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# Well-defined PDMAEA stars via Cu(0)-mediated reversible deactivation radical polymerisation

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## **Abstract**

The Cu(0)-mediated reversible deactivation radical polymerisation of *N,N'*-dimethylaminoethyl acrylate in DMSO and IPA at ambient temperature using Cu(0) wire is investigated. Tetra-functional and octa-functional initiators were utilised to facilitate the synthesis of well-defined PDMAEA star homo and block copolymers with a range of molecular weights ( $M_n \sim 5000-41000 \text{ g mol}^{-1}$ ). Both solvents demonstrated to be excellent media for the controlled polymerisation of DMAEA yielding narrow molecular weight distributions ( $\mathcal{D} \sim 1.1$ ) when the reactions were ceased at  $\sim 40\%$  conversion. Interestingly, at high conversions (typically  $> 55\%$ ) high and low molecular weight shoulders were evident by SEC when DMSO and IPA were used respectively, suggesting large extent of termination and/or side reactions at prolonged reaction times. Nevertheless, high end group fidelity could be maintained when immediate precipitation of the polymers (at lower conversion) was performed yielding low dispersed P(DMAEA-*b*-MA) star block copolymers ( $\mathcal{D} < 1.19$ ,  $M_n \sim 20000 \text{ g mol}^{-1}$ ).

Importantly, guidelines on how to prevent hydrolysis, termination and side reactions of PDMAEA as well as how to purify and store such materials are also provided and discussed.

## Introduction

Polyamines have attracted considerable interest due to the presence of cationic nitrogen atoms that allow for pH tuning and the formation of pH responsive nanoparticles structures that self-assemble in aqueous solution.<sup>1-3</sup> These properties render polyamines a good candidate for a wide range of applications such as gene delivery<sup>4</sup>, waste water treatment<sup>5</sup>, paper making<sup>6</sup> and cosmetics<sup>7</sup>. In comparison to the analogous methacrylate, poly(dimethylaminoethyl methacrylate) (PDMAEMA), poly(dimethylaminoethyl acrylate) (PDMAEA) has attracted further interest due to its ability to provide a timed release mechanism facilitated by its self-catalysed hydrolysis in water to polyacrylic acid and N,N'-dimethylaminoethanol.<sup>8,9</sup>

Several reversible-deactivation radical polymerisation (RDRP) methods have been employed in an attempt to provide PDMAEA with high end group fidelity and narrow molecular weight distributions (MWDs). Cunningham and co-workers<sup>10</sup> utilised nitroxide mediated polymerisation (NMP)<sup>11</sup> at 100°C to control the polymerisation of DMAEA, resulting in relatively low molecular weight polymers ( $M_n \sim 8800 \text{ g mol}^{-1}$ ,  $\mathcal{D} \sim 1.29$ ) and broad MWDs when a higher molecular weight was targeted ( $M_n \sim 13000 \text{ g mol}^{-1}$ ,  $\mathcal{D} \sim 1.47$ ). Importantly, the chain extension of the homopolymers/macroinitiator with butyl acrylate gave high dispersities ( $\mathcal{D} > 1.4$ ) and a significant low molecular weight shoulder, indicative of intense termination events and/or side reactions. High temperatures were used for all the experiments.<sup>10</sup> Reversible addition-fragmentation chain-transfer polymerisation (RAFT)<sup>12</sup> has also been employed for the controlled polymerisation of DMAEA. Monteiro and co-workers reported narrow MWDs ( $\mathcal{D} \sim 1.17-1.26$ ) for low molecular weight PDMAEA ( $M_n \sim 3000-8600 \text{ g mol}^{-1}$ ). However, no chain extensions or block copolymerisations were reported.<sup>13</sup> Perrier and co-workers also used RAFT

to polymerise DMAEA employing a PDMS macro chain transfer agent at 70 °C. Although narrow MWDS were reported ( $\mathcal{D} \sim 1.20$ ), again chain extensions were not studied.<sup>14</sup> Additional reports<sup>15</sup> on RAFT, also show a preference to incorporate PDMAEA as the second or third block, instead of using it as a macroinitiator.<sup>16,17</sup>

The polymerisation of DMAEA by copper-mediated RDRP techniques is somewhat problematic compared to other acrylates monomers.<sup>18,19</sup> This is attributed to the nucleophilic nature of the tertiary amine on the pendant groups that can react with the secondary halide on the polymer chain end. Thus, nucleophilic reactions can occur via intramolecular and/or intermolecular interactions.<sup>20</sup> Zhu and co-workers utilised atom transfer radical polymerisation (ATRP)<sup>21,22</sup> at 70 °C to synthesise PDMAEA homopolymers up to  $M_n \sim 10000$  with relatively broad MWDs ( $\mathcal{D} \sim 1.43$ ). Chain extension of PDMAEA macroinitiator was not reported.<sup>20</sup> Further ATRP reports utilised PDMAEA as the third block to yield well-defined materials.<sup>23</sup> High temperatures have been employed in all cases which could cause additional side reactions.

The use of Cu(0) in copper-mediated RDRP was reported by Matyjaszewski and co-workers in 1997<sup>24</sup> (and was later named as supplemental activator and reducing agent ATRP) and became popular in 2002<sup>25</sup> and 2006<sup>26</sup> by Percec and co-workers (named as single electron transfer living radical polymerisation and abbreviated SET-LRP), and has been successfully applied to the controlled polymerisation of acrylates<sup>18,27-29</sup> methacrylates<sup>30,31</sup> and acrylamides<sup>32-34</sup> at ambient temperatures or below with a broad range of architectures, including stars, combs, brushes and multiblock copolymers.<sup>35-37</sup> Although the role of Cu(0) has been the centre of a scientific debate, it is however outside of the scope of this current study.<sup>38-</sup>  
<sup>42</sup> Monteiro and co-workers utilised Cu (0) powder to successfully polymerise DMAEA, with narrow molecular weight distributions, although only for relatively low molecular weights. ( $M_n \sim 9000$ ,  $\mathcal{D} \sim 1.29$ ).<sup>43</sup> However, Cu(0) wire would perhaps be a better alternative as it offers many advantages as opposed to Cu(0) powder, including facile tuning of the reaction rate,

predictability, easy catalyst preparation and recyclability.<sup>44,45</sup> In addition, none of the aforementioned reports, including Cu(0)-mediated RDRP have been employed for the synthesis of PDMAEA star homo and block copolymers.

Star polymers are of particular interest both in academia and industry due to their potential applications as viscosity modifiers, catalyst supports, polymer therapeutics, drug carriers and additives.<sup>46-50</sup> In comparison to their linear counterparts, star polymers possess additional properties thanks to their compact structures and high arm density.<sup>47,51</sup> The major challenge in the synthesis of well-defined star polymers is bimolecular termination due to star-star coupling.<sup>52</sup> The high end group fidelity of Cu(0)-mediated RDRP suggests that it could potentially be an efficient tool for the synthesis of star polymers with narrow MWDs and low coupling.<sup>53-54</sup> Indeed, Cu(0)-mediated RDRP has already been employed to yield well-defined stars,<sup>55</sup> including the synthesis of stars homopolymers in a biphasic system, which was shown to suppress star-star coupling.<sup>56</sup> However, non-functional monomers have been employed (typically methyl acrylate) in all cases, thus limiting the applications of the resultant materials.<sup>57</sup>

Herein, we present the Cu(0)-mediated RDRP in dimethyl sulfoxide (DMSO) and isopropanol (IPA) solvents at ambient temperature to afford the synthesis of well-defined 4 and 8 arm PDMAEA stars. Polymerisation of DMAEA in either solvent using Cu(0) wire proceeds with controlled/living characteristics up to ~ 40% conversion, after which significant termination and/or side reactions start to occur as evidenced by SEC. This is highlighted in DMSO with a high molecular weight shoulder that increases throughout the polymerisation while in IPA a low molecular weight shoulder gradually forms suggesting loss of end group fidelity when longer reaction times are targeted. However, high end group fidelity can be maintained when the polymerisation is stopped at moderate conversions (35-50%) and the purified macroinitiator can subsequently facilitate the synthesis of well-defined block

copolymers. In addition, a range of molecular weights can be synthesised ( $M_n \sim 5000$ - 41000  $\text{g mol}^{-1}$ ), exhibiting narrow MWDs ( $\mathcal{D} \sim 1.1$ ) in all cases. Due to the high reactivity of the tertiary amine of PDMAEA, the first instructions on how to efficiently terminate these polymerisations and subsequently purify and store the PDMAEA stars are also presented.

