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RAFT Multiblock Reactor Telescoping: From Monomers to Tetrablock Copolymers in a Continuous Multistage Reactor Cascade

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Abstract

Well-defined multiblock copolymers were synthesized via reversible addition fragmentation chain transfer radical polymerization in a fully continuous multireactor cascade. The reactor is designed to accommodate a broad variety of monomers to be polymerized to various chain lengths to close to full monomer conversion under identical conditions. Based on theoretical considerations, reactor volumes and reactant concentrations were optimized, and reactions were carried out in reaction times of 40 min and 100 °C in most cases. A broad variety of homo-, diblock-, triblock and tetrablock copolymers were obtained. The reactor can be used for high throughput experimentation and can in principle be operated by non-specialists due to its automated character. Further, the setup allows for upscaling of reactions. The tetrablock copolymer P*n*BuA-*b*-PMA-*b*-PEA-*b*-P*t*BuA was obtained in quantities of 150 g in one day reactor runtime, illustrating the high potential and applicability of continuous flow processes for polymerizations.

Introduction

Today's polymer manufacturing is under pressure to provide tailor-made polymer materials with specific properties at low production costs.[1] Block copolymers are the most frequently sought-after structures, and synthesis costs are closely related to an in-depth understanding of reaction kinetics, thorough optimization and reaction monitoring, and mostly to manual labor. In this respect, the continuous flow manufacturing of functional block copolymers in microstructured reactors is highly desirable. Continuous flow techniques are not only efficient and inherently green approaches, but also allow for operation of reactors by non-specialists.[2] On industrial scale, block copolymers are often prepared via living anionic batch polymerizations.[3] Yet, the discovery of reversible-deactivation radical polymerization (RDRP)[4] made the synthesis of these complex architectures more accessible due to less stringent reaction conditions, even if only in recent years commercial production became more frequent.[5] Nitroxide mediated polymerization (NMP),[6,7] atom transfer radical polymerization (ATRP)[8,9] and reversible addition-fragmentation chain transfer (RAFT) polymerization[10-16] have already been employed for the synthesis of multiblock copolymers. RAFT polymerization is among these different methods the technique which gives access to the broadest range of functionalities, and is in this context the method of choice for multiblock copolymerizations.[10-16] Multiblock copolymerization via RAFT is very efficient when carried out under correct conditions,[12-15] and based on the fundament of previous RAFT multiblock copolymerization studies,[16] we extended the approach to continuous flow processing, making use of reactor telescoping.[17,18] Flow polymerizations offer an improved control over reaction parameters and allow for stable operation over extended periods of time. Designed to simplify the upscale, an ideal heat transfer and thus a uniform temperature distribution is assured throughout the tubes of the home-made flow reactor.[19-21] A combination of both – the RAFT polymerization technique and continuous flow processing – constitutes an ideal tool for the synthesis of functional multiblock copolymers with low dispersities and high end group fidelities, while suppressing possible side reactions related to backbiting and β-scission.[22]
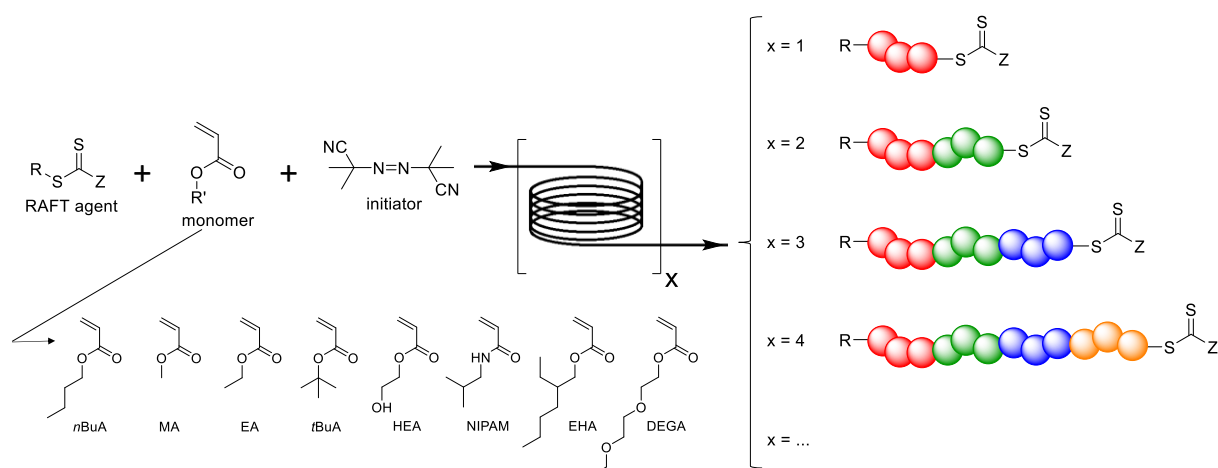
Figure 1. Multistage reactor concept for the synthesis of multiblock copolymers via RAFT.

As mentioned, the versatile RAFT polymerization is often a preferred polymerization technique to access multiblock copolymers.[5,10-14,16] In batch, Perrier and coworkers was the first to obtain an icosablock (20 blocks) copolymer with a narrow molecular weight distribution.[12] Later, the same team reduced the polymerization time from 24h per block to 2h,[13] and later even to 3 min per block.[14] Yet, the employed system is limited to few acrylamide monomers and is thus not applicable to a broader range of monomers, as we will also discuss below. The batch-wise approach also limits the scale of production, even if indeed already impressive amounts of polymer was made. Moad and coworkers investigated the development of high order quasi-block copolymer libraries *via* the use of an automated (batch) synthesizer, to assure a higher throughput.[10,11] Yet, the throughput can be increased even more by employing a flow process – which is not only beneficial for the volume output, but also enhances the polymer end group fidelity due to better isothermicity of flow reactors.[22] Naturally, all characteristics and limitations inherent to the polymerization (e.g. residual dispersity depending on initiator concentrations) itself will not change when transferring to a continuous flow process. The benefits of performing RAFT (homo)polymerizations in flow have been demonstrated by Diehl et al.[23] and Hornung et al.[24] Vandenbergh et al.[16] developed a RAFT pentablock copolymer *via* subsequent copolymerizations in a microchip reactor. A drawback of this process was, however, its sequential approach: after every polymerization step, the polymer is isolated whereby the solvent and residual monomer are evaporated. On the other hand, Hornung et al.[25] described a two-stage

continuous flow process for the synthesis of diblock copolymers without the purification or isolation of the first block. Yet, the use of a commercially available reactor set-up limits the employed reaction conditions drastically since the reactor volume of the second block cannot be adapted. Hence, the residence time for the second block is corresponding with the residence time for the first polymerization and vice versa, limiting the versatility of the system. More recently, Zhu and coworkers[26] reported a similar two-stage continuous flow process for the synthesis of a double hydrophilic block copolymer in water. Yet, reaction conditions were limited towards the synthesis of one specific hydrophilic diblock copolymer (based on 3-sulfopropyl methacrylate potassium salt (SPMA) and poly(ethylene glycol) methyl ether methacrylate (PEGMA)), rather than developing a standard procedure applicable for various multiblock copolymers.

