ACS Combinatorial Science

Technology Note

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Automated Parallel Freeze–Evacuate–Thaw Degassing Method for Oxygen-Sensitive Reactions: RAFT Polymerization

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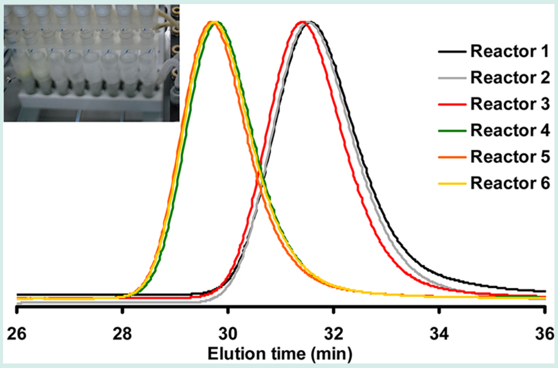
S *Supporting Information*

ABSTRACT: An automated and parallel freeze–evacuate–thaw degassing method in a commercially available synthesizer is disclosed and tested for its applicability to reversible addition–fragmentation chain transfer (RAFT) polymerization. The effectiveness of this method to eliminate oxygen in polymerization reactions is demonstrated by directly comparing it against experiments performed using conventional laboratory techniques. Apart from the demonstrated accuracy, the proposed method has also shown significant precision when performing RAFT polymerizations. The reported experimental technique can be easily adapted to other chemical systems where the removal of oxygen is mandatory. This new high-throughput method has the potential to significantly increase the productivity and/or research outcomes in laboratories where oxygen-sensitive reactions are carried out.



KEYWORDS: *RAFT, polymerization, automated parallel synthesizer, freeze–evacuate–thaw, degassing, oxygen sensitive reactions*

For many years, synthetic chemists have been made use of the "classical" one pot lab-scale approach to carry out oxygen sensitive reactions. For this purpose, degassing techniques such as refluxing, inert gas sparging, vacuum degassing and ultrasonic agitation,[1] had been proposed to remove traces of oxygen in reaction mixtures. However, these kinds of synthetic techniques can be time-consuming and often require additional experimental effort and care in order to be carried out in a proper and reliable manner. These rather demanding experimental methods can considerably limit the number of chemical reactions researchers can explore in a determined period of time. These restrictions can slow down the research and development process, negatively impacting on the duration, productivity and cost of a research project.

For instance, in oxygen or moisture sensitive polymerizations, limitations have been circumvented by developing suitable experimental protocols, which make use of the advantages of high-throughput experimentation (e.g., use of automation and parallel synthesis).[2−8] In this regard, anionic and cationic polymerization have been successfully performed in commercially available synthesizers using inert atmosphere techniques.[3−5] In the case of anionic polymerization, a convenient and automated chemical treatment was proposed to reach a homogeneous and suitable inert atmosphere level between the different reactors of a parallel synthesizer in order to obtain reproducible and reliable results.[4,5] This experimental protocol allowed the synthesis of block copolymer libraries,[5,9] synthesis of end-functionalized polymers,[10] and the rapid investigation of kinetic parameters[4] for one of the most demanding techniques in polymer synthesis. Similarly, in the case of cationic polymerization, the application of inert atmosphere techniques was sufficient enough for the polymerizations to be effectively performed in an automated and parallel fashion[3] allowing for kinetic investigations.[11] In addition, automated parallel synthesizers have been extensively utilized to perform controlled radical polymerizations (CRP), for example, nitroxide mediated polymerization (NMP),[12−15] atom transfer radical polymerization (ATRP),[16,17] macromolecular design via the interchange of xanthates (MADIX)[18] and reversible addition–fragmentation chain transfer polymerization (RAFT).[19−23] Nevertheless, and to the best of our knowledge, most reports pertaining to oxygen sensitive polymerizations undertaken in commercially available automated parallel synthesizers have utilized inert gas sparging techniques to eliminate oxygen from the corresponding reaction mixtures.[6,18−20] The precision and accuracy of this technique with respect to automated parallel synthesizers has been demonstrated to a certain extent.[18,19] One of the main drawbacks of using the inert gas sparging technique is that the concentration of reagents can be varied when the utilized chemicals or solvents are relatively volatile. These changes in concentration could be even more marked due to variations in temperature and time during the inert gas sparging, which can have an impact on the precision and accuracy of the obtained results (especially during kinetic investigations). Thus, this contribution discloses an automated freeze–evacuate–thaw

