Synthesis of RAFT block copolymers in a multi-stage continuous flow process inside a tubular reactor

Christian H. Hornung, Xuan Nguyen, Stella Kyi, John Chiefari, Simon Saubern*

CSIRO Materials Science & Engineering, Bag 10, Clayton South, Victoria 3169, Australia.
*Corresponding Author. E-mail: simon.saubern@csiro.au.

Abstract
This work describes a multi-stage continuous flow polymerization process for the synthesis of block copolymers using the RAFT method. The process retains all the benefits and versatility of the RAFT method and has been adapted for a series of monomer combinations, including acrylates, acrylamides and vinyl monomers. This resulted in polymers with molecular weights between 13500 and 34100 g/mol, and dispersities typically between 1.21 and 1.58. Different architectures were prepared (combinations of hydrophilic and hydrophobic blocks) which are soluble in a range of different solvents including aqueous and organic media.

Introduction
The Reversible Addition-Fragmentation chain Transfer (RAFT) method is a controlled radical polymerization (CRP) method, capable of controlling a broad range of different monomers to produce polymers with defined structures, narrow molecular weight distributions and defined end groups. One of the major advantages of the RAFT approach over other CRP processes is
its compatibility with most monomers (including (meth)acrylates, (meth)acrylamides, vinyl esters and acid and amine containing monomers) and reaction conditions suitable for the conventional free radical process.\textsuperscript{1-5} The capability of polymer chains, which contain thiocarbonylthio end groups (RAFT end groups), to be reinitiated and continue to grow, makes the RAFT method a very convenient and versatile technique for synthesizing complex architectures, such as blocks, stars, and others.\textsuperscript{6-13} The principal strategies and synthetic protocols used for radical polymerizations in general and controlled radical polymerizations, such as RAFT, in particular, have remained relatively unchanged over the last few decades. Only in the last few years, flow chemistry and microreactor technology\textsuperscript{14-21} has changed the way polymers are synthesized in the laboratory.\textsuperscript{22-26} In previous work, we have demonstrated that the RAFT process can be adapted for continuous flow processing using stainless steel tubular reactors.\textsuperscript{27-30} The small dimension of these reactors (typically 1 mm ID) ensure that the reaction is conducted at quasi-isothermal conditions, due to the excellent heat transfer characteristics of the reactor, and that the residence time distribution is very narrow, exhibiting a near plug-flow like profile.\textsuperscript{30,31} Herein, we demonstrate that additionally to the synthesis of homopolymers\textsuperscript{28} and subsequent removal of the RAFT end group,\textsuperscript{29} this continuous flow technology can also be used for the synthesis of block copolymers.

**Experimental Section**

*Materials and Analysis*

The initiators azobis(isobutyronitrile) (AIBN) and azobis(cyclohexanenitrile) (ACHN) were obtained from DuPont; the RAFT agent $S$-dodecyl $S$-(2-cyano-4-carboxy)but-2-yl trithiocarbonate, 1a (see Scheme 1), was synthesized in our group.\textsuperscript{32} RAFT agent cyanomethyl methyl(phenyl)carbamodithioate, 1b, was obtained from Aldrich. The monomers methyl acrylate (MA), $n$-butyl acrylate ($n$BA), hydroxylethyl acrylate (HEA), $N,N$-
dimethyl acrylamide (DMA), vinyl acetate (VAc) and N-vinylpyrrolidone (NVP) were pre-treated using polymer resin (for removal of monomethyl ether hydroquinone, Sigma Aldrich, Cat. No: 31,133-2) in order to remove the polymerization inhibitor. The monomer N-isopropyl acrylamide (NIPAM) was recrystallized in n-heptane before use. All monomers were obtained from Sigma Aldrich. The solvents acetonitrile (MeCN), dichloromethane (DCM), diethyl ether (Et₂O), ethyl acetate (EtOAc), isopropanol (iPrOH) and anisole were obtained from Merck KGaA or Sigma Aldrich and were used without further purification.