## Experimental part

### Materials

All materials were purchased from Sigma Aldrich or Fischer Scientific and used as received unless otherwise stated. DMAEA was used as it is. Distillation of DMAEA or passing the monomer through a column of alumina had no effect on the subsequent polymerisation (data not shown). HPLC IPA (99.9%) was used for all the experiments, including the chain extensions and the storage studies. Methyl acrylate was passed through a basic  $\text{Al}_2\text{O}_3$  chromatographic column prior to use to remove the inhibitor. *Tris*-(2-(dimethylamino)ethyl)amine ( $\text{Me}_6\text{-Tren}$ ), *octa-O*-isobutyryl bromide lactose (8-arm initiator)<sup>58</sup> and 1,1,1,1-*tetra*(methyl-2-methyl-2-bromopropionate (4-arm initiator)<sup>59</sup> were synthesised according to previously reported literature. Cu(0) (gauge 0.25 mm) wire was purchased from Comax Engineered wires and purified by immersion in conc. HCl for 15 minutes, subsequently rinsed with water and dried prior to use. NMR spectra were recorded on Bruker DPX-300 or DPX-400 spectrometers in  $\text{CDCl}_3$ . Chemical shifts are given in ppm downfield from the internal standard tetramethylsilane. Monomer conversions were determined via  $^1\text{H}$  NMR spectroscopy by comparing the integrals of monomeric vinyl protons to polymer signals. Size exclusion chromatography (SEC) measurements were conducted using an Agilent 1260 GPC-MDS fitted with a differential refractive index (DRI) detector equipped with 2 PLgel 5 mm mixed-D columns (300 7.5 mm), 1 PLgel 5 mm guard column (50 7.5 mm) and autosampler. Narrow linear poly(methyl methacrylate) standards ranging from 200 to  $1.0 \times 10^6$   $\text{g mol}^{-1}$  were

used as calibration standards. All samples were passed through a 0.45 mm PTFE filter prior to analysis. The mobile phase was chloroform with 2% triethylamine at a flow rate of 1.0 mL min<sup>-1</sup>. SEC data were analysed using Agilent GPC/SEC software (version 1.2). MALDI-TOF-MS was conducted using a Bruker Daltonics Ultraflex II MALDI-TOF mass spectrometer, equipped with a nitrogen laser delivering 2 ns laser pulses at 337 nm with positive ion ToF detection performed using an accelerating voltage of 25 kV. Solutions in tetrahydrofuran (50 µL) of trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propylidene] malonitrile (DCTB) as a matrix (saturated solution), sodium iodide as cationization agent (1.0 mg mL<sup>-1</sup>) and sample (1.0 mg mL<sup>-1</sup>) were mixed, and 0.7 µL of the mixture was applied to the target plate. Spectra were recorded in reflector mode calibrating PEG-Me 1900 kDa. ICP-MS samples were analysed on an Agilent 7500cx ICP mass spectrometer in no-gas mode, with an average of 3 replicates with RSD below 1%. Copper calibration standards were prepared from QMX SCP28 multi-element mix to cover a range from 1 ppb to 1 ppm. Polymer samples were solubilised in 4% nitric acid solutions.

## **Methods**

### **General procedure for a typical Cu(0)-mediated RDRP of DMAEA using the 4-arm initiator**

DMAEA (2.65 mL or 2.50 grams, 140 equiv.), pre-activated copper wire (5 cm), 4-arm initiator (0.0915 grams, 1 equiv.), CuBr<sub>2</sub> (0.0112 grams, 0.40 equiv. with respect to the 4-arm initiator or 0.10 equiv. with respect to each initiating site/arm) and IPA (2.65 mL) were added to a septum sealed vial. The copper wire was carefully wrapped around the stirrer bar and the mixture was subsequently degassed by purging with nitrogen for 15 min. Me<sub>6</sub>-Tren (0.024 mL, 0.72 equiv. with respect to initiator or 0.18 equiv. with respect to each initiating site/arm) was then introduced in the vial via a gas-tight syringe and the polymerisation was allowed to

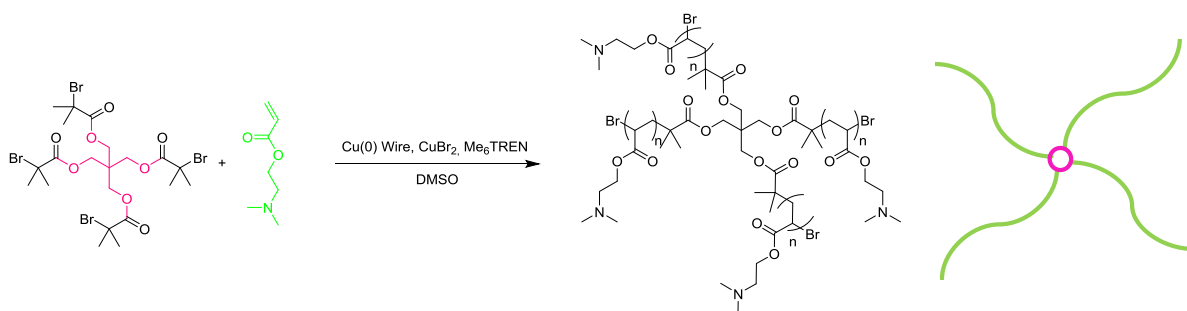
commence at ambient temperature. Samples were taken periodically under a nitrogen blanket and passed through a short column of neutral alumina to remove dissolved copper salts prior to analysis by  $^1\text{H}$  NMR. The reaction was terminated by dilution in IPA (another 2.65 mL) and the product was isolated via precipitation in cold hexane before being further characterised by NMR and SEC. An analogous procedure was followed when the 8-arm initiator was employed.

### General procedure for a typical chain extension/block copolymerisation using the 4-arm initiator

0.40 grams of the PDMAEA ( $M_n \sim 9100 \text{ g mol}^{-1}$ ) macroinitiator was synthesised and isolated as described in the previous section and was subsequently dissolved in IPA (1.85 mL). 1.76 grams of MA (targeting  $\text{DP} = 464$ ), 0.0039 grams of  $\text{CuBr}_2$  (0.4 equiv. with respect to the macroinitiator), and 5 cm of copper wire (wrapped around a stirrer bar) were also included in the polymerisation mixture and the vial was sealed via a septum. The polymerisation mixture was then degassed by purging with nitrogen for 15 min and  $\text{Me}_6\text{-Tren}$  (0.008 mL, 0.72 equiv. with respect to the macroinitiator) was subsequently introduced in the vial and the polymerisation was allowed to commence at ambient temperature under a nitrogen blanket. The diblock copolymer  $\text{P}(\text{DMAEA-}b\text{-MA})$  was stopped at  $\sim 58\%$  of conversion and was isolated via precipitation in heptane (3 times), followed by analysis by both  $^1\text{H}$  NMR and SEC.

## Results and discussion

### Synthesis of PDMAEA star homopolymers utilising an 4-arm initiator in DMSO





Scheme 1: Schematic representation of PDMAEA synthesis from a 4-arm initiator via Cu(0)-mediated RDRP.

Initially, the polymerisation of DMAEA was carried out in DMSO using Cu(0) wire, a *tetra*-functional initiator (1,1,1,1-*tetra*(methyl-2-methyl-2-bromopropionate), CuBr<sub>2</sub> and Me<sub>6</sub>-Tren at ambient temperature, under the following reaction conditions: [I]:[DMAEA]:[CuBr<sub>2</sub>]:[Me<sub>6</sub>-Tren]=[1]:[140]:[0.40]:[0.72] (Scheme 1). It should be noted that 0.10 equiv. of CuBr<sub>2</sub> and 0.18 equiv. of Me<sub>6</sub>-Tren were used relative to each initiating site as these ratios have been shown to maintain high end group fidelity.<sup>53</sup> Kinetic experiments revealed that the polymerisation proceeded with a relatively slow rate, when compared with other acrylate analogues such as methyl acrylate<sup>60, 61</sup> with 68% conversion achieved in 4 h and a final conversion of 86% even when the reaction was left to proceed overnight (Figures 1a & 1b, Table S1). Interestingly,  $\ln[M]_t/[M]_0$  increases linearly with time up until ~49% conversion (~ 2 h,  $\mathcal{D} \sim 1.13$ , Figures 1a & S1, Table S1) which is consistent with a constant concentration of propagating radicals suggesting a controlled/living polymerisation. SEC chromatograms (up to 2 h) indicate a monomodal distribution shifting to higher molecular weights with increasing conversion while the dispersities remain low ~ 1.10 (Figure 1c, Table S1). Whilst there is some deviation between the theoretical and experimental values, it is well known that star polymers adopt different hydrodynamic volumes than their linear counterparts which are typically used for SEC calibration.<sup>62, 63</sup> After 2 h a gradual broadening of the molecular weight distributions was observed with  $\mathcal{D} \sim 1.31$  (after 4 h) and a final dispersity of 2 (~ 86% conversion, Table S1). Importantly, SEC analysis revealed an obvious high molecular weight shoulder which is increasing throughout the reaction (Figure 1c). This was attributed to typical star-star coupling reactions commonly seen during the formation of star polymers, particularly at high conversions.<sup>64</sup> No low molecular weight shoulders were detected. Interestingly, when a linear initiator was employed, broad molecular distributions were also observed at higher conversions

(Figures S2-S10 and Tables S2-S4). This data suggest that the polymerization of this monomer using either a linear or a star initiator exhibit significant side reactions, although in the case of the star polymers additional coupling is observed. Although understanding the exact nature of the side reaction could be of interest, this is out of the scope of our contribution. In addition, MALDI-TOF MS was conducted where the main two polymer distribution correspond to PDMAEA terminated with a bromine end group (with either a sodium or hydrogen adduct) (Figures S11-S12).

