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Synthesis of cationic poly((3-acrylamidopropyl) trimethylammonium chloride) by SARA ATRP in ecofriendly solvent mixtures

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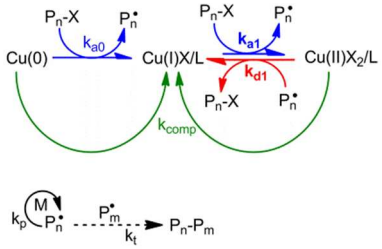
Supplemental activator and reducing agent atom transfer radical polymerization (SARA ATRP) of the cationic monomer (3-acrylamidopropyl)trimethylammonium chloride (AMPTMA) was successfully performed for the first time. The polymerizations were performed in water or ethanol/water mixtures at room temperature in the presence of Cu(0), using relatively low concentrations of soluble copper catalyst and an excess of ligand (Me_6TREN). The reaction conditions were optimized to give the best control over the polymerization under environmentally friendly conditions. The polymerization data showed good control over the molecular weights with narrow molecular weight distributions for the entire polymerization. The preservation of the chain-end functionality was confirmed by self-chain extension and the synthesis of a block copolymer containing AMPTMA and oligo(ethylene oxide) methyl ether acrylate (OEOA). SARA ATRP was also extended to the synthesis of alkyne-terminated poly-AMPTMA (PAMPTMA), which was subsequently functionalized, using copper(I) catalyzed azide-alkyne cycloaddition, with an azido-functionalized coumarin derivative.

Introduction

Reversible deactivation radical polymerization (RDRP) techniques are powerful tools for the synthesis of well-defined functional polymeric materials with complex structures. RDRP methods provide control over the polymers molecular weight and architecture, with low molecular weight dispersity ($Đ$) and high chain-end functionality.[1] Atom transfer radical polymerization (ATRP) is one of the most versatile RDRP techniques, as it can be applied to a wide range of monomers under mild conditions.[2-4] In ATRP, control over the molecular weight is gained through a dynamic equilibrium between radicals ($P_n^•$) and alkyl halide dormant species. ATRP uses transition metal complexes in a low oxidation state to activate the alkyl halide, giving a radical and the metal complex in a higher oxidation state.[5] The radical typically adds several monomer units before reacting with the higher oxidation state complex to return to the dormant alkyl halide species. Copper based complexes with nitrogen-based ligands are most often used in ATRP.[6, 7] Typically, high concentrations of the metal catalyst, often greater than 1000 parts per million (ppm), are required to perform normal ATRP reactions, which complicates the purification of the polymer. This issue is critically important for biomedical applications and also from the environmental standpoint. Therefore, new ATRP techniques[8-11] have been developed to reduce the amount of metal catalyst used in the polymerizations to less than 1000 ppm, as well as to avoid the use of organic solvents. One such method is the supplemental activator and reducing agent (SARA) ATRP, which uses zero-valent transition metals[11-15] or inorganic sulfites[16, 17] as both reducing agents and supplemental activators. When Cu(0) is used in the reaction, it slowly regenerates Cu(I)X species as a reducing agent, and it slowly generates radical and Cu(I)X by a supplemental activator (Scheme 1).[5]

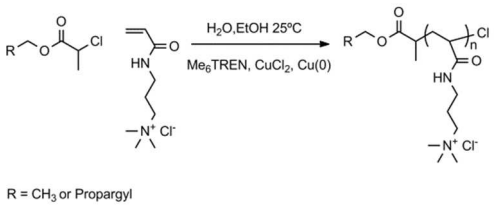


Scheme 1. General mechanism of SARA ATRP mediated by Cu(0) and Cu(II)X_2.

Apart from the low amount of catalyst used in SARA ATRP, this method is also very useful for the preparation of biomaterials, since polymerization can be conducted using environmentally friendly solvents/solvent mixtures at room temperature. Recently, SARA ATRP of acrylates and methacrylates was successfully performed in ethanol/water mixtures using sodium dithionite as a supplemental activator and reducing agent.[12] In addition, well controlled polymers of oligo(ethylene oxide) methyl ether acrylate (OEOA) were synthesized by SARA ATRP in water, using a combination of Cu(0) and $CuBr_2$/Me_6TREN with an excess of Me_6TREN (Me_6TREN: tris(2-(dimethylamino)ethyl)amine), and an excess of bromide salts.[18]

Cationic polymers have found extended biomedical applications due to their unique physicochemical properties. These polymers have been extensively studied for gene delivery, tissue engineering and antifouling surfaces.[19, 20] To maximize their therapeutic efficacy, well-defined polymers with precise architecture have been synthesized, mainly by RDRP methods or a combination of RDRP and "click" chemistry strategies.[21-23] Due to the anticipated demand for these products, it is important to develop ecofriendly ATRP systems for cationic monomers. The cationic monomer (3-acrylamidopropyl)trimethylammonium chloride (AMPTMA) has been investigated for various applications. AMPTMA has been included in temperature-responsive copolymers[24-26] with potential to be used as drug delivery systems,[27] and as a microcarrier for cell proliferation[28] or in gene delivery.[29, 30] The existing protocols for the ATRP of AMPTMA require more than 10000 ppm of CuCl or $CuCl_2$ coordinated with Me_6TREN, in DMF/water mixtures (DMF: dimethylformamide), using ethyl 2-chloropropionate (ECP) as the initiator.[24-30] To perform these reactions under more ecofriendly conditions, lower catalyst loadings and less toxic solvents are desired.

