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Improvement of the Control over SARA ATRP of 2-(Diisopropylamino)ethyl Methacrylate by Slow and Continuous Addition of Sodium Dithionite

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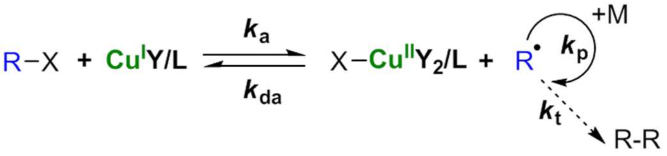
The kinetics and detailed mechanism of SARA ATRP of 2-(diisopropylamino)ethyl methacrylate (DPA) were investigated. Supplemental activator and reducing agent (SARA) atom transfer radical polymerization (ATRP) using sodium dithionite (Na2S2O4) was used to create well controlled polymers of PDPA. The influence of the initiator, solvent, structure and concentration of the catalyst, and the ratios of Na2S2O4 were adjusted to optimize the polymerization. Well controlled polymers required Na2S2O4 to be slowly and continuously fed to the reaction mixture, with 500 parts per million (ppm) of CuBr2 with tris(2-dimethyamino)amine (Me6TREN) as a ligand. The initial content of Na2S2O4 in the reaction mixture, the feeding rate and Cu catalyst concentration were optimized to provide polymers with narrow molecular weight distribution (Mw/Mn < 1.15) at high monomer conversion (~90%). Interestingly, the results revealed that when tris(2-pyridylmethyl)-amine (TPMA) was used as a ligand, the amount of copper required to achieve similar control of the polymerization could be decreased 5 times. This system was successfully extended to the polymerization of oligo(ethylene oxide) methyl ether methacrylate (OEOMA). The high conversion and preservation of the chain-end functionality allows the direct synthesis of POEOMA-b-PDPA block copolymers. The low catalyst concentrations and benign nature of the Na2S2O4 make this SARA ATRP method attractive for the synthesis of well controlled water soluble polymers for biomedical applications.

The synthesis of well-defined polymers, with predefined molecular weights (MW), narrow MW distributions, controlled composition and complex architectures is possible through reversible deactivation radical polymerization (RDRP) methods.[1, 2] Among the RDRP techniques reported in the literature, ATRP is one of the most robust and versatile methods to polymerize a wide range of monomers under mild reaction conditions.[3-6] In ATRP an alkyl halide is activated by a transition metal catalyst in a low oxidation state, typically Cu^I/L, to generate the corresponding radical and transition metal complex in its higher oxidation state, typically X-Cu^{II}/L (Scheme 1).[7] The radical propagates by adding monomer units until it is deactivated to the corresponding dormant alkyl halide by the transition metal complex in its higher oxidation state.[2] This dynamic equilibrium between propagating radicals and alkyl halides as dormant species ensures that the majority of chains grow at the same rate.[3, 8]



Scheme 1 General mechanism of copper catalyzed ATRP.

One limitation of traditional ATRP methods is that they require catalyst concentrations greater than 1000 parts per million (ppm) to maintain an acceptable rate of polymerization. [3]
The high catalyst loading leads to a significant contamination of the resulting polymer with often highly colored and toxic transition metal complexes. The high catalyst concentrations combined with the use of organic solvents makes traditional ATRP environmentally challenging. Over the last decade, several strategies have been developed to make ATRP more eco-friendly.[9] These strategies aim to decrease the amount of catalyst required, and to use green solvents such as water or alcohols. Several variations of the initial ATRP concept have been proposed to diminish the concentration of Cu needed in the reaction. In all cases the activator complex, namely Cu^I, is regenerated through a relatively slow reaction which compensates for termination events. Activator regeneration can be achieved by directly reducing the excess Cu^{II} as in activators regenerated by electron transfer (ARGET) ATRP,[10] using a continuous supply of radicals from the decomposition of a radical initiator as in initiator for continuous activator regeneration (ICAR) ATRP.[11] Other methods for ATRP with low catalyst concentrations include electrochemical reduction of Cu(II), photochemical activator regeneration, and an interesting system called supplemental activator and reducing

agent (SARA) ATRP.[12-14] SARA ATRP uses either sulfites or zerovalent transition metals (e.g Cu(0), Fe(0), Zn (0) or Mg (0)) to activate alkyl halides directly and to reduce excess Cu^{II} to Cu^{I} to compensate for radical termination.[15-18]

Inorganic sulfites, especially sodium dithionite ($Na_2S_2O_4$) have been reported as particularly effective additives in SARA ATRP[19, 20] and single electron transfer-degenerative chain transfer mediated living radical polymerization SET-DTLRP.[21-27] Sulfites are very efficient reducing agents for Cu^{II} species. In our previous work[28] SARA ATRP was described for the first time for the homopolymerization of the pH responsive poly(2-(diisopropylamino)ethyl methacrylate) (PDPA). Although the average MW in the original system was controlled, narrow MW distributions were not achieved, with M_w/M_n exceeding 1.2.

PDPA is a pH-responsive polymer with a pKa around 6.2[29, 30] typically used in biomedical applications.[31-36] PDPA-based copolymers have been widely used in the preparation of smart nanostructures for the controlled release of small molecules[33, 36, 37] complexation and delivery of genetic material,[38] specific targeting,[32, 34] or magnetic resonance imaging (MRI) contrast agents.[39]

These specific applications require narrow MW distributions, and the polymers should be synthesized with the lowest possible copper catalyst concentration, to facilitate purification after polymerization. In this paper, SARA ATRP with $Na_2S_2O_4$ was used to polymerize DPA in a mixture of isopropanol (IPA)/water at 40 °C. Several reaction parameters were optimized to give well-defined polymers with low copper concentrations. The method was extended to polymerize oligo(ethylene oxide) methyl ether methacrylate (OEOMA) and to prepare OEOMA-DPA block copolymers.