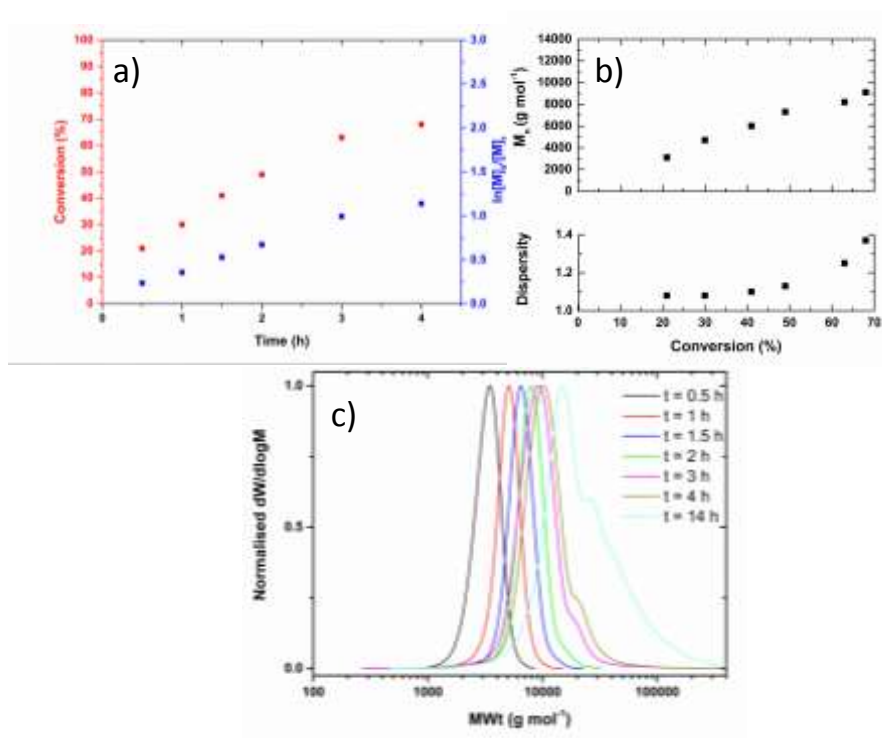


Figure 1: Kinetic data for the Cu(0)-mediated RDRP of DMAEA in DMSO utilising 4-arm initiator under the following reaction conditions  $[I]:[DMAEA]:[CuBr_2]:[Me_6-Tren]=[1]:[140]:[0.40]:[0.72]$ .

Thus it is apparent that to synthesise well-defined PDMAEA stars with narrow molecular weight distributions the reactions should be quenched at moderate conversions (up to 40%) in order to maintain low dispersities and good control over the polymerisation ( $M_n \sim 7300 \text{ g mol}^{-1}$ ,  $D \sim 1.13$ ). In order to probe the potential of Cu(0)-mediated RDRP in maintaining control for both lower and higher molecular weights a range of polymerisations were conducted

targeting degrees of polymerisation ( $DP_n$ ) from 35 to 560 ( $M_{n,th.} \sim 5000-80000 \text{ g mol}^{-1}$ ). The ratio of  $[I]:[DMAEA]:[CuBr_2]:[Me_6\text{-Tren}] = [1]:[DP_n]:[0.40]:[0.72]$  was kept for each polymerisation and the reactions were stopped typically between 40-50% of conversion in order to suppress star-star coupling reactions. In all cases, well-defined PDMAEA in various molecular weights ( $M_n \sim 3000-26000 \text{ g mol}^{-1}$ ) with dispersities as low as 1.10 (Table 1, Figure 2) could be attained demonstrating the advantages of Cu(0) wire over Cu(0) powder, which has previously employed by Monteiro and co-workers.<sup>43</sup>

Table 1:  $^1\text{H}$  NMR and SEC analysis of PDMAEA with various DP prepared via Cu(0)-mediated RDRP in DMSO.

<b>Target Molecular Weight (<math>\text{g mol}^{-1}</math>)</b>	<b>Conv. (%)*</b>	<b><math>M_{n,theory}</math> (<math>\text{g mol}^{-1}</math>)</b>	<b><math>M_{n,SEC}</math> (<math>\text{g mol}^{-1}</math>)</b>	<b><math>\mathcal{D}</math></b>
<b>5000</b>	50	2500	3200	1.10
<b>10000</b>	56	5600	6600	1.09
<b>20000</b>	49	9800	9700	1.10
<b>40000</b>	43	17200	14600	1.14
<b>80000</b>	44	35200	25500	1.20

\*as determined by  $^1\text{H}$  NMR

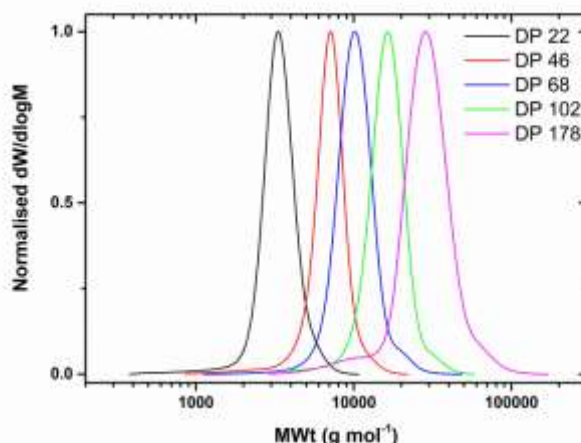


Figure 2: SEC analysis of PDMAEA with various DP prepared via Cu(0)-mediated RDRP in DMSO.

### Synthesis of PDMAEA star homopolymers utilising an 4-arm initiator in IPA

As longer reaction times leads to the loss of the constant radical concentration and star-star coupling, the polymerisation had to be ceased at ~ 40% followed by the purification of the macroinitiator in order to maintain the high end group fidelity required to facilitate the synthesis of block copolymers. However, purification of the polymers from DMSO was found to be challenging due to the low miscibility of this solvent with all the solvents employed for the precipitation of PDMAEA, including heptane, hexane and diethyl ether. In order to circumvent this issue IPA was utilised as an alternative reaction medium for the synthesis of PDMAEA as this solvent could be easily removed post polymerisation. In addition, due to the observed loss of control of the polymerisation, it was hypothesised that IPA may lead to slower polymerisation rates, either due to lower polarity of the solvent (in comparison to DMSO) or due to the lower amount of disproportionation of Cu(I)Br. We anticipated that the Cu(0)-mediated RDRP of DMAEA in IPA could be realised with success either via retention of the polymer solubility throughout the polymerisation or the capacity of IPA to support a self-generating biphasic system as previously reported.<sup>56</sup> Furthermore IPA was reported as a polar

solvent that has been used to reduce the dispersity of polymers synthesised by Cu(0)-mediated RDRP and does not undergo transesterification with DMAEA.<sup>65</sup>

When the same conditions used for the polymerisation in DMSO were employed for the polymerisation in IPA, ([I]:[DMAEA]:[CuBr<sub>2</sub>]:[Me<sub>6</sub>-Tren]=[1]:[140]:[0.40]:[0.72]), the reaction proceeded with slower polymerisation rates achieving 32% conversion in 2 h (as opposed to 49% conversion for DMSO) and 49% conversion in 4 h with a dispersity of 1.15. This slower polymerisation rate can be further illustrated by the lower  $k_p^{app}$  value in IPA, ( $k_p^{app}=5.53 \times 10^{-5} \text{ s}^{-1}$ ) in comparison to DMSO ( $k_p^{app}=9.20 \times 10^{-5} \text{ s}^{-1}$ ). Similarly to DMSO, when the polymerisation was sampled the following day broader MWDs ( $\mathcal{D} \sim 1.60$ ) were observed (Table S5). However, star-star coupling was significantly suppressed in the polymerisation with IPA and only a negligible high molecular weight shoulder could be observed on the SEC trace (Figure 3c). It is noted that the reaction mixture appears cloudy/heterogeneous post polymerisation, although the formation of two discrete phases was not observed. On the contrary, a low molecular weight shoulder was evident indicating a small extent of termination during the polymerisation which was further increased when the reaction was left to proceed overnight. Careful kinetic analysis of the polymerisation in IPA revealed a similar trend with the DMSO system, where a linear increase in  $M_n$  with conversion and a largely first order dependence on both monomer and propagating radical up to ~45% conversion (Figures 3a & b). The discrepancies between the theoretical and the experimental molecular weights are again attributed to the different hydrodynamic volumes of the star polymers.<sup>62, 63</sup> A range of molecular weights were also targeted, demonstrating the capacity of IPA to support the synthesis of well-defined PDMAEA of various DPs given that the conversions were maintained at moderate levels (30-50%) (Figure 3d, Table S6).