In this study, a simple and comparatively cheap home-made tubular reactor cascade was employed to produce multiblock copolymers *via* RAFT in continuous multistage 'one-flow' process (the flow equivalent to a 'one-pot' batch process). Full monomer conversions are targeted to avoid quasi-block copolymer formation and purification steps of macroRAFT agent.[10,11] A similar approach was already carried out to develop poly(2-oxazoline) triblock copolymers *via* the use of coupled glass chip reactors.[27] However, the use of a home-made tubular reactor cascade is more feasible in this extent, since every reactor volume – and thus the residence time of each separate block – can be adapted at any time. Hence, full monomer conversions and complete initiator consumptions (so called dead end polymerization conditions) will be targeted to avoid any isolation or purification step. Furthermore, the aim of this project is not to synthesize one specific multiblock copolymer, but to develop a more uniform continuous flow procedure towards a large variety of well-defined multiblock copolymers. In this sense, the reactor cannot only be used for facile upscaling and reduction of synthesis costs, but also to screen multiblock copolymer sequences and compositions in a high-throughput approach. In principle, a multistage reactor cascade allows to program the desired sequence at the start of the reaction, and hence fast synthesis of a broad polymer library for further testing. In this extent, a

theoretic approach was followed to determine the required reaction conditions. Important for a programmable sequence is that the reactor can be used under a strict set of conditions to fit all different monomers available for synthesis. In other words, a "one size fits all" strategy must be employed, in which all different monomers must be able to reach quasi-full conversion of monomer in the same reaction time. The use of RAFT polymerizations to synthesize different poly(acrylate)s are ideal for such approach. Yet, as we will show below, high propagation rates are required for successful flow polymerizations in the given setup, thus the methodology cannot be as easily applied to slower propagating monomers such as methacrylates or styrene and further optimization is required before it can be used for these systems. Since an exogenous initiator source is required, reaction times can be adjusted to the half-life time of the initiator, assuming that any polymerization will come to an end (full monomer conversion or not) after 4-5 half-life times as overall reactor residence times. The reactor sequence and individual stage operation can hence be adjusted to the *universal* initiator kinetics rather than the varying monomer propagation rates. In this view, the polymerization of seven different acrylates (*n*-butyl acrylate (*n*BuA), methyl acrylate (MA), ethyl acrylate (EA), *t*-butyl acrylate (*t*BuA), 2-hydroxyethyl acrylate (HEA), 2-ethylhexyl acrylate (EHA) and 2-(2-ethoxyethoxy)ethyl acrylate (DEGA)) was investigated and carried out under the exact same conditions. Acrylates offer a large range of functional groups, are easily tailorable *via* post-modification reactions[28] and are compatible with most organic solvents. To show the versatility of the system, an acrylamide (*N*-isopropyl acrylamide (NIPAM)) was included in the study as well. Next, systematic studies have been carried out on the di- and triblock copolymers with several well-defined sequences, based on these eight monomeric units. Generally, chain lengths of 10 monomer units were targeted during each chain extension, targeting block copolymers for biomedical and electronical applications.[12-14] Longer segment chain lengths can be achieved, but this must be traded off against an increase in dispersity. Different monomer/monomer ratios were targeted as well. The employed procedure could also be extended to synthesize a P*n*BuA-*b*-PMA-*b*-PEA-*b*-P*t*BuA tetrablock copolymer in large quantities (± 150 g) in 26h.

Experimental

Reactor set-ups

A home-made tubular reactor cascade was built, consisting of fluorinated gastight PFA tubing (Advanced Polymer Tubing GmbH, 1/16" OD, 0.75 mm ID), wrapped around a metal framework and placed in a silicon oil bath heated to 100°C on an IKA RCT basic hot plate. Reactor volumes could easily be adapted by varying the length of the reactor tubing. Reaction solutions were pumped into the reactor *via* Knauer Azura P 2.1S HPLC Pumps. Different reactor cascades were built by coupling several tubular reactors in a row *via* the use of a T-piece (Vici, ZT1, 0.75 mm bore, whereby both inlet flows were connected perpendicular to the outlet flow for mixing purposes). At the end of the reactor cascade, a back-pressure regulator of 100 psi was placed to ensure stable flow conditions. Here, a single 0.8 mL tubular reactor was employed for homopolymerizations. A 0.8 mL tubular reactor, was coupled to a 3.6 mL tubular reactor (as depicted in Figure 2) to target diblock copolymers. Triblock copolymerizations were carried out in a [0.8 mL + 3.6 mL + 5.2 mL] tubular reactor cascade, which could further be extended with a 6.8 mL tubular reactor when targeting tetrablock copolymers.
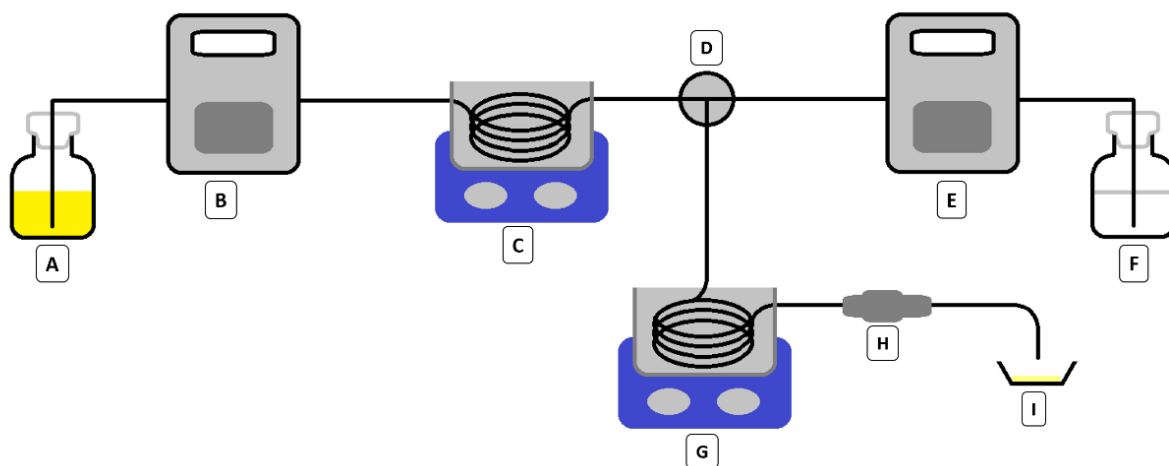
Figure 2: Schematic flow chart of a tubular reactor cascade, consisting of 2 reactor units. A. Stock solution of Monomer 1, DoPAT and AIBN; B. HPLC pump; C. 0.8 mL tubular reactor in a heated silicon oil bath; D. T-piece, inlet flows are connected perpendicular to the outlet flow; E. HPLC pump; F. Stock solution of Monomer 2 and AIBN; G. 3.6 mL tubular reactor in a heated silicon oil bath; H. Back pressure regulator and I. Sample collection.

