High Frequency sonoATRP of 2-Hydroxyethyl Acrylate in an Aqueous Medium

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High frequency ultrasound (490 kHz, 40 W) was applied for the controlled polymerisation of 2-hydroxyethyl acrylate (HEA) via sonochemially induced atom transfer radical polymerisation (sonoATRP). The synthesis of poly(HEA) (DP 100-800) was found to reach high conversions (>90%) in short times (<60 min) with excellent molecular weight distribution (*Đ*<1.1).

Reversible deactivation radical polymerisation (RDRP) techniques, such as atom transfer radical polymerization (ATRP),[1] nitroxide-mediated radical polymerization (NMP),[2] and reversible addition–fragmentation chain transfer (RAFT),[3] have allowed for the synthesis of polymers with targeted molecular weights, controlled end-group functionality, and narrow dispersities.[4–6] To provide a greater degree of temporal and spatial control, and to progress towards more scalable, environmentally-friendly, and straightforward procedures, external stimuli such as light,[7–9] redox,[10] electrical potentials,[11] and mechanical forces,[12] have been used to initiate and regulate RDRPs. While significant progress has been made, there remains room to prepare more versatile and scalable RDRP procedures to address current limitations.

Ultrasound (US) – defined as sound waves in the frequency range of 20 kHz to 20 MHz – has been widely used for drug delivery (i.e., sonodynamic therapy),[13–15] organic synthesis,[16] imaging,[17] and water treatment.[18] While polymer synthesis using US has been used for almost half a century,[19–27] RDRP using US as the polymerization stimulus has only recently been reported.[28–30] Historically, sonochemical polymerisation has been performed using low frequency US (20-100 kHz). At low frequencies, physical forces (e.g. shear) are dominant[31] and polymerisation can be achieved via mechano-responsive additives.[32–34] The seminal work by Esser-Kahn and co-workers showed that low frequency US treatment (20 kHz) of piezoelectric $BaTiO_3$ nanoparticles could mechanically activate an ATRP reaction.[33] However, the strong shear forces generated during low frequency US treatment resulted in polymer degradation and, as a result, polymer size was limited to <3.0 kDa. This was followed by Matyjaszewski and co-workers in which US (40 kHz) was used to prepare polymers of up to ~30 kDa using $BaTiO_3$[32] or ZnO[34] nanoparticles. In all cases the rate of polymerisation was slow, taking 4-16 hours to reach conversions above 80%.

The limitations of low frequency US (polymer degradation by shear forces) can be overcome by using higher frequencies (>200 kHz). At high frequencies chemical effects, stemming from cavitation-induced radical formation, become dominant, with negligible shear force generated.[31] The effect of US frequency on polymer degradation was demonstrated by Gogate and co-workers.[35] It was reported that low frequency (20 kHz) US treatment resulted in significant polymer degradation, whereas negligible degradation was observed at higher frequencies (204 and 694 kHz).

Our group recently discovered sonoRAFT, a process by which high frequency US (414 kHz) can be applied for the facile synthesis of well-defined water soluble polymers.[36] In this system, US generates radicals directly from the homolysis of water molecules, which initiate RAFT polymerisation. In this way, US can be used to prepare polymers with controlled molecular weights and narrow dispersities without the use of radical initiators or mechano-responsive additives, with no polymer degradation caused by the US treatment.

