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Controlled RAFT Polymerization in a Continuous Flow Microreactor

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ABSTRACT: Controlled radical polymerization using the reversible addition−fragmentation chain transfer approach (RAFT) was successfully conducted under continuous flow processing conditions, provided that steel tubing was used to prevent quenching of the radical process by oxygen. A series of different monomers, including acrylamides, acrylates, and vinyl acetate, were polymerized to high conversions (between 80 and 100%) at temperatures between 70 and 100 °C using various initiators, solvents, and RAFT agents. Low dispersities, typically between 1.15−1.20, and average molecular weights similar to those of batch RAFT polymerizations were obtained. The methodology provides a facile, alternative scale-up route to conventional batch polymerization, which can be challenging because of the oxygen-sensitive nature of the RAFT process.

INTRODUCTION

This paper describes investigations into the continuous flow processing of highly oxygen-sensitive radical polymerizations using a laboratory-scale tubular flow reactor system. Chemical laboratory flow reactors are devices containing fluidic pathways in the millimetre and micrometre range. Many designs have a single or multiple parallel channels with diameters between 10 and 1000 μm, where the chemical reaction takes place.[1−7] Several simple and cost-effective designs are based on microfluidic tubing made from polymer or steel which have the benefits of relatively low manufacturing cost and long reactor lengths when compared to chip-based microreactors. The long fluidic pathway of tubular reactors enables chemical reactions to be conducted with residence times of a few minutes to several hours in a single reactor unit. Hence, this class of microreactors is a suitable system for liquid-phase polymerizations, which can take several hours to provide high conversions.[8−10]

RAFT polymerization is arguably the most convenient and versatile of processes for reversible deactivation radical polymerization (RDRP), being compatible with most monomers amenable to radical polymerization, and allows the use of reaction conditions typical of the conventional process.[11−16] The mechanism of chain activation/deactivation is shown in Scheme 1, with the overall process involving insertion of monomer units into the C−S bond of a RAFT agent. With appropriate selection of reaction conditions the process takes on most of the characteristics of a living polymerization that allows the synthesis of polymers with narrow molecular weight distributions and defined end groups. It also allows the preparation of complex architectures (block, star, etc.).[11−14]

Other forms of RDRP, in particular nitroxide-mediated radical polymerization (NMP)[17−20] and atom transfer radical polymerization (ATRP),[21,22] have been successfully carried out in tubular flow reactors. RAFT differs from these processes in that the mechanism for control (chain equilibration) is a rapidly reversible chain transfer step involving reaction between macromolecular species. In NMP and ATRP the control mechanism is a reversible deactivation involving reaction between a macromolecular species and a small molecule (a nitroxide or a metal complex, respectively). A further difference is that, in RAFT, an added initiator is used. Several continuous flow RDRPs have been performed using mini-emulsion systems.[17,23,24] Mini-emulsion systems usually have lower viscosities than solution phase polymerisation however they often result in a higher polydispersity. In this work, we describe the first solution-phase RAFT polymerisation in a continuous flow capillary reactor.

A series of problems is often associated with the use of capillary reactors such as the susceptibility to blockage when using particulate systems or a high pressure buildup with highly viscous fluids, such as polymer solutions.[9] These problems limit the range of applications for these devices. The herein presented work on the synthesis of polymers in a continuous flow capillary system, also investigates the limitations of this reactor geometry for reactions that can present challenges because of their viscous nature.

CONTINUOUS FLOW REACTOR AND OPERATION METHODS

The flow experiments were performed in a commercially available tubular flow reactor (Vapourtec R2/R4 reactor heater), which allows continuous flow processing up to 250 °C (Figure 1). This reactor design has been used extensively for organic synthesis in academic groups such as the Ley group.[25−31] The use of microreactor technology for the synthesis of polymers or other highly viscous materials has been described in a series of publications to date.[8−10,17−24] These systems present a set of different challenges compared to most microreactor applications, which are generally based on homogeneous liquid-phase organic synthesis with water-like viscosities. In this set of experiments, two different flow reactor coils were investigated initially: a polymer coil made from perfluoroalkoxy polymer (PFA) and a stainless steel coil, both with an internal diameter of 1 mm and a total volume of 10 mL (Figure 1).

The flow reactions were performed in one of two different modes shown in Figure 2. For library synthesis, small amounts of

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starting material, (monomer, initiator, and RAFT agent) were processed in a series of plugs injected via a sample loop into a constant solvent stream. This mode, which in the following will be referred to as ‘segmented flow’, is generally suitable for processing several small samples in succession, with the goal to synthesize samples in practicable analytical quantities. Within this work, segmented flow has been used on a scale of 2 mL per sample. The second mode applied for the RAFT polymerization in the tubular reactors was continuous flow for the production of several grams of polymer. Here, samples typically ≥10 mL were processed under steady-state conditions. In both modes, starting material solutions were premixed and degassed. The reactions were performed at temperatures between 70 and 100 °C and flow rates between 0.08 and 0.33 mL/min, resulting in reaction times of 30−120 min. A 75 psi backpressure regulator, situated after the reactor coil, was used to provide a uniform flow. A series of different monomers, initiators, and RAFT agents were used for batch and flow experiments, as shown in Figures 3, 4, and 5 (detailed description of the experimental protocol can be found in the Experimental Section). The objective in these reactions was to achieve both high conversion within the limited residence time capabilities of the reactor and a relatively low viscous product solution. A too-high viscosity can result in pressure-drop complications created by the flow resistance inside the small-diameter tubing. For comparison, batch experiments were carried out on a laboratory reactor heated by microwave irradia-

Scheme 1. Mechanism for reversible addition−fragmentation chain transfer; R is a homolytic leaving group; R• must also be able to reinitiate polymerization

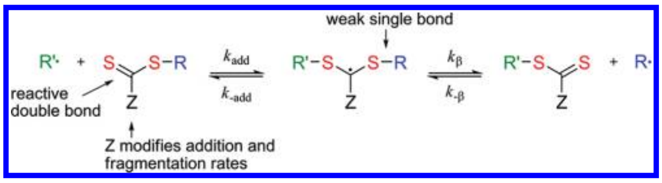

Figure 1. Flow reactor system using a PFA polymer tubing reactor in glass housing (left) or a stainless steel tubing reactor in high temperature, insulated housing (right). For use with the steel tubing reactor, the polymer tubing between pump and reactor and the sample loop were jacketed with a layer of aluminium foil and polymer film, in order to minimise oxygen ingress (right).