Reaction conversions were calculated from ¹H NMR spectra, which were recorded on a Bruker AC-400 spectrometer in deuterated chloroform (from Cambridge Isotope Laboratories Inc.). The residual solvent peak at δ = 7.26 ppm was used as an internal reference. The conversion of the polymerization process (first and second block) was determined by comparing a series of characteristic vinylic ¹H NMR peaks before and after reaction, which can be attributed to the monomer. The integrals of these monomer peaks were compared to those of the reference signal from the internal standard, 1,3,5-trioxane at δ = 5.1 ppm, and from the resulting relative values a conversion could be calculated by:

\[
\text{conv} = \frac{PI_{\text{before}} - PI_{\text{after}}}{PI_{\text{before}}},
\]

whereby, \( PI_{\text{before}} \) is the relative peak integral of the monomer signal (or series of signals) before end group removal and \( PI_{\text{after}} \) is the relative peak integral after reaction; e.g. for DMA, these monomer signals are at δ = 5.6 ppm (dd), δ = 6.2 ppm (dd) and δ = 6.5 ppm (dd).

Average molecular weight of the polymer, \( M_n \), and its dispersity index, \( D \), were measured using gel permeation chromatography (GPC). GPC was performed on a Shimadzu system equipped with a CMB-20A controller system, a SIL-20A HT autosampler, a LC-20AT tandem pump system, a DGU-20A degasser unit, a CTO-20AC column oven, a RDI-10A refractive index (RI) detector, and a PL Rapide (Varian) column. \( N,N\)-dimethylacetamide (DMAc) (containing 2.1 g·l⁻¹ LiCl) was used as eluent at a flow rate of 1 ml/min (pressure
range: 750-800 psi). The column temperature was set to 80 °C and the temperature at the RI detector was set to 35 °C. The GPC was calibrated with narrow dispersity poly(methyl methacrylate) standard, and molecular weights are reported as poly(methyl methacrylate) equivalents. $M_n$ and $D$ were evaluated using Shimadzu software. A polynomial was used to fit the log $M$ vs. time calibration curve, which was linear across the molecular weight ranges.

**Batch synthesis of RAFT block copolymers**

The following procedure is typical for the synthesis of a di-block copolymer with a 1:1 monomer ratio. A starting material solution of 397 mg (4 mmol) monomer (DMA), 1.97 mg (0.012 mmol) initiator (AIBN), 19.38 mg (0.048 mmol) RAFT agent 1a (see Scheme 1), in 1.6 ml of MeCN, was premixed and deoxygenated using nitrogen purging. The polymerization was conducted on a laboratory microwave reactor (Biotage Initiator) at 70 °C with a reaction time between 60 and 80 min. A yellow viscous polymer solution (first block) was obtained after reaction, from which conversion, molecular weight and dispersity were determined by NMR and GPC respectively. This polymer solution was then used as the PDMA macro-RAFT agent for subsequent block extension with methyl acrylate without purification. 344 mg (4 mmol) monomer (MA), 1.97 mg (0.012 mmol) initiator (AIBN) and 0.64 ml MeCN were added to the polymer solution. The mixture was deoxygenated using nitrogen purging and re-subjected to polymerization in the microwave reactor for a further 120 min at 80 °C. Following solvent removal and re-dissolving in DCM, the block copolymer product (pDMA-b-pMA) was precipitated into Et$_2$O, resulting in 650 mg of yellow polymer powder, after filtration and drying.

For di-block copolymers with a 1:5 monomer ratio, the concentrations of the two polymerization stages were adjusted accordingly. For example in one of these cases, the starting material solution of the first stage consisted of 297 mg (3 mmol) monomer (DMA), 1.48 mg (0.009 mmol) initiator (AIBN), 14.53 mg (0.036 mmol) RAFT agent 1a, and 1.2 ml
MeCN; and in the second stage 1291 mg (15 mmol) monomer (MA), 3.69 mg (0.023 mmol) initiator (AIBN) and 2.4 ml MeCN were added.