Here, we develop reaction conditions for the synthesis of well-defined PAMPTMA by SARA ATRP in water or ethanol/water mixtures at room temperature (25 ºC), using Cu(0) wire in combination with a small amount of $CuCl_2$ (Scheme 2). Importantly, the amount of soluble copper used the reaction was at least ten times lower than the one reported for the ATRP of AMPTMA.[24-30] In addition, DMF was replaced by ethanol (EtOH), which is a much less toxic solvent. The SARA ATRP method reported herein was also extended to the preparation of PAMPTMA-based block copolymer, as well as alkyne-terminated PAMPTMA, used to functionalized the chain-end with a dye molecule via copper(I) catalyzed azide alkyne cycloaddition.



Scheme 2. Synthesis of PAMPTMA by SARA ATRP.

Experimental

Materials

Acetone (Fisher Scientific), (3-acrylamidopropyl)trimethylammonium chloride (solution 75 wt. % in H_2O, Aldrich), alumina (basic, Fisher Scientific), anhydrous magnesium sulfate (99 %, Aldrich), 2-chloropropionyl chloride (97 %, Aldrich), copper (II) chloride (97 %, Aldrich), copper (II) sulfate pentahydrate (≥ 98 %, Aldrich), deuterated chloroform ($CDCl_3$, 99.8 % Cambridge Isotope Laboratories), deuterated (D_4) methanol (99.8 %, Euroisotop), deuterium oxide (99.9 %, Cambridge Isotope Laboratories), dichloromethane (DCM, HPLC grade, Fisher Scientific), DMF (Aldrich), EtOH (Fisher Scientific), ethyl 2-chloropropionate (ECP, 97 %, Aldrich), glacial acetic acid (Fisher Chemical), hydrochloric acid (Fisher Scientific), 2-hydroxyethyl 2-bromoisobutyrate (HBiB, 95 %, Aldrich), methanol (Fisher Scientific), propargyl alcohol (PgOH, 99 %, Aldrich), sodium ascorbate (crystalline, ≥ 98 %, Aldrich), sodium chloride (Fisher Scientific), triethylamine (TEA, ≥ 99 %, Sigma Aldrich), tris(2-aminoethyl)amine (TREN, 96 %, Aldrich) and water (HPLC grade, Fisher Scientific) were used as received.

CuCl (97%, Aldrich) was washed with glacial acetic acid, followed by 1 % aqueous HCl solution. Finally, it was washed with acetone and dried under nitrogen, to give a white powder.

Metallic copper (Cu(0), d = 1 mm, Alfa Aesar) was washed with HCl in methanol and subsequently rinsed with methanol and dried under a stream of nitrogen following the literature procedures.[31]

Oligo(ethylene oxide) methyl ether acrylate (OEOA, 99 %, average molecular weight 480, Aldrich) was passed over a column filled with basic alumina to remove inhibitor prior to use.

Tris[2-(dimethylamino)ethyl]amine (Me_6TREN),[32] tris(pyridin-2-ylmethyl)amine (TPMA)[32] and 3-azido-7-diethylaminocoumarin[33] were synthesized as reported in the literature.

Instrumentation

Monomer conversion was measured using ^{1}H NMR spectroscopy in D_2O using a Bruker Avance 500 MHz spectrometer at 27 °C, with spectra analyzed using MestRenova software version: 6.0.2-5475. The coumarin-functionalized PAMPTMA was analyzed by ^{1}H NMR spectroscopy in CD_3OD, using Bruker Avance III 400 MHz spectrometer, with a 5 mm TIX triple resonance detection probe.

Polymers number-average molecular weights (M_n^{SEC}) and dispersity ($Đ$) were determined by using a size exclusion chromatography (SEC) Water 2695 Series with a data processor (Empower Pro), equipped with three columns (Waters Ultrahydrogel Linier, 500 and 250), using 100 mM sodium phosphate buffer with 0.2 vol % trifluoroacetic acid (pH = 2) as an eluent at a flow rate 1.0 mL/min, with detection by a

refractive index (RI) detector. Before the injection (100 µL), the samples were filtered through a hydrophilic polyethersulfon (PES) membrane with 0.2 µm pore. The system was calibrated with six narrow poly(ethylene glycol) standards and the molecular weights were determined by conventional calibration.

Procedures

Synthesis of propargyl 2-chloropropionate (PgCP)

A mixture of PgOH (2.0 mL, 34 mmol), TEA (5.7 mL, 41 mmol) and dry DCM (15 mL) was added to a two-neck round flask, equipped with a magnetic stirrer bar. The solution was cooled to 0 ºC and purged with nitrogen. A mixture of 2-chloropropionyl chloride (4 mL, 41 mmol) and dry DCM (10 mL) was added dropwise to the flask under nitrogen. The mixture was allowed to react at 0 ºC for 2 h and then at room temperature overnight. The reaction mixture was filtered, washed with aqueous sodium chloride (100 mL, 3 times), water (100 mL, 2 times) and dried over anhydrous magnesium sulfate. The DCM was removed under reduced pressure and the crude product was purified by distillation under reduced pressure (2.1 g; 41.7 %). The purity of the compound was confirmed by ^{1}H NMR spectroscopy.