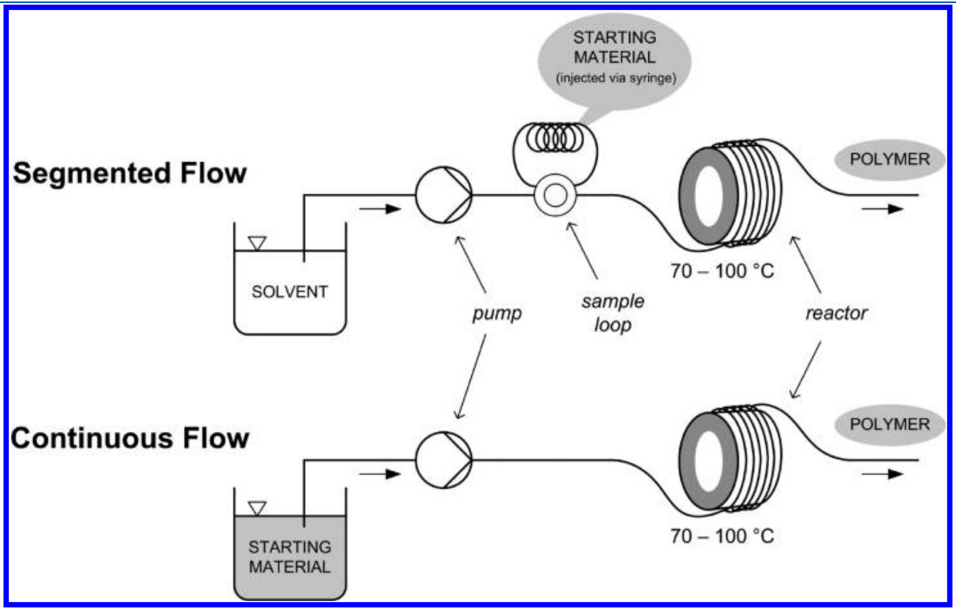

Figure 2. Different operation modes for the flow reactor. Segmented flow: monomer, initiator, and RAFT agent are preloaded in sample loop and injected into constant solvent stream as separated plug(s); continuous flow: starting materials are pumped directly into reactor as continuous stream.

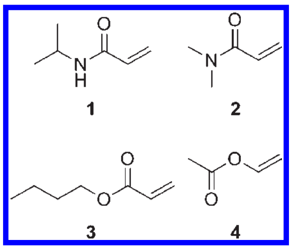

Figure 3. Monomers used in batch and flow radical polymerizations.

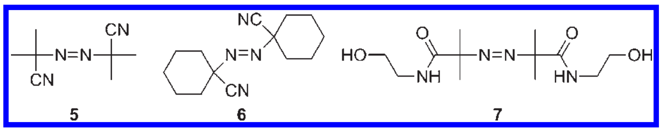

Figure 4. Initiators used in batch and flow radical polymerizations.

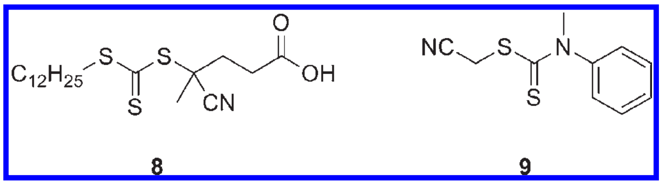

Figure 5. RAFT agents used in batch and flow radical polymerizations.

tion (Biotage Initiator) on a 2-mL scale, using the same preparation and degassing protocols as for the flow experiments. For this set of batch reactions, no rate acceleration caused by the microwave irradiation was observed when compared to conventional heating[32−36] (see Experimental Section). In both flow and batch modes, the reaction was quenched by cooling the product down to room temperature and exposing it to air.

■ INVESTIGATION ON THE EFFECT OF OXYGEN ON POLYMERIZATION

As the process was known to be extremely sensitive to any traces of oxygen which can quench the radical reactions, great care was taken not to entrain any air during preparation or polymerization, and the starting material solution was degassed carefully using three freeze−evacuate−thaw cycles. While all control experiments in batch using identical process parameters produced RAFT polymers in good conversions, initial experiments on the continuous flow polymerization in PFA polymer coils using various RAFT agents and monomers failed, and the reason for this was not immediately obvious. In order to investigate the influence of the flow reactor tubing material, comparative experiments were carried out, using the three previously described reactor geometries: the PFA polymer tubing reactor, the stainless steel tubing reactor, and the batch microwave reactor. A conventional free radical polymerization and a RAFT polymerization were compared in these three reactor systems. The conventional free radical polymerization of **1**, using initiator **7**, was conducted at 90 °C with a reaction time of 1 h, and the RAFT polymerization of **2**, using initiator **5** and RAFT agent **8**, was conducted at 80 °C with a reaction time of 2 h; details of both reactions are presented in the Experimental Section. Both reactions were processed under segmented flow conditions, injecting 2 mL of starting material solution per experiment. In the case of the RAFT polymerization, the reaction mixture was degassed using freeze−pump−thawing prior to injection, and the solvent which was used to wash the reactor in between reactions was degassed using nitrogen purging; in the