Experimental

Materials

2-(Diisopropylamino)ethyl methacrylate (DPA, 97%, Scientific Polymer Products Inc.), oligo(ethylene oxide) methyl ether methacrylate (OEOMA, 99%, average molecular weight 475, Aldrich) and 2-(dimethylamino)ethyl methacrylate (DMAEMA, 98%, Aldrich) were passed over a column of basic alumina to remove inhibitor prior to use. Sodium dithionite ($Na_2S_2O_4$, 85%, ACROS Organics), copper(II) bromide ($Cu^{II}Br_2$, 99.999%, Aldrich), ethyl α-bromophenyl acetate (EBPA, 97%, Alfa Aesar), water (HPLC grade, Fisher Scientific), isopropanol (IPA, ACS grade, Fisher Scientific), tetrahydrofuran (THF, ACS grade, Fisher Scientific), *tert*-butanol (≥ 99.5%, Sigma-aldrich), ethanol (95%, Pharmco-AAPER), diphenyl ether (≥ 99%,Aldrich), deuterated chloroform ($CDCl_3$) (99.8%, Cambridge Isotope Laboratories), anhydrous magnesium sulphate (99%, Aldrich) were used as received. Tris(2-(dimethylamino)ethyl)amine (Me_6TREN)[40] and tris(pyridin-2-ylmethyl)amine (TPMA) were synthesized as reported in the literature[41, 42].

Methods

A KDS Scientific, Legato 101 syringe pump was used for continuous feeding polymerizations. Monomer conversion was measured using ^1H NMR spectroscopy in $CDCl_3$ using a Bruker Avance 500 MHz spectrometer at room temperature. The number-average MW ($M_{n,GPC}$) and dispersity, ($Đ$) (M_w/M_n) of the synthesized polymers were determined by gel permeation chromatography (GPC). The GPC system used a Waters 515 HPLC pump and a Waters 2414 refractive index detector using PSS columns (Styrogel 10^2, 10^3, 10^5 Å) with tetrahydrofuran (THF) containing 10 mM $LiTf_2N$ and 10 mM 1-butylimidazole as the eluent, at a flow rate of 1 mL/min at 35 °C [43]. The GPC samples were prepared in THF with diphenyl ether as the internal standard.

Procedures

Typical procedure for the SARA ATRP of DPA. A mixture of $CuBr_2$ (1.05 mg, 4.70 μmol), Me_6TREN (2.16 mg, 9.40 μmol) and water (83μL) was placed in a Schlenk tube reactor that was sealed by using a rubber septa. $Na_2S_2O_4$ (1.92 mg, 9.40 μmol) and a mixture of DPA (1.00 g, 4.70 mmol) and EBPA (11.40 mg, 47.00 μmol) in IPA (3.17 mL) (previously bubbled with nitrogen for about 15 minutes) was added to the reactor and frozen in liquid nitrogen. The reaction mixture was deoxygenated by three freeze-pump-thaw cycles and purged with nitrogen. The Schlenk tube was placed in an oil bath at 40 °C with stirring (600 rpm). An aqueous solution of $Na_2S_2O_4$ (34.3 mM) (previous purged with nitrogen) was continuously injected into the reaction medium using a syringe pump at a rate of 116 nL/min (19.4 nmol/min). Samples were periodically withdrawn from the reaction mixture and analyzed by GPC and ^1H NMR.

Typical procedure for the SARA ATRP of OEOMA. The procedures for the SARA ATRP of OEOMA using $Na_2S_2O_4$ were similar to the DPA, but the monomer concentration was adjusted to 18% (w/w). A mixture of $CuBr_2$ (1.7 mg, 7.7 μmol), Me_6TREN (3.5 mg, 15.4 μmol) and water (125 μL) was placed in a Schlenk tube that was sealed by using a rubber septa. $Na_2S_2O_4$ (3.1 mg, 15.4 μmol) and a mixture of $OEOMA_{475}$ (1.01 g, 2.31 mmol) and EBPA (18.69 mg, 76.9 μmol) in IPA (4.74 mL) (previously bubbled with nitrogen for about 15 minutes) was added to the reactor and frozen in liquid nitrogen. The reaction mixture was deoxygenated by three freeze-pump-thaw cycles and purged with nitrogen. The additional $Na_2S_2O_4$ aqueous solution (125 μL, 37.8mM) was slowly feed into the reaction mixture using a syringe pump at a feed rate 87 nL/min (16.1nmol/min). Samples were periodically withdrawn from the reaction mixture and analyzed by GPC and ^1H NMR.

Synthesis of a POEOMA-*b*-PDPA Block Copolymer. A mixture of $CuBr_2$ (2.58 mg, 11.5 μmol), Me_6TREN (5.31 mg, 23.1 μmol) and water (125μL) was placed in a Schlenk tube reactor that was sealed by using a rubber septa. $Na_2S_2O_4$ (4.72 mg, 23.1 μmol) and a mixture of OEOMA (1.01 g, 2.31 mmol) and EBPA (28.03 mg, 0.12 mmol) in IPA (4.74 mL) (previously bubbled with nitrogen for about 15 minutes) was added to the reactor and frozen in liquid nitrogen. The reaction mixture was deoxygenated by three freeze-pump-thaw cycles and purged with nitrogen. The additional $Na_2S_2O_4$ aqueous solution (125 μL, 37.8mM) was slow feed into the reaction mixture using a syringe pump at a feed rate 87 nL/min

(16.1nmol/min). The polymerization proceeded for 12h at 25 °C (87% conversion, $M_{n,th}$= 8.570 x10^{-3} gmol^{-1}, $M_{n,GPC}$= 11.75 x 10^{-3} gmol^{-1}, M_w/M_n = 1.18). After that, the DPA (1.23 g, 5.76 mmol), previously bubbled with nitrogen for about 15 minutes, was added and allowed to polymerize for 12h.

Results and Discussion

The use of $Na_2S_2O_4$ in SARA ATRP of DPA was recently reported[28]. $Na_2S_2O_4$ acts as a powerful reducing agent for X-Cu^{II}/L species allowing efficient regeneration of Cu^I/L species, as well as generating radicals by its role as a supplemental activator. For the homopolymerization of DPA, unless otherwise specified, all the reactions were performed at 40 °C, using a monomer to solvent ratio 1/3 (v/v) and a solvent mixture of IPA/water of [95/5 (v/v)]. In the following sections the effects of various reaction parameters are investigated to determine the most suitable conditions for the polymerization.