Received: April 16, 2012
Revised: June 11, 2012
Published: June 19, 2012

method as performed in a commercially available parallel synthesizer as an alternative degassing procedure to perform parallel oxygen-sensitive reactions in a reliable manner. It is demonstrated that the proposed experimental technique is very effective in eliminating oxygen from reaction mixtures and allows for RAFT polymerization to be carried out in an accurate and precise manner in the utilized apparatus. The reported experimental protocol was directly compared to a conventional freeze−evacuate−thaw method carried out in sealed ampules (and under high vacuum conditions)[24,25] indicating that the method can be as effective as traditionally used "one at a time" manual approaches. It is envisaged that the reported experimental technique can easily be adapted and utilized in other chemical systems where the removal of oxygen is mandatory, such as is the case with RAFT polymerization.[26] This new high-throughput method can significantly increase the productivity and/or research outcomes in laboratories where oxygen-sensitive reactions are carried out.

The experimental setup (automated parallel synthesizer) utilized in this investigation was a Chemspeed Swing-SLT automated synthesizer (Figure 1). The synthesizer is equipped with a glass reactor block consisting of 16 reaction vessels (13 mL) with thermal jackets connected in series through the reaction block and connected to a heating/cooling system (Hüber, −90 to 140 °C). In addition, all reaction vessels are equipped with coldfinger reflux condensers (~7 °C). Mixing is achieved by vortex agitation (up to 1400 rpm). Liquid transfers were handled by a 4-needle head (4-NH) capable of four simultaneous sample transfers. The 4-NH was connected to a reservoir bottle (degassed solvent) for needle rinsing after each liquid transfer step. This solvent reservoir is degassed by continuous sparging with nitrogen and is also utilized to prime the tubing lines of the 4-NH. When experiments are carried out, the synthesizer is maintained under an inert atmosphere by supplying a constant flow of nitrogen into the hood of the synthesizer. A nitrogen atmosphere is also applied to reactors and stock solutions at all times. Prior to the synthetic experiment, the reaction vessels are heated to 135 °C and subjected to 10 cycles of vacuum (2 min each) and filling with nitrogen (2 min each) to ensure the elimination of oxygen. After this pretreatment, a typical oxygen-sensitive reaction utilizing a proposed automated parallel freeze−evacuate−thaw procedure is carried out as explained below. Stock solutions or pure chemicals are prepared and placed inside the automated synthesizer. Aliquots of stock solutions and corresponding solvent from the reservoir are transferred into the reactors with the automated liquid handling system to provide the desired concentrations of reagents. After the liquid transfers are completed, the reaction solutions are degassed through three automated freeze−evacuate−thaw cycles carried out as follows: The reaction mixtures are cooled to −90 °C,[27] while applying vortex to the reaction block (200 rpm, 2 min). Vacuum (~5 mbar) is then applied to the reactor block while heating the reactors up to −10 °C (or up to the reaction mixture melts) with vortex (600 rpm, 2 min). Thereafter, the reactors are sealed under a nitrogen atmosphere and heated to desired reaction temperature while applying vortex to the reaction block (typically 300 rpm); the temperature of the reflux condensers on top of the reactors is normally set at 7 °C.