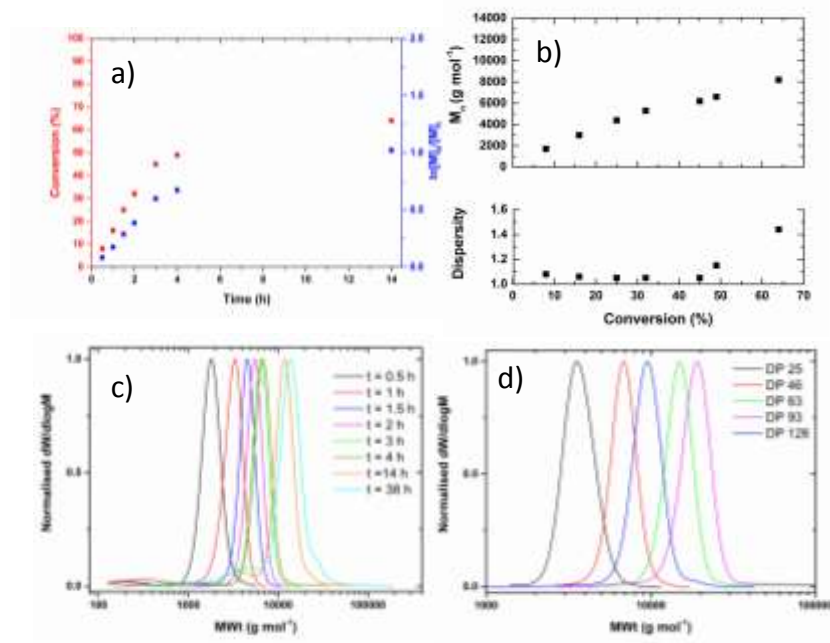


Figure 3a-c): Kinetic data for the Cu(0)-mediated RDRP of DMAEA in IPA utilising the *tetra*-functional initiator under the following reaction conditions [I]:[DMAEA]:[CuBr<sub>2</sub>]:[Me<sub>6</sub>Tren]=[1]:[140]:[0.40]:[0.72] and d) SEC analysis of purified PDMAEA with various DP prepared via Cu(0)-mediated RDRP in IPA.

### Synthesis of P(DMAEA-*b*-MA) star copolymers utilising an 4-arm initiator

Switching from DMSO to IPA allowed for the straightforward isolation of the PDMAEA by precipitation (see subsequent section for further details) at ~ 40% of conversion ( $M_n \sim 9100 \text{ g mol}^{-1}$ ,  $\mathcal{D} \sim 1.07$ ) which was subsequently employed as the macroinitiator for the block polymerisation with methyl acrylate (MA). The PDMAEA homopolymer was successfully chain extended (chain extension was also performed in IPA) with SEC revealing a nearly complete shift of the molecular weight after 3 h whilst maintaining low dispersity ( $\mathcal{D} \sim 1.15$ ) and a final  $M_n$  of  $\sim 23500 \text{ g mol}^{-1}$  (Figures 4 & S13, Table S7). Thus, well-defined P(DMAEA-*b*-MA) star copolymers could be obtained for the first time and in a facile manner. Interestingly, the reduced star-star coupling observed in both the -homo and copolymerisation

further confirms the advantage of heterogeneous systems for the controlled polymerisation of star copolymers in comparison with homogeneous media.<sup>56</sup>

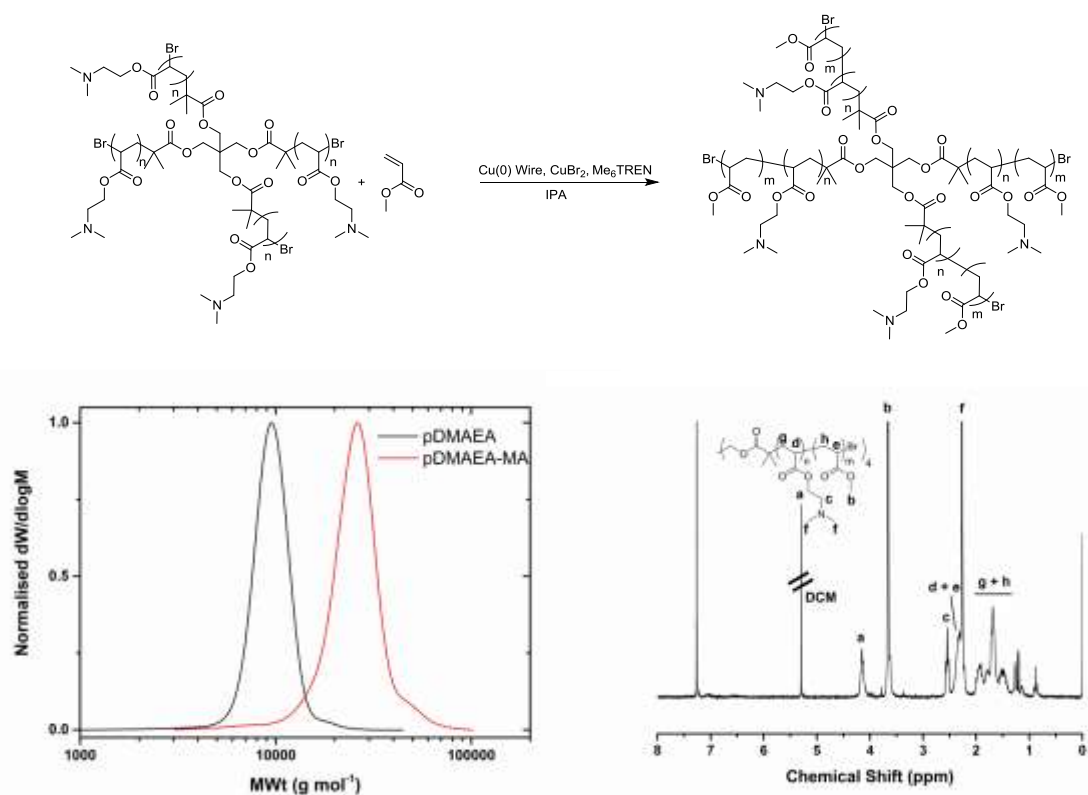


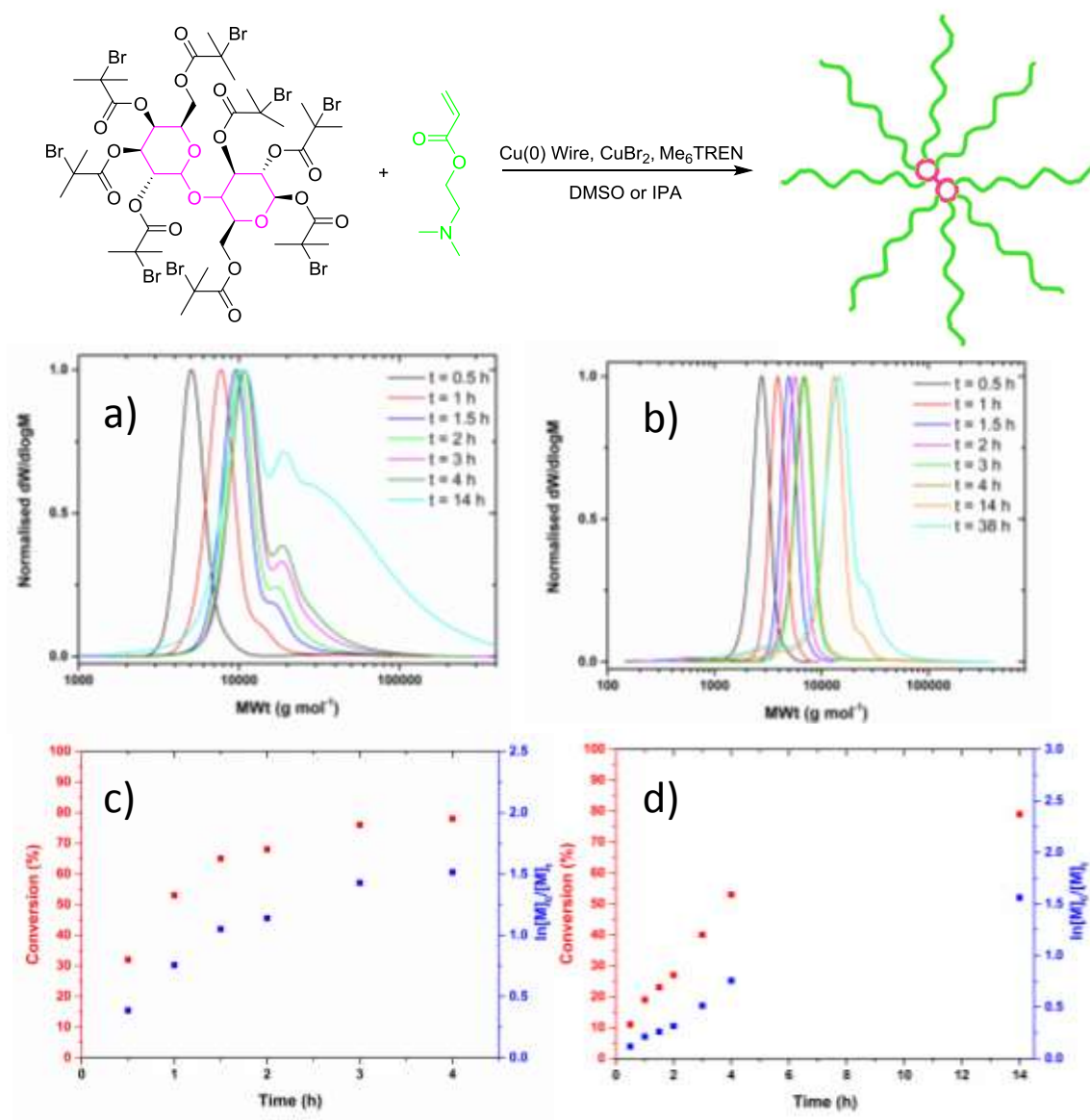
Figure 4: SEC and NMR of the block copolymerisation from a PDMAEA macroinitiator in IPA via Cu(0)-RDRP utilising a 4-arm initiator.