Influence of the initiator structure and concentration

One of the most important factors to consider in ATRP is matching the initiator and monomer structures. Two different ATRP initiators were evaluated for the SARA ATRP of DPA using $Na_2S_2O_4$, with α-bromophenyl acetate (EBPA) being more active than ethyl 2-bromoisobutyrate (EBiB)[44] (Fig. 1). Therefore, the initiation was expected to be more efficient with EBPA than with EBiB. The reaction conditions used for kinetics in Fig. 1(a) are the same for both EBPA and EBiB, because $Na_2S_2O_4$ most probably generates carbon centered radicals rapidly from the initiator species (as a supplemental activator to Cu(I) species). As a result, the rate of polymerization is controlled by the rate of activator regeneration[15]. Although EBPA is a more active initiator than EBiB, both systems showed good agreement with the theoretical MW with M_w/M_n values between 1.25 and 1.3. The evolution of well controlled MW distributions for the EBPA initiated polymerization is confirmed in Fig. 1(c). As expected, by decreasing the initiator concentration, the M_n measured by GPC increases (supporting information, Fig. S1, effect of target DP on the SARA ATRP of DPA). At lower alkyl halide concentration, radical concentration is also lower and hence polymerization slows down.

Effect of the solvent mixture

Previously, it was shown that for SARA ATRP of DPA with $Na_2S_2O_4$, the water content in the solvent mixture should be kept at 5% (v/v)[28]. Here, IPA, ethanol and *tert*-butanol were examined as solvents for the polymerization of DPA with 5 % water mixtures. As seen in Fig. 2(a) and Fig. 2(c), the rate of polymerization is the same in all three solvents. Fig. 2(b) and Fig. 2(d) indicate that the evolution of M_n is similar in all three cases, regardless of the initiator used. While ethanol and IPA gave similar control over the polymer's MW, and M_w/M_n values in the order of 1.3-1.4 (Fig. 2(b)), *tert*-butanol gave molecular weights above the theoretical line and M_w/M_n values greater than 2 (Fig. 2(d)). This fact could be related with the decrease of solubility of the resultant PDPA in the polymerization mixture for tert-butanol, since the polymer partially precipitates at high monomer conversions. In the remainder part of this work, IPA was used as the solvent.

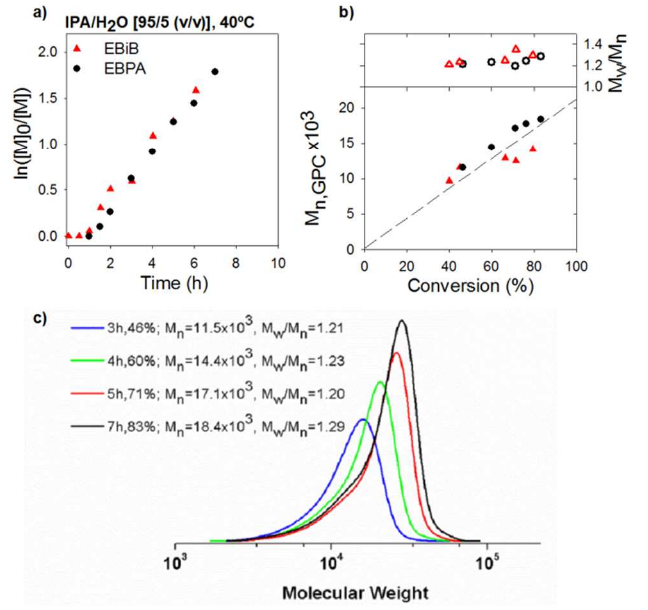


Fig. 1 Effect of the ATRP initiator on the SARA ATRP of DPA in IPA/water = 95/5 (v/v) at 40 °C. (a) First-order kinetic plot, (b) evolution of MW and M_w/M_n with conversion (the dashed line represents theoretical MW at a given conversion, and (c) GPC traces with conversion for the reaction with EBPA. Reaction conditions: $[DPA]_0/[initiator]_0/[Na_2S_2O_4]_0/[CuBr_2]_0/[Me_6TREN]_0$=100/1/0.5/0.1/0.1 (molar).

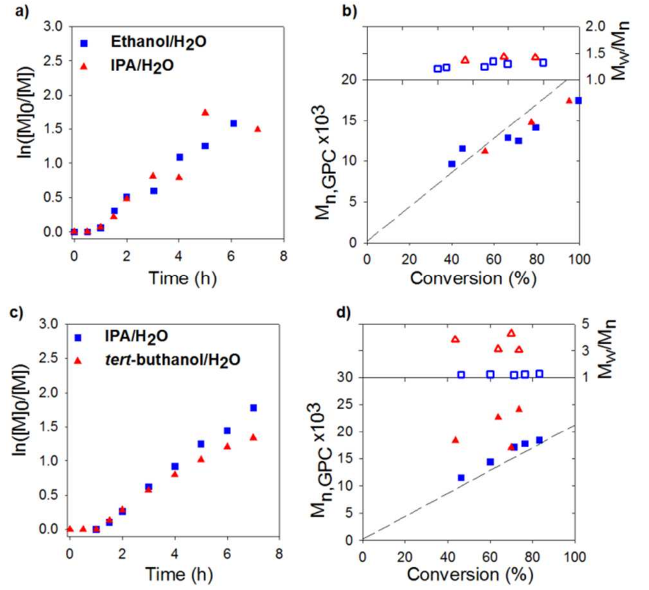


Fig. 2. Effect of solvent mixture in the SARA ATRP of DPA, IPA/water = 95/5 (v/v), ethanol/water = 95/5 (v/v) and *tert*-butanol/water = 95/5 (v/v) at 40 °C. (a,c) First-order kinetic plot, (b,d) evolution of MW and M_w/M_n with conversion (the dashed line represents theoretical MW at a given conversion). Reaction conditions: $[DPA]_0/[EBiB]_0/[Na_2S_2O_4]_0/[CuBr_2]_0/[Me_6TREN]_0$=100/1/0.5/0.1/0.1 (molar) (a,b); $[DPA]_0/[EBPA]_0/[Na_2S_2O_4]_0/[CuBr_2]_0/[Me_6TREN]_0$ =100/1/0.5/0.1/0.1 (molar) (c,d).