Typical procedure for SARA ATRP of AMPTMA

A series of aqueous SARA ATRP reactions were carried out with systematically varied conditions to determine optimal conditions for SARA ATRP of AMPTMA. Generally, the SARA ATRP of AMPTMA followed this procedure: AMPTMA (2.0 mL, 7.26 mmol), a solution of $CuCl_2$ (2.9 mg, 22 µmol) and Me_6TREN (10 mg, 44 µmol) in water (2.4 mL) and a solution of ECP (9.9 mg, 73 µmol) in ethanol (2.0 mL) were added to a 10 mL Schlenk flask equipped with a magnetic stirrer bar. Next, Cu(0) wire (l = 10 cm; *d* = 1 mm) was added to the Schlenk flask, which was sealed with a glass stopper, deoxygenated with three freeze-vacuum-thaw cycles and purged with nitrogen. The reaction was allowed to proceed with stirring (700 rpm) at room temperature (25 ºC). Different reaction mixture samples were collected during the polymerization. The samples were analyzed by ^{1}H NMR spectroscopy in order to determine the monomer conversion, and by aqueous SEC to determine the molecular weights and dispersity of the polymers. The final reaction mixture was dialyzed against deionized water and the polymer was obtained after freeze drying.

Typical "one-pot" chain extension of PAMPTMA-Cl

AMPTMA (0.5 mL, 1.8 mmol), a solution of $CuCl_2$ (2.4 mg, 18 µmol) and Me_6TREN (8.4 mg, 36 µmol) in water (0.5 mL) and a solution of ECP (5.0 mg, 36 µmol) in ethanol (0.6 mL) were added to a 10 mL Schlenk flask equipped with a magnetic stirrer bar. Next, Cu(0) wire (*l* = 5 cm; *d* = 1 mm) was added to the Schlenk flask, which was sealed with a glass stopper, deoxygenated with three freeze-vacuum-thaw cycles and purged with nitrogen. The reaction was allowed to proceed with stirring (700 rpm) at room temperature. When the monomer conversion reached more than 90 %, a degassed mixture of AMPTMA (1 mL, 5.4 mmol), water (740 µL) and ethanol (740 µL) were added to the Schlenk flask under nitrogen. The monomer conversion was determined by ^{1}H NMR spectroscopy and the molecular weights and dispersities were determined by aqueous SEC.

Typical block copolymerization of AMPTMA and OEOA

AMPTMA (0.5 mL, 1.8 mmol), a solution of $CuCl_2$ (4.9 mg, 36 µmol) and Me_6TREN (16.7 mg, 73 µmol) in water (0.5 mL) and a solution of ECP (9.9 mg, 73 µmol) in ethanol (0.6 mL) were added to a 25 mL Schlenk flask equipped with a magnetic stirrer bar. Next, Cu(0) wire (*l* = 5 cm; *d* = 1 mm) was added to the Schlenk flask, which was sealed with a glass stopper, deoxygenated with three freeze-vacuum-thaw cycles and purged with nitrogen. The reaction was allowed to proceed with stirring (700 rpm) at room temperature. When the monomer conversion reached more than 90 %, a degassed mixture of OEOA (1.6 mL, 3.6 mmol), previously passed over a basic alumina column, water (3.9 mL) and ethanol (3.9 mL) were added to the Schlenk flask under nitrogen. The monomer conversion was determined by ^{1}H NMR spectroscopy and the molecular weights and dispersities were determined by aqueous SEC.

"Click" reaction between alkyne-terminated PAMPTMA and (3-azido-7-diethylaminocoumarin)

An alkyne-terminated PAMPTMA sample (M_n^{SEC} = 5000; *Đ* = 1.17) was purified through dialysis against water and the polymer was obtained after freeze drying. A solution of (3-azido-7-diethylaminocoumarin) (3.1 mg; 12 µmol), alkyne-terminated PAMPTMA (50 mg; 10 µmol) and $CuSO_4.5H_2O$ (1.2 mg; 5 µmol) in water (100 µL) and EtOH (500 µL) was placed in a round-bottom flask equipped with a magnetic stirrer bar, which was sealed with a rubber septum. The mixture was bubbled with nitrogen for 20 min to remove the oxygen. Finally, a degassed stock solution of sodium ascorbate in water (125 mM; 100 µL) was injected into the flask under nitrogen atmosphere. The reaction was allowed to proceed with stirring (700 rpm) at room temperature for 72 h. The product was purified through dialysis against water, followed by dialysis against ethanol. The organic solvent was evaporated under reduced pressure and the functionalized polymer was analyzed by ^{1}H NMR spectroscopy, and the fluorescence confirmed by irradiation at 366 nm.