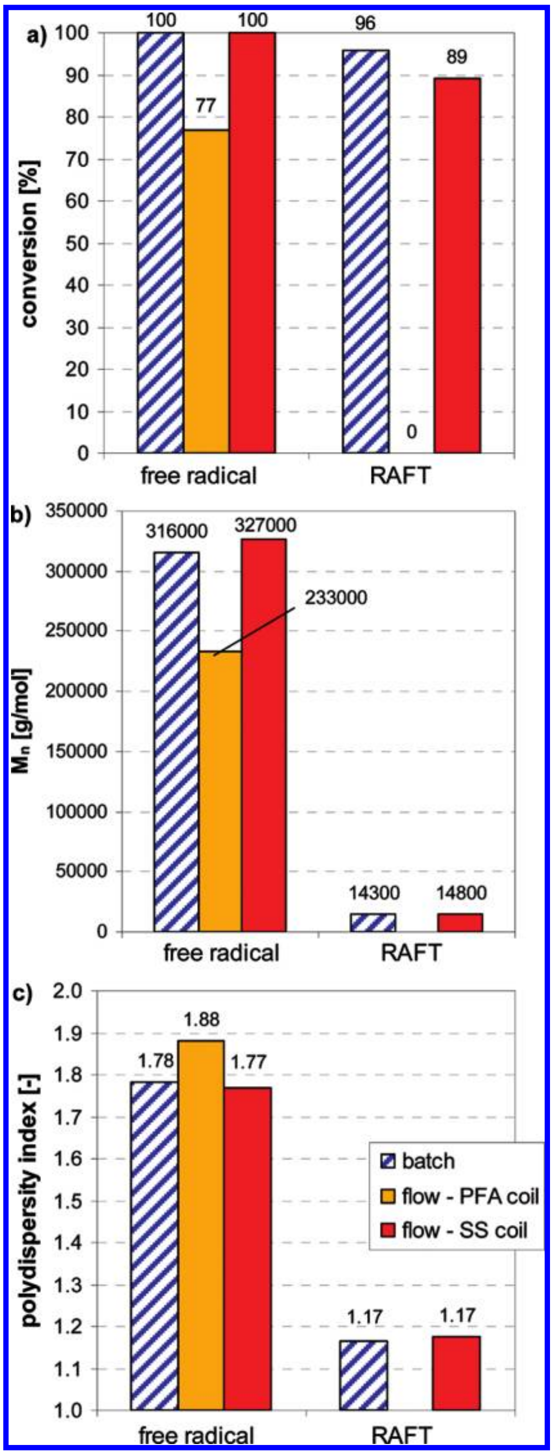

Figure 6. Comparison of reactor performance in three different reactors for a free radical polymerization (left set of columns) and a RAFT polymerization (right set of columns): batch microwave reactor (blue/white, left column), PFA tubing flow reactor (orange, central column), steel tubing reactor (red, right column); (a) conversion, (b) number average molecular weight, (c) polydispersity index; flow experiments were carried out in segmented flow.

case of the conventional free radical polymerization, starting material solution and solvent were not degassed.

Figure 6 shows the results of the comparative experiments carried out in the three reactor geometries. While the batch microwave reactor and the steel tubing flow reactor perform almost identically, the PFA tubing flow reactor results in a significantly lower conversion in the free radical polymerization and does not produce any polymer in the RAFT process. Experiments using different monomers, such as **1**, and glycidyl methacrylate under various different conditions and in different solvents also failed in the PFA reactor; hence, the oxygen permeability of the polymer tubing was believed to be responsible for these results. As the initiator concentration in RAFT polymerizations is in the order of 1−5·μmol/L, very small amounts of molecular oxygen led to termination of the polymerisation reaction. To verify this assumption qualitatively, we evaluated the stability of a solution of samarium(II) iodide in THF[37,38] in the polymer reactor coil, as a model for a highly oxygen-sensitive species which undergoes a colour change that could easily be visualized while inside the reactor. For these experiments, two stock solutions of SmI_2 in THF were prepared at concentrations of 0.048 mol/L and 0.024 mol/L (thus of a much higher concentration than in the active species in the radical polymerization reactions). After the injection of 2 mL of each stock solution into two polymer reactor coils, the ends of the reactor coils were blocked, and they were gently warmed to 50 °C by circulating air. If oxygen permeated through the tubing wall as warm air was blown over the tubing containing the stationary sample, the solution would discolour by oxidation of the blue samarium(II) complex to yellow samarium(III). A series of time-related photos were taken at various stages of the experiment, and a selection of these images is shown in Figure 7. The right coil in these images was filled with the high-concentration stock solution (0.048 mol/L), and the left coil, with the low-concentration stock solution (0.024 mol/L).

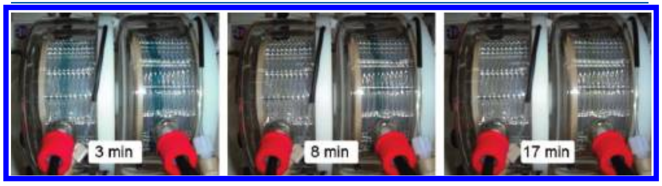

Figure 7. Photographic images of 2-mL samples of SmI_2 solution inside a PFA tubing reactor coil; concentration in left coil = 0.024 mol/L, concentration in right coil = 0.048 mol/L. Images were taken at different times after injection.

Around 3 min into the heating process, both samples still showed an intense blue colour, which started to fade away first for the low-concentration sample (around 8 min) and then for the higher concentrated solution (around 17 min). The observed complete discoloration of SmI_2 after just 17 min under these conditions was attributed to the uptake of oxygen by the reagent solution through the polymer wall,[39,40] which clearly shows the limitation of the PFA polymer material for the handling of oxygen-sensitive reagents. As initiator concentrations in RAFT polymerizations are substantially lower than these SmI_2 solutions, typically by a factor of 10, this effect is believed to greatly influence the polymerization inside such a polymer tubing reactor. These qualitative results do not allow for an accurate quantification of the oxygen permeation process, as the experiments are potentially influenced by a series of artefacts associated with the sensitivity of the compound, especially during the transfer process between the preparation flask and the reactor coil, where air is likely to be introduced. However, the fact that the less concentrated sample (0.024 mol/L) which is half the concentration of the more concentrated sample (0.048 mol/L) takes approximately half the time to discolour indicates that these artefacts are either minimal or reproducible. These results were repeated at room temperature, and we observed total discoloration after 90−110 min, which is still within the time frame of a polymerization reaction. As a result of these findings, future RAFT polymerizations were carried out only in the steel reactor, including minor changes to the experimental configuration. In order to minimise the oxygen uptake of the sample prior to entry into the steel reactor, all PFA tubing components between pump and reactor coil were jacketed with a layer of aluminium foil and a polymer film with good oxygen barrier properties (Parafilm M), including the 2-mL sample loop (see Figure 1).

■ CONTINUOUS FLOW RAFT POLYMERIZATION IN A STEEL MICROREACTOR

For a continuous flow polymerisation inside a microreactor system, pressure buildup due to an increase of viscosity during reaction can be problematic. The choice of monomer and process conditions has a large effect on the length of the synthesised polymer chains, which in turn is mainly responsible for the viscosity of the product solution. Due to the flow resistance of the small-diameter tubing, flow of highly viscous liquids can result in a high pressure drop. For Newtonian liquids, this pressure drop can be estimated using general fluid mechanic principles,[41] but for a polymer solution which is forming inside