Herein, we progress upon the use of high frequency US for RDRP and report a new procedure for sonochemically-induced aqueous ATRP (sonoATRP) performed at 490 kHz. Controlled polymerisation was achieved via the reduction of Cu(II) to Cu(I) by US generated radicals, thereby activating the ATRP. SonoATRP was realised with low Cu loading (250 ppm) and resulted in polymers with tailored molecular weights and low dispersities (*Đ*<1.1). Importantly, polymerisation was rapid, reaching high conversions (60 min, >90% conversion) for an illustrative acrylate monomer. A degree of temporal control was demonstrated, with clear attenuation of the

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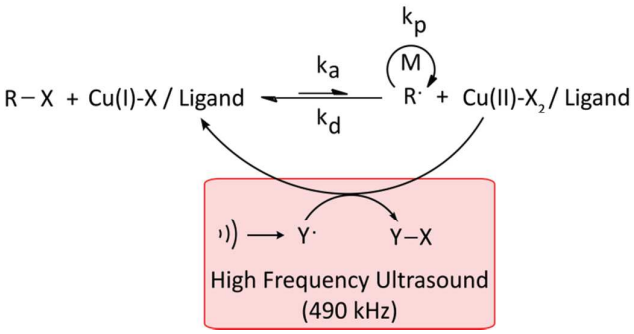


Scheme 1 Proposed mechanism of sonoATRP (according to the concept of "initiators for continuous activator regeneration", or ICAR). US treatment of solvent water molecules forms radicals (Y·) which reduce Cu(II) to Cu(I) and forms a small amount of brominated-by-product (Y-X). Examples of reducing radical species include monomer-derived carbon-centred radicals and hydrogen radicals.

polymerisation being observed in the absence of US. Moreover, high chain-end fidelity was evidenced by matrix-assisted laser desorption ionisation time-of-flight (MALDI-ToF) mass spectrometry, as well as an *in-situ* chain extension experiment for the synthesis of pseudo-block copolymers.

It is known that radical formation and sonochemical reactions are the result of "acoustic cavitation" which occurs during US treatment.[37,38] Cavitation refers to the formation of gaseous bubbles in the liquid medium, their expansion, and eventual implosion, which creates localised regions of extreme pressure and heat (up to 5000 K and 500 atm) within the solution. It is this intense temperature/pressure which can degrade molecules (solvent or other) into radical species. If the solution is water, the main products are hydroxyl and hydrogen radicals. Our previous study determined the optimal conditions which produce the highest rate of hydroxyl radicals to induce controlled polymerisation via sonoRAFT (414 kHz, 40 W, producing hydroxyl radicals at a rate of ~15 μM min^{-1}).[36] Therefore, similar conditions were used for the following sonoATRP experiments (490 kHz, 40 W).

Unlike RAFT, controlled polymerisation via ATRP relies on the equilibrium between activating Cu(I) and deactivating Cu(II) species.[1] Continuous regeneration of Cu(I) from Cu(II) is often employed in order to minimize the required Cu catalyst complex concentration, as the *ratio* of Cu(I) (activator) to Cu(II) (deactivator) is the critical factor in determining the rate and 'control' of the reaction. The reduction of Cu(II) to Cu(I) has previously been reported through photoreduction[39,40] or the addition of reducing agents.[41] Here, we propose that radicals formed by the US-induced cavitation of aqueous solutions can reduce Cu(II) to Cu(I) (Scheme 1). Reducing radicals, including primary radicals derived from the direct pyrolysis of solvent/solute molecules and secondary radicals formed via H-abstraction or radical addition, (Y·, Scheme 1) form during US treatment. Various pathways for the reduction of dissolved metal ions involving hydroxyl, hydrogen, and organic radicals