Results and discussion

The ATRP system described in the literature for the polymerization of AMPTMA, employed more than 10000 ppm of CuCl (or CuCl/$CuCl_2$) coordinated with Me_6TREN in a DMF/H_2O = 50/50 (v/v) mixture.[25, 29] It is known that CuX/Me_6TREN complexes (X – halide) undergo rapid

disproportionation in the presence of water, producing soluble CuX_2/Me_6TREN and Cu(0) particles.[34] The Cu(I) disproportionation could occur even during the preparation of the reaction system, prior to the polymerization.[34] However, recent investigations on the polymerization of water soluble monomers, catalyzed by $Cu(0)/CuBr_2/Me_6TREN$, in aqueous medium, revealed that the polymerization is governed by SARA ATRP mechanism.[5, 18] This is because the very high activity of Cu(I) toward the activation of alkyl halides ensures that Cu(I) is the major activator.[5, 18] Furthermore, due to the high activity of Cu(I) in activating alkyl halides, its concentration is at so low levels that disproportionation occurs at a very slow rate and can be neglected during polymerization.[18] In this case, Cu(0) acts as a supplemental activator and a reducing agent, to slowly regenerate Cu(I) and radicals. In this system, the majority of alkyl halide activation events and deactivations of growing radicals are ruled by the ATRP equilibrium.[31, 35] To the best of our knowledge, detailed kinetic studies on the ATRP of AMPTMA[29] have never been discussed in the literature.

The initial experiments employed Cu(0) wire in combination with $CuCl_2$ as a catalyst in the polymerization of AMPTMA. These experiments were designed to confirm that the SARA ATRP mechanism governs the process, and that similar results to the ones in the literature could be obtained using Cu(0) wire rather than relying on predisproportionation of Cu(I) species.[29] The initial reactions were performed in a DMF/H_2O = 50/50 (v/v) mixture at room temperature, targeting degree of polymerization (DP) of 100, using ethyl 2-chloropropionate (ECP). After 1.5 h of polymerization, the monomer conversion was approximately 90 % and the control achieved over the PAMPTMA molecular weight was similar for both polymerization methods, with dispersity around 1.2 (Figure 1). The SARA ATRP method, using Cu(0) and $Cu(II)X_2$, is attractive, since lower copper catalyst concentration can be used than in normal ATRP systems. In addition, because it starts with the oxidatively stable $Cu(II)X_2$ deactivator species, the polymerization is tolerant to a limited amount of oxygen, especially if oxygen is removed prior to the polymerization.[11-14, 36] Therefore, a series of variables associated with SARA ATRP were investigated in this work, to allow the synthesis of well-defined PAMPTMA under environmentally friendly reaction conditions.

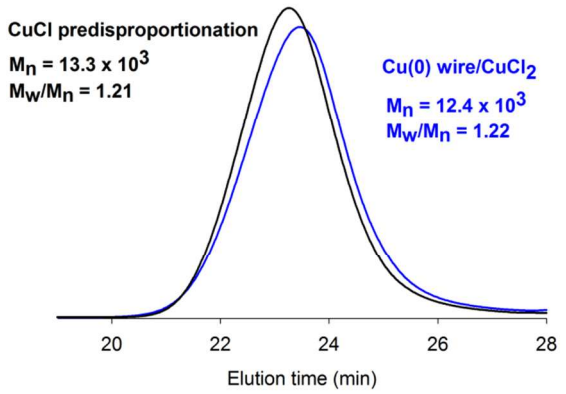


Figure 1. SEC traces of the polymers obtained by the use of predisproportionation of CuCl: $[AMPTMA]_0/[ECP]_0/[CuCl]_0/[Me_6TREN]_0$ = 100/1/1/1; DMF/H_2O = 50/50 (v/v); $V_{solvent}$ = 2 mL; (black line) and Cu(0) wire/$CuCl_2$: $[AMPTMA]_0/[ECP]_0/[CuCl_2]_0/[Me_6TREN]_0/Cu(0)$ wire = 100/1/0.5/1.0/Cu (0) wire; DMF/H_2O = 50/50 (v/v); Cu(0) wire: *l* = 5 cm; *d* = 1 mm; $V_{solvent}$ = 2 mL (blue line) of AMPTMA during 1.5 h at room temperature.

Effect of the water content in the solvent mixture

It is commonly accepted that water is the best solvent from the environmental point-of-view and it is attractive for industrial applications due to its low toxicity. The use of polar organic solvents or their mixtures with water are sometimes inevitable due to solubility issues of monomers, polymers and catalysts. Ideally, only benign solvents should be used. In this work, DMF was replaced by EtOH, since EtOH solubilizes both the monomer and the polymer and EtOH is less toxic than DMF. The effect of the content of water in the alcohol/water reaction mixture was varied from 50 % to 70 %, on the SARA ATRP of AMPTMA was investigated. In all cases, the monomer conversion reached 90 % in less than 1 h and the kinetics were first-order with respect to monomer conversion (Figure 2 (a)). Changing the ratio of H_2O to EtOH had minimal influence on the control over the molecular weights (Figure 2 (b)), since the experimental number average molecular weights were in good agreement with the predicted values and the dispersity values were low ($Đ \approx$ 1.3) throughout the reaction.

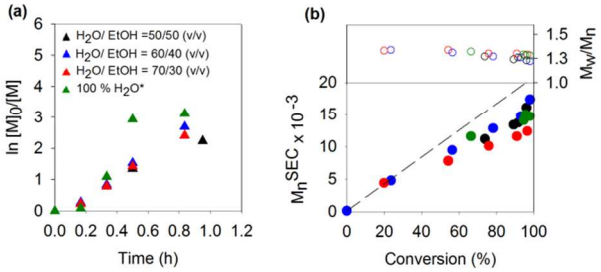


Figure 2. (a) Kinetic plots of $\ln[M]_0/[M]$ *vs.* time and (b) plot of number–average molecular weights (M_n^{SEC}) and *Đ* (M_w/M_n) *vs.* monomer conversion (the dashed line represents theoretical molecular weight at a given conversion) for the SARA ATRP of AMPTMA initiated by ECP or $HBiB^*$ (green symbols), for different water contents in the $EtOH/H_2O$ (v/v) solvent mixture. Conditions: $[AMPTMA]_0/[ECP \text{ or } EBiB^*]_0/[CuCl_2]_0/[Me_6TREN]_0/Cu(0)$ wire = 100/1/0.5/1.0/Cu(0) wire; $[AMPTMA]_0$ = 1.45 M; Cu(0) wire: *l* = 10 cm; *d* = 1 mm; $V_{solvent}$ = 5 mL.