Table 1. Reaction conditions and starting materials for RAFT polymerization; all reactions were performed under identical conditions in both batch processing in a microwave reactor and in segmented or continuous flow in a steel microreactor (with the exception of entry 6, which was only performed in batch)

entry	monomer [mol/L]/[%][a]	initiator [mmol/L][a]	RAFT agent [mmol/L][a]	solvent	temperature [°C]
1	**1**, 1.8/23	**5**, 5.4	**8**, 9	EtOAc	70
2	**1**, 1.8/23	**5**, 5.4	**8**, 9	EtOAc	80
3	**1**, 1.8/23	**6**, 5.4	**8**, 9	EtOAc	90
4	**1**, 1.8/23	**6**, 5.4	**8**, 9	EtOAc	100
5	**2**, 1.8/28	**5**, 5.4	**8**, 9	MeCN	80
6	**2**, 1.8/21	**5**, 5.4	**8**, 9	dioxane	80
7	**3**, 1.8/35	**5**, 5.4	**8**, 9	EtOAc	80
8	**4**, 3.0/40	**5**, 12.0	**9**, 48	EtOAc	100

[a] First figure refers to species: (see Figures 3, 4, and 5); second figure refers to amount: monomer content is given as concentration in mol/L and wt % (mass of monomer per mass of solvent); initiator and RAFT agent contents are given as concentration in mmol/L.

the reactor with a highly non-Newtonian character, a pressure drop estimation is more complex. For this reason, first a series of batch reactions were performed, and on the basis of these results the starting material concentrations for the flow processes were chosen. Using pressure monitoring and process control and by carefully choosing starting material concentrations, the pressure increase inside the flow reactor could be kept below 4 bar (pressure difference between value measured during polymerization and with pure solvent), with the maximum system pressure never exceeding 8 bar. The starting material solutions for these experiments were prepared at relatively moderate concentrations between 1.8 and 3 mol/L, resulting in water-like viscosities. The product solutions greatly varied in viscosity but were generally much more viscous.

A series of different RAFT polymerisation examples were conducted in the stainless steel reactor and the batch microwave reactor, using the monomers *N*-isopropylacrylamide (NIPAM), **1**; *N,N*-dimethyl acrylamide (DMA), **2**; *n*-butyl acrylate (nBA), **3**; and vinyl acetate (VAc), **4**, (Figure 3); the initiators **5**−**7** (Figure 4), RAFT agents **8** and **9** (Figure 5), and different solvents: ethyl acetate (EtOAc), acetonitrile (MeCN), and 1,4-dioxane at a reaction time of 2 h. The resulting polymer solutions were analyzed. Table 1 presents an overview of the process parameters of a set of these experiments which were performed under identical conditions in batch and flow.

Figure 8 compares the performance of the continuous flow reactor using segmented flow with the batch process (segmented flow, F is left bar, batch, B is right bar in column pair), for conversion of monomer (Figure 8a), number average molecular weight of polymer, $\overline{M}_n$ (Figure 8b) and polydispersity index, Đ (Figure 8c). It shows a selection of polymers synthesized at temperatures between 70 and 100 °C and a reaction time of 2 h (see Table 1 for reaction conditions).

Polymers made in batch and segmented flow processing generally show similar conversion, average molecular weight, and Đ. In most cases, conversions in segmented flow are lower, but generally only by less than 5%; Đ is generally higher by 0.02−0.08. This leads to the conclusion that both reactor types produce similar results for the investigated polymerization conditions and that the narrow dispersity and relatively high conversion in segmented flow show that RAFT polymerization is generally suitable for flow processing in steel tube microreactors. These results are comparable to work on nitroxide-mediated radical polymerisation in steel tube microreactors by Enright[17] and Rosenfeld[18] who report styrene homopolymers with Đ between 1.17 and 1.50. Compared to results from miniemulsion RAFT polymerisations in continuous flow by Russum,[23] that lie in the range of 1.5−1.7, our results are significantly lower, suggesting that the continuous solution-phase process has a better control over polydispersity than the miniemulsion process. Figure 8b shows a comparison between measured (columns) and theoretical values (black diamonds) for the average molecular weight. These predictions were calculated using eq 1.[11]

$$\overline{M}_n(\text{calc}) \approx \frac{c_{\text{mon},0} - c_{\text{mon},2\text{h}}}{c_{\text{RAFT},0}} \cdot M_{\text{mon}} \qquad (1)$$

Here $c_{\text{mon},0}$ and $c_{\text{RAFT},0}$ are the initial concentrations of monomer and RAFT-agent respectively, $c_{\text{mon},2\ \text{h}}$ is the concentration of monomer left after 2 h of reaction and M_{mon} is the molecular weight of the monomer. Figure 8b shows that for polymers made from NIPAM and VAc (entries 1−4, 8), values for predicted and experimental molecular weight are generally in good agreement. The discrepancies between experimental and theoretical values observed for the polymer made from DMA and nBA (entries 5 and 7) can partially be attributed to inaccuracies resulting from the GPC measurement protocol (see Experimental Section).