For kinetic studies, small samples of the reaction mixture for $^1$H NMR and GPC were removed through the septum of the microwave reactor glass vial using a syringe. For this the microwave reaction was stopped at various points in time over the course of the reaction, e.g. at 30, 60, 100, 130, 183 and 220 min.

*Continuous flow synthesis of RAFT block copolymers*

The following procedure is typical. A starting material solution of 991 mg (10 mmol) monomer (DMA), 4.93 mg (0.03 mmol) initiator (AIBN), 48.44 mg (0.12 mmol) RAFT agent 1a (see Scheme 1) in 4 ml MeCN was premixed and deoxygenated by nitrogen purging. The washing solvent (MeCN) was also degassed. The starting material solution was injected via a 5 ml sample loop into a Vapourtec R2/R4 flow reactor, containing two 1.0 mm ID stainless steel reactor coil modules in series (10 ml each – total reactor volume: 20 ml). The polymerization was conducted at 70°C and flow rates between 0.24 and 0.4 ml·min$^{-1}$, which resulted in a reaction time of 83 to 50 min. 5 ml of yellow polymer solution (first block) was collected and used as the PDMA macro-RAFT agent for subsequent block extension with NIPAM without purification. 1132 mg (10 mmol) monomer (NIPAM), 4.93 mg (0.03 mmol) initiator (AIBN) and 1.2 ml MeCN were added to the polymer solution. The mixture was deoxygenated using nitrogen purging and a 5 ml aliquot was injected into the flow reactor for polymerisation at 80 °C for a further 83 min. Following solvent removal and re-dissolving in DCM, the block copolymer product (pDMA-$b$-pNIPAM) was precipitated into Et$_2$O, resulting in 1890mg of yellow polymer powder, after filtration and drying.

*Results and Discussion*
The herein presented solution phase synthesis of RAFT di-block-copolymers follows the general reaction pathway shown in Scheme 1. In a first stage, monomer A, is reacted with RAFT-agent, 1, and initiator in an appropriate solvent to form a homo-polymer, 2, which still contains the RAFT end-group. In the second stage, this homo-polymer (which can also be considered as a macro-RAFT agent) is reinitiated with fresh initiator and a second block is grown by adding monomer B. The final product is a RAFT di-block copolymer, 3. The integrated continuous flow process for the two-stage synthesis of RAFT di-block copolymers does not allow for simple removal of unreacted monomer after the first polymerization step. Hence, no purification or isolation of the first block, 2, was conducted for all herein presented continuous flow and batch reactions.

Scheme 1. Synthesis of di-block copolymers using the RAFT approach and the following monomers: MA, nBA, DMA, NIPAM, HEA, VAc and NVP.

Before investigating continuous flow processing for multi-stage synthesis of RAFT block copolymers, we first undertook kinetic studies of various di-block combinations in batch. These experiments were carried out on a batch microwave reactor system (see experimental
section) at temperatures between 80 and 110 °C in preparation for the more complex flow process. The monomers used for these experiments were MA, DMA and NIPAM; the RAFT agent was 1a; the solvents were MeCN and anisole, and the initiators AIBN or ACHN depending on the reaction temperature. The ratio of block A to B for these copolymers was adjusted to 2:1. Figure 1 shows the results plotted as conversion over time.

![Graph showing conversion profiles of batch microwave reactions for the synthesis of RAFT di-block copolymers (ratio monomer A / monomer B = 2:1), dotted line: addition of monomer B and fresh initiator.](image)

**Figure 1.** Conversion profiles of batch microwave reactions for the synthesis of RAFT di-block copolymers (ratio monomer A / monomer B = 2:1), dotted line: addition of monomer B and fresh initiator.