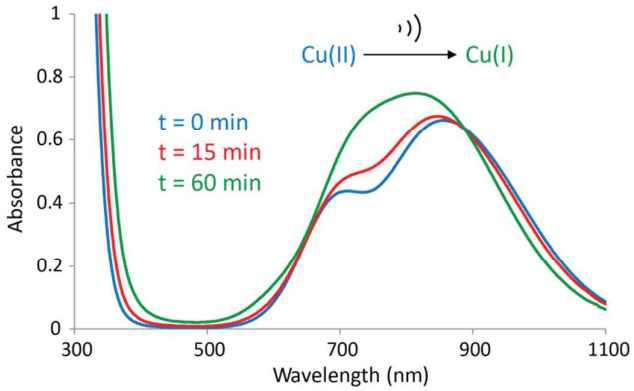


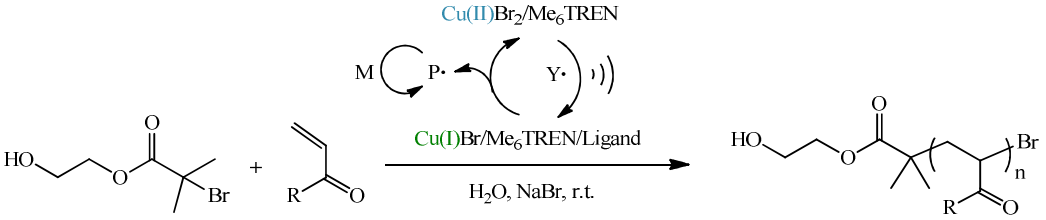
Fig. 1 UV-Vis spectrum of a $Cu(II)Br_2/Me_6TREN$ solution (10 mM $Cu(II)Br_2$, 1:6 [Cu]:[Me_6TREN]) before (green) and after 15 min (red) or 1 hr (green) of sonication (490 kHz, 40 W).

have been proposed.[42–44] It is likely that the main mechanism of Cu(II) reduction involves the formation of monomer-derived carbon-centred radicals (produced via direct pyrolysis in the cavitation bubble or from the reaction between monomers with US-generated hydroxyl/hydrogen radicals) which then reduce the Cu(II) to Cu(I), forming a small amount of brominated side-product (Y-X, Scheme 1). Additionally, it is possible for hydrogen radicals to directly reduce Cu(II), forming H-Br (See Fig. S1 for proposed reaction pathways of Cu(II) reduction).

The ability to reduce Cu(II) to Cu(I) via US was initially investigated through UV-Vis spectroscopy (Fig. 1). Significant changes in the absorbance spectrum of a degassed $Cu(II)Br_2/Me_6TREN$ solution (10 mM $Cu(II)Br_2$, 1:6 [Cu]:[Me_6TREN]) was observed during sonication. Prior to sonication two peaks at approximately 880 and 690 nm are clearly seen. However, following sonication the peak at 690 nm increases in intensity and starts to overlap with the peak at 880 nm, which itself undergoes a slight blue-shift. These changes in absorbance are consistent with previous studies on the reduction of $Cu(II)Br_2/Me_6TREN$ complexes in DMF.[33] Although this is not a direct observation of the formation of Cu(I) it does indicate a change in the Cu(II) complex, potentially forming Cu species of lower oxidation states or perhaps also other new oxo-species.

With a strong indication that the reduction of Cu(II) to Cu(I) can be achieved via US, ATRP of the water-soluble monomer 2-hydroxyethyl acrylate (HEA) was examined. The polymerisation was undertaken using 2-hydroxyethyl 2-bromoisobutryate (HEBriB) as initiator, and $Cu(II)Br_2/Me_6TREN$ (1:6 [Cu]:[Me_6TREN]) as the pre-catalyst complex. As this complex is known to be photoactive,[40] control experiments were performed to quantify the rate of polymerisation initiated by ambient light. Following conditions outlined for photoinduced ATRP ([M]:[I]:[Me_6TREN]:[$Cu(II)Br_2$] = 200:1:0.12:0.02)[40] we observed minimal polymerisation when no US was applied. When left on the benchtop, under laboratory lights, conversion via photoinduced ATRP reached 11.5% after 4 hrs. In the dark, conversion reached 16% after 24 hrs. When in the

Table 1 Characterisation data for polymers prepared via sonoATRP.