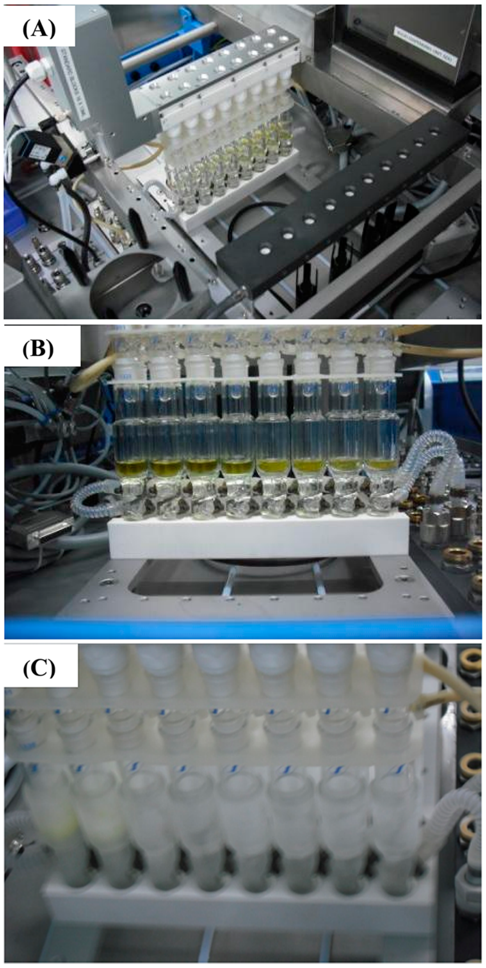


Figure 1. (A) Overview of a glass block reactor with thermal jackets in the Chemspeed automated synthesizer. (B) Parallel reactors containing RAFT polymerization reaction mixtures. (C) Overview of a parallel RAFT polymerization experiment during the proposed freeze−evacuate−thaw degassing method.

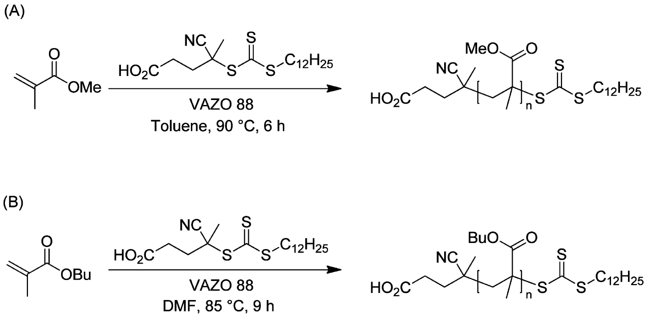
To verify the precision of the proposed method a series of RAFT polymerization reactions were performed in the automated synthesizer (see Experimental Procedures for details), which were subjected to the automated parallel freeze−evacuate−thaw procedure. For this purpose, 3 different experiments were undertaken (2 RAFT polymerizations of MMA and 1 RAFT polymerization of BuMA with each performed in triplicate. The reaction conditions for these experiments are summarized in Scheme 1.

Table 1 summarizes the results obtained from the precision experiments of Scheme 1 and Figure 2 displays the SEC traces of these experiments. Table 1 and Figure 2 demonstrate that the apparatus and the proposed automated parallel freeze−evacuate−thaw procedure are very precise when performing RAFT polymerizations as very similar number average molar masses (M_n) (which are in good agreement to the theoretical values) and monomer conversions for the 3 repetitions of each experiment are obtained.

To demonstrate the accuracy of the proposed automated parallel freeze−evacuate−thaw method, a RAFT polymerization experiment was performed in the synthesizer and directly compared with experiments carried out in "conventional" sealed glass ampules using a high-vacuum technique as a degassing method as reported elsewhere.[24,25] The reaction conditions for these experiments are summarized in Scheme 2.

Table 2 shows the obtained results of the accuracy experiments (Scheme 2), from which it can be observed that

Scheme 1. (A) Schematic Representation of the Polymerization of MMA (6.55 M in toluene) with VAZO-88 Initiator (1.80×10^{-3} M) and RAFT 1 at 90 °C for 6 h,[a] and (B) Schematic Representation of the Polymerization of BuMA (2.14 M in DMF) with VAZO-88 Initiator (4.29×10^{-4} M) and RAFT 1 (4.29×10^{-2} M) at 85 °C for 9 h[b]



[a]The concentration of RAFT 1 was varied at 2 different levels in the experiments: Reactors 1−3 (4.95×10^{-2} M) and reactors 4−6 (2.48×10^{-2} M). [b]The polymerizations were carried out utilizing the proposed automated parallel freeze−evacuate−thaw procedure.