Effect of the initial concentration of $Na_2S_2O_4$

In the literature, the reported SARA reactions were performed by adding the total amount of the $Na_2S_2O_4$ at the beginning of the reaction, with the molar ratio initiator/$Na_2S_2O_4$ = 1/1.[19, 20, 28] However, such higher concentrations of the $Na_2S_2O_4$ salt can lead to very high rate of activator (re)generation and to accelerated termination reactions, leading to a significant decrease in the end-group functionality. Therefore it is essential to choose a $Na_2S_2O_4$ concentration in the reaction system that provides a sufficiently fast rate of activator (re)generation that the polymerization occurs in a reasonable time frame, without being too fast, as the high radical concentration could lead to a significant loss of end group functionality. Several reactions were performed in which the concentration of reducing agent in the polymerization mixture was varied from 0.3 to 1 equivalents to the alkyl halide (Fig. 3). The decrease of concentration of $Na_2S_2O_4$ from 1 to 0.5, led to similar polymerization rate, MW and M_w/M_n. This observation suggests that above a certain concentration, adding more of the dithionite salt does not contribute to increase the polymerization rate. One possibility is that the $Na_2S_2O_4$ salt is only partially soluble in the reaction mixture, and therefore increasing the amount added above the saturation concentration leads to minimal improvement in the rate of reaction. A possible explanation for the very slow rate of reaction with 0.3 equivalents of $Na_2S_2O_4$ to alkyl halide is that a large fraction of the $Na_2S_2O_4$ is consumed reducing Cu^{II} to Cu^I, implying that there is only a small amount left to maintain the SARA ATRP reaction. In fact, the polymerization only starts after 6 hours and the monomer reaches 50% of conversion after 24h ($M_{n,GPC}$ = 8,300 g/mol; M_w/M_n=1.4) (supporting information, Fig. S2). However, using 0.3 to 1 equivalent of $Na_2S_2O_4$ leads to similar control over the MW and M_w/M_n.

Feeding of $Na_2S_2O_4$

$Na_2S_2O_4$ is a powerful reducing agent that quickly converts Cu^{II} to Cu^I species[19]. However, due to the poor solubility of $Na_2S_2O_4$ in alcohols, the water content in the system could be a key factor when considering the SARA ATRP of DPA using $Na_2S_2O_4$. In water, the $Na_2S_2O_4$ forms Na^+ and $S_2O_4^{2-}$ and the dissociation of the $S_2O_4^{2-}$ will form two molecules of the $SO_2^{-\bullet}$ radical anion (scheme 2)[45]. A higher fraction of water in the system promotes the efficient dissolution of the dithionite salt and consequently its dissociation into $SO_2^{-\bullet}$.[20, 28] It is important to note that the dissociation constant of $S_2O_4^{2-}$ in water is very small, $K_d \sim 10^{-6}$ mM[45, 46] but it increases with the decreasing of polarity of the solvent.[47] Nevertheless, the data in Fig. 4 suggest that the limited solubility of $Na_2S_2O_4$ in the reaction mixture has a great influence on the polymerization rate perhaps greater than the dissociation of the $S_2O_4^{2-}$. The data in Fig. 4 suggest that the formation of $SO_2^{-\bullet}$ is very rapidly followed by the radical anion acting as a supplemental activator and reducing agent.

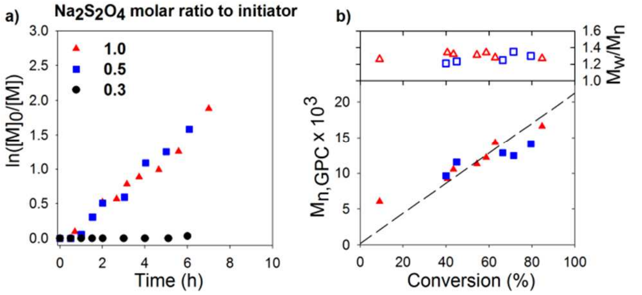


Fig. 3 Effect of the ratio of $Na_2S_2O_4$ on the SARA ATRP of DPA in IPA/water = 95/5 (v/v) at 40 °C. (A) First-order kinetic plot, (B) evolution of MW and M_w/M_n with conversion (the dashed line represents theoretical MW at a given conversion). Reaction conditions: $[DPA]_0/[EBiB]_0/[Na_2S_2O_4]_0/[CuBr_2]_0/[Me_6TREN]_0$=100/1/$Na_2S_2O_4$/0.1/0.1 (molar).

$$Na_2S_2O_4 \rightleftharpoons 2Na^+ + S_2O_4^{2-} \rightleftharpoons 2Na^+ + 2SO_2^{-\bullet}$$

Scheme 2. Scheme of the sodium dithonite decomposition.

Even though the preliminary results showed that a SARA ATRP of DPA proceeded in a controlled manner, adding all of $Na_2S_2O_4$ at the beginning of the reaction could produce high radical concentrations in the early phase of the reaction, possible leading to undesired termination reactions. This effect is mostly visible in the polymer GPC traces, with a prominent low MW tail (Fig. 1(c)). We envisaged a solution for this issue by adding small amounts of reducing agent over an extended period of time to maintain its relatively low concentration over the whole polymerization.

In an attempt to understand the significance of the feeding on the control over SARA ATRP of DPA using $Na_2S_2O_4$, the reactions were performed with different feeding rates at which an aqueous solution of $Na_2S_2O_4$ was fed into the system. Several feeding rates of the $Na_2S_2O_4$ aqueous solution ($FR_{Na2S2O4}$) and initial concentrations of the salt in the solvent mixture ($IR_{Na2S2O4}$) were tested. In all experiments the reaction started with 2.5% (v/v) of water in the polymerization mixture and the feeding was conducted so that the final water content in the polymerization mixture was 5% (v/v). The feeding was stopped when the total molar ratio of $Na_2S_2O_4$ added in the solution reached 0.5 molar (molar ratio to initiator), which is the same ratio as in well-controlled experiments without feeding, using one single $Na_2S_2O_4$ addition.

The reaction was very slow in experiments where the initial concentration of $Na_2S_2O_4$ was zero, and $Na_2S_2O_4$ fed at a rate of $FR_{Na2S2O4}$ = 39.1 nmol/min (139 nL/min) was the only source of dithionite salts, with an induction period of 5 hours (supporting information, Fig. S3). The reaction only started when the concentration of the $Na_2S_2O_4$ in the solution mixture reached a 0.25 molar ratio to initiator, which corresponds to 50% of the total amount of $Na_2S_2O_4$ added. After this point the polymerization proceeded rapidly, reaching within 5 hours 60% conversion. The GPC data also show that this polymerization with feeding of $Na_2S_2O_4$ gives similar control over the M_n and M_w/M_n values as experiments without feeding, with good agreement between theoretical and experimental MW and M_w/M_n =1.2-1.25.

To further investigate the effect of feeding $Na_2S_2O_4$ the initial concentration of $Na_2S_2O_4$ in the polymerization mixture was established 50% of the total $Na_2S_2O_4$ (0.25 molar ratio to initiator) and the feeding rate of the $Na_2S_2O_4$ solution was varied from 8 to 33nmol/min. To ensure that the same amount of $Na_2S_2O_4$ was added to the reaction mixture these feeding rates correspond to 6 to 24h reactions times (Fig. 4).