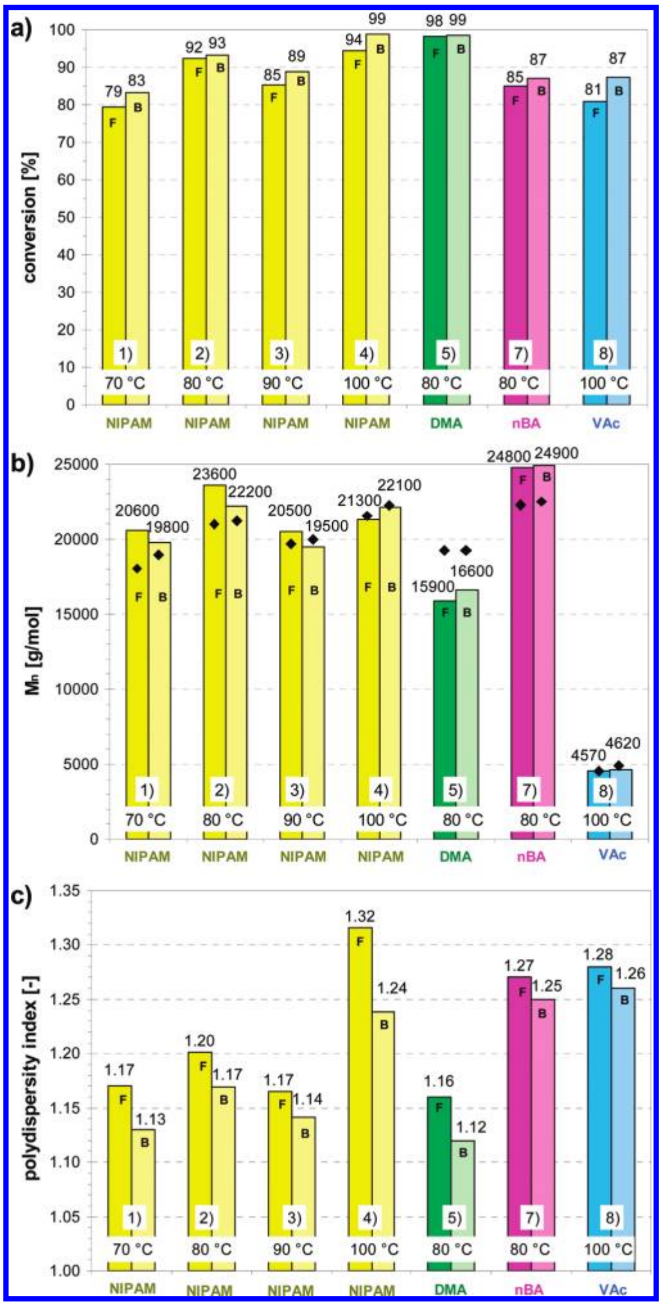

Figure 8. RAFT polymers synthesized in batch and segmented flow after 2-h reaction time, four different monomers (NIPAM, DMA, nBA, VAc) polymerized at temperatures between 70 and 100 °C, detailed conditions given in Table 1, comparison between segmented flow (left columns, F) and batch (right columns, B), (a) conversion, (b) number average molecular weight (columns are experimental values/black diamonds are theoretical values), (c) polydispersity index.

The average molecular weight for the NIPAM, DMA, and nBA polymers lay in between 15000 and 25000 g/mol. The conditions chosen for these reactions were modified from standard batch-type RAFT polymerizations, in that a relatively low ratio of RAFT agent to initiator was chosen as well as a low concentration

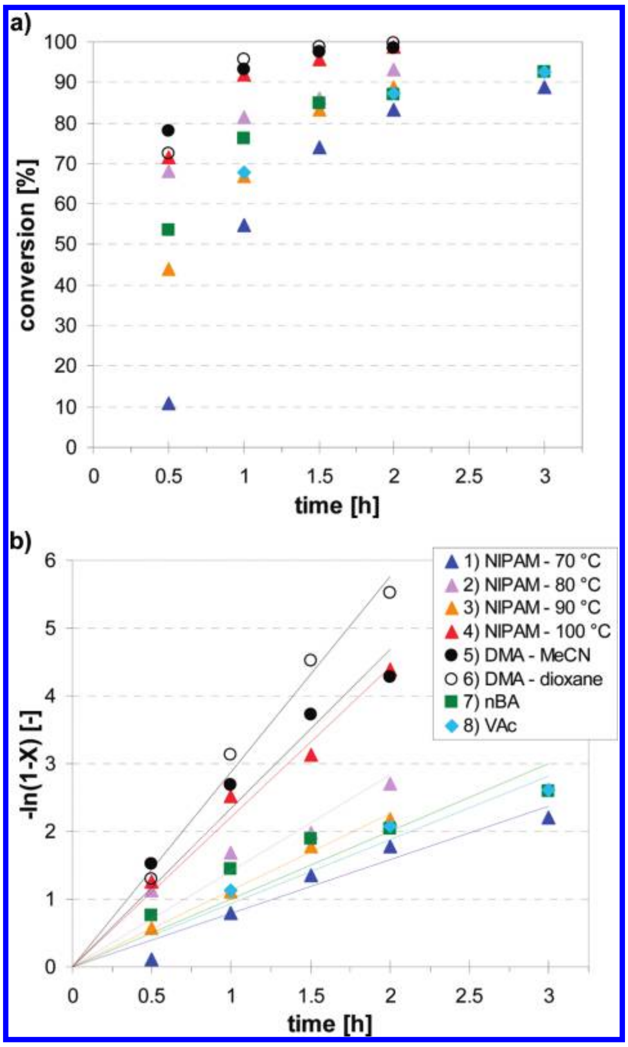

Figure 9. RAFT polymerization of a series of monomers in batch processing; polymerization temperature and solvent were varied in between experiments; details on individual reaction conditions can be found in Table 1, (a) linear conversion in %, (b) logarithmic values where X = conversion (including linear best fit), both plotted over time.

of monomer. The low ratio of RAFT agent to initiator was necessary in order to achieve fast polymerization with relatively high conversions within 2 h, as the residence time inside the flow reactor was limited. The low monomer concentration was necessary in order to produce a polymer solution with low enough viscosity so that it would flow through the reactor without pressure buildup complications. Both these modifications to standard RAFT polymerization protocols are believed to have an influence on the control of polymerization. The 'less-activated' monomer VAc had an average molecular weight of 4500 g/mol, which is significantly lower than for the other polymers. This is believed to be due in part to the higher concentration of monomer and RAFT agent (see Table 1), which had to be chosen in this particular case in order to achieve fast polymerization. Controlled radical polymerization of less-activated monomers, such as VAc can be problematic and is often significantly slower than polymerizations of more activated monomers under comparable conditions. Less active RAFT agents, such as dithiocarbamates and xanthates usually provide the best results; hence, **9** was chosen for the polymerization of VAc.[42]

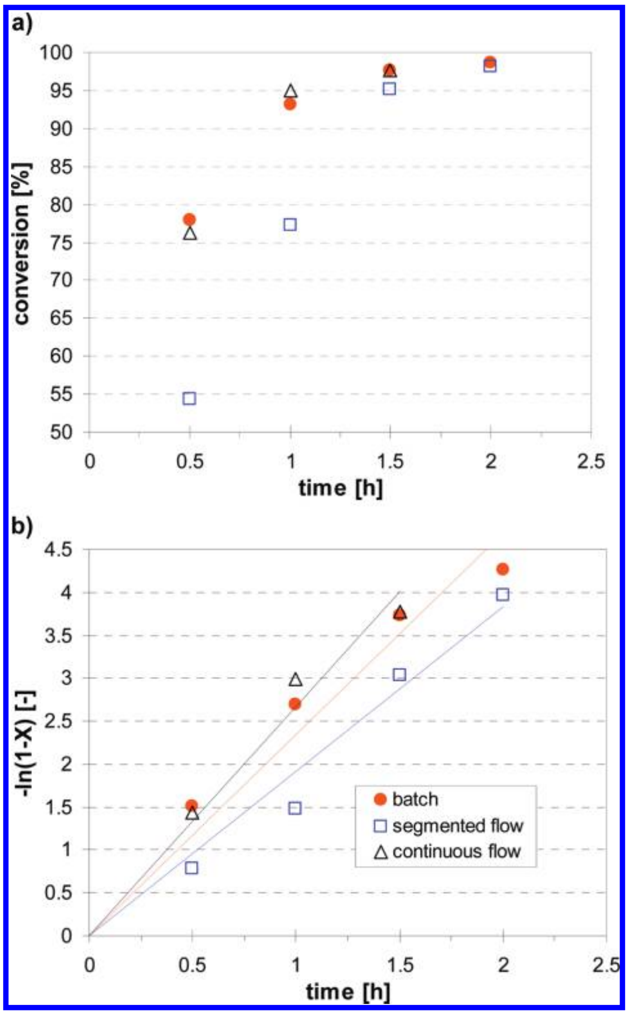

Figure 10. RAFT polymerization of DMA, comparison between batch processing in a microwave reactor and segmented and continuous flow in a steel microreactor; (a) linear conversion in %, (b) logarithmic values where X = conversion (including linear best fit), both plotted over time.