Table 1. M_n, Polydispersity Index Values, and Monomer Conversions for PMMA (Reactors 1−6)[a] and PBuMA (Reactors 7−9)[b] Obtained According to Scheme 1

reactor	M_n [g mol^{-1}]	M_w/M_n	conversion [%][c]	M_n (theory) [g mol^{-1}][d]
1	7300	1.16	51	7160
2	7500	1.16	52	7293
3	8200	1.13	57	7955
4	17200	1.13	63	17063
5	17700	1.14	63	17063
6	17500	1.14	59	16005
7	6600	1.14	93	7016
8	6500	1.14	93	7016
9	6600	1.13	92	6945

[a]M_n and polydispersity index were estimated by SEC using THF as eluent; values are reported as linear PMMA equivalents. [b]Number average molar mass and polydispersity index were estimated by SEC using DMAc as eluent; values are reported as linear PMMA equivalents. [c]The monomer to polymer conversions were determined by ^{1}H NMR in CDCl$_3$ (see Experimental Procedures). [d]M_n (theory) was estimated using the following formula: $M_n \text{ (theory)} = [([M]_o/[RAFT]_o) \times M_{monomer} \times \% \text{ conversion}] + M_{RAFT}$; where $M_{monomer}$ and M_{RAFT} are the molar masses of the corresponding monomer and RAFT agent, respectively.

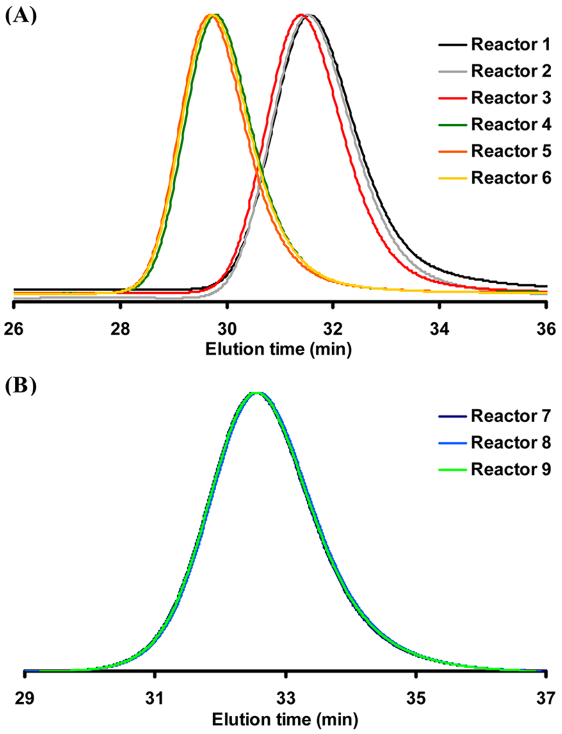
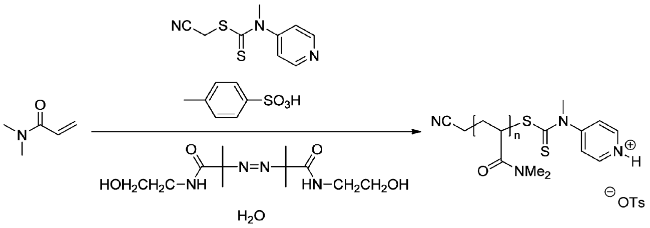


Figure 2. SEC traces demonstrating the precision of the proposed automated parallel freeze−evacuate−thaw procedure and the automated synthesizer. (A) PMMA and (B) PBuMA obtained according to Scheme 1 and the information of Table 1.

Scheme 2. Schematic Representation of the Polymerization of DMA (1.83 M in H$_2$O) with VA-086 Initiator (1.83×10^{-3} M), TsOH (1.83×10^{-2} M), and RAFT 2 (1.83×10^{-2} M) at 80 °C[a]



[a]The polymerization was carried out in the automated parallel synthesizer utilizing the proposed freeze−evacuate−thaw procedure and in sealed glass ampules using a high-vacuum technique as a degassing method.[24]

the automated parallel freeze−evacuate−thaw procedure yields very similar M_n and monomer conversion data to those obtained using "conventional" freeze−evacuate−thaw in sealed glass ampules. Note that the discrepancy between M_n (theory) and M_n obtained via SEC is mainly due to the difference in the hydrodynamic volume of poly(*N*,*N*-dimethylacrylamide) (PDMA) and the PS standards. In the comparison summarized in Table 2, time zero (t_0) in the automated synthesizer was considered to be at the moment the reactor reached the desired reaction temperature (80 °C). At the pre-estimated times (36 and 66 min), monomer conversions and molecular weights of the formed polymers were followed by sampling aliquots 75 (μL) from the reaction mixture with the automated liquid handling system into NMR tubes and SEC vials. SEC and NMR samples for analysis were prepared with the automated liquid handling system of the synthesizer at the end of the experiment by adding the corresponding SEC and NMR solvents. In the case of the "conventional" sealed glass ampules, two identical ampules were prepared and placed into a preheated oil bath at the desired reaction temperature (80 °C); this time was considered as time zero (t_0) for the purposes of comparison with the experiments performed in the automated synthesizer. In this latter case, the first ampule was withdrawn from the oil bath at 30 min and the second one at 60 min. It is worth mentioning that for these comparison experiments same stock solutions for preparing the reaction mixtures were utilized for both discussed approaches.