Continuous tetrablock copolymerizations

The first stock solution was prepared by dissolving 40 mmol (5.127 g, 10 equiv., 4 M) *n*BuA, 4 mmol (1.402 g, 1 equiv.) DoPAT and 0.2 mmol (33 mg, 0.05 equiv.) AIBN in *n*-butanol. The solution was kept in a sealed Duran flask, connected to the reactor set-up *via* the first HPLC pump and purged with Ar prior to use. In a second stock solution, 50 mmol (4.305 g, 10 equiv., 5 M) MA and 0.45 mmol (74 mg, 0.09 equiv.) AIBN were dissolved in *n*-butanol. The solution was kept in a sealed Duran flask at 0°C and protected from light. The solution was connected to the reactor set-up *via* a second HPLC pump and purged with Ar prior to use. A third stock solution was prepared by dissolving 50 mmol (5.006 g, 10 equiv., 5 M) EA and 0.65 mmol (107 mg, 0.13 equiv.) AIBN in *n*-butanol. The solution was kept in a sealed Duran flask at 0°C and protected from light. The solution was connected to the reactor set-up *via* a third HPLC pump and purged with Ar prior to use. In a fourth stock solution, 50 mmol (6.409 g, 10 equiv., 5 M) *t*BuA and 0.85 mmol (140 mg, 0.17 equiv.) AIBN were dissolved in *n*-butanol. The solution was kept in a sealed Duran flask at 0°C and protected from light. The solution was connected to the reactor set-up *via* a fourth HPLC pump and purged with Ar prior to use. A [0.8 mL + 3.6 mL + 5.2 mL + 6.4 mL] tubular reactor cascade was employed for the polymerizations. By carefully choosing the reactor volume of the third block, and its corresponding flow rate, a 1:1:1:1 ratio between monomer 1, 2, 3 and 4 could be achieved. Hence, residence times of 16 min, 40 min, 40 min and 40 min were employed for the first, second, third and fourth block respectively (0.050 mL min^{-1} flow rate 1, 0.040 mL min^{-1} flow rate 2, 0.040 mL min^{-1} flow rate 3 and 0.040 mL min^{-1} flow rate 4). Monomer conversions of the fourth block were determined *via* ^{1}H NMR (92%) and molecular weight distributions were analyzed *via* SEC (2990 g mol^{-1}, Đ = 1.47) (calibrated using PS standards, calculations based on the Mark-Houwink parameters of P*n*BuA). By employing the described reactor-set-up and collecting for 26 h 05 min, 152.4 g product could be obtained (after solvent removal).
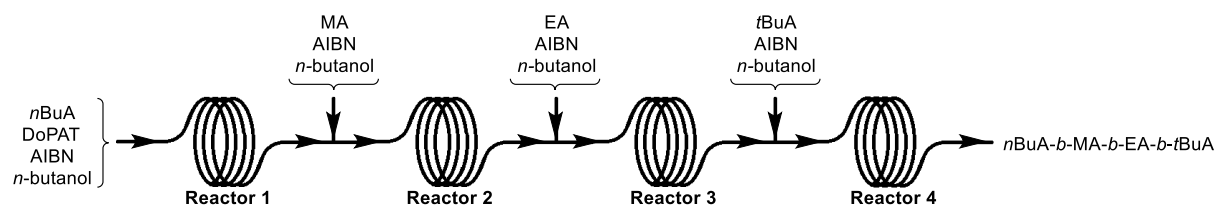
Figure 3: Schematic overview of the continuous synthesis of a P*n*BuA-*b*-PMA-*b*-PEA-*b*-P*t*BuA polymer.

Results and discussion

<u>Theoretical calculations</u>

To develop multiblock copolymers *via* RAFT in one continuous process, reaction conditions must be chosen to assure full monomer conversions and complete initiator consumptions. Every chain extension towards a new block – hence every separate polymerization step – must reach full monomer conversion to avoid quasi-block copolymer formation through residual monomer being present from the previous stage.[10,11] As mentioned above, this can be reached by adjusting the reactor length and volume to the half-life time of the initiator. Assuming that all monomer will have reacted before all initiator is depleted (a non-trivial assumption), will give access to a broadly applicable reactor. Important to note is that should all monomer have been reacted before the initiator is consumed, then radicals are generated on a non-polymerizing system. This can in principle have negative impact on dispersity and chain end fidelity. As Perrier and coworkers had demonstrated before, it is hence important to keep overall initiator levels at an absolute minimum. A balance must be found between minimum initiator concentration and at the same time avoidance of so-called premature dead-end polymerizations, where polymerizations end at intermediate monomer conversion due to full depletion of initiator. To solve this riddle, calculations were carried out to find optimal reaction conditions for a general acrylate homopolymerization (where k_p is typically above 10 000 L mol^{-1} s^{-1}) to reach almost full conversion in a reasonable time scale ($\leq$ 40 min). Ideally, RAFT polymerization is identical in kinetics to a free radical polymerization, as rates of initiation, propagation and termination are not affected by the RAFT equilibrium. Hence, rate calculations of RAFT polymerizations (and hence calculations on required initiator concentrations) can be performed based on free radical polymerization kinetics. Knowledge of RAFT specific rate coefficients is hereby not required. Based on the kinetics of an ideal radical chain polymerizations, equation (**1**) can be applied for dead-end polymerizations.[29] Aiming for 99% conversion, $\ln\frac{[M]_t}{[M]_0} \left[= \ln(1-x)\right]$ should be -4.6. Five times the initiator half-life time is chosen for $t_\mathrm{end} \left[= \frac{5\ln 2}{k_\mathrm{d}}\right]$ to assure full initiator consumption. Assuming an

initiator efficiency f of 0.6 and an overall termination rate k_t of 10^8 L mol^{-1} s^{-1} (dilute conditions), equation (2) is derived, correlating the rate of propagation (k_p) (monomer dependent), the initiator dissociation rate constant and initial initiator concentration (k_d and $[I]_0$) for the desired monomer conversion.