Generally, the results show that the chosen process conditions present a good compromise, as they result in high conversions within the residence time and pressure limits given by the reactor geometry and sufficient control over the polymerization.

In addition to the experiments carried out at 2 h reaction time (Figure 8), all batch reactions and some flow reactions were also performed at shorter and longer reaction times. Figure 9 presents the conversion of these polymerizations over time for the experiments carried out in batch. The graphs show trends expected from theoretical polymerization kinetics, with DMA (entries 5 and 6) polymerizing faster than NIPAM (entry 2) or nBA (entry 7) under identical or similar conditions.

Figure 10 shows a comparison of conversion over time between batch, segmented flow, and continuous flow conditions for one example using DMA (entry 5). This graph shows that there are no significant differences between batch and continuous flow processing, but segmented flow conditions result in lower conversions at short reaction times before they reach similar values at 1.5−2 h. These results indicate that a small plug of only a few millilitres injected via a sample loop (segmented flow) is not processed under the same conditions as in continuous flow. The drop in conversion, which is also

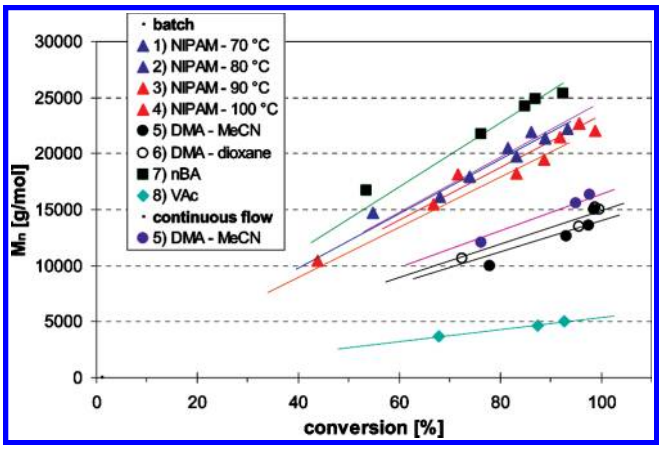

Figure 11. RAFT polymerization of a series of monomers in batch and continuous flow processing; polymerization temperature and solvent were varied in between experiments; details on individual reaction conditions can be found in Table 1, average molecular weight plotted over conversion (including linear best fit).

reflected in the dispersity index for these samples, could have one or a combination of the following reasons. As shown above, the RAFT polymerization is a very oxygen- sensitive reaction, and when a small sample of monomer solution is injected with a syringe, small amounts of oxygen are entrained before and after the reagent plug. When pumped through the reactor coil, this oxygen diffuses into the reagent plug and partially quenches the reaction. Another reason could be the flow-induced dispersion of reagents inside the reactor from the starting material plug into the solvent proceeding and following the plug.[43] This dispersion effect, also called axial diffusion, results in a locally lower concentration at the boundaries of the plug compared to that at the centre of the plug. As this effect is generally believed to be small for the given flow geometries, it is questionable if it would affect the conversion of the RAFT polymerization process. However, only more detailed investigations into the residence time distribution of this reaction system could verify this assumption.

In Figure 11, $\overline{M}_n$ is plotted over conversion for the batch and continuous flow experiments from Figures 9 and 10; this data shows a generally linear trend. The polydispersity index, Đ, for the polymerization of DMA (entry 5) lies between 1.10 and 1.15 in the batch experiments and between 1.09 and 1.16 for the continuous flow experiments. Generally, these results show that it is possible to produce larger amounts of RAFT polymer inside a continuous flow stainless steel microreactor with no difference in reactor performance compared to that of batch. The produced polymers have a narrow dispersity, and the process can be run in high conversions (>95%) at a residence time of 60−90 min.

CONCLUSIONS

This paper reports the first solution-phase synthesis of RAFT polymers with narrow molecular weight distribution (Đ = 1.1 to 1.3) and conversions between 80 and 100% in a continuous flow process using a stainless steel tubing microreactor. A series of different monomers including acryl amides, acrylate and vinyl acetate, different initiators, solvents, and RAFT agents were polymerized at temperatures between 70 and 100 °C. Two different flow modes were compared to batch processing in a microwave reactor. The choice of monomer and process conditions greatly influences the properties of the polymer product, such as the average molecular weight and the dispersity. The length of the polymer chains is mainly responsible for the viscosity of the product solution. As the polymer is formed, the viscosity of the solution increases whilst travelling downstream inside the reactor. While all the starting material solutions had a water-like viscosity, the viscosity of the product was significantly higher and non-Newtonian, and this needed to be accounted for in the design of the process in order to avoid a pressure buildup greater than the pressure limit of the device. The long length of the reactors, with a total volume of 10 mL, enabled the investigation of residence times between a few minutes and several hours; hence, the polymerizations could be performed with high conversions in 2 h. Experiments conducted in segmented flow generally show more similar results than batch processing for the final product obtained after 2 h, with marginally better results in batch. However, experiments carried out at shorter reaction times in both flow modes and in batch showed a difference between segmented and continuous flow. While batch and continuous flow produced the same results, segmented flow performed noticeably worse, which was explained by the way these samples were processed. The herein presented work shows that it is possible to synthesise RAFT polymers on a multigram scale in a commercially available laboratory flow reactor, despite the high oxygen sensitivity of the reaction. When harnessing the numbering-up potential of the technology, this process could potentially be transferred to a small production scale;[1−4,6,44] by using sequential processing it could be modified for the synthesis of block copolymers in a continuous fashion.

