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Benchtop Flow-NMR for Rapid Online Monitoring of RAFT and Free Radical Polymerisation in Batch and Continuous Reactors

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A "Benchtop" NMR spectrometer is used for detailed monitoring of controlled and free radical polymerisations performed in batch and continuous reactors both offline and in real-time. This allows detailed kinetic analysis with unprecedented temporal resolution for reactions which reach near completion in under five minutes.

Real-time online monitoring presents a range of opportunities to synthetic chemists for chemical discovery and reaction/process optimisation. Data obtained from this type of analysis can be used to conduct autonomous complex synthetic chemistry which typically involves feedback loops where data is processed/analysed and returned into the system to refine process parameters (i.e. self-optimisation).[1–5]

In the context of polymerisation, the extent of reaction (or conversion), can be monitored by a range of techniques, including titration, gravimetry, IR and UV/vis spectroscopy and NMR spectroscopy.[6–10] NMR is perhaps most useful given its near-universal applicability, the absence of any sample-to-sample calibration required, but most importantly its ability to provide much more detail regarding the chemical structure. As the complexity of polymeric materials and polymerisation processes increases – such as self-assembling block copolymers, sequence defined polymers and complex polymerisation formulations – the need for effective and facile reaction monitoring becomes more and more important.[11–16] This is particularly relevant for polymerisation formulations where high conversions are achieved in increasingly shorter times.[17–19]

The limits of NMR have primarily been the cost and cumbersome nature of conventional instrumentation – meaning more complex utilisation, such as the powerful continuous (online) flow NMR, has generally been confined to dedicated research facilities.[20–23] The advent of cheaper, lower-field ("benchtop") spectrometers based upon permanent magnets rather than the cryogenically cooled superconducting magnets seen in conventional instruments presents an opportunity to widen the availability both in industry and academia.[2,24,25] The only report of the use of low-field NMR to monitor a polymerisation (butyl acrylate by emulsion polymerisation) was much hindered by the limited resolution afforded by an older generation of spectrometer.[26] Analysis by direct integration of peaks was not used; however, through judicious post-processing and a deuterated solvent, it was possible to obtain some kinetic information from peak width measurements.

Herein we demonstrate for the first time, that benchtop Flow-NMR is an extremely convenient and powerful tool for real-time monitoring of both controlled and free radical polymerisation techniques. This includes ultrafast (<10 minute) syntheses of well-defined homopolymers via RAFT solution polymerisation and diblock copolymer nanoparticles via RAFT dispersion polymerisation, and a traditional free radical solution polymerization. Furthermore, by integrating the NMR instrumentation into a continuous-flow platform we show it is possible to obtain detailed kinetic information under a range of conditions.

An initial study showed the validity of low-field measurements, when compared to a conventional 400 MHz instrument (Figure SI1), for the monitoring of the RAFT synthesis of polydimethylacrylamide (PDMAm – Figure 1c). Though differences in signal splitting were observed, calculated conversion was found to be roughly equivalent, giving very similar kinetic traces. This initial study used traditional NMR sample preparation and the default spectrometer settings (i.e. dilution in deuterated solvent (D_2O) to 7.5 % w/w and analysis performed in NMR tubes), though subsequently it was shown that the use of hydrogenated solvent had no impact (outside of experimental error) on the calculated conversion (see Figure SI2). For all NMR data, it is important to perform phase and baseline corrections prior to evaluation. In most cases, these corrections are ignored, or performed manually. Here, automated processing is used in order to increase throughput and reduce workload – for more details see SI.[27] Following these initial off-line studies, the effectiveness of on-line measurements was investigated – both from a traditional batch reaction and using a flow reactor based on that previously used by this group (Figure 1).[28]