### Synthesis of PDMAEA star homo and copolymers utilising an 8-arm initiator

In order to obtain stars with an increased number of arms, an 8-arm lactose initiator (*octa-O-isobutyryl bromide lactose initiator*) was utilised by adjusting the previously employed reaction conditions for 8 initiating sites ( $[I]:[DMAEA]:[CuBr_2]:[Me_6-Tren]=[1]:[140]:[0.80]:[1.44]$ ). The polymerisations were carried out in both DMSO and IPA, where a higher rate of polymerisation was evident for both solvents in comparison with the 4-arm star analogues. It is noted that increased  $k_p^{app}$  values are obtained for the 8-arm star polymers, which is due to the higher concentration of radicals generated in these systems. For example in DMSO  $k_p^{app}$  for the 8-arm star polymer is  $1.32 \times 10^{-4} \text{ s}^{-1}$ , in comparison to  $9.20 \times 10^{-5}$

$5 \text{ s}^{-1}$  for the 4-arm star and  $3.04 \times 10^{-5} \text{ s}^{-1}$  for the linear polymer. This was attributed to the greater concentration of bromines which results in higher concentration of radicals during polymerisation. Specifically, in DMSO 53% conversion was attained within 1 h ( $\mathcal{D} \sim 1.16$ ) as opposed to 30% conversion when the 4-arm initiator was employed). Similarly, when IPA was utilised as the solvent slightly higher polymerisation rates were attained (19% conversion). Kinetic experiments were also performed, mirroring the results obtained for the 4-arm star initiator (Figures 5, S14 & S15 and Tables S8 & S9). When the synthesis of the 8-arm stars was performed in DMSO, a high molecular weight shoulder could be observed in the SEC which increased throughout the reaction yielding polymers with very broad molecular weight distributions when left to react for prolonged periods of time (90%  $\mathcal{D} \sim 2.75$ , Figures 5a & 5c). However, when the reaction was stopped at 53% conversion, well-defined PDMAEA stars could be obtained with  $M_n \sim 7800 \text{ g mol}^{-1}$  and a final dispersity of 1.16. In contrast to DMSO, IPA facilitates the synthesis of PDMAEA stars with less pronounced high molecular weight shoulders and lower final dispersities ( $\mathcal{D} \sim 1.48$  after 16 h of reaction, Figures 5b & 5d), further highlighting the capability of IPA to reduce star-star coupling when phase separation occurs during the polymerisation. It should however be noted that a small, yet reproducible, low molecular weight shoulder could be observed in this solvent suggesting premature termination events. Nevertheless, when the reaction was stopped at  $\sim 53\%$  conversion, PDMAEA stars with low dispersities could be obtained ( $\mathcal{D} \sim 1.08$ ,  $M_n \sim 6800 \text{ g mol}^{-1}$ ). Higher molecular weight polymers were subsequently obtained by targeting higher degrees of polymerisation, yielding well-defined polymers up to  $M_n \sim 41000$  and  $\mathcal{D} \sim 1.08$  (Figures S16 & S17, Tables S10 & S11). Chain extension of PDMAEA ( $\mathcal{D} \sim 1.16$ ,  $M_n \sim 11100 \text{ g mol}^{-1}$ ) with MA yielded well-defined P(DMAEA-*b*-MA) with  $\mathcal{D} \sim 1.19$  and  $M_n \sim 19000 \text{ g mol}^{-1}$  (Figures S18 & S19, Table S12), demonstrating high end group fidelity of PDMAEA 8-arm macroinitiator.





Figures 5 a-d): Kinetic data for the Cu(0)-mediated RDRP of DMAEA utilising an 8 arm initiator under the following reaction conditions [I]:[DMAEA]:[CuBr<sub>2</sub>]:[Me<sub>6</sub>-Tren]=[1]:[140]:[0.80]:[1.44]. DMSO is represented in the left hand column (a, c) and IPA in the right hand one (b, d).

### Guidelines for termination and purification of PDMAEA stars

As these polymers present broader MWDs with increasing reaction time (especially in the case of DMSO), it is essential to terminate the reaction at an early stage. In order to identify the best way to terminate, 4 different samples were conducted after ~1.5 h of polymerisation of DMAEA in DMSO (Figures 6b, Table S13). The first sample was analysed instantly by

NMR and SEC revealing ~42% of conversion and  $\mathcal{D} \sim 1.05$  respectively. The second sample was stored in a vial at ambient temperature for ~ 18 h prior to NMR and SEC analysis. Despite the exposure in oxygen and the absence of copper wire from the system, ~57% of conversion was confirmed by NMR while SEC presented a highly dispersed polymer with significant high molecular weight shoulder ( $\mathcal{D} \sim 1.92$ ). This could be attributed to the slow generation of radicals via light and the subsequent free radical polymerisation of DMAEA.<sup>66, 67</sup> However, when the sample was kept in the dark the same phenomenon was observed suggesting continuation of the polymerisation even in the presence of oxygen. We managed to circumvent this by diluting the third and fourth sample with  $\text{CHCl}_3$  and IPA respectively, where analysis of the two samples the following day showed that the low dispersities ( $\mathcal{D} \sim 1.05$ ) and the conversion (~ 42%) were maintained in both cases. This suggests that a side reaction is occurring, probably either an intermolecular or intramolecular substitution, which is slowed down by dilution. ICP-MS analysis was also conducted revealing <1 % of the initial copper content (5.9 ppm) and thus suggesting that copper might be associated to the side reaction, although the mechanism is unknown and out of the scope of our current contribution. Alternatively, TEMPO can be used to end cap the polymer chain end which also resulted in maintaining narrow MWDs (Figure S20, Table S14).<sup>68</sup> It is noted that for the case of IPA, no significant high molecular weight shoulder is observed and there is no further increase in the conversion despite the 4 different ways to store this material. (Table S15).

As termination and purification of these materials can be rather challenging, we would like to provide some guidelines on how to remove the remaining monomer, as well as how to precipitate low molecular weight tailing when the polymerisation of DMAEA is performed in IPA. Once the desired conversion is reached (*e.g.* ~ 40%), the vial/flask should be frozen in liquid nitrogen to ensure the cessation of the polymerisation. The reaction mixture should be subsequently diluted with IPA (if started with 4 mL IPA/DMAEA (50% v/v) add another 4 mL

of IPA) while still keeping the vial in liquid nitrogen. After allowing the polymerisation mixture to thaw, IPA should be removed via flushing with nitrogen (avoid using air instead as this induces hydrolysis, read subsequent section) until the polymer becomes viscous. Precipitation in cold hexane 3 times will ensure the removal of monomer and side-products as evident by the disappearance of all the monomer peaks in  $^1\text{H}$  NMR and the low molecular weight material in SEC, respectively (Table S16 & Figures S21-S23). Please note, the viscous polymer mixture should be added to hexane or vigorous shaking is required in the reverse scenario (addition of hexane to polymer) so to remove all monomer. During the precipitations a small amount of IPA can be used to collect the precipitated polymer which can then be removed by flushing with nitrogen prior to the next precipitation.