EXPERIMENTAL SECTION

Initiators **5**−**7** were obtained from Acros, Dupont, and Wako, respectively. RAFT agent **8** was synthesised in-house,[45,46] and RAFT agent **9** was purchased from Sigma Aldrich. Monomer **1** was used as obtained, and monomers **2**−**4** were pretreated using polymer resin (for removal of hydroquinone and monomethyl ether hydroquinone, Sigma Aldrich, cat. no: 31,133-2) in order to remove the polymerization inhibitor. Solvents were obtained from Merck KGaA and were used without further purification.

Conversions were calculated from ^{1}H NMR spectra using 1,3,5-trioxane as an internal standard. ^{1}H NMR spectra were recorded on a Bruker AC-400 spectrometer in deuterated chloroform (solvent residual as internal reference: δ = 7.26 ppm). Average molecular weight of the polymer, $\overline{M}_n$, and its polydispersity index, Đ, were measured using gel permeation chromatography (GPC). Đ was calculated from experimental data using eq 2.[13]

$$Đ = \frac{\overline{M}_w}{\overline{M}_n} = \frac{\sum w_i M_i / \sum w_i}{\sum n_i M_i / \sum n_i} = \frac{\sum n_i M_i^2 / \sum n_i M_i}{\sum n_i M_i / \sum n_i} \qquad (2)$$

Here $\overline{M}_w$ is the weight average molecular weight, $\overline{M}_n$ is the number average molecular weight and w_i, n_i, and M_i are the weight, number, and molecular weight of chains of length i respectively. GPC of polymers from **1** and **2** was performed on a system comprising a Waters 590 HPLC pump and a Waters 410 refractive index detector equipped with three Waters Styragel columns (HT2, HT3, HT4, each 300 mm ×7.8 mm providing an effective molecular weight range of 100−600000). The eluent was *N,N*-dimethylformamide (DMF) (containing 0.45% w/v LiBr) at 80 °C (flow rate: 1 mL/min). GPC of polymers from **3** and **4** was performed on a system using a Waters 2695 Separation Module, with tetrahydrofuran (1.0 mL/min) used as eluent. The GPCs were calibrated with narrow dispersity polystyrene standards, and molecular weights are reported as polystyrene equivalents. $\overline{M}_n$ and $\overline{M}_w$ were evaluated using Waters Millennium software. A polynomial was used to fit the log M vs time calibration curve, which was linear across the molecular weight ranges.

In order to validate our microwave-induced batch reactions, one RAFT reaction system using monomer **2** was performed in both, the microwave reactor and by conventional heating in an oil bath, as a control. The polymerisation was carried out on a 2-mL scale with identical conditions in these two batch reaction vessels. We did not observe any nonthermal microwave effects accelerating the reaction,[32−36] as the experiments resulted in comparable conversions after 30 min (oil bath: 91%; microwave: 90%) and 2 h (oil bath: 99%; microwave: 99%).

Free Radical Polymerization of *N*-Isopropylacrylamide, 1, in Batch and Segmented Flow (Comparison between a PFA and a Steel Reactor Coil). A starting material solution of 596 mg of monomer, **1**, 87 mg of initiator, **7**, in 6882 mg water was premixed, but not degassed. The polymerization was conducted at 90 °C with a reaction time of 1 h. For batch processing, 2 mL of starting material solution was processed in a laboratory microwave reactor (Biotage Initiator). For segmented flow, 2 mL of starting material solution was injected into a constant solvent stream (water) at 0.17 mL/min on a Vapourtec R2/R4 reactor heater, using either a PFA polymer coil or a stainless steel coil. A clear, viscous polymer solution was obtained after reaction.

RAFT Polymerization of *N,N*-Dimethylacrylamide, 2, in Batch and Segmented Flow (Comparison between a PFA and a Steel Reactor Coil). A starting material solution of 1630 mg of monomer, **2**, 18 mg of initiator, **5**, 44 mg of RAFT agent, **8**, in 8 mL of ethyl acetate (EtOAc) was premixed and degassed using three freeze−evacuate−thaw cycles. The process solvent in between reagent plugs used for segmented flow was degassed using nitrogen purging. The polymerization was conducted at 80 °C with a reaction time of 2 h. For batch processing, 2 mL of starting material solution was processed in a laboratory microwave reactor (Biotage Initiator). For segmented flow, 2 mL of starting material solution was injected into a constant solvent stream (EtOAc) at 0.08 mL/min on a Vapourtec R2/R4 reactor heater, using either a PFA polymer coil or a stainless steel coil. A yellow, viscous polymer solution was obtained after reaction.

RAFT Polymerization of *N,N*-Dimethylacrylamide, 2, in Batch, Segmented and Continuous Flow (Steel Reactor Coil). A starting material solution of 8564 mg of monomer, **2**, 42 mg of initiator, **5**, 175 mg of RAFT agent, **8**, in 39 mL of acetonitrile (MeCN), was premixed and degassed using nitrogen purging. The washing solvent for continuous flow mode and the process solvent used in between reagent plugs for segmented flow mode were also degassed using nitrogen. The polymerizations were conducted at 80 °C with reaction times between 30 min and 2 h. For batch processing, 2 mL of starting material solution were processed on a laboratory microwave reactor (Biotage Initiator). For segmented flow, 2 mL of starting material solution were injected into a constant solvent stream (MeCN) at flow rates between 0.08 and 0.33 mL/min on a Vapourtec R2/R4 reactor heater, using a stainless steel coil. For continuous flow, a total of 35 mL of starting material solution were processed at flow rates between 0.08 and 0.33 mL/min on a Vapourtec R2/R4 reactor heater, using a stainless steel coil. A yellow, viscous polymer solution was obtained after reaction. This general procedure was used for all entries in Table 1 with the noted alterations to the process conditions.

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REFERENCES

(1) Hessel, V.; Renken, A.; Schouten, J. C.; Yoshida, J.; editors. *Micro Process Engineering: A Comprehensive Handbook, 3 Vol. Set*, Wiley-VCH: Weinheim, 2009.

(2) Hessel, V.; Hardt, S.; Löwe, H.; Müller, A.; Kolb, G. *Chemical Micro Process Engineering*; Wiley-VCH: Weinheim, 2005.

(3) Wirth, T. *Microreactors in Organic Synthesis and Catalysis*; Wiley-VCH: Weinheim, 2008.

(4) Ehrfeld, W.; Hessel, V.; Löwe, H. *Microreactors: New Technology for Modern Chemistry*; Wiley-VCH: Weinheim, 2000.

(5) Seeberger, P. H.; Blume, T. *New Avenues to Efficient Chemical Synthesis, Emerging Technologies*; Springer: Berlin, 2007.