$$-\ln\frac{[M]_t}{[M]_0} = 2\,k_p\left(\frac{f\,[I]_0}{k_d k_t}\right)^{\frac{1}{2}}\left(1 - e^{-0.5\,k_d t_{\,end}}\right) \quad (1)$$

$$k_p = 2.8\left(\frac{k_d}{1.2\ 10^{-8}[I]_0}\right)^{\frac{1}{2}} \quad (2)$$

Via equation (2), for any given initiator concentrations ($[I]_0$), the propagation constant (k_p) and the dissociation constant (k_d) are directly correlated, showing which pair of parameters will yield the desired result (99 % conversion in 5τ). These correlation graphs for various $[I]_0$ are depicted on the l.h.s. of Figure 4. As example, fast-propagating monomers (e.g. k_p = 25 000 L mol^{-1} s^{-1}) in combination with a slowly decomposing initiator (e.g. k_d ~ 0.001 s^{-1}) require a low initiator concentration (e.g. $[I]_0$ ~ 0.001 mol L^{-1}). Slow-propagating monomers on the other hand (e.g. k_p = 5 000 L mol^{-1} s^{-1}), combined with a fast-decomposing initiator (e.g. k_d ~ 0.004 s^{-1}) require a higher initiator concentration (e.g. $[I]_0$ ~ 0.1 mol L^{-1}) to reach the same high conversion before the dead-end case is reached (as would be the case of methacrylates). In practice, too high initiator concentrations are unpractical, as the RAFT agent concentration must be chosen accordingly to the initiator concentration (ensuring good control). High $[I]_0$ would lead to too concentrated polymer solutions, which in turn leads to reactor channel blockages. Aiming for the polymerization of acrylates (k_p typically above 10 000 L mol^{-1} s^{-1} at elevated temperatures) in a reasonable time frame ($t_{\,end}$ ≤ 40 min and thus k_d ~ 0.0014 s^{-1}), it can be concluded that an optimal $[I]_0$ should be at least 0.01 M.
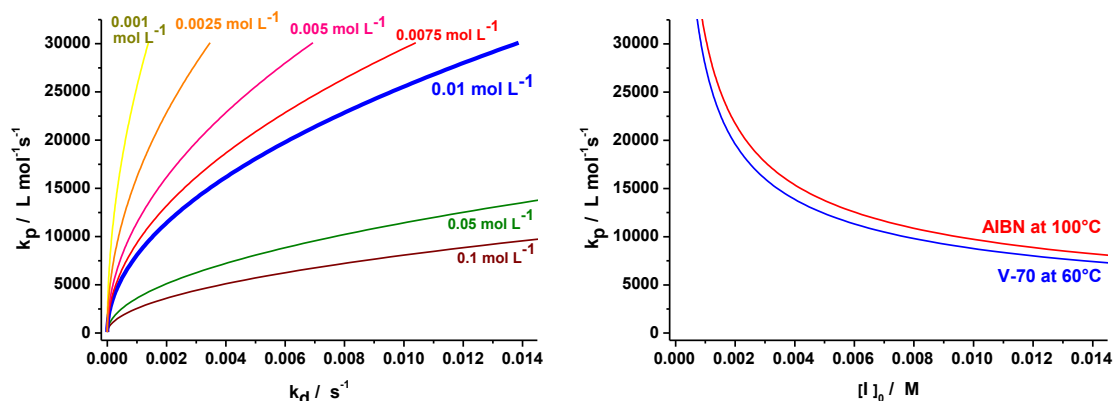
Figure 4: l.h.s.: correlation of k_p in function of k_d at different initiator concentrations. r.h.s.: correlation of k_p in function of $[I]_0$ for given k_d.

Slowly propagating monomers such as methacrylates or styrene – as can be seen from Figure 4 – would require the use of initiators with very low k_d, which in turn would result in very long reaction times that are unpractical for flow operation. Hence, we limited ourselves in the present study to the acrylate family. In this extent, a thermal initiator can be chosen based on the desired dissociation constant (k_d ~ 0.0014 s^{-1}) to fulfill the time limitation ($t_{end} \leq 40$ min). As long as k_d values match, the choice of the initiator itself does not have a significant influence, as can be seen in Figure 4, r.h.s. For example V-70, would require $[I]_0 = 0.0077$M (with $k_d = 0.001178$ s^{-1} at 60°C) to reach the set minimum k_p. A slower initiator, such as AIBN (1,1'-azobis(isobutyronitrile)), would require a higher temperature but also requires $[I]_0 = 0.0095$M (with $k_d = 0.001449$ s^{-1} at 100°C).[30] Since acrylates are typically associated with activation energies for the rate of propagation in the range of 17-20 kJ mol^{-1}, higher temperatures are favorable, and hence AIBN was chosen for all further experiments at 100 °C. It is thereby pure coincidence that AIBN – the probably most used thermal initiator in the realm of radical polymerization – was found to be the most suitable initiator for the purpose of the RAFT multiblock copolymerizations. A note must be made on the targeted chain length. The above calculations do not take the RAFT agent concentration into account as they are only concerned with the rate of polymerization. In RAFT, however, the RAFT to initiator concentration is crucial for aiming at low dispersity polymers. Increasing the targeted chain length (be it in homo- or block copolymers) will lead to a lowering of the RAFT concentration compared to monomer concentration, which in turn yields lower RAFT to initiator ratios

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when the overall polymerization rate is kept constant. RAFT is thus inherently better suited for

polymerization of multiblock copolymers with short block lengths.

<u>Reactor Design</u>

To assure a flexible and easily variable reactor set-up, home-made tubular reactors were employed as described in the experimental section. Therefore, fluorinated gastight PFA tubing was wrapped around a metal framework and placed in a silicon oil bath for heating purposes. Reactor volumes are adjusted by varying the length of reactor tubing. Initial studies focused on the reaction kinetics of a *n*BuA homopolymerization carried out in a standardized home-made 1 mL reactor. Identical results were obtained for a residence time of 16 min (twice the half-life time of AIBN at 100°C) and a residence time of 40 min (five times the half-life time of AIBN at 100°C). It should be noted that this is no contradiction of the calculations presented above. Butyl acrylate is a relatively "fast" monomer and the propagation rate coefficient is significantly larger than the limiting 10 000 L mol^{-1} s^{-1}. The reactor is though chosen to also accommodate slower monomers. Hence, in a later stage, a dedicated tubular reactor of 0.8 mL (1.81 m length) was built to carry out the polymerization of the first block at a reasonable flow rate of 0.050 mL min^{-1} (well-above the pump limitation). Depending on these choices to carry out the polymerization of the first block, the reactor volumes and flow rates in the following reactors were chosen. To provide a 1:1 ratio between the first and the second block, an equimolar flow rate was chosen between both monomers. Hence, the second stock solution was added with a flow rate of 0.040 mL min^{-1} (5 M monomer concentration – giving a 0.2 mmol min^{-1} flow rate of monomer 2, equimolar to monomer 1) into a 3.6 mL reactor to provide a residence time of 40 min (0.090 ml min^{1} in total). According to this similar strategy, each following reactor was designed to match equimolar flow rates and 40 min residence times. Hence, reactors of 5.2 mL and 6.4 mL were employed for the third and fourth block respectively. In addition, experimental tests and theoretic simulations via PREDICI® were carried out to investigate the effect of sequential dosing of initiator via additional inlets. Yet, sequential dosing of initiator has no advantageous effect over propagation kinetics. (A total amount $[I]_{\text{tot}}$, dosed at the beginning of the reactor or divided over multiple inlets, gives the same conversion in all cases, in simulations as well as in experiments). Also the mixing effect at the (second) reactor inlet was tested during chain extension experiments. An inefficient mixing might lead to a

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broadening of the molecular weight distribution and to uncontrolled polymerization of the added monomer. Therefore the effect of mixing was tested experimentally by linking, two reactors to each other via the use of a T-piece (with both inlet flows connected perpendicular to the outlet flow) (Vici, ZT1, 0.75 mm bore) or via the use of a static mixing tee (Upchurch Scientific, U-466, swept volume of 2.2 μL). The static mixer should provide significantly better mixing, especially when dealing with monomer injection into a polymer solution. Yet, no differences were observed in the resulting diblock copolymer, so the cheapest and easiest solution, a T-piece, was employed further in the reactor cascades.