The next step involved the polymerization in aqueous system (green symbols in Figure 2), using the water soluble 2-bromoisobutyrate (HBiB) as the initiator. It is known that aqueous ATRP systems present some challenges that can contribute to poor level of control, mainly due to the high activity of Cu(I) species as well as the dissociation of the halide anion from the X-Cu(II) deactivator complex, which gives a free halide anion and a Cu(II) complex that cannot deactivate radicals.[37] These challenges can be overcome by slowly regenerating Cu(I) species, and adding an excess of halide salt to promote the formation of the X-Cu(II) deactivator complex.[18, 38-40] Since the AMPTMA monomer inherently contains a chloride anion, well-controlled polymerization in aqueous medium was achieved, without adding any external halide salt, as shown in Figure 2 (b) (green symbols) by the narrow molecular weight distributions. After the induction period the reaction was very fast, reaching 95 % conversion in 30 min. Control experiments using different concentrations of NaCl were performed and showed no effect on the polymerization control. The use of the heterogeneous Cu(0) wire as a reducing agent for the (re)generation of Cu(I)X species in aqueous medium is an attractive feature of the SARA ATRP method reported here.

Effect of the ligand nature and concentration

The next parameters investigated were the structure and concentration of ligand used in the polymerization. The performance of tris(pyridin-2-ylmethyl)amine (TPMA) was compared to Me_6TREN, since TPMA forms very stable Cu(I) complexes, which prevents disproportionation, although Me_6TREN complexes are more active.[41] Figure FS1 (b) showed that TPMA could also mediate the SARA ATRP of AMPTMA providing good control over the molecular weight. However, the polymerization was considerably slower than with Me_6TREN and the maximum monomer conversion was limited to 35 % (Figure FS1 (a)). The decrease of the polymerization rate when TPMA complexes are used in the presence of high concentration of salt has been previously reported for other ATRP systems.[39, 40] Therefore, Me_6TREN was used for all subsequent experiments aiming to achieve high monomer conversion, while ensuring the synthesis of well-defined polymers.

The ligand concentration is an important parameter to consider in SARA ATRP reactions. The ligand concentration should be high enough to coordinate with the all soluble copper in the reaction mixture, to ensure good control over the polymers molecular weight. Since the concentration of soluble Cu increases during the reaction, the ligand is often used in a large excess compared to the initial amount of soluble copper. However, the ligand could lead to undesired side reactions and could affect the livingness of the polymers and control over the reaction.[42-44] In this work, three different copper to ligand ratios (1/1.2, 1/2 and 1/4) were studied. As shown in Figure 3, the rate of polymerization increased with the Me_6TREN concentration, while the control over polymer structure was similar in all cases. Using the copper to ligand ratio of 1/2 (red symbols in Figure 3) it was possible to reach a fast reaction and high monomer conversion, obtaining polymers with low dispersity. Increasing the ligand concentration above that value leads to a slight improvement in the polymerization rate with negligible improvement in the control over the molecular architecture. Therefore, for this particular system, two-fold excess of Me_6TREN to $CuCl_2$ (molar) seems to be the optimum ratio.

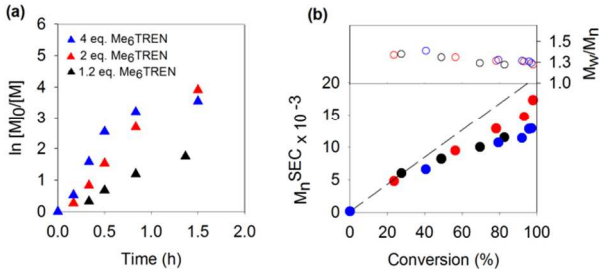


Figure 3. (a) Kinetic plots of $\ln[M]_0/[M]$ *vs.* time and (b) plot of number–average molecular weights (M_n^{SEC}) and $Đ$ (M_w/M_n) *vs.* monomer conversion (the dashed line represents theoretical molecular weight at a given conversion) for the SARA ATRP of AMPTMA initiated by ECP, for different amounts of ligand. Conditions: $[AMPTMA]_0$ = 1.45 M; $[AMPTMA]_0/[ECP]_0$ = 100; $[CuCl_2]_0$ = 5000 ppm; Cu(0) wire: l = 10 cm; d = 1 mm; $V_{solvent}$ = 5 mL.