(6) Jähnisch, K.; Hessel, V.; Löwe, H; Baerns, M. *Angew. Chem., Ind. Ed.* **2004**, *43*, 406–446.

(7) Ley, S. V.; Baxendale, I. R. *Chimia* **2008**, *62*, 162–168.

(8) Iwasaki, T.; Kawano, N.; Yoshida, J. *Org Process Res. Dev.* **2006**, *10* (6), 1126–1131.

(9) Wilms, D.; Nieberle, J.; Klos, J.; Löwe, H; Frey, H. *Chem. Eng. Technol.* **2007**, *30* (11), 1519–1524.

(10) Florence Bally, F.; Serra, C. A; Hessel, V.; Hadziioannou, G. *Macromol. React. Eng.* **2010**, *4* (9−10), 543–561.

(11) Moad, G.; Rizzardo, E.; Thang, S. H. *Aust. J. Chem.* **2005**, *58*, 379–410.

(12) Moad, G.; Rizzardo, E.; Thang, S. H. *Aust. J. Chem.* **2006**, *59*, 669–692.

(13) Moad, G.; Rizzardo, E.; Thang, S. H. *Polymer* **2008**, *49*, 1079–1131.

(14) Moad, G.; Rizzardo, E.; Thang, S. H. *Aust. J. Chem.* **2009**, *62*, 1402–1472.

(15) Bicciocchi, E.; Chong, Y. K.; Giorgini, L.; Moad, G.; Rizzardo, E.; Thang, S. *Macromol. Chem. Phys.* **2010**, *211* (5), 529–538.

(16) Jenkins, A. D.; Jones, R. I.; Moad, G. *Pure Appl. Chem.* **2010**, *82*, 483–491.

(17) Enright, T. E.; Cunningham, M. F.; Keoshkerian, B. *Macromol. React. Eng.* **2010**, *4* (3−4), 186–196.

(18) Rosenfeld, C.; Serra, C.; Brochon, C.; Hadziioannou, G. *Chem. Eng. Sci.* **2007**, *62* (18−20), 5245–5250.

(19) Zitlalpopoca-Soriano, A. G.; Vivaldo-Lima, E.; Flores-Tlacuahuac, A. *Macromol. React. Eng.* **2010**, *4* (8), 516–533.

(20) Zitlalpopoca-Soriano, A. G.; Vivaldo-Lima, E.; Flores-Tlacuahuac, A. *Macromol. React. Eng.* **2010**, *4* (9−10), 599–612.

(21) Chan, N.; Boutti, S.; Cunningham, M. F.; Hutchinson, R. *Macromol. React. Eng.* **2009**, 3 (5−6), 222–231.

(22) Chan, N.; Cunningham, M. F.; Hutchinson, R. A. *Macromol. React. Eng.* **2009**, *4* (6−7), 369–380.

(23) Russum, J. P.; Jones, C. W.; Schork, F. J. *Ind. Eng. Chem. Res.* **2005**, *44* (8), 2484–2493.

(24) Schork, F. J.; Guo, J. *Macromol. React. Eng.* **2008**, *2* (4), 287–303.

(25) Baxendale, I. R.; Ley, S. V.; Mansfield, A. C.; Smith, C. D. *Angew. Chem., Int. Ed.* **2009**, *48* (22), 4017–4021.

(26) Baxendale, I. R.; Schou, S. C.; Sedelmeier, J.; Ley, S. V. *Chem.—Eur. J.* **2009**, *16* (1), 89–94.

(27) Baumann, M.; Baxendale, I. R.; Martin, L. J.; Ley, S. V. *Tetrahedron* **2009**, *65*, 6611–6625.

(28) Baumann, M.; Baxendale, I. R.; Ley, S. V. *Synlett* **2008**, *14*, 2111–2114.

(29) Qian, Z.; Baxendale, I. R.; Ley, S. V. *Synlett* **2010**, *4*, 505–508.

(30) Hornung, C. H.; Mackley, M. R.; Baxendale, I. R.; Ley, S. V. *Org. Process Res. Dev.* **2007**, *11* (3), 399–405.

(31) Hornung, C. H.; Hallmark, B.; Baumann, M.; Baxendale, I. R.; Ley, S. V.; Hester, P.; Clayton, P.; Mackley, M. R. *Ind. Eng. Chem. Res.* **2010**, *49* (10), 4576–4582.

(32) Paulus, R. M.; Becer, C. R; Hoogenboom, R.; Schubert, U. S. *Aust. J. Chem.* **2009**, *62* (3), 254–259.

(33) Roy, D.; Ullah, A.; Sumerlin, B. S. *Macromolecules* **2009**, *42* (20), 7701–7708.

(34) Hernández-Ortiz, J. C.; Jaramillo-Soto, G.; Palacios-Alquisira, J.; Vivaldo-Lima, E. *Macromol. React. Eng.* **2010**, *4* (3−4), 210–221.

(35) Hoogenboom, R.; Schubert, U. S. *Aust. J. Chem.* **2009**, *62* (3), 181–183.

(36) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107* (6), 2563–2591.

(37) Namy, J.-L.; Kagan, H. B. *Nouv. J. Chim.* **1977**, *1*, 5–7.

(38) Girard, P.; Namy, J.-L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.

(39) Souppe, J.; Namy, J.-L.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 2869–2872.

(40) Namy, J.-L.; Colomb, M.; Kagan, H. B. *Tetrahedron Lett.* **1994**, *35*, 1723–1726.

(41) Hornung, C. H.; Hallmark, B.; Hesketh, R. P.; Mackley, M. R. *J. Micromech. Microeng.* **2006**, *16*, 434–447.

(42) Moad, G.; Rizzardo, E.; Thang, S. H. *Acc. Chem. Res.* **2008**, *41*, 1133–1142.

(43) Hornung, C. H.; Mackley, M. R. *Chem. Eng. Sci.* **2009**, *64*, 3889–3902.

(44) Vankayala, B. K.; Löb, P.; Hessel, V.; Menges, G.; Hofmann, C.; Metzke, D.; Krtschil, U.; Kost, H.-J. *Int. J. Chem. React. Eng.* **2007**, *5*, A91.

(45) Thang, S. H.; Chong, Y. K.; Mayadunne, R.; Moad, G.; Rizzardo, E. *Tetrahedron Lett.* **1999**, *40*, 2435–2438.

(46) Moad, G.; Chong, Y. K.; Rizzardo, E.; Postma, A.; Thang, S. H. *Polymer* **2005**, *46*, 8458–8468.