Entry	Monomer	US Frequency (kHz)	Power (W)	[Cu] (ppm)	DP	T (min)	Conv. (%)[a]	$M_{n,th}$ (Da)[b]	$M_{n,GPC}$ (Da)[c]	PDI[c]
1	HEA	490	40	50	200	60	32.8	7,622	133,600	2.16
2	HEA	490	40	250	200	60	90.1	20,937	27,430	1.08
3	HEA	490	40	500	200	60	91.0	21,146	38,580	1.06
4	HEA	490	40	1000	200	60	90.0	20,913	54,750	1.10
5	HEA	490	40	250	100	60	84.7	9,919	17,960	1.13
6	HEA	490	40	250	400	60	93.0	43,024	50,480	1.08
7	HEA	490	40	250	800	60	90.1	83,101	100,500	1.10
8	HEA	490	20	250	200	60	84.4	19,759	21,110	1.14
9	HEA	45	230	250	200	60	18.7	4,378	17,530	1.22

All polymerisations were conducted in an aqueous NaBr solution (10 mM) at [HEA] = 0.75 M. [a]Determined from ^{1}H-NMR spectroscopy. [b]Defined as: $M_{n,th}$ = (conv. x DP) x MW_{mon} + MW_I, where DP=$[M]_0/[I]$. [c]Calculated using GPC-MALS with ASTRA software.

dark, conversion is potentially caused by the reduction of Cu(II) to Cu(I) by Me_6TREN, as has been demonstrated for other nitrogen-based ligands.[45] As the rate of polymerisation via photoinduced ATRP or ligand reduction under ambient light conditions was very slow we decided to continue with the $Cu(II)Br_2/Me_6$TREN complex for our sonoATRP investigations.

SonoATRP was performed in a sonochemical bath with an irradiating frequency of 490 kHz and applied power of 40 W, corresponding to an intensity of ~1.6 W cm^{-2} (for experimental setup see SI). Consistent with our previous work on sonoRAFT, a HEA concentration of 0.75 M was chosen to maintain a workable reaction viscosity.[36] Initial experiments revealed the importance of halide salts, sodium bromide (NaBr), for controlling the aqueous ATRP. Without NaBr, experimental molecular weights were found to be significantly higher than theoretical values (Fig. S3). The addition of NaBr to improve aqueous ATRP has been reported and is thought to give control by increasing the concentration of deactivating species and limiting hydrolysis of the brominated initiator/growing polymer chains.[39] Accordingly, all future experiments were performed in a 10 mM NaBr aqueous solution.

SonoATRP performed in a 10 mM NaBr solution without the $Cu(II)Br_2/Me_6$TREN complex and/or without HEBriB resulted in uncontrolled polymerisation. The polymers formed were of very high molecular weights (>1 million Da) and high dispersities (1.3-1.6) (Figure S4). This confirmed that controlled ATRP under our conditions requires both copper and initiator. Further, it indicates that the concentration of any active brominated species, formed via the abstraction of bromine by carbon-centred radicals (Y-X, Scheme 1), which may act as additional initiators, is too low to give control over the polymerisation. Hence, free radical polymerisation is dominant. Further investigations on the role, if any, of *in-situ* US generated initiators in sonoATRP are currently underway.

Initial sonoATRP was performed at a target DP of 200, i.e. [HEA]:[I]=200:1. The copper concentration was varied to examine the effect of copper loading on the rate and degree of control of the polymerisation. At the lowest concentration ([Cu(II)] = 50 ppm) the polymerisation was uncontrolled and a high molecular weight polymer with broad dispersity was observed at low monomer conversions (Table 1 entry 1, Fig. 2c). This is similar to the uncontrolled US polymerisation of HEA observed previously.[36] Increasing the copper concentration to between 250-1000 ppm was found to result in controlled ATRP (Table 1 entries 2-4, Fig. 2c-d). In all cases, minor tailing towards low molecular weights was observed in the GPC traces which indicate a small amount of irreversible termination occurring during the initial stages of the polymerisation. Regardless, under the optimum conditions (250 ppm Cu) narrow dispersities (< 1.2) were observed throughout the polymerisation. A very fast initial rate of polymerisation was observed which reached approximately 65-80% conversion after the first 10 min (Fig. 2b). The plot of $\ln([M]_0/[M]_t)$ vs conversion was found to be linear during this period, indicating a constant concentration of active radicals (Fig. 2a). After 10 mins, the rate of polymer growth was found to decrease. Conversions reached between 82 – 90% after 30 min and slightly above 90% after 1 hr (Fig. 2b). The reduction in the rate of polymerisation was observed previously for sonoRAFT[36] and is thought to be due to the increase in viscosity of the solution, caused by the growing polymer chains, which reduces the efficiency of cavitation induced radical production.[46]

The optimal copper concentration was found to be 250 ppm,

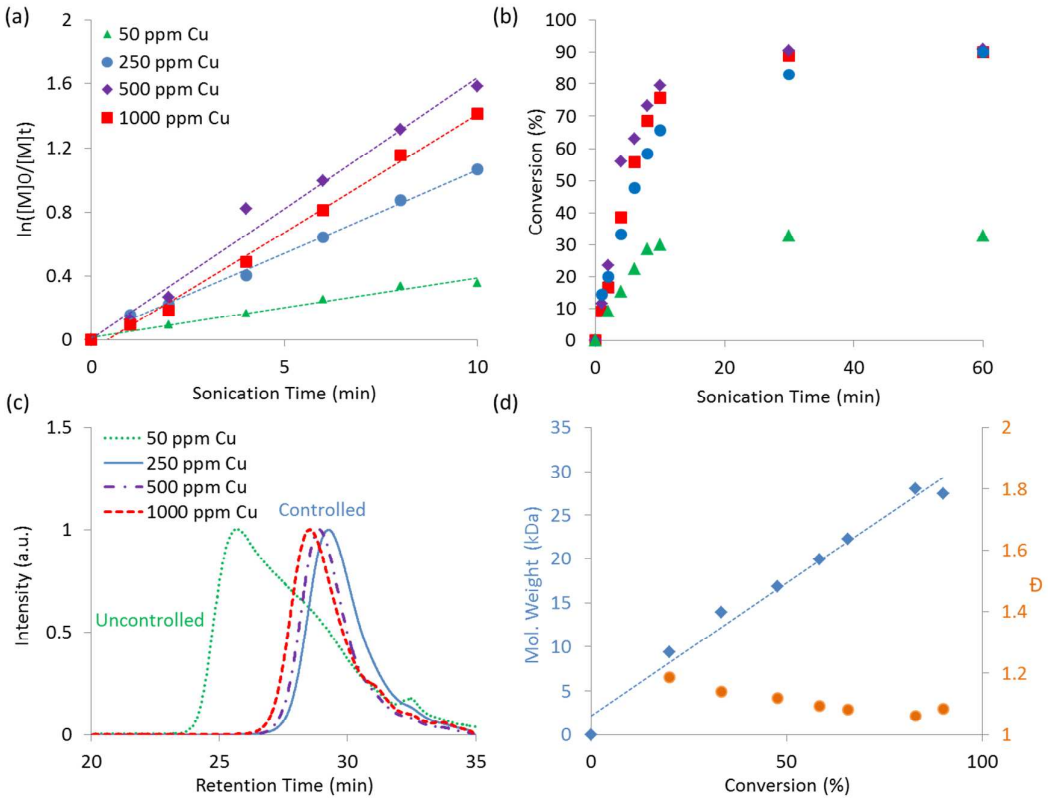


Fig. 2 (a) Reaction kinetics of sonoATRP (490 kHz, 40W) of HEA ([M]:[I]:[Me_6TREN]:[$CuBr_2$] = 200:1:6X:X, [HEA] = 0.75 M) with varying amounts of Cu (50 – 1000 ppm). All reactions were performed in a 10 mM NaBr aqueous solution; (b) Conversion vs sonication time for sonoATRP reactions with varying amounts of Cu (50 – 1000 ppm); (c) GPC traces of polymers formed after 60 min ultrasonic irradiation with different amounts of Cu; (d) GPC molecular weight characterisation of poly(HEA) prepared via sonoATRP with 250 ppm Cu.

with experimental molecular weights closest to their theoretical values. Further, a linear increase in molecular weight with monomer conversion was observed, while maintaining low dispersity (Table 1 entry 2, Fig. 2d).

Increasing the Cu concentration to 500 or 1000 ppm increased the rate of polymerisation (Fig. 2a), but the experimental molecular weights became significantly higher than theoretical values (Table 1 entries 3 and 4). At the highest copper concentration examined (1000 ppm) chain-end coupling was observed at high monomer conversions, as evidenced by a sudden jump in the observed molecular weight. (Table 1 entry 4) (see Fig. S5-7 for kinetic analysis). In light of this, a copper concentration of 250 ppm was used for all subsequent experiments.

To examine whether sonoATRP could be used to prepare polymers of various molecular weights, a range of DPs were investigated. Polymerisation for 1 hr led to the synthesis of poly(HEA) with targeted DPs of 100, 200, 400, or 800, each reaching between 84-93% monomer conversion with low dispersity in this time (Table 1 entries 2,5-7, Fig. 3a). SonoATRP consistently resulted in polymers with experimental molecular weights above their theoretical value. We believe this is due to the high radical concentration formed in the early stages of the reaction. A high concentration of radicals leads to an increase in the number of radical termination events which results in “dead” polymer chains and causes the effective ratio of [M]:[I] to increase leading to experimental molecular weights above theoretical.

As the application of US is required to form the radical species necessary for activating the ATRP by reducing Cu(II) to Cu(I), we sought to investigate the temporal control of the sonoATRP by performing an ON/OFF experiment (Fig. 3b). In the initial stages of the reaction, during the ON periods, the rate of polymerisation was rapid, consistent with results discussed earlier. As the reaction proceeds and conversion increases past 60% the rate of polymerisation slows, as expected due to the increase in viscosity. Some continuation of polymerisation is observed during the OFF periods, however the polymerisation rate is significantly attenuated compared with the ON periods. Polymerisation during the OFF cycles is almost completely attributed to the accumulation of activating Cu(I) species which remain in the reaction mixture following the ON/OFF transition. The small amount of residual Cu(I) can cause an increase in conversion in the absence of US until it is oxidised to Cu(II) via participation in the ATRP. As the rate of polymerisation through either photoinduced ATRP or ligand reduction is very slow (11.5% conversion after 4 hrs), and as timescale of the ON/OFF reaction is very short (2 min time intervals), any contribution to the polymerisation from these competing reactions is negligible. Regardless, a clear effect on