Effect of the soluble copper concentration

In developing "green" ATRP systems it is important to consider the total amount of soluble copper present in the reaction medium, since Cu complexes are mildly toxic and often require additional processes to remove them. In this work, the $CuCl_2$ concentration was decreased from 5000 ppm to 1000 ppm (determined as the initial molar ratio of $CuCl_2$ to the monomer). Figure 4 shows that the rate of polymerization as well as the control over the polymer decreased with the decrease in the initial concentration of $CuCl_2$. Despite these the decrease in rate and control over the polymer, Figure 4 shows that even using 1000 ppm of $CuCl_2$ gave a reasonable rate of polymerization, reaching 65% in an hour, and relatively well controlled polymers with $Đ \approx 1.4$ at high conversion. Therefore a tradeoff exists between the rate and control over the polymerization and total amount of soluble copper species in the polymerization. For certain applications polymers with narrow molecular weight distributions are necessary, and in these cases higher catalyst loadings may be required. For other applications tolerating broader molecular weight distributions, lower catalyst loadings can be used.

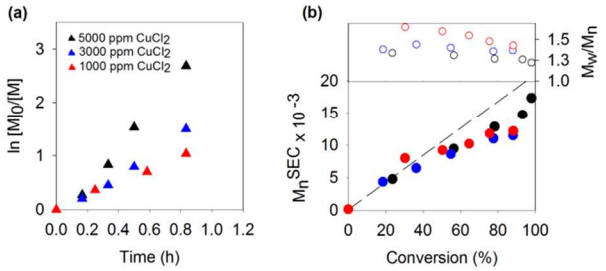


Figure 4. (a) Kinetic plots of $\ln[M]_0/[M]$ *vs.* time and (b) plot of number–average molecular weights (M_n^{SEC}) and $Đ$ (M_w/M_n) *vs.* monomer conversion for the SARA ATRP of AMPTMA initiated by ECP, for different amounts of initial soluble copper. Conditions: $[AMPTMA]_0$ = 1.45 M; $[AMPTMA]_0/[ECP]_0$ = 100; $[Me_6TREN]_0/[CuCl_2]_0$ = 2/1; Cu(0) wire: *l* = 10 cm; *d* = 1 mm; $V_{solvent}$ = 5 mL.

Effect of the Cu(0) wire length

Typically, the Cu(0) wire surface influences the rate of activation of alkyl halide by Cu(0) as well as the rate of copper comproportionation, leading to faster polymerizations with higher Cu(0) surface area.[18, 34, 45, 46] In this section, the Cu(0) wire length was decreased from 10 cm to 2.5 cm in the SARA ATRP of AMPTMA (Cu(0): *d* = 1 mm). Table 1 summarizes the rate of polymerization as well as the polymers molecular weights obtained after 30 min of reaction. The rate of polymerization was fast when 10 cm of Cu(0) wire was used (Table 1, entry 1), reaching 55 % in 30 min. Interestingly, when the copper surface area was decreased 4 times (Table 1, entry 2), the reaction still maintained a high rate of polymerization, reaching 49 % in 30 min. These results suggest that, in this system, it is possible to use a low surface area of copper wire without compromising the rate of polymerization. Further, the control of the reaction was similar in both polymerizations, with final dispersities around 1.4. Kinetic plots of the polymerizations are shown in the Supporting Information (Figure SF2).

Table 1. SARA ATRP of AMPTMA initiated by ECP, for different lengths of Cu(0) wire. Conditions: $[AMPTMA]_0/[ECP]_0/[CuCl_2]_0/[Me_6TREN]_0$/Cu(0) wire = 100/1/0.3/0.6/Cu (0) wire; EtOH/H_2O = 40/60 (v/v); T = 25 ºC.; $[AMPTMA]_0$ = 1.45 M; $V_{solvent}$ = 5 mL, t_{rx} = 30 min.

Entry	Cu(0) length[1] (cm)	Cu (0) SA[2] (cm^2)	m $_{Cu(0)}$/SA (g/cm^2)	k_p^{app} (h^{-1})	Conv. (%)	M_n^{SEC} x 10^{-3}	$Đ$
1	10	3.14	0.703	1.578	55	8.6	1.40
2	2.5	0.78	0.176	1.308	49	8.2	1.37

[1] Cu(0) wire: *d* = 1 mm; [2] SA: surface area

Chain "livingness" and preparation of copolymers

The livingness of the PAMPTMA chains was evaluated by a "one-pot" chain extension experiment with the same monomer. The first block (targeted DP of 50) was synthesized using SARA ATRP in EtOH/H_2O = 50/50 (v/v) mixture at ambient temperature. After the monomer reached high conversion (> 90 %), a degassed solution of AMTPMA in EtOH/H_2O = 50/50 (v/v) was injected into the reaction mixture. Figure 5 (a) shows a clear shift on the SEC trace towards high molecular weight (lower retention volume), upon the formation of the extended polymer. However, a low molecular weight tailing was noticeable and was attributed to some terminated chains formed during the first polymerization. Nevertheless, the control over the molecular weight was good, as the extended polymer presented narrow molecular weight distribution ($Đ$ = 1.27).