<u>Homopolymerization</u>

Based on the rational outlined above, AIBN was applied as initiator at 100°C to assure full-conversion dead-end polymerization within 40 min residence time for practical any acrylate monomer. Targeting a DP 10 homopolymer, a monomer/RAFT agent/initiator ratio of 10/1/0.05 was employed to avoid the loss of chain end functionality.[31] To reduce the mid-chain radical formation (and hence to speed up the overall polymerization), *n*-butanol was used as solvent.[32] *n*-Butanol is known to cause reduced mid-chain radical formation rates, resulting in higher actively propagating radical species concentrations. Maximum monomer concentrations – taking into account the limited solubility of the RAFT agent to assure homogeneous reaction conditions - turned out to be 4 M for *n*-butyl acrylate (*n*BuA), methyl acrylate (MA), ethyl acrylate (EA), *t*-butyl acrylate (*t*BuA) and 2-hydroxyethyl acrylate (HEA). (Due to the bulkiness of 2-ethylhexyl acrylate (EHA) and 2-(2-ethoxyethoxy)ethyl acrylate (DEGA), lower monomer concentrations had to be employed. In these cases 2.7 M and 3 M respectively.) The corresponding initiator concentrations are hence 0.02 M (or 0.0135 M and 0.015 M in the EHA and DEGA system respectively). These values are all well above the theoretically calculated lower limit for the initiator concentration (0.0095 M). Despite these highly concentrated solutions, no viscosity problems were encountered. For the homopolymerizations, monomer conversions were screened using in-line-FT-IR spectroscopy. Almost full conversions were already obtained after 16 min, where FT-IR showed the absence of the typical acrylate monomer peaks. More accurate monomer conversions were further determined *via* NMR (Table 1), confirming the in-line measurements. For practical reasons, 90% conversion were in the framework of the current study be set as sufficient experimental limit. This means that block copolymers obtained in the following are associated with a slight gradient (so-called *quasi*-block copolymers), but a 10 % contamination seems justifiable, as small gradients do not affect self-assembly behavior of polymers significantly. Most monomers allow to polymerize significantly above 90 %, only EHA did not reach this conversion limit, due to the lower monomer (2.7 M instead of 4 M) and initiator concentrations (0.0135 M instead of 0.02 M).

Table 1: Continuous homopolymerization of 7 different acrylates via the use of DoPAT (2-(dodecylthiocarbonothioylthio)propionic acid) as a RAFT agent. A 0.8 mL tubular reactor was employed to carry out each polymerization at 100°C and 16 min residence time. M_n^{theor} is calculated for full monomer conversion. Determinations of M_n^{app} are based on the Mark-Houwink parameters of PnBuA.

Polymer	$[M]_0$ / M	M / RAFT / I ratio	Conversion / %	Đ	M_n^{app} / g · mol^{-1}	M_n^{theor} / g · mol^{-1}
PnBuA	4	10 / 1 / 0.05	95	1.11	1630	1630
PMA	4	10 / 1 / 0.05	93	1.15	1110	1210
PEA	4	10 / 1 / 0.05	91	1.14	1240	1350
PtBuA	4	10 / 1 / 0.05	97	1.12	1610	1630
PHEA	4	10 / 1 / 0.05	98	1.14	1100	1510
PEHA	2.7	10 / 1 / 0.05	87	1.12	2040	2190
PDEGA	3	10 / 1 / 0.05	95	1.16	2030	2230

To vary the chain length of the first block, different monomer/RAFT agent ratios were injected into the reactor set-up, employing otherwise identical conditions. Monomer concentrations were kept constant at 4 M (except for DP 5 where $[M]_0$ = 2 M, corresponding to a maximum DoPAT concentration of 0.4 M given by solubility constrains). Again, no viscosity problems were encountered in the reactor. The corresponding decrease of the RAFT agent and initiator concentration led to a lower monomer conversions for longer chains (Figure 5) and thus a larger deviation from the theoretic molecular weights (calculated for 100 % monomer conversion). The increase of the molecular weight distributions can easily be followed by SEC (Figure 5). The homopolymerization procedure is thus highly versatile and show the complete formation of a first block, allowing for chain extension towards diblock copolymers, but limits must be respected with respect to the desired chain length. As described above, when longer chain segments are targeted, the RAFT to initiator concentration ratio is changed to more unfavorable conditions, leading to a slight detoriation of the RAFT endgroup fidelity. The increase in dispersity is hence not an effect of the flow conditions, but is inherent to the RAFT mechanism. This effect is more limiting to the present technique than viscosity issues.
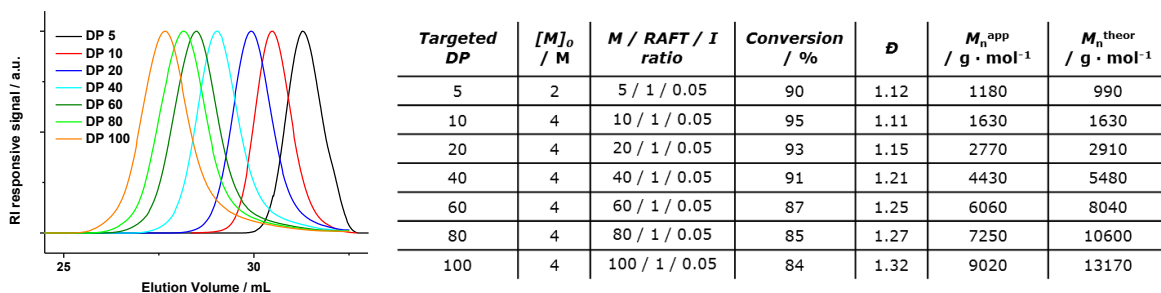
Targeted DP	$[M]_0$ / M	M / RAFT / I ratio	Conversion / %	Đ	M_n^{app} / g · mol^{-1}	M_n^{theor} / g · mol^{-1}
5	2	5 / 1 / 0.05	90	1.12	1180	990
10	4	10 / 1 / 0.05	95	1.11	1630	1630
20	4	20 / 1 / 0.05	93	1.15	2770	2910
40	4	40 / 1 / 0.05	91	1.21	4430	5480
60	4	60 / 1 / 0.05	87	1.25	6060	8040
80	4	80 / 1 / 0.05	85	1.27	7250	10600
100	4	100 / 1 / 0.05	84	1.32	9020	13170

Figure 5: Molecular weight distributions of nBuA homopolymers with different chain lengths, polymerized in a 0.8 mL tubular reactor, at 100°C and 16 min residence time. M_n^{theor} is calculated for full monomer conversion. Determinations of M_n^{app} are based on the Mark-Houwink parameters of PnBuA.