(a) Batch Polymerization **(b) Continuous Polymerization**

Polydimethylacrylamide

Polydimethylacrylamide –*b*-
Poly(diacetone acrylamide)
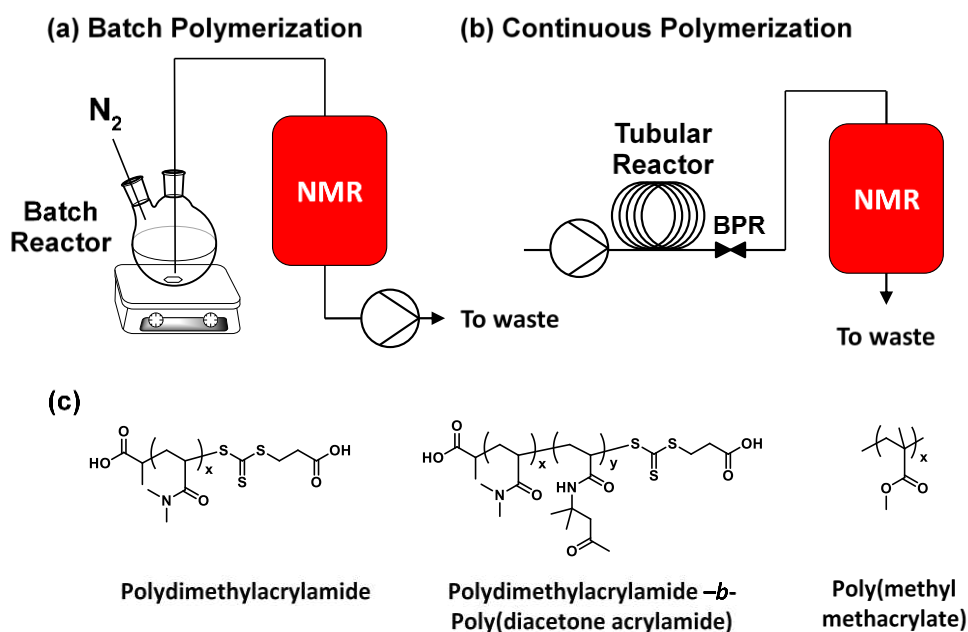
Poly(methyl methacrylate)

Figure 1. Schematics for reactor setups: (a) batch; (b) flow and (c) the target polymers in this study

NMR spectroscopy of flowing liquids can introduce complexity relative to static samples. A detailed treatment of the complications is given by Dalitz *et al.*[29] The impact of flow rate upon the signal intensities was investigated in a similar way to that described by Zientek *et al.*[27] (using a 30 % w/w solution of DMAm), and the maximum flow rates for a glass flow cell and perfluoroalkane (PFA) tubing were found to be 0.75 mL min^{-1} and 0.5 mL min^{-1} respectively (see Figure SI3). In the same experiment, it was shown that using a presaturation water suppression method lead to a reduced error in the measurement of the integral of the vinyl peak, seen in the reduction of scatter in the normalised integral. This initial experiment relied upon a feed of constant composition – when the glass flow cell was used for reaction monitoring, deviations from expected behaviour was observed. The observed rate of reaction was significantly reduced where the glass flow cell was used compared to batch sampling (Figure SI4). Problems with the residence time distributions of such flow cells have been reported, due to the expansion and subsequent contraction of the bore.[27,29] This issue is likely to be exacerbated by the increase in viscosity caused by polymerisation. Therefore, PFA tubing was used for all the flowed studies, ensuring the flow rate was limited to <0.5 mL min^{-1}.

It has previously been reported that polymerisation of fast-propagating acrylamide monomers can be accelerated by using 2,2′-Azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride (VA-044 – which has a 10h half-life in water at 44 °C) as an initiator at higher temperatures.[17] Here, we polymerised dimethylacrylamide in the presence of VA-044, giving high conversions in under 10 minutes. Monitoring the reaction using online flow-NMR enabled the collection of detailed kinetic profiles for a batch reaction and a transient flow study (Figure 3a). The waterfall plot of the NMR spectra recorded (Figure 3b) highlights the temporal resolution which is offered by flow NMR and shows the qualitative power of the technique.

The variation in kinetic profile that might be expected from the enhanced heat transfer using flow techniques is shown by the faster initial reaction in the flow system (125-250 s) – this change would not otherwise be observed in the same detail. For the batch reaction, there is a delay associated with the time taken for the reaction vessel to reach the reaction temperature which is eliminated with the flow reactor. A subsequent slight acceleration is often observed because of an increase in temperature, caused by a combination of reaction exotherm and an overcompensation by the hotplate to bring the system back to the reaction temperature. However, across the range of the reaction, similar rates were obtained for both routes, irrespective of sampling methodology.