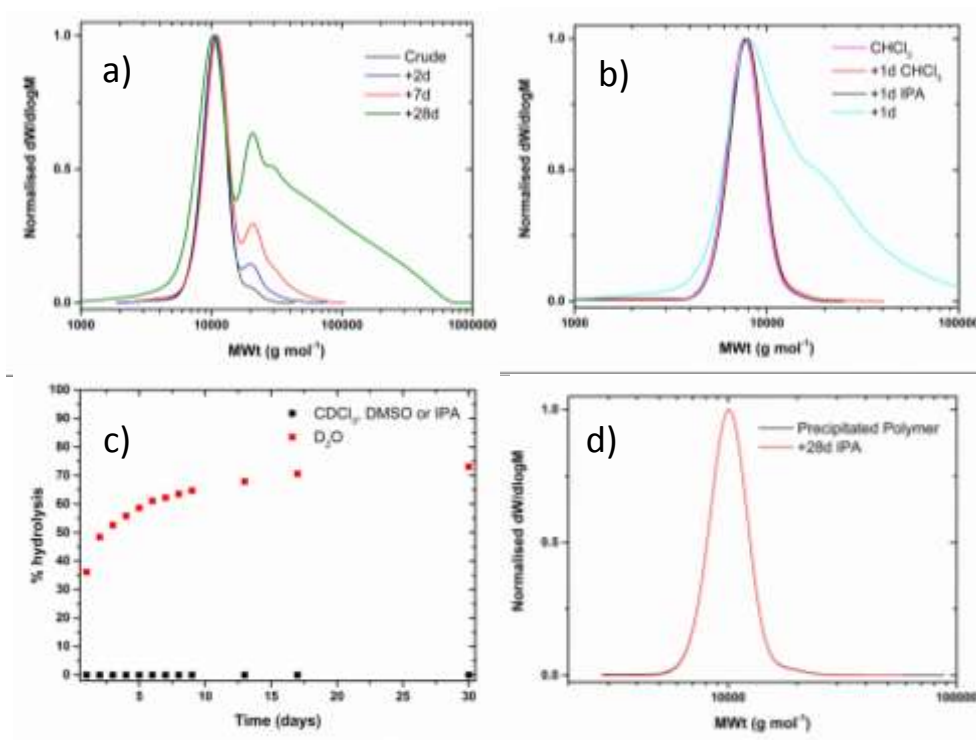


Figure 6: a) Monitoring the reaction via SEC with increasing conversion, b) Diluting the reaction with either  $\text{CHCl}_3$  or IPA demonstrating the elimination of the star-star coupling and c) hydrolysis study in  $\text{CHCl}_3$ , IPA, DMSO and  $\text{H}_2\text{O}$ . d) Storage study of the purified polymer in IPA

### Hydrolysis and storage of PDMAEA stars

As PDMAEA is known to hydrolyse to polyacrylic acid and  $N,N'$ -dimethylaminoethanol, (Scheme S1) the choice of the appropriate polymerisation solvent is crucial. In order to verify this, different solvents were screened to ascertain the degree of hydrolysis of PDMAEA including water, DMSO, IPA, and  $CHCl_3$ . (Figure 6c, Table S17). A PDMAEA of  $M_n \sim 10500 \text{ g mol}^{-1}$  was synthesised in IPA utilising a 4-arm initiator and isolated via purification (as described in previous section, reaction stopped at 48% conversion) with  $\bar{D} \sim 1.04$ . The purified polymer (24 mgs) was subsequently diluted with 0.6 mL of each solvent and the degree of hydrolysis was measured by  $^1H$  NMR. Water revealed a significant amount of hydrolysis after 1 day ( $\sim 36\%$ ). A further increase in the extent of hydrolysis was observed in more prolonged times, albeit with a much slower rate, with 73% hydrolysis after 4 weeks for water. Thus, water is an unsuitable solvent for the polymerisation of DMAEA. On the contrary, DMSO,  $CHCl_3$  and IPA showed no hydrolysis, even after 30 days, which suggests that they are better candidates for the controlled polymerisation of DMAEA. However,  $CHCl_3$  was not selected as the polymerisation solvent due to the potential of this molecule to act as an initiator, in addition to the multi-functional initiator. As such, IPA was chosen as the ideal polymerisation solvent.

Another interesting observation is the challenge in storing such materials. Once precipitated, the purified PDMAEA ( $M_n \sim 10000 \text{ g mol}^{-1}$ ,  $\bar{D} \sim 1.08$ ) was placed in a vial, and sealed with a cap. After 2 days, a small, yet visible, high molecular weight shoulder was evident in the SEC with an observed increase in the dispersity from 1.08 to 1.15. After one week the dispersity was further increased to 1.25 while after 1 month multimodality was dominant revealing broad molecular weight distributions ( $\bar{D} \sim 3.57$ ) (Figure 6a, Table S18). Hence, it is evident that PDMAEA 4-arm stars cannot be efficiently stored in a vial, even when they are kept under a nitrogen atmosphere. As shown earlier during the hydrolysis study, both  $CHCl_3$  and IPA showed negligible, if any, hydrolysis which suggests that both of the solvents could

facilitate the successful safe storage of these materials (Figures 6d & S24 and Tables S19 & S20). In addition to that, both solvents have already demonstrated to efficiently terminate the polymerisation (by dilution as shown in previous section) and eliminate star-star coupling. As such, the purified PDMAEA 4-arm star ( $M_n \sim 10600 \text{ g mol}^{-1}$ ,  $\mathcal{D} \sim 1.06$ ) was stored separately in IPA and  $\text{CHCl}_3$  for one month, after which period both samples were analysed by both NMR and SEC. No sign of hydrolysis could be detected by NMR while neither low nor high molecular weight shoulders could be seen in the SEC chromatogram and the initially low dispersity ( $\mathcal{D} \sim 1.06$ ) was maintained. Therefore, it was shown that both IPA and  $\text{CHCl}_3$  can be used for the effective storage solvents for PDMAEA stars by preventing both termination and side reactions.

## Conclusions

In summary, the synthesis of well-defined PDMAEA stars in a range of molecular weights ( $M_n \sim 5000\text{-}41000 \text{ g mol}^{-1}$ ) was described. Cu(0)-mediated RDRP using Cu(0) wire was successfully employed to control the polymerisation of DMAEA at ambient temperature. DMSO and IPA were investigated as reaction media, showing slightly different findings. The polymerisation in DMSO proceeded under purely homogeneous conditions in a controlled manner up to  $\sim 40\%$  conversion with narrow molecular weight distributions attained ( $\mathcal{D} \sim 1.1$ ). When the polymerisation was left to proceed for longer reaction times, high molecular weight shoulders were observed by SEC and the dispersity increased significantly ( $\mathcal{D} \sim 2$ ). On the contrary, under heterogeneous conditions (IPA) less star-star coupling is observed while a low molecular weight shoulder appears, indicating terminated polymer chains at the earlier stage of the polymerisation, when the conversion exceeds 55%. Nevertheless, when the macroinitiator is isolated up to  $\sim 40\%$  conversion, well defined block copolymers can be obtained ( $\mathcal{D} < 1.19$ ,  $M_n \sim 20000 \text{ g mol}^{-1}$ ), demonstrating that high end group fidelity can be maintained up when moderate conversions are targeted. Crucially, a detailed way of how to

terminate and purify these materials is also presented by immediate dilution of the reaction mixture into either  $\text{CHCl}_3$  or IPA which effectively stops the polymerisation. In addition, the storage of PDMAEA stars in these solvents could also be demonstrated, eliminating hydrolysis and preventing star-star coupling.

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## References

1. Bütün, V.; Armes, S. P.; Billingham, N. C., Selective quaternization of 2-(dimethylamino) ethyl methacrylate residues in tertiary amine methacrylate diblock copolymers. *Macromolecules*, **2001**, 34 (5), 1148-1159.
2. Lee, H.; Son, S. H.; Sharma, R.; Won, Y.-Y., A Discussion of the pH-Dependent Protonation Behaviors of Poly (2-(dimethylamino) ethyl methacrylate)(PDMAEMA) and Poly (ethylenimine-ran-2-ethyl-2-oxazoline)(P (EI-r-EOz)). *J. Phys. Chem. B*, **2011**, 115 (5), 844-860.
3. Truong, N. P.; Quinn, J. F.; Dussert, M. V.; Sousa, N. B.; Whittaker, M. R.; Davis, T. P., Reproducible Access to Tunable Morphologies via the Self-Assembly of an Amphiphilic Diblock Copolymer in Water. *ACS Macro Lett.*, **2015**, 4 (4), 381-386.
4. Akhtar, S.; Hughes, M. D.; Khan, A.; Bibby, M.; Hussain, M.; Nawaz, Q.; Double, J.; Sayyed, P., The delivery of antisense therapeutics. *Adv. Drug. Deliv. Rev.*, **2000**, 44 (1), 3-21.

5. Joo, D. J.; Shin, W. S.; Choi, J.-H.; Choi, S. J.; Kim, M.-C.; Han, M. H.; Ha, T. W.; Kim, Y.-H., Decolorization of reactive dyes using inorganic coagulants and synthetic polymer. *Dyes Pigments*, **2007**, 73 (1), 59-64.
6. Obokata, T.; Yanagisawa, M.; Isogai, A. Characterization of polyamideamine-epichlorohydrin (PAE) resin: Roles of azetidinium groups and molecular mass of PAE in wet strength development of paper prepared with PAE, *J. Appl. Polym. Sci.*, 2005, **97**, 2249.
7. Choi, S. W.; Lee, S. K.; Kim, E. O.; Oh, J. H.; Yoon, K. S.; Parris, N.; Hicks, K. B.; Moreau, R. A., Antioxidant and antimelanogenic activities of polyamine conjugates from corn bran and related hydroxycinnamic acids. *J. Agric. Food Chem.*, **2007**, 55 (10), 3920-3925.
8. Truong, N. P.; Jia, Z.; Burges, M.; McMillan, N. A.; Monteiro, M. J., Self-catalyzed degradation of linear cationic poly (2-dimethylaminoethyl acrylate) in water. *Biomacromolecules*, **2011**, 12 (5), 1876-1882.
9. Tran, N. T.; Truong, N. P.; Gu, W.; Jia, Z.; Cooper, M. A.; Monteiro, M. J., Timed-release polymer nanoparticles. *Biomacromolecules*, **2013**, 14 (2), 495-502.
10. Bian, K.; Cunningham, M. F., Nitroxide-mediated radical polymerization of 2-(dimethylamino) ethyl acrylate and its sequential block copolymerization with styrene and N-butyl acrylate. *J. Polym. Sci. A Polym. Chem.*, **2006**, 44 (1), 414-426.
11. Solomon, D. H.; Rizzardo, E.; Cacioli, P., Polymerization process and polymers produced thereby. Google Patents: 1986.
12. Chiefari, J.; Chong, Y.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. P.; Mayadunne, R. T.; Meijs, G. F.; Moad, C. L.; Moad, G., Living free-radical polymerization by reversible addition-fragmentation chain transfer: the RAFT process. *Macromolecules*, **1998**, 31 (16), 5559-5562.
13. Truong, N. P.; Jia, Z.; Burgess, M.; Payne, L.; McMillan, N. A.; Monteiro, M. J., Self-catalyzed degradable cationic polymer for release of DNA. *Biomacromolecules*, **2011**, 12 (10), 3540-3548.
14. Suchao-in, N.; Chirachanchai, S.; Perrier, S., pH-and thermo-multi-responsive fluorescent micelles from block copolymers via reversible addition fragmentation chain transfer (RAFT) polymerization. *Polymer*, **2009**, 50 (17), 4151-4158.