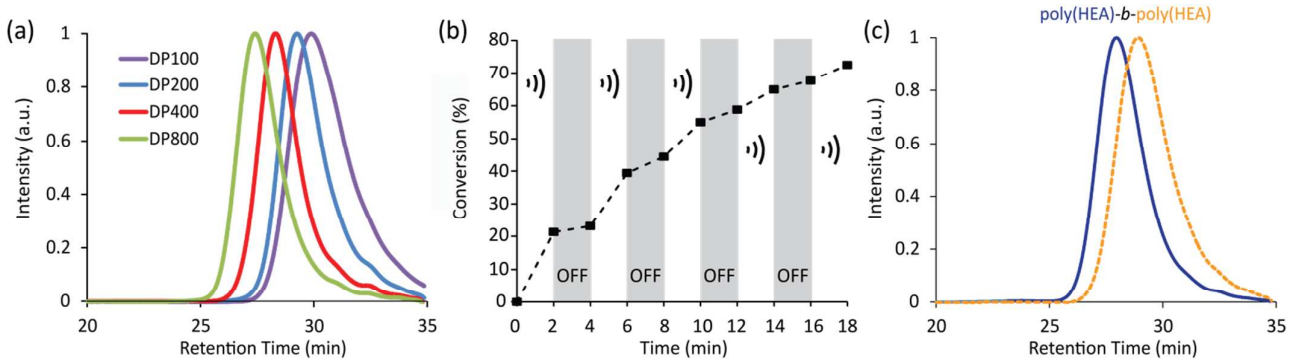


Fig. 3 (a) Different target DPs of poly(HEA) prepared via sonoATRP; (b) Monomer conversion with alternating ON/OFF periods of applied US; (c) GPC traces of the chain extension of poly(HEA) (orange dashed trace = homopolymer, blue solid trace = pseudo block co-polymer). All sonoATRP procedures were performed at frequency = 490 kHz, power = 40 W, [HEA] = 0.75 M.

the rate of polymerisation with the application of US could be observed.

MALDI-ToF spectroscopic analysis was performed to assess the structural fidelity of the synthesized ATRP polymers. The major peak series (separated by the exact mass of the HEA repeat unit (116.047 g mol^{-1})) corresponded to the in-tact, predicted polymer structure (initiated by HEBriB) confirming very high chain-end fidelity (Fig. 4). A smaller secondary series can also be observed in the MALDI-TOF spectra, albeit with an extremely low relative intensity. This is ascribed to the hydrolysed chain-end product, with a close match between the observed and theoretical mass values for this species calculated (Fig. 4). This indicates that the direct initiation of polymer chain-growth by the US generated radicals is negligible in this system, with initiation occurring exclusively via Cu(I)-activation of the alkyl bromide.

As MALDI-ToF analysis revealed high chain-end fidelity, the "livingness" of the polymers was further explored by performing an *in-situ* chain extension on the "macroinitiator" prepared by sonoATRP (Fig. 3c). Initially, chain extension was

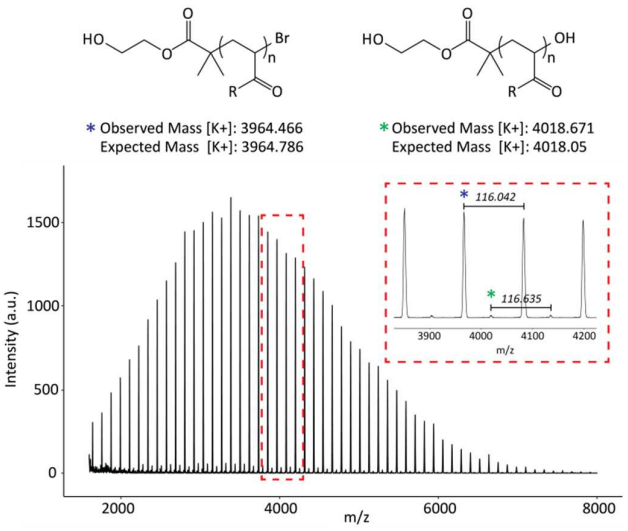


Fig. 4 MALDI-ToF of poly(HEA) confirming high chain-end fidelity.

performed on a poly(HEA) sample synthesised following the previously optimised procedure (60 min US at ambient temperature). However, chain extension of this sample led to a bimodal GPC trace indicating a significant amount of chain-end loss, likely via hydrolysis of the terminal bromine (Fig. S8). To minimise chain-end hydrolysis, sonoATRP was performed at a reduced temperature (<5 °C)[47] and allowed to react for 30 mins.

Under these conditions, conversion reached 82% and the molecular weight was found to be 36 kDa with a dispersity of 1.14. To this polymer solution an equivalent mass of monomer in a degassed aqueous NaBr solution (10 mM) was added directly. US treatment for a further hour revealed excellent continued chain growth, indicating good pseudo-blocking efficiency and a high degree of "livingness" (Fig. 3c).

