Boyer, C.; Nystrom, F.; Zetterlund, P. B.; Whittaker, M. R. *J. Am. Chem. Soc.* **2011**, *133*, 11128−11131.

(61) Anastasaki, A.; Waldron, C.; Wilson, P.; Boyer, C.; Zetterlund, P. B.; Whittaker, M. R.; Haddleton, D. *ACS Macro Lett.* **2013**, 896−900.

(62) Gody, G.; Maschmeyer, T.; Zetterlund, P. B.; Perrier, S. *Nat. Commun.* **2013**, *4*, 2505.

(63) Wu, Y.; Wang, Q. *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 2425−2429.

(64) Keddie, D. J.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **2012**, *45*, 5321−5342.

(65) Keddie, D. J. *Chem. Soc. Rev.* **2013**, *43*, 496−505.

(66) Gody, G.; Maschmeyer, T.; Zetterlund, P. B.; Perrier, S. *Macromolecules* **2014**, *47*, 639−649.

(67) Zhong, M. J.; Matyjaszewski, K. *Macromolecules* **2011**, *44*, 2668−2677.

(68) McLeary, J. B.; Calitz, F. M.; McKenzie, J. M.; Tonge, M. P.; Sanderson, R. D.; Klumperman, B. *Macromolecules* **2004**, *37*, 2383−2394.

(69) Barner-Kowollik, C.; Buback, M.; Charleux, B.; Coote, M. L.; Drache, M.; Fukuda, T.; Goto, A.; Klumperman, B.; Lowe, A. B.; McLeary, J. B.; Moad, G.; Monteiro, M. J.; Sanderson, R. D.; Tonge, M. P.; Vana, P. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 5809−5831.

(70) van den Dungen, E. T. A.; Matahwa, H.; McLeary, J. B.; Sanderson, R. D.; Klumperman, B. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 2500−2509.

(71) Smith, G. B.; Russell, G. T.; Yin, M.; Heuts, J. P. A. *Eur. Polym. J.* **2005**, *41*, 225−230.