Diblock copolymerization

To extend the reactor to two stages, the 0.8 mL reactor employed for homopolymerizations was coupled to a second 3.6 mL reactor. Reactor volumes are carefully chosen based on the flow rates and monomer concentrations to provide a 1/1 monomer/monomer ratio. To perform a systematic study, nBuA, MA, HEA and DEGA were each polymerized as first block and immediately chain extended with 7 different acrylates (nBuA, MA, EA, tBuA, HEA, EHA, DEGA) and an acrylamide (N-isopropylacrylamide (NIPAM)). The results of all PnBuA-containing diblock copolymers are given in Table 2. The results of the other 24 diblocks can be found in Table S1-S3. High monomer conversions (≥ 90%) were obtained for most diblock copolymers. Molecular weight distributions were determined from SEC using universal calibration, based on PnBuA Mark-Houwink parameters. Dispersities between 1.19 and 1.27 were observed, underpinning that control is still good even after renewed injection of initiator. The slight broadening of the molecular weight distributions cause a small deviation between the apparent and the theoretic average molecular weight, whereby the observed peak molecular weights are corresponding well.

Table 2: Diblock copolymers based on P*n*BuA as first block, obtained from a [0.8 mL + 3.6 mL] tubular reactor cascade without intermediate purification or isolation. The first block was obtained at 100°C and 16 min residence time, the second block at 100°C and 40 min residence time. M_n^{theor} is calculated for full monomer conversion. M_n^{app} and M_p^{app} are determined via SEC, based on the Mark-Houwink parameters of P*n*BuA.

Entry	*Polymer*	$[M]_0$ / M	*Conversion* / %	*Đ*	M_n^{app} / g · mol^{-1}	M_p^{app} / g · mol^{-1}	M_n^{theor} / g · mol^{-1}
1	P*n*BuA	-	95	1.11	1630	1840	1630
2	P*n*BuA-*b*-P*n*BuA	5	92	1.19	2750	3260	2910
3	P*n*BuA-*b*-PMA	5	96	1.21	1950	2450	2490
4	P*n*BuA-*b*-PEA	5	92	1.19	2300	2750	2630
5	P*n*BuA-*b*-P*t*BuA	5	94	1.23	2480	2960	2910
6	P*n*BuA-*b*-PHEA	5	97	1.27	1990	2470	2790
7	P*n*BuA-*b*-PNIPAM	3.3	91	1.27	2210	2510	2760
8	P*n*BuA-*b*-PEHA	3.3	91	1.20	2710	3270	3470
9	P*n*BuA-*b*-PDEGA	3.3	93	1.26	2800	3340	3510

So far, flow rates were chosen carefully to provide a 1/1 monomer/monomer ratio. Yet, to show the versatility of the system the flow rate of the second monomer was adapted, allowing the synthesis of a "10/10", a "10/20" and a "10/40" P*n*BuA-*b*-PMA diblock copolymer (on a DP 10 P*n*BuA block). Molecular weight distributions of these diblock copolymers, in comparison to the P*n*BuA homopolymer, are shown in Figure 6. Naturally, this approach is not limited to P*n*BuA-*b*-PMA diblock copolymers. Also a variety of P*n*BuA-*b*-PHEA and P*n*BuA-*b*-PDEGA diblock copolymers was targeted (Table S4). The procedure towards diblock copolymers is thus highly versatile, even though the same trend is observed as for the homopolymers; with increasing chain length of the block, a broadening of the distributions is observed.
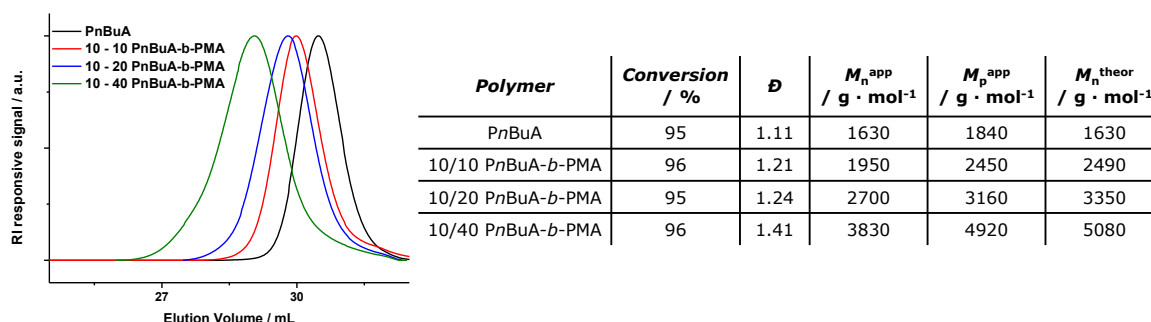

Polymer	Conversion / %	Đ	M_n^{app} / g · mol^{-1}	M_p^{app} / g · mol^{-1}	M_n^{theor} / g · mol^{-1}
P*n*BuA	95	1.11	1630	1840	1630
10/10 P*n*BuA-*b*-PMA	96	1.21	1950	2450	2490
10/20 P*n*BuA-*b*-PMA	95	1.24	2700	3160	3350
10/40 P*n*BuA-*b*-PMA	96	1.41	3830	4920	5080

Figure 6. Molecular weight distributions of P*n*BuA-*b*-PMA diblock copolymers (monomer ratio 10/10, 10/20 and 10/40) in comparison to the initial P*n*BuA homopolymer. For conditions see Table 2. M_n^{theor} is calculated for full monomer conversion. M_n^{app} and M_p^{app} are determined via SEC, based on the Mark-Houwink parameters of P*n*BuA.

<u>Tri- and Tetrablock copolymerization</u>

After the successful implementation of continuous diblock copolymer formation, the cascade was further extended with a 5.2 mL reactor. Reaction conditions were slightly adapted: 0.09 eq and 0.13 eq of AIBN were added in the second and third reactor respectively, to provide 0.02M AIBN concentration throughout the whole reaction. On one hand, this increased AIBN concentrations provides a slight increase of conversion in the second block and a higher conversion in the third reactor making multiblock copolymer formation more feasible. On the other hand, this also leads to a broadening of the molecular weight distribution due to the adapted monomer/macroRAFT/initiator ratio (10/1/0.09 and 10/1/0.13 respectively) (decrease of the end-group fidelity).[31] Yet, to limit quasi-block copolymer formation, maximum conversions were preferred over more narrow molecular weight distributions. Again, triblock copolymer formation was studied systematically. Based on PnBuA-b-PMA block copolymers, triblock copolymers were successfully synthesized with the same variety in acrylate monomers as above (Table 1). Almost complete monomer conversions were observed (*via* the use of CH_2Br_2 as internal standard in NMR). The molecular weight distributions are broader than for the diblock copolymers (1.29 ≤ *Đ* ≤ 1.35), which is directly connected to the higher overall initiator concentration. Again, the observed peak molecular weight corresponds well to theoretic molecular weight distribution.