15. Cotanda, P.; Wright, D. B.; Tyler, M.; O'Reilly, R. K., A comparative study of the stimuli-responsive properties of DMAEA and DMAEMA containing polymers. *J. Polym. Sci. A Polym. Chem.*, **2013**, 51 (16), 3333-3338.
16. Zhao, W.; Fonsny, P.; FitzGerald, P.; Warr, G. G.; Perrier, S., Unexpected behavior of polydimethylsiloxane/poly (2-(dimethylamino) ethyl acrylate)(charged) amphiphilic block copolymers in aqueous solution. *Polym. Chem.*, **2013**, 4 (6), 2140-2150.
17. Tran, N. T.; Jia, Z.; Truong, N. P.; Cooper, M. A.; Monteiro, M. J., Fine tuning the disassembly time of thermoresponsive polymer nanoparticles. *Biomacromolecules*, **2013**, 14 (10), 3463-3471.
18. Lligadas, G.; Percec, V., Synthesis of perfectly bifunctional polyacrylates by single-electron-transfer living radical polymerization. *J. Polym. Sci. A Polym. Chem.*, **2007**, 45 (20), 4684-4695.
19. Dong, H.; Matyjaszewski, K., ARGET ATRP of 2-(dimethylamino) ethyl methacrylate as an intrinsic reducing agent. *Macromolecules*, **2008**, 41 (19), 6868-6870.
20. Zeng, F.; Shen, Y.; Zhu, S., Atom-Transfer Radical Polymerization of 2-(N, N-Dimethylamino) ethyl Acrylate. *Macromol. Rapid Commun.*, **2002**, 23 (18), 1113-1117.
21. Kato, M.; Kamigaito, M.; Sawamoto, M.; Higashimura, T., Polymerization of methyl methacrylate with the carbon tetrachloride/dichlorotris-(triphenylphosphine) ruthenium (II)/methylaluminum bis (2, 6-di-tert-butylphenoxide) initiating system: possibility of living radical polymerization. *Macromolecules*, **1995**, 28 (5), 1721-1723.
22. Wang, J.-S.; Matyjaszewski, K., Controlled/" living" radical polymerization. Atom transfer radical polymerization in the presence of transition-metal complexes. *J. Am. Chem. Soc.*, **1995**, 117 (20), 5614-5615.
23. Feng, C.; Shen, Z.; Li, Y.; Gu, L.; Zhang, Y.; Lu, G.; Huang, X., PNIPAM-b-(PEA-g-PDMAEA) double-hydrophilic graft copolymer: Synthesis and its application for preparation of gold nanoparticles in aqueous media. *J. Polym. Sci. A Polym. Chem.*, **2009**, 47 (7), 1811-1824.
24. Matyjaszewski, K.; Coca, S.; Gaynor, S. G.; Wei, M.; Woodworth, B. E., Zerovalent Metals in Controlled/"Living" Radical Polymerization. *Macromolecules*, **1997**, 30 (23), 7348-7350.



25. Percec, V.; Popov, A. V.; Ramirez-Castillo, E.; Monteiro, M.; Barboiu, B.; Weichold, O.; Asandei, A. D.; Mitchell, C. M., Aqueous room temperature metal-catalyzed living radical polymerization of vinyl chloride. *J. Am. Chem. Soc.*, **2002**, 124 (18), 4940-4941.
26. Percec, V.; Guliashvili, T.; Ladislaw, J. S.; Wistrand, A.; Stjerndahl, A.; Sienkowska, M. J.; Monteiro, M. J.; Sahoo, S., Ultrafast synthesis of ultrahigh molar mass polymers by metal-catalyzed living radical polymerization of acrylates, methacrylates, and vinyl chloride mediated by SET at 25 C. *J. Am. Chem. Soc.*, **2006**, 128 (43), 14156-14165.
27. Samanta, S. R.; Sun, H.-J.; Anastasaki, A.; Haddleton, D. M.; Percec, V., Self-activation and activation of Cu (0) wire for SET-LRP mediated by fluorinated alcohols. *Polym. Chem.*, **2014**, 5 (1), 89-95.
28. Zhang, Q.; Anastasaki, A.; Li, G.-Z.; Haddleton, A. J.; Wilson, P.; Haddleton, D. M., Multiblock sequence-controlled glycopolymers via Cu (0)-LRP following efficient thiol-halogen, thiol-epoxy and CuAAC reactions. *Polym. Chem.*, **2014**, 5 (12), 3876-3883.
29. Basuki, J. S.; Esser, L.; Duong, H. T.; Zhang, Q.; Wilson, P.; Whittaker, M. R.; Haddleton, D. M.; Boyer, C.; Davis, T. P., Magnetic nanoparticles with diblock glycopolymer shells give lectin concentration-dependent MRI signals and selective cell uptake. *Chem. Sci.*, **2014**, 5 (2), 715-726.
30. Nguyen, N. H.; Leng, X.; Percec, V., Synthesis of ultrahigh molar mass poly (2-hydroxyethyl methacrylate) by single-electron transfer living radical polymerization. *Polym. Chem.*, **2013**, 4 (9), 2760-2766.
31. Samanta, S. R.; Anastasaki, A.; Waldron, C.; Haddleton, D. M.; Percec, V., SET-LRP of methacrylates in fluorinated alcohols. *Polym. Chem.*, **2013**, 4 (22), 5563-5569.
32. Zhang, Q.; Wilson, P.; Li, Z.; McHale, R.; Godfrey, J.; Anastasaki, A.; Waldron, C.; Haddleton, D. M., Aqueous copper-mediated living polymerization: exploiting rapid disproportionation of CuBr with Me6TREN. *J. Am. Chem. Soc.*, **2013**, 135 (19), 7355-7363.
33. Jones, G. R.; Li, Z.; Anastasaki, A.; Lloyd, D. J.; Wilson, P.; Zhang, Q.; Haddleton, D. M., Rapid Synthesis of Well-Defined Polyacrylamide by Aqueous Cu (0)-Mediated Reversible-Deactivation Radical Polymerization. *Macromolecules*, **2016**, 49 (2), 483-489.
34. Aksakal, R.; Resmini, M.; Becer, C. R., Pentablock star shaped polymers in less than 90 minutes via aqueous SET-LRP. *Polym. Chem.*, **2016**, 7 (1), 171-175.