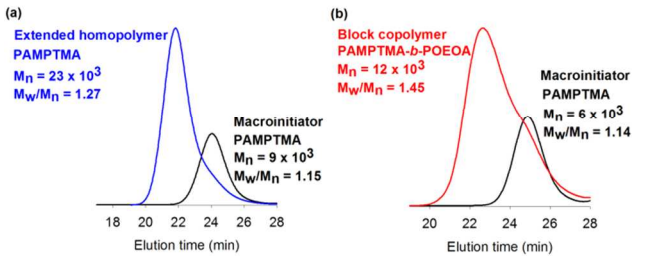


Figure 5. SEC traces of PAMPTMA before and after: (a) self-chain extension: first block - $[AMPTMA]_0/[ECP]_0/[CuCl_2]_0/[Me_6TREN]_0$/Cu(0) wire = 50/1/0.5/1.0; conversion = 92 %; second block - $[AMPTMA]_0$ = 1.45 M; $[AMPTMA]_0/[ECP]_0$ = 150; conversion = 94 %; (b) extension with $OEOA_{480}$: first block - $[AMPTMA]_0/[ECP]_0/[CuCl_2]_0/[Me_6TREN]_0$/Cu(0) wire = 25/1/0.5/1.0; conversion = 97 %; second block - $[OEOA]_0$ = 0.4 M; $[OEOA]_0/[ECP]_0$ = 50; conversion = 90 %. Both chain extensions were done by "one-pot" SARA ATRP, in EtOH/H_2O = 50/50 (v/v) at 25 ºC; Cu(0) wire: *l* = 5 cm; *d* = 1 mm; $[AMPTMA]_0$ (first block) = 1.45 M; $V_{solvent}$ (first block) = 1.25 mL.

The SARA ATRP system was also extended to block copolymers containing two distinct monomers. In this case the first block was PAMPTMA, and the second block contained poly(oligo(ethylene oxide) acrylate) (POEOA) and this block copolymer could find application in the biomedical field. The method proved to be suitable for the preparation of water-soluble block copolymer with a relatively low dispersity of 1.45, as shown in Figure 5 (b). A PAMPTMA-*b*-POEOA sample was purified by dialysis and its structure was confirmed by ^{1}H NMR spectroscopy (Figure SF3).

Preparation of alkyne-functionalized PAMPTMA by SARA ATRP

To further explore the potential of the SARA ATRP, the system was used for the preparation of alkyne-functionalized PAMPTMA, using the alkyne bearing initiator propargyl 2-chloropropionate (PgCP). The alkyne functionality allows the polymer to be coupled with a wide library of azide-containing molecules by "click" chemistry, which could be employed in the design of well-defined copolymers and different architectures or containing different functional groups.

The concentration of PgCP was varied to prepare alkyne-functionalized PAMPTMA with several chain lengths. As expected, the rate of polymerization decreased with the increase of the targeted DP (Figure 6 (a)), since the supplemental activation, which is often rate determining,[47] reaction rate is dependent on the initiator concentration. The polymerizations showed first-order kinetics (Figure 6 (a)) and good control over PAMPTMA molecular weight, with low dispersity values

throughout the polymerizations (Figure 6 (b)). These results suggest that the SARA ATRP is a robust method to prepare well-defined end-functional polymers.

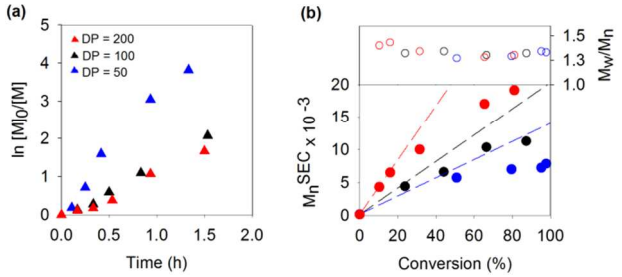


Figure 6. (a) Kinetic plots of $\ln[M]_0/[M]$ *vs.* time and (b) plot of number–average molecular weights (M_n^{SEC}) and $Đ$ (M_w/M_n) *vs.* monomer conversion (the dashed lines represent theoretical molecular weight at a given conversion) for the SARA ATRP of AMPTMA initiated by alkyne-terminated initiator (PgCP), for different DP values. Conditions: $[AMPTMA]_0/[ECP]_0/[CuCl_2]_0/[Me_6TREN]_0$/Cu(0) wire = DP/1/0.5/1.0/Cu (0) wire; $[AMPTMA]_0$ = 1.45 M; Cu(0) wire: *l* = 10 cm; *d* = 1 mm; $V_{solvent}$ = 5 mL.

The molecular structure of the alkyne-terminated PAMPTMA prepared by SARA ATRP was characterized by ^{1}HNMR spectroscopy (Figure 7). The characteristic signals of the polymer assigned agree with those reported in the literature.[29, 30] Additionally, the presence of the active chain-end at 4.14 ppm (h) (1H, –CHCl) and the presence of the alkyne moiety at 2.73 ppm (a) (1H, HC≡C–) were identified.

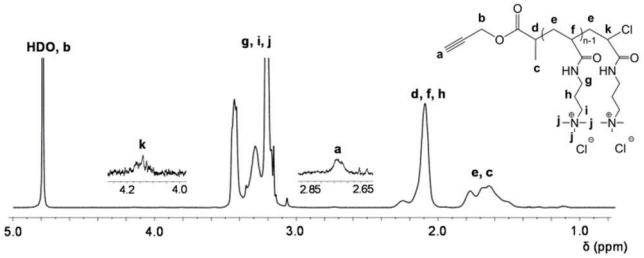


Figure 7. 500 MHz ^{1}H NMR spectrum, in D_2O, of purified alkyne-terminated PAMPTMA (M_n^{SEC} = 9600; $Đ$ = 1.17) obtained by SARA ATRP. Reaction conditions: $[AMPTMA]_0/[ECP]_0/[Me_6TREN]_0/[CuCl_2]_0$ = 50/1/0.5/1.0; $[AMPTMA]_0$ = 1.45 M; Cu(0) wire: *l* = 10 cm; *d* = 1 mm; $V_{solvent}$ = 5 mL; EtOH/H_2O = 40/60 (v/v).