The graph shows similar trends for the conversion of the first blocks; these follow regular conversion curves for this type of monomers, up until 100 min (1.67 h) reaction time. At that point monomer B together with fresh initiator was added to the mixture and the second block was grown. For experiments where the conversion of the first block was between 80 and 90% (monomer A = MA or NIPAM) there is an additional step in the conversion curve for...
monomer A at this point caused by the addition of fresh initiator. The curves for monomer B follow the regular trend. These results gave an initial understanding of the polymerization kinetics of the chosen RAFT / monomer systems, and based on this data we selected the reaction conditions for the subsequent experiments.

At high conversion, for controlled free radical polymerization processes, such as RAFT and ATRP, chain termination reactions arising from radical-radical reactions may lead to considerable amounts of “dead” polymer chains. The extent that these reactions occur depends on the type of monomer and reaction conditions. The consequence of these radical-radical termination reactions is that the polymer loses the end group fidelity i.e. the polymer chain is no longer living. The loss of end group fidelity means that these polymer chains cannot be extended into a block and hence a product reacted under these conditions will consist of a mixture that contains the homo-polymer. In order to examine this effect more closely, a series of batch reactions was conducted, synthesizing pDMA-$b$-pMA at different reaction conditions and with different monomer ratios. The reaction conditions, together with conversion, $M_n$ and $D$ of these experiments are presented in Table 1. Figure 2 contains GPC traces of these experiments: Figure 2a shows results of di-blocks from experiments, where both monomers where used in equal amounts (monomer ratio 1:1, entries 2 to 4) and Figure 2c shows results from experiments using five times as much second monomer (MA) than the first (DMA) (monomer ratio 1:5, entries 5 to 8). The two graphs on the right show one example of each of these two groups, together with the GPC trace of the respectable homo-polymer (first block), before growing the DMA-block in the second stage: Figure 2b shows results from entry 3 and Figure 2d shows results from entry 5.

Table 1. Reaction conditions, concentrations and results for the batch synthesis of pDMA-$b$-pMA using RAFT.

<table>
<thead>
<tr>
<th>entry</th>
<th>monomer ratio DMA/MA</th>
<th>T [°C]</th>
<th>t [min]</th>
<th>monomer conversion [%]</th>
<th>$M_n$ [g·mol$^{-1}$]</th>
<th>$D$ [-]</th>
</tr>
</thead>
</table>
The following molar ratios of monomer to RAFT agent to initiator were used for the synthesis of the first polymer block (DMA): entries 1 to 4: 100/1.2/0.3 (monomer concentration: 2 mol/L in MeCN), entries 5 to 7: 40/1.2/0.3 (monomer concentration: 2 mol/L in MeCN); the following molar ratios of monomer to RAFT-agent to initiator were used for the synthesis of the second polymer block (MA): entries 1 to 4: 100/1.2/0.3 (monomer concentration: 1.33 mol/L in MeCN), entries 5 to 7: 200/1.2/0.3 (monomer concentration: 1.33 mol/L in MeCN); reaction temperature for synthesis of first / second block; for all entries the initiator AIBN and the RAFT agent 1a was used; reaction time for synthesis of first / second block; monomer conversion of the first block (DMA) / second block (MA); average molecular weight of first / second block, measured in pMMA equivalents; dispersity of first / second block.
Figure 2. GPC of di-block copolymers from Table 1: a) polymers with monomer ratio (DMA:MA) 1:1, Table 1, entries 2 to 4; b) Table 1, entry 3, di-block and homopolymer; c) polymers with monomer ratio (DMA:MA) 1:5, Table 1, entries 5 to 8; d) Table 1, entry 5, di-block and homopolymer.