35. Rosen, B. M.; Percec, V., Single-electron transfer and single-electron transfer degenerative chain transfer living radical polymerization. *Chem. Rev.*, **2009**, 109 (11), 5069-5119.
36. Anastasaki, A.; Nikolaou, V.; Nurumbetov, G.; Wilson, P.; Kempe, K.; Quinn, J. F.; Davis, T. P.; Whittaker, M. R.; Haddleton, D. M., Cu (0)-mediated living radical polymerization: a versatile tool for materials synthesis. *Chem. Rev.*, **2015**, 116 (3), 835-877.
37. Anastasaki, A.; Waldron, C.; Wilson, P.; Boyer, C.; Zetterlund, P. B.; Whittaker, M. R.; Haddleton, D., High molecular weight block copolymers by sequential monomer addition via Cu (0)-mediated living radical polymerization (SET-LRP): An optimized approach. *ACS Macro Lett.*, **2013**, 2 (10), 896-900.
38. Wang, Y.; Zhong, M.; Zhu, W.; Peng, C.-H.; Zhang, Y.; Konkolewicz, D.; Bartolomei, N.; Isse, A. A.; Gennaro, A.; Matyjaszewski, K., Reversible-deactivation radical polymerization in the presence of metallic copper. Comproportionation–disproportionation equilibria and kinetics. *Macromolecules*, **2013**, 46 (10), 3793– 3802.
39. Peng, C. H.; Zhong, M.; Wang, Y.; Kwak, Y.; Zhang, Y.; Zhu, W.; Tonge, M.; Buback, J.; Park, S.; Krys, P.; Konkolewicz, D.; Gennaro, A.; Matyjaszewski, K., Reversible-Deactivation Radical Polymerization in the Presence of Metallic Copper. Activation of Alkyl Halides by Cu<sup>0</sup>. *Macromolecules*, **2013**, 46 (10), 3803– 3815.
40. Konkolewicz, D.; Wang, Y.; Zhong, M.; Krys, P.; Isse, A. A.; Gennaro, A.; Matyjaszewski, K., Reversible-deactivation radical polymerization in the presence of metallic copper. A critical assessment of the SARA ATRP and SET-LRP mechanisms. *Macromolecules*, **2013**, 46 (22), 8749– 8772.
41. Alsubaie, F.; Anastasaki, A.; Nikolaou, V.; Simula, A.; Nurumbetov, G.; Wilson, P.; Kempe, K.; Haddleton, D. M., Investigating the Mechanism of Copper(0)-Mediated Living Radical Polymerization in Organic Media. *Macromolecules* **2015**, 48, 5517– 5525.
42. Konkolewicz, D.; Wang, Y.; Krys, P.; Zhong, M.; Isse, A. A.; Gennaro, A.; Matyjaszewski, K., SARA ATRP or SET-LRP. End of controversy? *Polym. Chem.* **2014**, 5, 4396– 4417
43. Truong, N. P.; Gu, W.; Prasad, I.; Jia, Z.; Crawford, R.; Xiao, Y.; Monteiro, M. J., An influenza virus-inspired polymer system for the timed release of siRNA. *Nat. Commun.*, **2013**, 4, 1902.

44. Nguyen, N. H.; Percec, V., Dramatic acceleration of SET-LRP of methyl acrylate during catalysis with activated Cu (0) wire. *J. Polym. Sci. A Polym. Chem.*, **2010**, 48 (22), 5109-5119.
45. Nguyen, N. H.; Rosen, B. M.; Lligadas, G.; Percec, V., Surface-dependent kinetics of Cu (0)-wire-catalyzed single-electron transfer living radical polymerization of methyl acrylate in DMSO at 25 C. *Macromolecules*, **2009**, 42 (7), 2379-2386.
46. Herfurth, C.; de Molina, P. M.; Wieland, C.; Rogers, S.; Gradzielski, M.; Laschewsky, A., One-step RAFT synthesis of well-defined amphiphilic star polymers and their self-assembly in aqueous solution. *Polym. Chem.*, **2012**, 3 (6), 1606-1617.
47. Wu, W.; Wang, W.; Li, J., Star polymers: Advances in biomedical applications. *Prog. Polym. Sci.*, **2015**, 46, 55-85.
48. Khanna, K.; Varshney, S.; Kakkar, A., Miktoarm star polymers: advances in synthesis, self-assembly, and applications. *Polym. Chem.*, **2010**, 1 (8), 1171-1185.
49. Gao, H.; Matyjaszewski, K., Synthesis of functional polymers with controlled architecture by CRP of monomers in the presence of cross-linkers: from stars to gels. *Prog. Polym. Sci.*, **2009**, 34 (4), 317-350.
50. Voit, B. I.; Lederer, A., Hyperbranched and Highly Branched Polymer Architectures □ Synthetic Strategies and Major Characterization Aspects. *Chem. Rev.*, **2009**, 109 (11), 5924-5973.
51. Hirao, A.; Hayashi, M.; Loykulant, S.; Sugiyama, K.; Ryu, S. W.; Haraguchi, N.; Matsuo, A.; Higashihara, T., Precise syntheses of chain-multi-functionalized polymers, star-branched polymers, star-linear block polymers, densely branched polymers, and dendritic branched polymers based on iterative approach using functionalized 1, 1-diphenylethylene derivatives. *Prog. Polym. Sci.*, **2005**, 30 (2), 111-182.
52. Barner-Kowollik, C.; Davis, T. P.; Stenzel, M. H., Synthesis of star polymers using RAFT polymerization: what is possible? *Aust. J. Chem.*, **2006**, 59 (10), 719-727.
53. Nyström, F.; Soeriyadi, A. H.; Boyer, C.; Zetterlund, P. B.; Whittaker, M. R., End-group fidelity of copper (0)-mediated radical polymerization at high monomer conversion: an ESI-MS investigation. *J. Polym. Sci. A Polym. Chem.*, **2011**, 49 (24), 5313-5321.
54. Soeriyadi, A. H.; Boyer, C.; Nyström, F.; Zetterlund, P. B.; Whittaker, M. R., High-order multiblock copolymers via iterative Cu (0)-mediated radical polymerizations (SET-LRP):

toward biological precision. *J. Am. Chem. Soc.*, **2011**, 133 (29), 11128-11131.55. Boyer, C.; Derveaux, A.; Zetterlund, P. B.; Whittaker, M. R., Synthesis of multi-block copolymer stars using a simple iterative Cu (0)-mediated radical polymerization technique. *Polym. Chem.*, **2012**, 3 (1), 117-123.

56. Waldron, C.; Anastasaki, A.; McHale, R.; Wilson, P.; Li, Z.; Smith, T.; Haddleton, D. M., Copper-mediated living radical polymerization (SET-LRP) of lipophilic monomers from multi-functional initiators: reducing star–star coupling at high molecular weights and high monomer conversions. *Polym. Chem.*, **2014**, 5 (3), 892-898.

57. Whittaker, M. R.; Urbani, C. N.; Monteiro, M. J., Synthesis of linear and 4-arm star block copolymers of poly (methyl acrylate-*b*-solketal acrylate) by SET-LRP at 25° C. . *J. Polym. Sci. A Polym. Chem.*, **2008**, 46 (18), 6346-6357.

58. Limer, A. J.; Rullay, A. K.; San Miguel, V.; Peinado, C.; Keely, S.; Fitzpatrick, E.; Carrington, S. D.; Brayden, D.; Haddleton, D. M., Fluorescently tagged star polymers by living radical polymerisation for mucoadhesion and bioadhesion. *React. Funct. Polym.*, **2006**, 66 (1), 51-64.

59. Jones, M.-C.; Ranger, M.; Leroux, J.-C., pH-sensitive unimolecular polymeric micelles: synthesis of a novel drug carrier. *Bioconjugate Chem.*, **2003**, 14 (4), 774-781.

60. Jiang, X.; Rosen, B. M.; Percec, V., Mimicking “nascent” Cu (0) mediated SET-LRP of methyl acrylate in DMSO leads to complete conversion in several minutes. *J. Polym. Sci. A Polym. Chem.*, **2010**, 48 (2), 403-409.

61. Lligadas, G.; Rosen, B. M.; Bell, C. A.; Monteiro, M. J.; Percec, V., Effect of Cu (0) particle size on the kinetics of SET-LRP in DMSO and Cu-mediated radical polymerization in MeCN at 25 C. *Macromolecules*, **2008**, 41 (22), 8365-8371.

62. Daoud, M.; Cotton, J., Star shaped polymers: a model for the conformation and its concentration dependence. *J. Phys.*, **1982**, 43 (3), 531-538;

63. Stenzel-Rosenbaum, M. H.; Davis, T. P.; Chen, V.; Fane, A. G., Synthesis of poly (styrene) star polymers grown from sucrose, glucose, and cyclodextrin cores via living radical polymerization mediated by a half-metallocene iron carbonyl complex. *Macromolecules*, **2001**, 34 (16), 5433-5438.

64. Ohno, K.; Wong, B.; Haddleton, D. M., Synthesis of well-defined cyclodextrin-core star polymers. *J. Polym. Sci. A Polym. Chem.*, **2001**, 39 (13), 2206-2214.
65. Bories-Azeau, X.; Armes, S. P., Unexpected transesterification of tertiary amine methacrylates during methanolic ATRP at ambient temperature: a cautionary tale. *Macromolecules*, **2002**, 35 (27), 10241-10243.
66. Anastasaki, A.; Nikolaou, V.; Zhang, Q.; Burns, J.; Samanta, S. R.; Waldron, C.; Haddleton, A. J.; McHale, R.; Fox, D.; Percec, V., Copper (II)/tertiary amine synergy in photoinduced living radical polymerization: Accelerated synthesis of  $\omega$ -functional and  $\alpha$ ,  $\omega$ -heterofunctional poly (acrylates). *J. Am. Chem. Soc.*, **2014**, 136 (3), 1141-1149.
67. Frick, E.; Anastasaki, A.; Haddleton, D. M.; Barner-Kowollik, C., Enlightening the mechanism of copper mediated photoRDRP via high-resolution mass spectrometry. *J. Am. Chem. Soc.*, **2015**, 137 (21), 6889-6896.
68. Bon, S. A.; Steward, A. G.; Haddleton, D. M., Modification of the  $\omega$ -bromo end group of poly (methacrylate) s prepared by copper (I)-mediated living radical polymerization. *J. Polym. Sci. A Polym. Chem.*, **2000**, 38 (15), 2678-2686.