Another key benefit of online real-time analysis is the enabling of high throughput screening of a range of process parameters. The transient flow methodology is particularly suited to this type of screening - Figure 3c & 2d shows the expected increase in rate for increasing temperature.[28] The increased resolution makes a deviation from linearity for the 90 °C semi-logarithmic plot clearly discernible (Figure 3d). Obtaining such detailed data without the need for laborious sample preparation and data processing demonstrates the potential for unprecedented insight into a wide range of polymerisation kinetics.
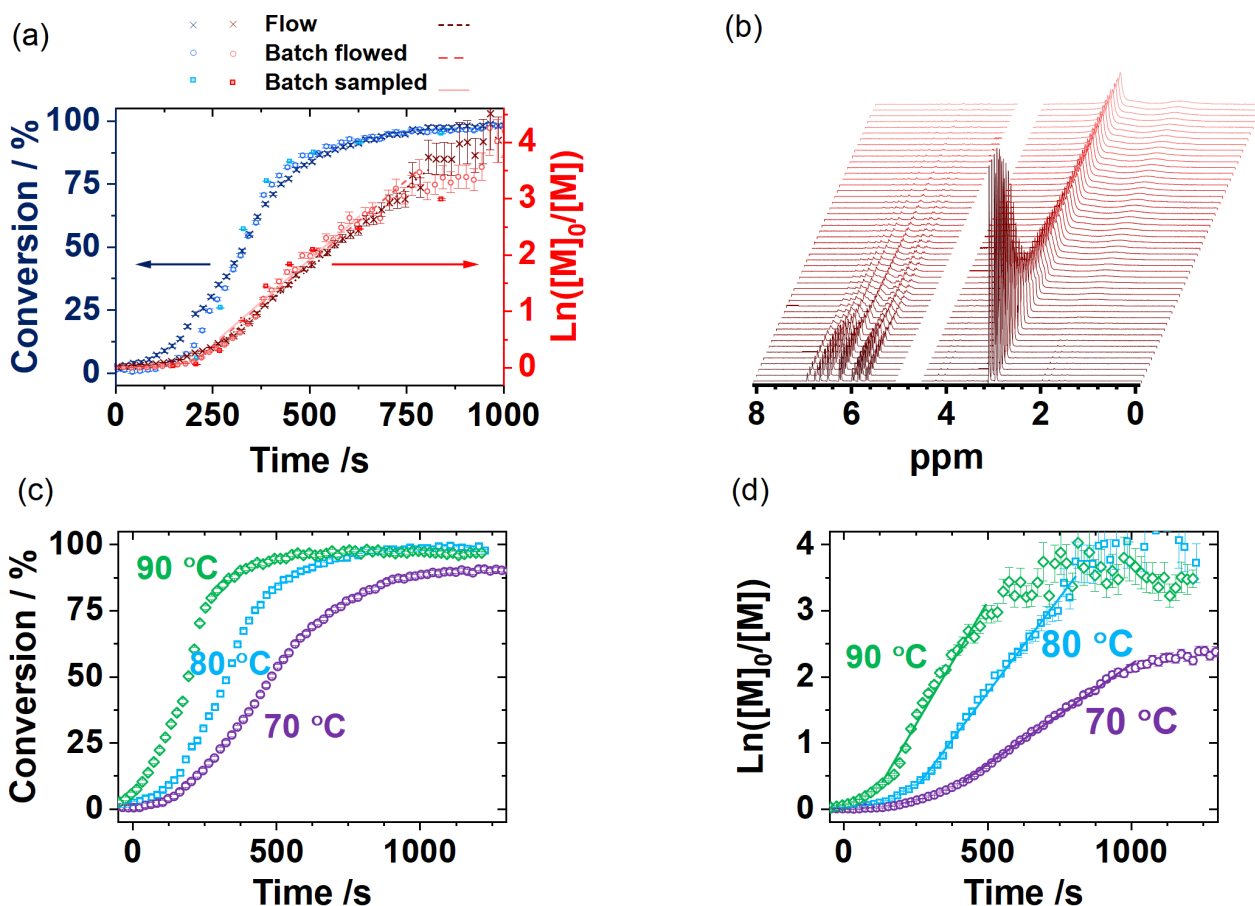
Figure 3. (a) Kinetic plot of batch and transient flow RAFT polymerisations of dimethylacrylamide at 80 °C, sampled continuously using the setups detailed in Figure 1, and by more traditional batch sampling. Semi-log plot shown with time. (b) Example NMR waterfall for the polymerisation of DMAm. A scan was recorded every 20 s. (c) Conversion and (d) semi-logarithmic plots for RAFT polymerisation of dimethylacrylamide at 70, 80 and 90 °C, using a flow reactor. Errors are propagated from the standard deviation of integral measurements on a sample of constant composition.

Often more complex polymeric materials are synthesised using complicated multiphase systems such as the preparation of block copolymer particles (e.g. polymerisation induced self-assembly (PISA)).[12] Figure 2 shows the versatility of flow-NMR, in monitoring the RAFT dispersion polymerisation of diacetone acrylamide in the presence of PDMAm$_{95}$ macro-CTA. An internal standard (3-(Trimethylsilyl)-1-propanesulfonic acid sodium salt) was used to improve the accuracy of conversion measurements, since the solid core of the spherical particles formed by the PDAAm block is not visible in the NMR spectra, making the conversion methodology used in the macro-CTA synthesis impossible (a full discussion of the methods available to calculate conversion is given in the SI). In spite of the rapid reaction, the high temporal resolution enables precise determination of the onset of rate acceleration typically observed for PISA systems – which is driven by locally high monomer concentrations in the self-assembled nanostructures.[12,30] The lack of a peak relating to the polymer in the NMR is the cause of the increased magnitude of error at high conversions – since the measurement relies on the small signal for remaining monomer. However, the errors only become unacceptably high at conversions above 90 %.