To ensure the complete removal of oxygen, all the RAFT polymerizations discussed above were subjected to two degassing methods, performed in tandem: (1) sparging the

Table 2. M_n, Polydispersity Index Values, and Monomer Conversions for PDMA Obtained According to Scheme 2[a]

exp.	reaction time [min]	conversion [%][b]	M_n [g mol^{-1}][c]	M_w/M_n[c]	M_n (theory) [g mol^{-1}][d]
synthesizer	36	79	11000	1.08	7900
ampoule	30	73	9200	1.13	7300
synthesizer	66	92	12100	1.07	9200
ampoule	60	95	11500	1.11	9500

[a] Results from sealed ampules experiments have also been reported elsewhere.[24] [b] The monomer to polymer conversions were determined by ^{1}H NMR in D_2O (see Experimental Procedures). [c] Number average molar mass and polydispersity index were estimated by SEC using DMF as eluent; values are reported as linear PS equivalents. [d] M_n (theory) was estimated using the following formula: M_n (theory) = $[([M]_o/[RAFT]_o) \times M_{monomer} \times \%\ \text{conversion}] + M_{RAFT}$; where $M_{monomer}$ and M_{RAFT} are the molar masses of the corresponding monomer and RAFT agent, respectively.

stock solutions with nitrogen for 15 min at room temperature prior to the automated liquid transfers (NB = concentration changes in this step were considered negligible since the reagents utilized in these experiments have relatively low volatility at room temperature) and (2) the reported automated parallel freeze−evacuate−thaw method, after the reaction mixtures were prepared via the liquid handling system. Additional experiments carried out in the automated synthesizer for the RAFT polymerization of BuMA (Scheme 1), utilizing either degassing method individually, demonstrated that both approaches are suitable to obtain precise results in the apparatus (see SEC traces in Supporting Information). In a recent investigation describing a comparison of different degassing methods for RAFT polymerizations, we have observed that both discussed techniques are comparable.[28] However, we regard the automated freeze−evacuate−thaw method of the present contribution as the superior approach, as it allows implementation in an unattended and parallel fashion. Further to this sparging with inert gas can display some shortcomings. These include changes in concentration when relatively volatile substances are present, derived from variations in temperature, time and flow rate of the inert gas. This drawback can undermine the accuracy of the experimental obtained results, particularly when undertaking kinetic investigations.

To summarize, the reported automated and parallel freeze−evacuate−thaw degassing method is a very convenient, precise and accurate approach to perform unattended oxygen-sensitive chemical reactions. The presented experimental procedure can easily be adapted or utilized in other chemical systems where the removal of oxygen is mandatory. Thus, an important experimental technique in conventional chemical synthesis has been successfully established in a high-throughput fashion, which has been used to undertake detailed kinetic investigations during RAFT polymerization.[24,25] This new experimental approach can increase the productivity and/or research outcomes in laboratories where oxygen-sensitive reactions are carried out and provide sufficient experimental data to efficiently model this kind of chemical reaction.[29] Current efforts in this direction are focused on utilizing this new high-throughput technique to build libraries of polymeric materials made by RAFT technology, which will be reported in the near future.