Table 1. Results for the synthesis of various triblock copolymers based on PnBuA-b-PMA macroRAFT agents. The third block was directly polymerized in a 5.2 mL reactor at 100°C and 40 min residence time. M_n^{theor} is calculated for full monomer conversion. M_n^{app} and M_p^{app} are determined via SEC, based on the Mark-Houwink parameters of PnBuA.

Entry	Polymer	$[M]_0$ / M	Conversion / %	Đ	M_n^{app} / g · mol^{-1}	M_p^{app} / g · mol^{-1}	M_n^{theor} / g · mol^{-1}
1	PnBuA	-	95	1.11	1630	1840	1630
2	PnBuA-b-PMA	-	95	1.23	1960	2490	2490
3	PnBuA-b-PMA-b-PnBuA	5	91	1.35	2730	4000	3770
4	PnBuA-b-PMA-b-PMA	5	91	1.35	2260	3200	3350
5	PnBuA-b-PMA-b-PEA	5	92	1.34	2380	3330	3490
6	PnBuA-b-PMA-b-PtBuA	5	94	1.29	2820	3800	3770
7	PnBuA-b-PMA-b-PHEA	5	96	1.30	3470	3350	3650
8	PnBuA-b-PMA-b-PNIPAM	3.3	92	1.34	2150	2930	3620
9	PnBuA-b-PMA-b-PEHA	3.3	91	1.29	3200	4290	4330
10	PnBuA-b-PMA-b-PDEGA	3.3	93	1.35	2790	4020	4370

The complete formation of the third block allows for chain extension towards tetrablock copolymers *via* the use of a [0.8 mL + 3.6 mL + 5.2 mL + 6.8 mL] reactor cascade. Stock solutions were prepared in a similar way to the triblock copolymers. Again a higher amount of AIBN (0.17 eq) was added into the fourth reactor to provide an initiator concentration of 0.02 M. As example, a P*n*BuA-*b*-PMA-*b*-PEA-*b*-P*t*BuA tetrablock copolymer was targeted. (Also other tetrablock copolymers with different variations can be targeted though, see Figure S3.) The employed reactor set-up, the molecular weight distributions and the results of the synthesis of the tetrablock copolymer are depicted in Figure 7. The copolymer was obtained with a dispersity of 1.47, at almost complete *t*BuA conversion. In contrast to batch procedures, this reactor set-up and experimental procedure could be used to synthesize a significant amount of the tetrablock copolymer by just extending the reactor run time and thus avoiding batch-to-batch variations. By collecting for 26 h, ± 150 g of the P*n*BuA-*b*-PMA-*b*-PEA-*b*-P*t*BuA tetrablock copolymer could be obtained, which is very close to the theoretically expected amount of polymer under such runtime.
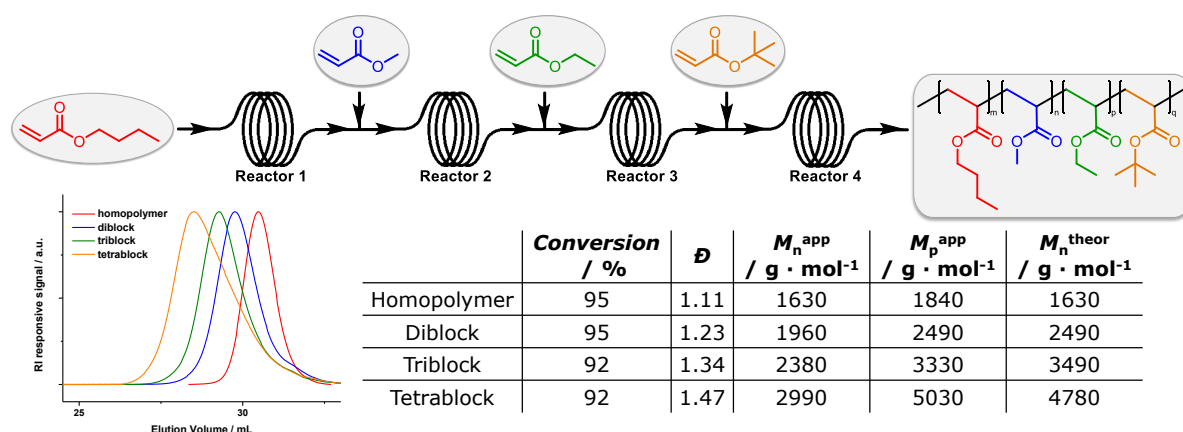

	Conversion / %	Đ	M_n^{app} / g · mol^{-1}	M_p^{app} / g · mol^{-1}	M_n^{theor} / g · mol^{-1}
Homopolymer	95	1.11	1630	1840	1630
Diblock	95	1.23	1960	2490	2490
Triblock	92	1.34	2380	3330	3490
Tetrablock	92	1.47	2990	5030	4780

Figure 7. Schematic representation of the synthesis of a P*n*BuA-*b*-PMA-*b*-PEA-*b*-P*t*BuA tetrablock copolymer *via* the use of a [0.8 mL + 3.6 mL + 5.2 mL + 6.8 mL] reactor cascade. M_n^{theor} is calculated for full monomer conversion. M_n^{app} and M_p^{app} are determined via SEC, based on the Mark-Houwink parameters of P*n*BuA.

With the described setup, practically any tetrablock copolymer can be obtained, as long as the individual block length is kept within reason. In principle, a further extension of the cascade towards pentablock or higher block copolymers is in principle possible, yet such set-up would require an even larger amount of pumps and mixer units. Further, the obtained tetrablock copolymers can be reinjected in the first stage in iterative manner. First results for such approach have been encouraging, yet a further broadening of molecular weight distributions and increasing issues with maximal polymer concentration and viscosity must be expected.