The GPC traces from the experiments where the second block was five times as large as the first one (monomer ratio 1:5, entries 5 to 8), are especially revealing (Figures 2c and 2d). In these cases, the retention times of homo-polymer and di-block copolymer differ substantially so that the two peaks are clearly separated (Figure 2d), unlike in the case of a 1:1 di-block, where these two peaks are not fully separated (Figure 2b). Figure 2d also shows, that in this particular case, a small fraction of homo-polymer is retained in the final product. The majority of this polymer is a di-block (solid line, major peak at log $M_n = 4.4$), with a minor second fraction (solid line, small peak at log $M_n = 3.7$), which has the same molecular weight as the homo-polymer trace (dotted line, peak at log $M_n = 3.7$). In this case, the polymerization of the first block was pushed to almost full conversion (99%, see entry 5) by reacting it for a comparably long reaction time (80 min). Entries 6 to 8, which were reacted for shorter times (77 to 65 min), but otherwise identical conditions, do not show any traces of homo-polymer (see Figure 2c). This leads to the conclusion that only at very high conversions of the first stage of the di-block synthesis, the effect of chain termination is significant and measurable. If the first block is reacted to 90% or lower (entries 6 to 8), there is no significant amount of dead chain homo-polymer present in the final product. As a result of these preliminary experiments, it was decided to choose reaction conditions for the continuous process that would give conversions between 80 and 90% for the first block. This is a compromise between very high conversions, which lead to a large number of dead chains, and low conversions, which lead to contamination of the second block with monomer A. This is necessary since the multi-stage continuous flow process, unlike the batch process, does not allow for a simple and practical separation of unreacted monomer A in between the two
reaction stages (see Figure 3). The results from these initial experiments were used to design the continuous flow operation.

![Figure 3. Experimental configuration of the two-stage continuous flow process for the synthesis of RAFT di-block copolymers.](image)

The reactor configuration shown in Figure 3 was used to synthesize a series of di-blocks continuously, and some of these experiments were compared to a batch process under identical processing conditions (see Table 2).

### Table 2. Conditions, reagents and results for the synthesis of RAFT di-block copolymers in batch and continuous flow. The following molar ratio of monomer A to monomer B to RAFT-agent to initiator was used: 100/100/1.2/0.3.

<table>
<thead>
<tr>
<th>entry</th>
<th>processing method</th>
<th>monomer A</th>
<th>monomer B</th>
<th>solvent</th>
<th>T [°C]</th>
<th>t [min]</th>
<th>conversion of B [%]</th>
<th>$M_n$ [g·mol$^{-1}$]</th>
<th>$D$ [-]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td>batch DMA MA MeCN</td>
<td>70 / 80 83 / 111</td>
<td>90 18900 1.39</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2$^b$</td>
<td>cont. DMA MA MeCN</td>
<td>70 / 80 83 / 111</td>
<td>90 19400 1.35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3$^b$</td>
<td>batch DMA MA MeCN</td>
<td>110 / 110 83 / 111</td>
<td>92 14100 1.51</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4$^b$</td>
<td>cont. DMA MA MeCN</td>
<td>110 / 110 83 / 111</td>
<td>91 13500 1.56</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>cont. DMA $n$BA MeCN</td>
<td>70 / 80 83 / 83</td>
<td>83 22400 1.24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>cont. DMA NIPAM MeCN</td>
<td>70 / 80 83 / 83</td>
<td>88 27100 1.22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>cont. NIPAM DMA MeCN</td>
<td>70 / 70 83 / 120</td>
<td>81 28400 1.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>cont. NIPAM $n$BA MeCN</td>
<td>70 / 80 83 / 83</td>
<td>88 34100 1.21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>batch HEA DMA $i$PrOH</td>
<td>70 / 70 83 / 83</td>
<td>94 9800 1.58</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>cont. HEA DMA $i$PrOH</td>
<td>70 / 70 83 / 83</td>
<td>87 12800 1.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>batch VAc NVP EtOAc$^c$</td>
<td>100 / 105 60 / 60</td>
<td>96 15100 2.84</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>cont. VAc NVP EtOAc$^c$</td>
<td>100 / 105 50 / 60</td>
<td>93 15800 2.26</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
a) Entries 1-10 were synthesized using RAFT agent 1a, entries 11 and 12 were using 1b (see Scheme 1). b) Preliminary results of these experiments were presented at two scientific conferences.\textsuperscript{34,35} c) The following monomer concentrations were used for the synthesis of the first polymer block: entries 1-10: 2 mol/L, entries 11 and 12: 5 mol/L. d) The following monomer concentrations were used for the synthesis of the second polymer block: entries 1-10: 1.33 mol/L, entries 11 and 12: 1.89 mol/L. e) The first block (pVAc) was synthesized in EtOAc, the second (pNVP) in a mixture of EtOAc and MeOH. f) Reaction temperature for synthesis of first / second block; for entries 1,2,5-10 the initiator AIBN was used, for the others ACHN was used; g) reaction time for synthesis of first / second block; h) average molecular weights were measured in pMMA equivalents.