Fig. 4(a) indicates that the lower feeding rates led to a decrease in the polymerization rate. The reaction with $FR_{Na2S2O4}$=33 nmol/min has one hour of induction period and reached a conversion of 80% after 5 hours. Slowing the $FR_{Na2S2O4}$ to 16 nmol and 8 nmol/min increased the induction period to 3 h. After 12h reaction, the reaction with $FR_{Na2S2O4}$=16 nmol/min reached 92% conversion. For the reaction with $FR_{Na2S2O4}$=8 nmol/min after 12h reaction, the monomer conversion was 77%. This is expected based on the fact that the SARA reactions of the dithionite species control the rate of reaction. In all cases Fig. 4 (b) shows good agreement between the theoretical M_n and the $M_{n,GPC}$, and M_w/M_n values in between 1.15 and 1.4. Although reducing the rate at which $Na_2S_2O_4$ is fed into the system decreased the polymerization rate, the control over the polymerization improved, as measured the M_w/M_n values. In particular, going from a $FR_{Na2S2O4}$ = 33 nmol/min to $FR_{Na2S2O4}$ = 16 nmol/min the dispersities dropped from approximately 1.4 for the system with $FR_{Na2S2O4}$ = 33 nmol/min to 1.2-1.3 for the system with $FR_{Na2S2O4}$ = 16 nmol/min. Interestingly, Fig. 4 (b), shows that the reaction with $FR_{Na2S2O4}$=8 nmol/min demonstrated no increase in the M_w/M_n values at higher monomer conversions which could be due to the smaller influence of termination reactions in this system, although the $M_{n,GPC}$ values are slightly below the theoretical ones. In subsequent studies, the initial concentration of $Na_2S_2O_4$ in the polymerization mixture was then reduced to 40% of the total $Na_2S_2O_4$ added (0.2 molar ratio to initiator) and two feeding rates were evaluated (39.0 and 19.4 nmol/min) that corresponds to 6 and 12 hour feeding times. The kinetics is presented in Fig. 5(a). Both reactions had a 2 hour induction period, and as expected, the polymerization rate decreased with the slower feeding rate. Fig. 5(b) presents the GPC traces of the reaction that starts with 0.2 molar ration of $Na_2S_2O_4$ to initiator, and $FR_{Na2S2O4}$=19 and 39 nmol/min. The GPC data indicate that the reaction with $FR_{Na2S2O4}$=19 nmol/min had very narrow MW distributions throughout the whole polymerization (M_w/M_n = 1.1-1.2) and the $M_{n,GPC}$ values were in excellent agreement with the theoretical ones. The GPC traces in Fig. 5(c) show the evolution of the M_w/M_n for the polymerization starting with 40% of the total $Na_2S_2O_4$ added with a remainder fed at 19 nmol/min. The absence of low MW tailing is evident in the traces in Fig. 5(c), which is not the case for the polymerizations without feeding of $Na_2S_2O_4$ (Fig. 1(b)). The effect of the feeding rate on the polymerization rate is given in Fig. S4 (supporting information) The data in Fig. S4 shows that the rate of the polymerization, measured by the slope of the semilogarithmic plot, is proportional to the square-root of the feeding rate. This is consistent with the 0.5 order observed for ICAR ATRP, or other processes where activator regeneration, combined with radical termination, is the rate determining step.[9, 15, 48, 49]

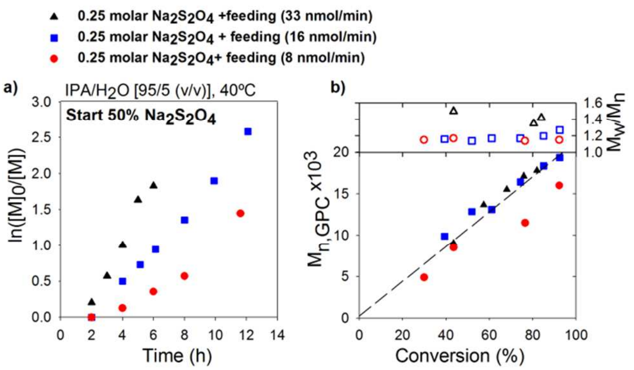


Fig. 4 Effect of the different feeding rates of $Na_2S_2O_4$ solution in SARA ATRP of DPA, starting with 50% of $Na_2S_2O_4$ in the solvent mixture, IPA/water = 95/5 (v/v) at 40 °C. (a) First-order kinetic plot, (b) evolution of MW and M_w/M_n with conversion (the dashed line represents theoretical MW at a given conversion). Reaction conditions: $[DPA]_0/[EBPA]_0/[Na_2S_2O_4]_0/[CuBr_2]_0/[Me_6TREN]_0$=100/1/feeding/0.1/0.2 (molar).

Variation of copper concentration

Whenever a polymer is to be applied in the biomedical field, it is important to remove contaminants and toxic compounds, including the residual copper catalysts. Therefore, it is

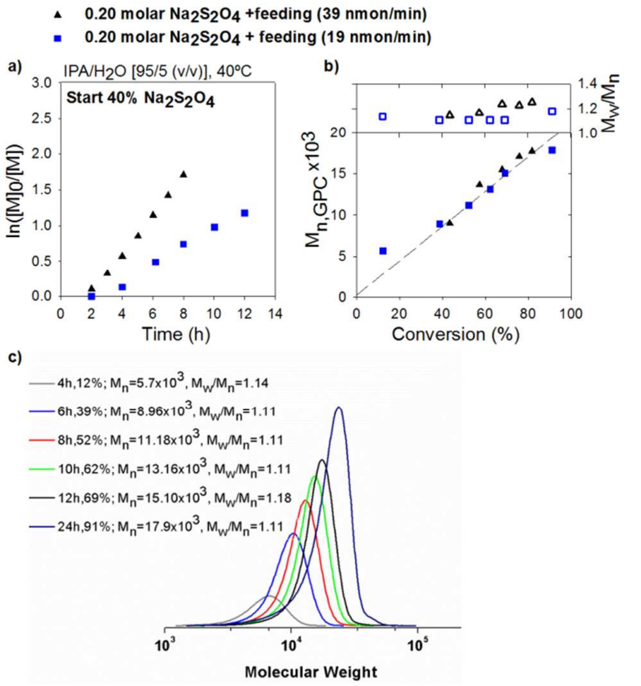


Fig. 5 Effect of the feeding rates of $Na_2S_2O_4$ solution in SARA ATRP of DPA, starting with 40% of $Na_2S_2O_4$ in the solvent mixture, IPA/water = 95/5 (v/v) at 40 °C. (a) First-order kinetic plot, (b) evolution of MW and M_w/M_n with conversion (the dashed line represents theoretical MW at a given conversion) and, (c) GPC traces with conversion for reaction $IR_{Na2S2O4}$=40% and $FR_{Na2S2O4}$= 19 nmol/min. Reaction conditions: $[DPA]_0/[EBPA]_0/[Na_2S_2O_4]_0/[CuBr_2]_0/[Me_6TREN]_0$=100/1/feeding/0.1/0.2 (molar).

advantageous to synthesize polymers with lowest catalyst concentrations to simplify the polymer purification. Fig. 6 shows the effect of lowering the catalyst concentration on the polymerization, the copper concentration was varied from 1000 to 250 ppm with 40% of the total $Na_2S_2O_4$ added initially and $FR_{Na2S2O4}$= 19 nmol/min. Fig. 6 suggests that it is possible to reduce the amount of Cu to 250 ppm while maintaining a similar rate of polymerization and control over the MW and M_w/M_n. There is a slight increase in dispersity at 250 ppm of Cu, compared to the higher catalyst loadings.

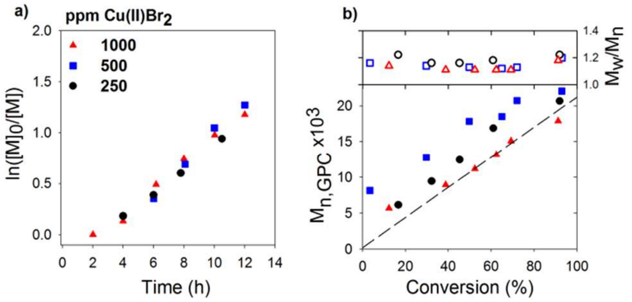


Fig. 6 Effect of the copper concentration in the SARA ATRP of DPA with feeding rate of aqueous solution of $Na_2S_2O_4$, 19.4nmol/min, starting with 40% of $Na_2S_2O_4$ in the solvent mixture, IPA/water = 95/5 (v/v) at 40 °C. (a) First-order kinetic plots, (b) evolution of MW and M_w/M_n with conversion (the dashed line represents theoretical MW at a given conversion). Reaction conditions: $[DPA]_0/[EBPA]_0/[Na_2S_2O_4]_0/[CuBr_2]_0/[Me_6TREN]_0$=100/1/0.2/CuBr₂/Me₆TREN (molar).

Effect of the ligand

Another parameter that can be varied in Cu-mediated polymerizations is the nature, activity and stability of the catalyst, by varying the ligand structure. Interestingly, substituting Me_6TREN for a stronger binding ligand, tris(2-pyridylmethyl)-amine (TPMA),[44, 50] allowed for similar control over the polymerization with only 100 ppm of Cu (Fig.7), compared to the 500 ppm needed to achieve similar control using Me_6TREN as the ligand.

The polymerization rate with 100 ppm of Cu/TPMA catalyst was slightly faster than the reaction with Me_6TREN and 250 ppm of Cu, and the control over the molecular weights was similar, with lower dispersities Furthermore, the M_w/M_n values were similar for 250 ppm of Cu/Me_6TREN catalyst and 100 ppm of Cu/TPMA catalyst, typically M_w/M_n = 1.1-1.2, with the TPMA system leading to slightly narrower MW distributions.

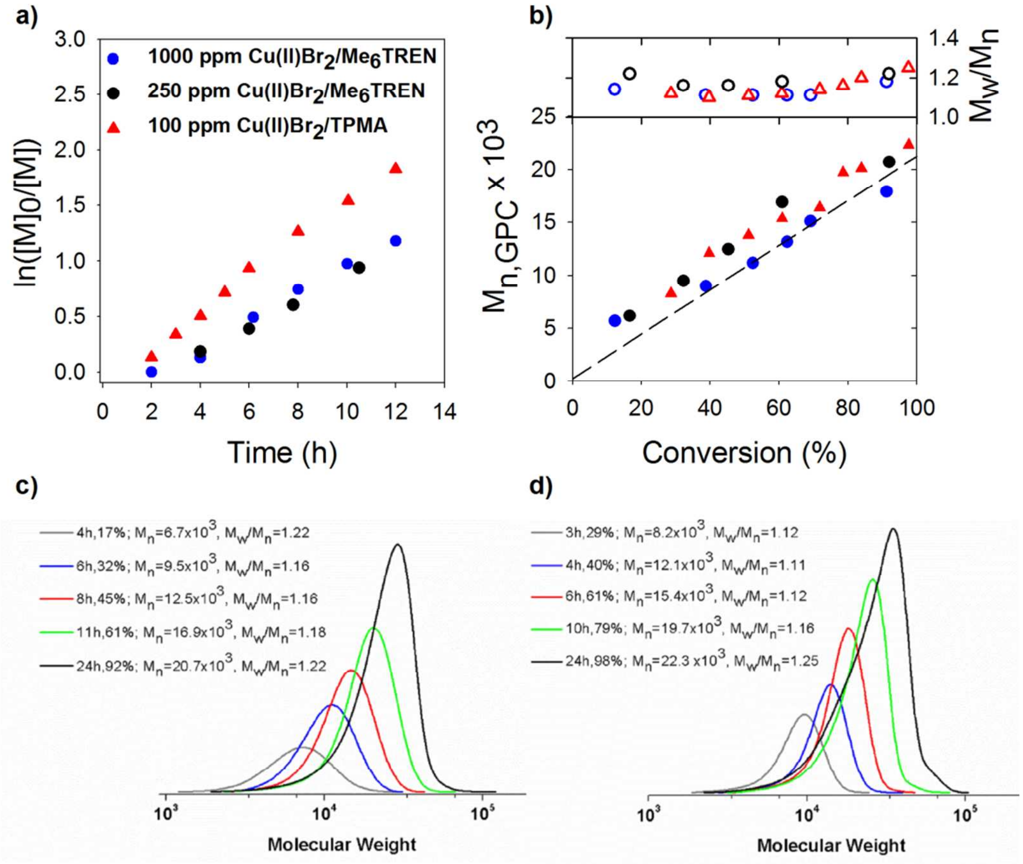


Fig.7 Influence of ligand and the Cu concentration in the SARA ATRP of DPA with feeding rate of aqueous solution of $Na_2S_2O_4$, 16nmol/min, starting with 40% of $Na_2S_2O_4$ in the solvent mixture, IPA/water = 95/5 (v/v) at 40 °C. (a) First-order kinetic plots, (b) evolution of MW and M_w/M_n with conversion (the dashed line represents theoretical MW at a given conversion), (c) GPC traces with conversion for reaction with Me_6TREN and 250ppm of Cu and (d) TPMA with 100ppm of Cu. Reaction conditions: $[DPA]_0/[EBPA]_0/[Na_2S_2O_4]_0/[CuBr_2]_0/[ligand]_0$=100/1/0.2/l/2l (molar) (l=0.1 or 0.025 for Me_6TREN and l=0.01 for TPMA).

Table 1. SARA ATRP of PDA with $Na_2S_2O_4$, in IPA/water = 95/5 (v/v) at 40 °C. Reaction conditions: $[DPA]_0/[EBPA]_0/[Na_2S_2O_4]_0/[CuBr_2]_0/[Me_6TREN]_0$ = 100/1/$IR_{Na2S2O4}$/0.1/0.2 (molar).

Entry	$IR_{Na2S2O4}$, %^{a}	$FR_{Na2S2O4}$, nmol/min	Feeding time, h	Time^b	Conv^b, %	k_p^{app}, h^{-1}	$M_{n,th}{}^b$ x 10^3	$M_{n,GPC}{}^b$ x 10^3	$M_w/M_n{}^a$	Cu^c, ppm
1^d	100	-	-	7	85	0.254	18.4	16.6	1.27	1000
2^d	50	-	-	24	99	0.289	20.92	17.50	1.32	1000
3^d	30	-	-	48	88	0.044	17.40	18.57	1.43	1000
4	50	-	-	7	83	0.301	17.71	18.4	1.28	1000
5	0	39.1	10	22	93	0.141	20.3	17.30	1.23	1000
6	50	32.6	6	6	84	0.472	18.59	18.57	1.42	1000
7	50	16.3	12	12	92	0.235	20.31	19.34	1.27	1000
8	50	8.15	24	24	92	0.149	20.17	15.98	1.15	1000
9	40	39.0	6	8	82	0.272	17.78	17.76	1.25	1000
10	40	19.4	12	24	91	0.124	19.9	17.9	1.18	1000
11^e	40	19.4	12	24	93	0.157	20.41	22.08	1.20	500
12^f	40	19.4	12	24	92	0.117	20.05	20.70	1.22	250
13^g	40	19.4	12	24	98	0.170	21.20	22.3	1.25	100

$IR_{Na2S2O4}$: Initial ratio of $Na_2S_2O_4$ to the initiator (0.5 molar max); $FR_{Na2S2O4}$: Feeding rate of $Na_2S_2O_4$; ^{a} molar ratio to initiator; ^{b}values obtained from the last sample from the kinetic study; ^{c}calculated by the initial molar ration of $CuBr_2$ to the monomer; ^{d}EBiB was used as initiator; $^e[CuBr_2]_0/[Me_6TREN]_0$ = 0.05/0.1; $^f[CuBr_2]_0/[Me_6TREN]_0$ = 0.025/0.1; ^{g}TPMA was used as ligand, $[CuBr_2]_0/[TPMA]_0$ = 0.01/0.02.

A summary of all experiments performed to optimize the polymerization is shown in Table 1. The main conclusion of the data in Table 1 is that SARA ATRP of DPA can yield well controlled polymers if the $Na_2S_2O_4$ solution is slowly and continuously fed into the reaction mixture. As expected, higher feeding rates led to faster polymerizations with inferior control. Another key conclusion from these experiments is that the initial concentration of $Na_2S_2O_4$ should not be too high, since this will cause a large amount of termination early in the reaction, as evidenced by low MW tailing in the GPC traces and higher dispersities. The results in Table 1 also indicate that very well-controlled polymers can be synthesized using just 100 ppm of the $Cu^{II}Br_2$/TPMA complex, and that $Cu^{II}Br_2/Me_6TREN$ at 250 ppm gives similar results to those at 100 ppm of $Cu^{II}Br_2$/TPMA.

Polymerization of OEOMA & the synthesis of poly(OEOMA) containing block copolymers

Although DPA is an important monomer for biomedical applications, it is also important to investigate other water soluble functional methacrylates, and determine whether the conditions developed can be used to control the polymerization of a wide range of functional monomers. Therefore, the Cu/Me_6TREN system was applied to OEOMA, as a representative methacrylic monomer. The reactions were performed using the conditions: IPA/water = 95/5 (v/v), $[EBPA]_0/[Na_2S_2O_4]_0/[CuBr_2]_0/[Me_6TREN]_0$ = 1/0.2/0.1/0.2 (molar) and slow feed of $Na_2S_2O_4$, but the monomer concentration was adjusted to 18% (w/w). In the case of OEOMA, more diluted solutions were used, since the literature shows that higher concentrations of oligo(ethylene oxide) based monomers can lead to broader MW distributions.[51] The kinetic plots for the homopolymerization of OEOMA are presented in Fig. 8, and they show linear first order kinetics. Additionally, the evolution of MW is linear with conversion, and dispersities were close to 1.1 throughout the polymerization. The GPC traces, Fig. 8 (c), show a shift to higher MW with conversion.

One of the key advantages of RDRP methods over conventional radical processes is their ability to create polymers with active chain-ends, which can be extended with either the same or a different monomer. The chain-end functionality of the synthesized polymers was confirmed by chain extension of a poly(OEOMA) macroinitiator with DPA, through a one-pot

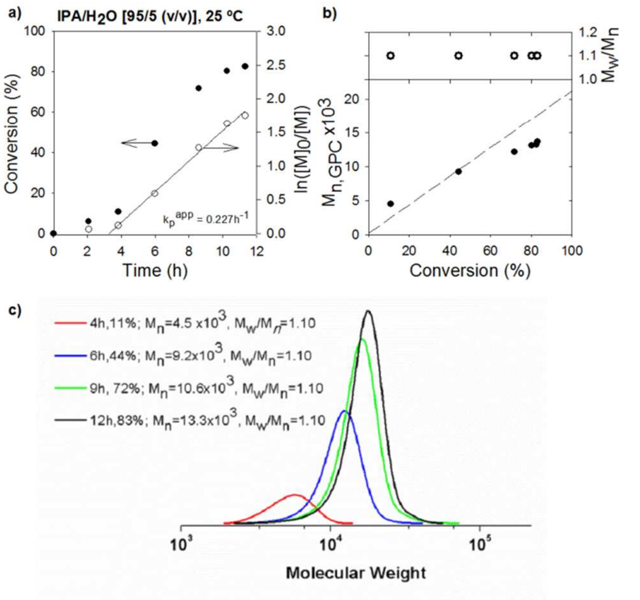
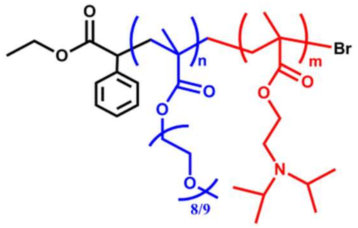