Finally, the parameters of the US treatment were varied to examine the effect of US frequency and power on the rate and control of the sonoATRP. Firstly, the power was reduced from 40 to 20 W while maintaining the frequency at 490 kHz. The reduction in the US power resulted in a slower rate of polymerisation (Fig. S9 and S10), consistent with the reduced rate of radical production expected under these conditions.[36] After 60 mins, polymerisation at 20 W had reached a similar conversion (84.4%) to that performed at 40 W (90.1%) (Table 1 entry 8). Importantly, the agreement between theoretical and experimental molecular weight was far closer at 20 W (Table 1, entry 8, $M_{n,th}$: 19,759 Da, $M_{n,GPC}$:21,110 Da) than at 40 W (Table 1, entry 2, $M_{n,th}$: 20,937 Da, $M_{n,GPC}$: 27,430 Da). We attribute this to the lower rate of radical formation at 20 W which reduces the concentration of radicals in the reaction, minimising termination events and maintaining a [M]:[I] ratio closer to the targeted value. Hence, by varying the US intensity the radical concentration may be manipulated to affect the polymerisation.

In the preparation of this manuscript, a similar concept for sonoATRP was reported by Matyjaszewski and co-workers in which polymerization was achieved using low frequency ultrasound (40 kHz, 110 W) with 400 ppm copper.[48] Polymerisation of oligo(ethylene oxide) methyl ether methacrylate was found to reach good conversions (up to

88%) within four hours. The polymerisation of HEA however, reached a maximum of only 59% conversion after 6 hrs.

To compare our sonoATRP procedure at a lower frequency, we conducted a polymerisation in a 45 kHz bath (230 W). After one hour of ultrasonic irradiation a conversion of only 19% was reached (Table 1 entry 9, Fig. S11). This is significantly lower than the conversion reached using the higher frequency (490 kHz) for the same time period (60 min, 90% conversion). The reduced rate of polymerisation at 45 kHz is presumably due to the much slower rate of radical formation, leading to a slower rate of reduction of Cu(II) to Cu(I).

MALDI-ToF analysis of the polymer prepared at 45 kHz revealed also good chain-end fidelity with the major peak series corresponding to the intact polymer initiated by HEBriB (Fig. S12). Similar to the polymer prepared at 490 kHz, a small secondary series associated with chain-end hydrolysis of the terminal bromine atom is also observed.

Here, sonoATRP was restricted to solutions of low monomer concentration (0.75 M) in order to minimise the increase in viscosity caused by polymer growth. We understand this may be a limitation for some industrial applications. However, achieving controlled sono-polymersations with higher monomer concentrations may be achieved by various means including increasing the applied power or through emulsion or semi-batch polymerisation. Work is continuing to develop sonoATRP for more industrially relevant purposes.

In summary, the use of high frequency US for controlled ATRP has been demonstrated. US treatment of an aqueous solution of monomer, alkyl halide initiator, and a pre-catalyst complex (Cu(II)/L) was found to produce radicals which serve to reduce Cu(II) to Cu(I) and initiate ATRP. High frequency sonoATRP was demonstrated for a water-soluble monomer (HEA) with polymers of different molecular weights being prepared in rapid rates and with low dispersities. US provides a green and scalable means of polymer synthesis, and further studies are ongoing to develop this technique further for the synthesis of a wide variety of polymers and complex molecular architectures.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

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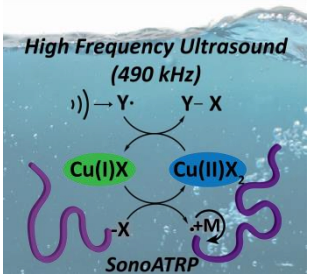
High Frequency sonoATRP of 2-Hydroxyethyl Acrylate in an Aqueous Medium

TOC:



Controlled aqueous ATRP (sonoATRP) of 2-hydroxyethyl acrylate using high frequency ultrasound is presented for the first time.