A broad range of different monomer and RAFT agent combinations were investigated for various conditions. Because of the fully enclosed design of the two-stage flow process, only conversion of monomer B could be monitored, by analyzing the final di-block copolymer product. This conversion lay between 80 and 96%, and in all cases there was no monomer A present in the final product. The average molecular weight of these polymers ranged between 10000 and 34000 g mol\(^{-1}\) and \(D\) was in between 1.2 and 2.3, strongly depending on the monomer system. Monomer combinations of DMA, NIPAM and \(n\)BA (entries 5 to 8) showed the lowest \(D\) with values around 1.2, while HEA / DMA (entries 9 and 10) had a \(D\) above 1.5. The polymerization of VAc is a very reactive system, leading to side reactions and therefore it can be difficult to obtain good control. This is reflected in the high values of \(D\) of above 2 for the VAc / NVP system (entries 11 and 12). For the examples where a batch comparison reaction under identical conditions was performed (entries 1, 3, 9 and 11), no significant difference to the flow process in conversion, \(M_n\) and \(D\) was observed. The flow experiments resulted in marginally lower conversions but also lower dispersities. Some of the flow reactions in Table 2 were processed in a two-stage fashion as depicted in figure 3, where two reactors in series were used and monomer for the second block was fed into the system inline after the first reactor; for some others, only one reactor was used, and after passing through it the first time the reaction mixture (first block) was collected, monomer B was added, the mixture than degassed and fed through the reactor again. Both these operation modes of the continuous flow system result effectively in the same conditions and thus the polymer
products are as good as identical; this was verified by repeating the continuous flow synthesis of pDMA-\textit{b}-pMA (entry 2) for both operation modes, giving similar results: The integrated two reactor process produced polymer with $M_n$ of 18900 g/mol and $D$ of 1.38 in 90% conversion; the single reactor approach produced polymer with $M_n$ of 19800 g/mol and $D$ of 1.32 in 90% conversion (average: $M_n = 19400$ g/mol, $D = 1.35$, conversion = 90%). In general, it can be said that the continuous flow process gives good control over the RAFT polymerization, resulting in di-block copolymers with narrow polymer size distribution.

**Conclusion**

Above, we have demonstrated the synthesis of di-block copolymers in a two-stage continuous flow reactor using the RAFT approach. The use of continuous flow processing allows for large quantities of polymer to be generated in a reactor system with significantly smaller footprint than a comparable batch reactor. The small dimensions of our tubular flow reactor of around 1 mm ID ensure that heat and mass transport is efficient and that the reactor can be operated quasi isothermally, resulting in more uniform reaction conditions than a batch stirred tank reactor. Our reactor was capable of producing RAFT block copolymers continuously in an integrated process, without the need for handling of intermediates. The process is robust and has performed reliably for a series of different monomer combinations, RAFT agents, solvents and reaction conditions. Using the described technology, it is possible to synthesize these polymers on scales ranging from a few milligrams to potentially several kilograms, and with a greatly improved reproducibility when compared to a corresponding batch process.

**Acknowledgements**

The authors thank Ezio Rizzardo, San Thang and Graeme Moad for helpful discussions.
References


Graphical Abstract: