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Microwave-Assisted Synthesis of Block Copolymer Nanoparticles via RAFT with Polymerization-Induced Self-Assembly in Methanol

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A comparative study of microwave-assisted (MA) and conductive heating in RAFT dispersion polymerization formulations in MeOH that result in polymerization-induced self-assembly is detailed. A beneficial kinetic effect is seen in MA formulations, especially in lower concentration systems, with benzyl- and 2-phenylethyl methacrylate comonomers and poly[oligo(ethylene glycol) methyl ether methacrylate] macro-CTAs.

Recently there has been significant interest in reversible addition-fragmentation chain transfer dispersion polymerization (RAFTDP) formulations that result in polymerization-induced self-assembly (PISA)[1] giving nanoparticles of variable and complex morphology including spheres, worms and vesicles. RAFTDP-PISA offers several important advantages over traditional approaches for preparing soft matter nanoparticles. These include the ability to prepare nanoparticles at high solids contents (≥ 50% w/w is possible), low solution viscosities, often improved polymerization kinetics especially in aqueous-based systems, and since nanoparticle formation occurs *in situ* it does not require any post-polymerization processing steps.

The current interest in RAFTDP-PISA has been driven by recent work from the groups of Armes,[2-9] Pan,[10-17] Zhang[18-27] as well as others.[28-42] There is now an impressive body of work detailing numerous RAFTDP-PISA formulations, especially in aqueous media, but also in various lower alcohols, non-polar organic media (typically *n*-alkanes), ionic liquids[43] and supercritical CO_2[44-48] with heating being accomplished by traditional conductive (CH) methods.

Microwave-assisted (MA) syntheses in small molecule chemistry were first described by Gedye and co-workers in the mid 1980's.[49] Since this time, and with the subsequent development of dedicated research-grade microwave reactors, MA syntheses have evolved into a standard approach for mediating chemical processes,[50-54] including polymerization,[55-59] although it is still relatively under-utilized in the polymer science community compared to traditional CH methods.

This is particularly pertinent given the potential benefits of MA syntheses which are well-documented and include, but are not limited to, a) broad applicability, i.e. few limitations to its use; b) increased reaction rates (up to 1000x in best cases); c) applicability in solution and solid phase syntheses; d) improved product yields; e) scalability; f) access to chemical transformations not achievable by conductive heating, and g) it represents a controlled, uniform method of heating.

MA syntheses have been utilized in a variety of chain and step growth polymerization processes under both homogeneous and heterogeneous (dispersed media) conditions although literature reports are inconsistent due, mainly, to the significant difference in experimental setup. Of relevance here are those MA polymerizations performed in traditional dispersion[55, 56] polymerization processes as well as those conducted under homogeneous reversible addition fragmentation chain transfer (RAFT) conditions.[60, 61] While MA syntheses via these two different processes are known there is, to the best of our knowledge, only one example in which MA synthesis has been employed in a RAFT polymerization in dispersed media. In this instance the process was employed to prepare double hydrophilic block copolymers or nanogels and no basic evaluation, or comparative studies, of the effect of MA polymerization was presented.[62]

We have an interest in RAFTDP-PISA, especially in lower alcohols, utilizing a variety of aryl methacrylates as comonomers and have recently been examining MA-RAFTDP-PISA employing an Anton-Paar monomodal MONOWAVE 300 high performance microwave reactor with temperature monitoring via an infrared sensor. Herein we report our results regarding a comparative evaluation of the formation of AB diblock copolymers based on poly[oligo(ethylene glycol) methyl ether methacrylate] (pOEGMA, stabilizing block) with benzyl methacrylate (BzMA) or 2-phenylethyl methacrylate

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(PEMA) in MeOH under RAFTDP-PISA conditions utilizing MA and CH methods, Scheme 1. The emphasis in this report is on observable beneficial kinetic effects under MA conditions rather than a detailed elucidation of phase diagrams/nanoparticle formation for these particular methanolic RAFTDP-PISA formulations.
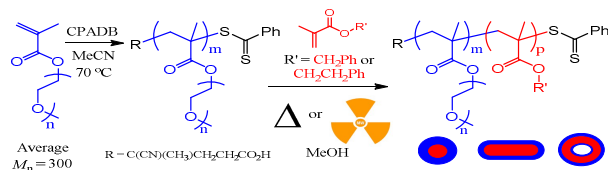
Scheme 1. General outline for the synthesis of p(OEGMA$_{22}$-*b*-aryl methacrylate) copolymers, and their associated nanoparticles, via traditional conductive heating (CH) and under microwave-assisted (MA) conditions.

pOEGMA macro-CTAs with an average degree of polymerization, $\bar{X}_n$, of 22 were first prepared in MeCN at 70 °C under homogeneous RAFT conditions yielding two species with SEC measured $\bar{M}_w$ and $Đ_M$ values of 5,200, 5,600, 1.17 and 1.14 respectively.

In the first series of experiments we examined the block copolymerization of BzMA with a pOEGMA$_{22}$ macro-CTA in 10, 20, 30 and 40% w/w methanolic formulations under MA and CH conditions for a target $\bar{X}_n$ of BzMA of 85 at quantitative conversion. Figure 1A shows the BzMA conversion vs. time plots for these eight polymerizations.
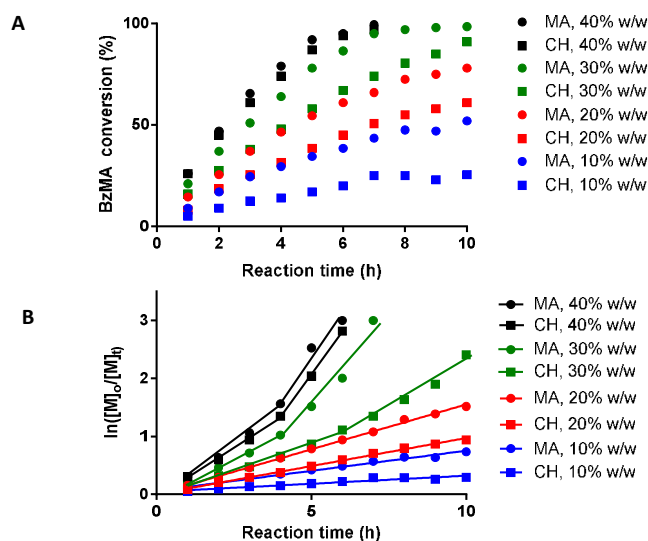

Figure 1. (A) Conversion vs. time plots for the block copolymerization of BzMA with a pOEGMA$_{22}$ macro-CTA in MeOH under MA and CH conditions for 10, 20, 30 and 40% w/w formulations, and (B) the corresponding pseudo-first-order kinetic plots for the same series of copolymerizations. All copolymerizations were conducted at 70 °C.

Several features are worth noting. First, and not unexpected, the higher the concentration of the formulation the faster the BzMA conversion regardless of the method of heating. Second, in *all* instances the MA polymerizations gave a faster rate of BzMA conversion compared to the CH systems

conducted under otherwise identical conditions. This demonstrates that there is, indeed, a positive kinetic effect associated with MA heating in RAFT dispersion formulations. Third, and perhaps most intriguingly, the magnitude of this rate effect appears to be concentration dependent and is more pronounced in lower concentration formulations. For example, in the case of the 10% w/w formulation we observe a BzMA conversion of ca. 26 % after 10 h under CH conditions while under MA conditions the BzMA conversion, as determined by ^{1}H NMR spectroscopy, was 52 %, i.e. exactly double that observed under more traditional conditions. In contrast, in the 40% w/w formulation there appears to be little, if any, difference in the fractional conversion of BzMA under both heating conditions with the two block copolymerizations reaching essentially quantitative conversion of BzMA after 7 h.

The origin of rate effects in MA syntheses are still not entirely clear. In general, the fundamental causes are referred to as 'thermal effects' and 'non-thermal microwave effects'. Thermal effects arise from the rapid and uniform temperatures attainable upon microwave irradiation, conditions that can be difficult to duplicate via CH especially for reactions performed at very high temperatures, whereas microwave effects are associated with direct material-wave interactions (note, additional thermal effects can arise from superheating capabilities in fully sealed systems). Since it is not the primary aim of this communication to elucidate the origin or nature of the observed rate effects we will simply note that currently the general consensus is thermal effects are the primary (if not exclusive) cause for any observed rate enhancement in MA syntheses and such arguments can likewise be invoked to explain the observations reported here.

An examination of the pseudo-first-order kinetic plots for the same series of MA- and CH-mediated polymerizations, Figure 1B, also reveals an additional interesting, concentration dependent, feature. In the case of the 10 and 20% w/w formulations the pseudo-first-order kinetic plots are linear over the entirety of the block copolymerization (at least over the time period examined). In contrast, the 30 and 40% w/w formulations exhibit two distinct rate regimes – far more pronounced for the MA-assisted formulation at 30% w/w but also evident in *both* the MA- and CH-polymerizations at 40% w/w. Similar observations have been reported previously, especially in (mixed) aqueous RAFTDP-PISA formulations (even in 10% w/w formulations),[9, 21, 42] but we believe this is the first time it has been reported in a wholly alcoholic-based RAFTDP-PISA system. The cause of the increase in rate of monomer consumption has been linked to the point at which micellar nucleation occurs, i.e. the onset of block copolymer self-assembly and the creation of an aggregate core environment suitable for monomer solubilisation/sequestration. Partitioning of unreacted monomer into the core of the newly formed nanoparticles results in an increase in the local effective concentration of BzMA and hence the observed increase in rate. The up-turn in kinetics in the 40% w/w formulation, for example, occurs after ca. 4 h. This corresponds to a BzMA conversion of 79% (MA) and 74 % (CH), which in turn suggests critical BzMA $\bar{X}_n$'s of 67 and 63, i.e.

aggregation appears to occur reasonably late in these particular formulations given that the final targeted $\overline{X}_n$ for the pBzMA block is 85. Since the 10 and 20% w/w formulations do not reach this critical conversion after the 10 h time frame examined we do not observe any increase in the rate in the pseudo-first-order kinetic plots.

It has been noted that MA polymerizations can yield (co)polymers with narrower molecular weight distributions (lower, $Đ_M$'s), compared to the same materials prepared under CH conditions. In the case of the p(OEGMA$_{22}$-b-BzMA$_x$) formulations we did not observe any particular benefit, or trend, in this respect with all formulations yielding block copolymers with low final dispersities with $1.12 \leq Đ_M \leq 1.26$.

Subsequently, we performed a similar comparative experiment substituting BzMA for 2-phenylethyl methacrylate (PEMA), an aryl methacrylate we have previously demonstrated to be a suitable comonomer in alcoholic RAFTDP-PISA formulations.[37] Figure 2A shows the conversion vs. time plots (with BzMA added for comparative purposes) and 2B shows the pseudo-first-order kinetic data. Consistent with the first series of experiments with BzMA the MA-RAFTDP-PISA of PEMA with a pOEGMA$_{22}$ macro-CTA proceeds at a faster rate than the corresponding CH-mediated copolymerization. The data does suggest a more significant effect for PEMA vs BzMA with a near 100% increase in PEMA conversion in these 20% w/w formulations after 10 h vs. ca. 50% in the case of BzMA. Interestingly, we also observed evidence for a two-regime kinetic profile in the case of the MA copolymerization of PEMA, a feature that is absent in the remaining three copolymerizations as well as the 20% w/w formulation in the first series of experiments. In this instance, we observe an up-turn, albeit less pronounced, in the kinetic profile at ca. 70% PEMA conversion, a value that is consistent with the first series of experiments where the change in kinetic profile was seen at ca 65-70% BzMA conversion.

As noted above, while the primary aim of this communication is the evaluation of MA synthesis conditions on the RAFTDP-PISA process we note that the polymerizations do proceed to give soft matter nanoparticles with various morphologies. For example, Figure 3 shows representative TEM images of the nanoparticles obtained in the case of the p(OEGMA$_{22}$-b-PEMA$_x$) MeOH formulation conducted at 20% w/w under MA conditions. We observe a clear transition in nano-object morphology with increasing $\overline{X}_n$ of the pPEMA block. In the case of p(OEGMA$_{22}$-b-PEMA$_{36}$), Figure 3A, we observe a pure spherical phase in which the nanoparticles have a DLS-measured hydrodynamic diameter of 37.6 nm (DLS polydispersity = 0.087). Interestingly, in the case of p(OEGMA$_{22}$-b-PEMA$_{47}$) a predominant worm phase is observed although a small population of spheres as well as a number of relatively narrow size distribution toroidal species, 3B, are also present. We are not aware that the latter have been previously reported/observed in RAFTDP-PISA formulations. Finally, in the case of the p(OEGMA$_{22}$-b-PEMA$_{57}$) sample a predominantly vesicular morphology is observed, 3C. These results confirm that the MA conditions do not have a detrimental effect on accessible nano-object morphologies

and may, in fact, afford access to species not readily accessible otherwise.
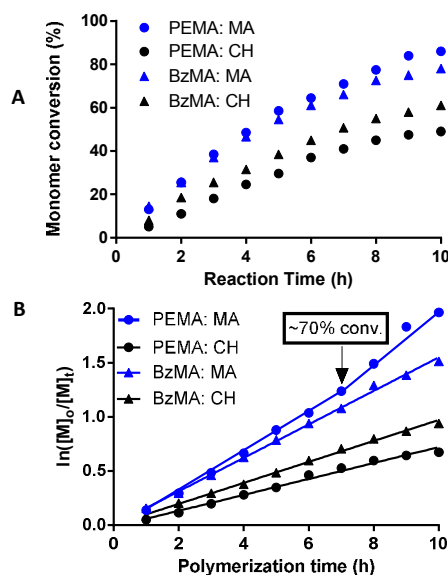

Figure 2. (A) Conversion vs. time profiles for the MA RAFTDP-PISA of BzMA and PEMA with a pOEGMA$_{22}$ macro-CTA in MeOH at 70 °C at 20% w/w, and (B) the corresponding pseudo-first-order kinetic plots. Final 10 h SEC measured molecular weights and dispersities were 14,400 and 1.22 for the MA PEMA copolymerization and 10,200 and 1.16 for the CH PEMA copolymerization.

Figure 3. Representative TEM images of nano-objects formed in MeOH at 20% w/w
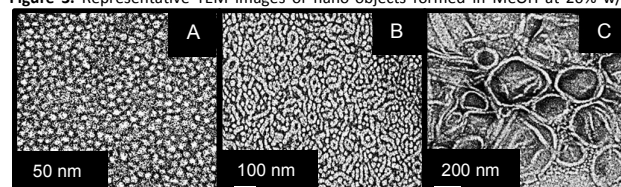
under MA conditions (A) p(OEGMA$_{22}$-b-PEMA$_{36}$), spheres; (B) p(OEGMA$_{22}$-b-PEMA$_{47}$), worm-based species, and (C) p(OEGMA$_{22}$-b-PEMA$_{57}$), vesicles.

In summary, we have reported the first evaluation of the effect of microwave mediated conditions on the kinetics of the synthesis of soft matter nano-objects via reversible addition-fragmentation chain transfer dispersion polymerization with polymerization-induced self-assembly (RAFTDP-PISA). We have demonstrated that there is a clear beneficial kinetic effect in the formulations examined that appears to be concentration dependent as evidenced by the conversion vs time and pseudo-first-order kinetic plots, with the latter also highlighting two-regime type kinetic behaviour under certain conditions and especially in the MA formulations. These results suggest that MA-RAFTDP-PISA represent a useful addition to the range of experimental conditions under which such formulations can be conducted conferring positive beneficial kinetic effects. We are currently expanding our studies to include more detailed evaluations of MA-RAFTDP-PISA in a variety of different media utilizing different macro-CTAs and comonomers.

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