Conclusion

In a self-made tubular reactor cascade multiblock copolymers were synthesized *via* RAFT polymerization in a single setup without the requirement of intermediate polymer isolation or purification. Theoretic calculations were carried out to target full monomer conversions in order to avoid quasi-block copolymer formation (while few percent statistical copolymer cannot be fully avoided). The use of AIBN as initiator at 100°C, with an initiator concentration of at least 0.0095 M, provides full monomer conversion within residence times of 40 min. The (homo)polymerizations of seven different acrylates (*n*-butyl acrylate (*n*BuA), methyl acrylate (MA), ethyl acrylate (EA), *t*-butyl acrylate (*t*BuA), 2-hydroxyethyl acrylate (HEA), 2-ethylhexyl acrylate (EHA) and 2-(2-ethoxyethoxy)ethyl acrylate (DEGA)) were carried out successfully, under the exact same reaction conditions, showing that the reactor designed is very versatile and does not require reoptimization towards different acrylates. The chain length of these polymers could easily be varied. Practically full monomer conversions allowed for chain extension towards diblock copolymers, which were based on the same seven acrylates and *N*-isopropylacrylamide (NIPAM). Continuation of the concept allows to obtain up to tetrablock copolymers whereby the position of the different acrylates in the block structure and the length of the blocks (with a upper limit of ~40 units per block) can be chosen freely. Generally, an increase in chain (or block) length results in slight broadening of the distributions, which is inherent to the process in circumstances where the dispersity is limited by the extent of termination, if polymerization rates are meant to be kept constant as is here the case. The reactor can hence be used for high-throughput screening as it allows to synthesize a large number of different block copolymers in short time, under very reproducible reaction conditions. In total, for this study a number of 55 diblock, triblock and tetrablock copolymers (based on 7 different acrylates and an acrylamide) were obtained. Further, the reactor also allows for facile upscaling of the reactions, making the desired block copolymers also available to extensive mechanical testing. P*n*BuA-*b*-PMA-*b*-PEA-*b*-P*t*BuA tetrablocks were obtained as proof of principle in very significant amount (± 150 g in 26 h). The developed procedure is thus highly versatile, allows for a stable production over extended period of

time and can in principle easily be employed for even further chain extensions. As a final note, in view of literature describing block copolymers with ten or more segments, a tetrablock copolymer might appear to be small in size. It should, however, be noted that our method is wide in scope and not limited to certain very fast monomers or very few monomer unit insertions, and due to its automated nature is available to scientists outside the field of synthetic macromolecular chemistry. Further, theoretical understanding of self-assembly effects of multiblock copolymers is highly complex, and 4 consecutive blocks with variable chain length is more than sufficient to advance the field of research in this area.

Acknowledgement

References

(1) Ruzette, A.-V.; Leibler, L. *Nat Mater* **2005**, *4*, 19.

(2) Junkers, T. *Macromolecular Chemistry and Physics* **2017**, *218*, 1600421.

(3) Szwarc, M. *Journal of Polymer Science Part A: Polymer Chemistry* **1998**, *36*, IX.

(4) Jenkins, A. D.; Jones, R. G.; Moad, G. In *Pure and Applied Chemistry* 2009; Vol. 82, p 483.

(5) Keddie, D. J. *Chemical Society Reviews* **2014**, *43*, 496.

(6) Hawker, C. J.; Bosman, A. W.; Harth, E. *Chemical Reviews* **2001**, *101*, 3661.

(7) Nicolas, J.; Guillaneuf, Y.; Lefay, C.; Bertin, D.; Gigmes, D.; Charleux, B. *Progress in Polymer Science* **2013**, *38*, 63.

(8) Matyjaszewski, K. *Macromolecules* **2012**, *45*, 4015.

(9) Noda, T.; Grice, A. J.; Levere, M. E.; Haddleton, D. M. *European Polymer Journal* **2007**, *43*, 2321.

(10)   Haven, J. J.; Guerrero-Sanchez, C.; Keddie, D. J.; Moad, G. *Macromolecular Rapid Communications* **2014**, *35*, 492.

(11)   Haven, J. J.; Guerrero-Sanchez, C.; Keddie, D. J.; Moad, G.; Thang, S. H.; Schubert, U. S. *Polymer Chemistry* **2014**, *5*, 5236.

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

(13)   Gody, G.; Maschmeyer, T.; Zetterlund, P. B.; Perrier, S. *Macromolecules* **2014**, *47*, 3451.

(14)   Gody, G.; Barbey, R.; Danial, M.; Perrier, S. *Polymer Chemistry* **2015**, *6*, 1502.

(15)   Gemici, H.; Legge, T. M.; Whittaker, M.; Monteiro, M. J.; Perrier, S. *Journal of Polymer Science Part A: Polymer Chemistry* **2007**, *45*, 2334.

(16)   Vandenbergh, J.; de Moraes Ogawa, T.; Junkers, T. *Journal of Polymer Science Part A: Polymer Chemistry* **2013**, *51*, 2366.

(17)   Webb, D.; Jamison, T. F. *Chemical Science* **2010**, *1*, 675.

(18)   J.-C. M. Monbaliu, N. E. a. R. G. *Chimie Nouvelle* **2016**, *122*, 18.

(19)   Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angewandte Chemie International Edition* **2004**, *43*, 406.

(20)   Wilms, D.; Klos, J.; Frey, H. *Macromolecular Chemistry and Physics* **2008**, *209*, 343.

(21)   Tonhauser, C.; Natalello, A.; Löwe, H.; Frey, H. *Macromolecules* **2012**, *45*, 9551.

(22)   Derboven, P.; Van Steenberge, P. H. M.; Vandenbergh, J.; Reyniers, M.-F.; Junkers, T.; D'Hooge, D. R.; Marin, G. B. *Macromolecular Rapid Communications* **2015**, *36*, 2149.

(23)   Diehl, C.; Laurino, P.; Azzouz, N.; Seeberger, P. H. *Macromolecules* **2010**, *43*, 10311.

(24)   Hornung, C. H.; Guerrero-Sanchez, C.; Brasholz, M.; Saubern, S.; Chiefari, J.; Moad, G.; Rizzardo, E.; Thang, S. H. *Organic Process Research & Development* **2011**, *15*, 593.

(25)   Hornung, C. H.; Nguyen, X.; Kyi, S.; Chiefari, J.; Saubern, S. *Australian Journal of Chemistry* **2013**, *66*, 192.

(26)   Li, Z.; Chen, W.; Zhang, L.; Cheng, Z.; Zhu, X. *Polymer Chemistry* **2015**, *6*, 5030.

(27)   Baeten, E.; Verbraeken, B.; Hoogenboom, R.; Junkers, T. *Chemical Communications* **2015**, *51*, 11701.

(28)   Gauthier, M. A.; Gibson, M. I.; Klok, H.-A. *Angewandte Chemie International Edition* **2009**, *48*, 48.

(29)   Odian, G. *Principles of polymerization*; fourth edition ed.; John Wiley & Sons, 2004.

(30)   Van Hook, J. P.; Tobolsky, A. V. *Journal of the American Chemical Society* **1958**, *80*, 779.

(31)   Vandenbergh, J.; Junkers, T. *Macromolecules* **2014**, *47*, 5051.

(32)   Liang, K.; Hutchinson, R. A.; Barth, J.; Samrock, S.; Buback, M. *Macromolecules* **2011**, *44*, 5843.

TOC Figure