Fig. 8 SARA ATRP of OEOMA with feeding rate of aqueous solution of $Na_2S_2O_4$, 16nmol/min, starting with 40% of $Na_2S_2O_4$ in the solvent mixture, 18wt%, IPA/water = 95/5 (v/v) at 25 °C. (a) First-order kinetic plot, (b) evolution of MW and M_w/M_n with conversion (the dashed line represents theoretical MW at a given conversion), (c) GPC traces with conversion for reaction with ratio molar. Reaction conditions: $[OEOMA]_0/[EBPA]_0/[Na_2S_2O_4]_0/[CuBr_2]_0/[Me_6TREN]_0$=30/1/0.2/0.1/0.2 (molar).



Scheme 3. POEOMA-*b*-PDPA block copolymer synthesized by SARA ATRP with $Na_2S_2O_4$.

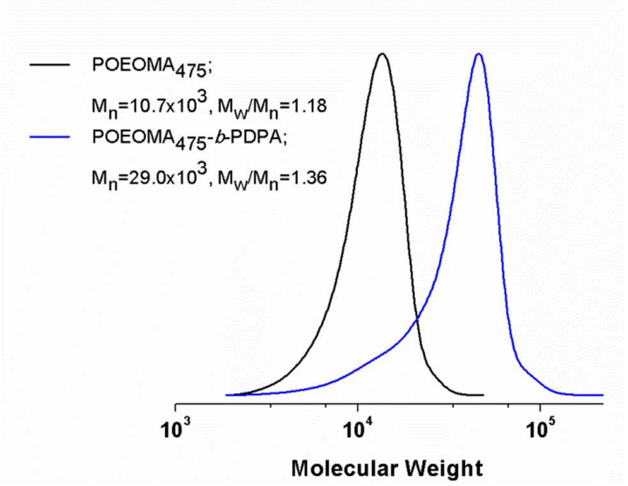


Fig. 9 GPC chromatographs of the poly(OEOMA) before (black curve) and after the chain extension with DPA, poly(OEOMA-*b*-DPA) (blue curve). Reaction conditions:$[OEOMA]_0/[EBPA]_0/[Na_2S_2O_4]_0/[CuBr_2]_0/[Me_6TREN]_0$=30/1/0.2/0.1/0.2 (molar), OEOMA 18wt%, in 6 mL of IPA/water =95/5 (v/v) and slow feeding of $Na_2S_2O_4$ solution (16nmol/min), 25 °C; $[DPA]_0/[POEOMA]$=100/1 (molar).

polymerization reaction. This method allows the direct synthesis of a stimuli-responsive POEOMA-b-PDPA block copolymer (Scheme 3). POEOMA macroinitiator was synthesized in a mixture IPA/water [95/5 (v/v)] using the SARA ATRP with slow feeding of $Na_2S_2O_4$ (16.1nmol/min). The second monomer, DPA, was injected into the system, when the first monomer reached high conversion, and the same feeding conditions were used for the chain extension reaction. The formation of the block copolymer was confirmed by a clear shift of the GPC trace towards high MW (Fig. 9).

The ^1H NMR spectrum of poly(OEOMA-*b*-DPA) is presented in the supporting information (Fig. S5). The system reported was extended to other reaction conditions, and is a reliable method for preparing different block copolymers, as highlighted in Table 2.

Conclusions

Well defined (co)polymers of a pH responsive monomer, DPA, were synthesized through SARA ATRP in the presence of $Na_2S_2O_4$ and $Cu(II)Br_2$/Ligand complex. The preferred reaction medium was a mixture of isopropanol and water (95/5 (v/v)). The polymerization conditions of this eco-friendly and inexpensive SARA ATRP system were enhanced to prepare well-controlled polymers using relatively low copper catalyst concentrations. The slow and continuous feeding of $Na_2S_2O_4$ solution into the reaction mixture improves the control over the polymerization. Slower feeding rates reduced the polymerization rate, but the control over the polymerization was enhanced. Furthermore, the use of TPMA as ligand allowed polymerization to be carried out in the presence of only 100 ppm of copper, reaching 80% of monomer conversion after 10h ($M_{n,GPC}$=19.7 x 10^3; M_w/M_n= 1.16). The present method was also applied in the synthesis of well controlled poly(OEOMA-*b*-DPA) block copolymers by one-pot polymerization reaction. Due to the reduced catalyst concentration this is a promising method for the synthesis of pH responsive (co)polymers, that could be used in the biomedical field.

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Table 2: Copolymers prepared by SARA ATRP with Na_2S_2O by one-pot polymerization reaction. Reaction conditions: $[OEOMA]_0/[EBPA]_0/[Na_2S_2O_4]_0/[CuBr_2]_0/[Me_6TREN]_0$ = DP/1/0.2/0.1/0.2 (molar), OEOMA 18wt%, IPA/water =95/5 (v/v) and slow feeding of $Na_2S_2O_4$ solution (16nmol/min), 40 °C.

	1st segment			2nd segment		
Copolymer	$M_{n,th}$ x10^3	$M_{n,GPC}$ x10^3	M_w/M_n	$M_{n,th}$ x10^3	$M_{n,GPC}$ x10^3	M_w/M_n
$POEOMA_{30}$-*b*-$PDPA_{50}$	14.60	13.24	1.18	22.46	27.00	1.33
$POEOMA_{20}$-*b*-$PDPA_{50}$	8.57	11.75	1.18	18.06	23.20	1.29
$POEOMA_{20}$-*b*-$PDPA_{100}$	8.60	10.70	1.18	25.35	28.95	1.36
$POEOMA_{20}$-*b*-$PDMAEMA_{50}$	8.50	9.72	1.17	15.58	14.63	1.23

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