The use of low-field NMR is not only of interest to flow scientists studying complex systems. We demonstrate that the system can also analyse simple systems such as the free radical
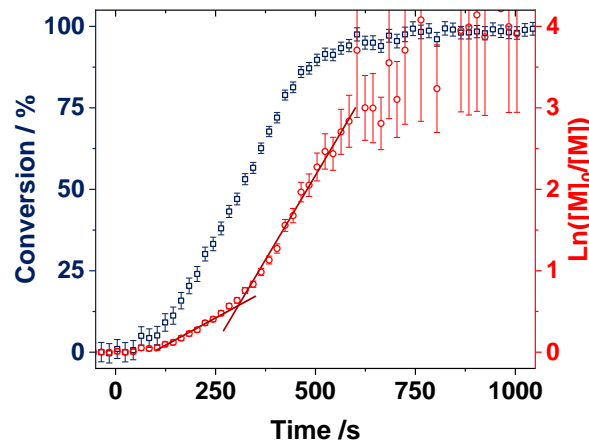

Figure 2. Kinetic plot of RAFT dispersion polymerisation of diacetone acrylamide (DAAm) in the preparation of (P(DMAm$_{100}$-b-DAAm$_{200}$). The rate acceleration caused by self-assembly is seen at 300 s. Errors are propagated from the standard deviation of integral measurements on a sample of constant composition. (NMR waterfall shown in Figure SI6a)

polymerisation of methyl methacrylate (Figure 4). NMR analysis using traditional sampling (i.e. withdrawal using a syringe and placing sample in NMR tube) gave a linear semi-logarithmic plot – indicating the expected pseudo-first order kinetics. (Each analysis uses neat reaction solution and only takes one minute
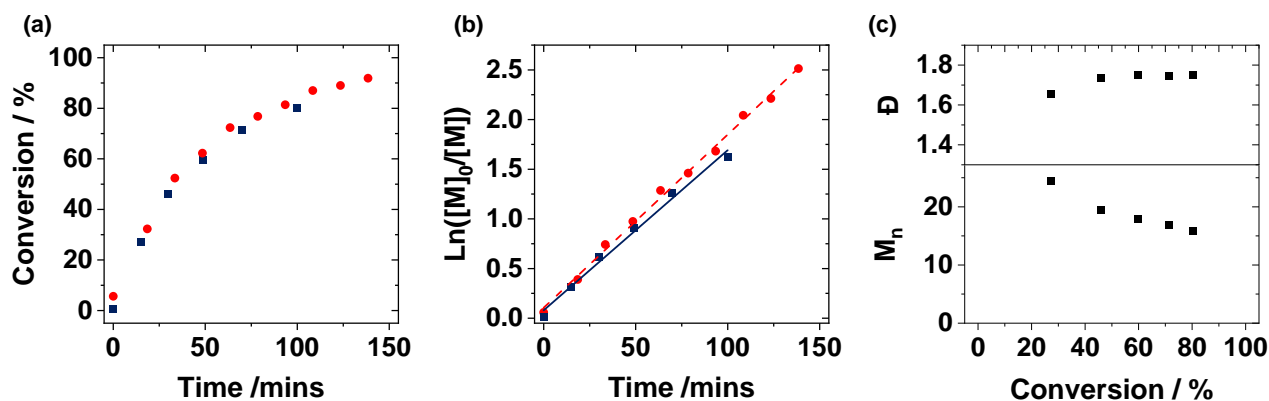
Figure 4. (a) Conversion, (b) semilogarithmic plot and (c) molecular weight development for the solution free radical polymerisation of methyl methacrylate (MMA) in 1,4-dioxane. Analysis was performed on the benchtop instrument both offline (■) and online (● – using the setup as detailed in Figure 1a). GPC chromatograms are shown in Figure SI7.

to record – much faster than a conventional routine). Molecular weight development as measured by offline GPC was characteristic for free-radical polymerisation – with high MW polymer obtained even at low conversion, a slight decrease in MW as the reaction progressed (since monomer concentration is reduced) and higher molar mass dispersities. The same polymerisation was analysed in real-time by flow-NMR using the setup detailed in Figure 1a – and the same kinetics observed regardless of the sampling methodology. Since the time scale of reaction is much longer than the RAFT polymerization of DMAm, stopped flow sampling was used rather than a constant slow withdrawal to conserve material.

To summarise, the power of using benchtop NMR spectrometers for online flow applications has been demonstrated through several polymerization reactions. Continuing development in this area will provide an important step in achieving effective high-throughput and self-optimising platforms for polymer synthesis. Furthermore, the versatility of the benchtop instruments is demonstrated with analysis of a free radical system. The lower price of these instruments will improve access to the NMR spectroscopy in general and the reduced sample preparation/time taken for analysis will increase research output.

There are no conflicts to declare.

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