■ EXPERIMENTAL PROCEDURES

Materials. Butyl methacrylate (BuMA), methyl methacrylate (MMA), *N,N*-dimethylacrylamide (DMA) monomers were purchased from Aldrich and purified by stirring in the presence of inhibitor-remover for hydroquinone or hydroquinone monomethyl ether (Aldrich) for 30 min prior to use. DMA was additionally distilled under reduced pressure immediately before use. RAFT agents: 4-cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl]pentanoic acid[30−32] (RAFT 1) and cyanomethyl methyl(pyridine-4-yl)-carbamodithioate[32,33] (RAFT 2) were prepared according to reported literature procedures. 1,1′-Azobis-(cyclohexanecarbonitrile) (VAZO-88) initiator (DuPont) was used as received. 2,2′-Azobis[2-methyl-*N*-(2-hydroxyethyl)-propionamide] (VA-086) was purchased from Wako chemicals and used as received. *p*-Toluenesulfonic acid monohydrate (TsOH) was purchase from Aldrich and used as received. *N,N*-Dimethylformamide (DMF), toluene (AR grade, Merck) and Milli-Q water (H_2O) (18.2 MΩ cm) were degassed by sparging nitrogen for at least 15 min prior to use.

Characterization Techniques. Proton nuclear magnetic resonance (^{1}H NMR) (400 MHz) spectra were recorded using a Bruker Av400 spectrometer at 25 °C either in deuterated chloroform ($CDCl_3$) or in deuterium oxide (D_2O) to determine monomer to polymer conversions.

The monomer to polymer conversion for the polymerizations of MMA was determined by comparing the integration of resonance peaks in the δ 3.77 ppm region, corresponding to the $-CH_2$ protons of the MMA monomer, with that of the peaks in the δ 3.63 ppm region, pertaining to the $-CH_2$ protons of the repeat units of the poly(methyl methacrylate) PMMA polymer. The conversion was then calculated using the following equation: % MMA conversion = $[\int 3.62/(\int 3.77 + \int 3.62)] \times 100$; where $\int 3.77$ and $\int 3.62$ are the integral values for the $-CH_2$ protons of the MMA monomer and of the PMMA polymer, respectively.

The monomer to polymer conversion for the polymerizations of BuMA was determined by comparing the integration of resonance peaks in the δ 4.0 ppm region, corresponding to the $-CH_2$ protons of the BuMA monomer, with that of the peaks in the δ 3.8 ppm region, pertaining to the $-CH_2$ protons of the repeat units of the poly(butyl methacrylate) (PBuMA) polymer. The conversion was then calculated using the following equation: % BuMA conversion = $[\int 3.8/(\int 4.0 + \int 3.8)] \times 100$; where $\int 4.0$ and $\int 3.8$ are the integral values for the $-CH_2$ protons of the BuMA monomer and of the PBuMA polymer, respectively.

The monomer to polymer conversion for polymerization of DMA was determined by comparing the integrals of the side chain methyl groups (2.75−3.20 ppm) with respect to the integrals of the vinylic protons (5.65−6.70 ppm). The conversion was then calculated using the following equation: % DMA conversion = $[\int(2.75\text{−}3.20\ \text{ppm}) - 2 \times (\int (5.65\text{−}6.70\ \text{ppm})]/ \int (2.75\text{−}3.20\ \text{ppm}) \times 100$.

Size exclusion chromatography (SEC) was performed on a Waters system or on a Shimadzu system. The Waters system is equipped with a differential refractometer and 3 × mixed E PLgel column (each 7.5 × 300 mm) from Polymer Laboratories and uses tetrahydrofuran (THF) as eluent with a flow rate of 1 mL min^{-1} at 22 ± 2 °C. The Shimadzu system is 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 detector and with 4 × Waters Styragel columns (HT2, HT3, HT4, HT5 each 300 mm ×7.8 mm providing an effective molar mass range of 100−4000000), and uses *N,N*-dimethylacetamide (DMAc) (with 2.1 g L^{-1} of lithium chloride (LiCl)) or DMF (with 0.45% w/v of lithium bromide (LiBr)) as eluent with a flow rate of 1 mL min^{-1} at 80 °C. For both systems, the molar mass of the samples was obtained from a calibration curve constructed with PMMA standards (Polymer Laboratories) or polystyrene (PS) standards (Polymer Laboratories) of low polydispersity index value. A third-order polynomial was used to fit the log M_p versus time calibration curve, which was linear across the molar mass ranges.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

SEC traces of additional experiments carried out in the automated synthesizer utilizing two different degassing methods individually. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge the Capability Development Fund of CSIRO Materials Science and Engineering for financial support. D.J.K. acknowledges the Office of the Chief Executive of CSIRO for partial funding.

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