To confirm that these polymers can participate in "click" reactions, an alkyne-terminated PAMPTMA sample was coupled with an azide-terminated non-fluorescent coumarin derivative (3-azido-7-diethylaminocoumarin), through Huisgen 1,3-dipolar cycloaddition. Coumarin was chosen since it is often used in the biomedical field.[48] Moreover, upon the formation of the triazole ring, the 3-azido-7-diethylaminocoumarin becomes fluorescent (Figure SF4), which makes the material applicable to imaging applications.[33] The success of the "click" reaction was confirmed by the appearance of the triazole ring proton signal (e) at 8.59 ppm[49] in the ^{1}H NMR spectrum of the purified product (Figure 8).

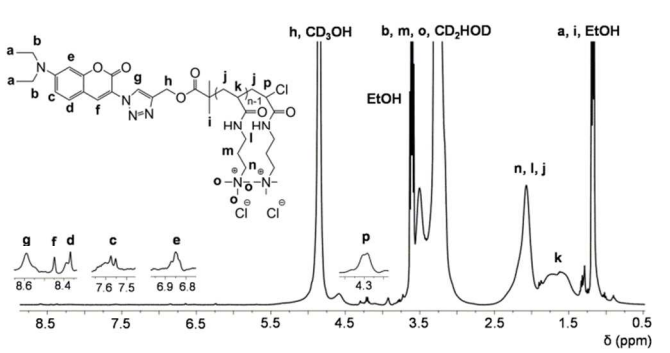


Figure 8. 400 MHz ^{1}H NMR spectrum, in CD_3OD, of purified coumarin-functionalized PAMPTMA obtained by a "click" reaction.

Conclusions

Well controlled polymers of AMPTMA were synthesized under environmentally friendly conditions using SARA ATRP. The conditions for the polymerization of AMPTMA were optimized for various targets such as low catalyst concentrations or narrow molecular weight distributions. Remarkably, the reaction could be performed in aqueous medium, using a relatively low amount of soluble $CuCl_2$ (1000 ppm) with 2-fold excess of Me_6TREN ligand, at ambient temperature. In addition to narrow molecular weight distributions, the polymers had a high degree of livingness as confirmed by both self-blocking chain extension and preparation of a well-defined PAMPTMA-*b*-POEOA block copolymer. Finally, a reactive moiety was introduced onto the initiator giving PAMPTMA with an end-group. This alkyne group was subsequently reacted with an azido- functionalized coumarin derivative using "click" chemistry giving a fluorescent PAMPTMA molecule.

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Notes and references

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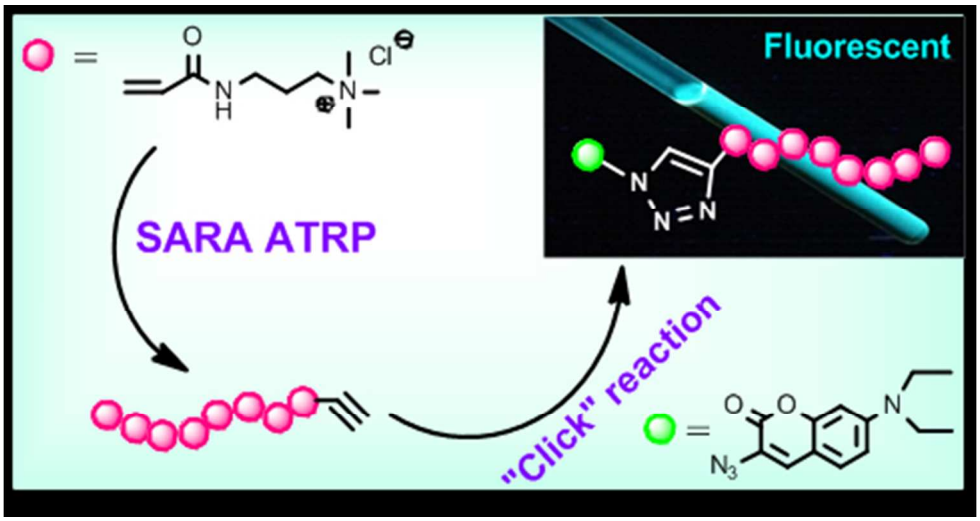
Electronic Supplementary Information (ESI) available: kinetic plots of the SARA ATRP of AMPTMA for different ligands and Cu(0) wire lengths; ^{1}H NMR spectrum of the PAMPTMA-*b*-POEOA.See DOI: 10.1039/b000000x/

1. W. A. Braunecker and K. Matyjaszewski, *Prog. Polym. Sci.*, 2007, **32**, 93-146.
2. M. Kamigaito, T. Ando and M. Sawamoto, *Chem. Rev.*, 2001, **101**, 3689-3746.
3. K. Matyjaszewski and N. V. Tsarevsky, *Nat. Chem.*, 2009, **1**, 276-288.
4. K. Matyjaszewski and J. Xia, *Chem. Rev.*, 2001, **101**, 2921-2990.
5. T. Guliashvili, P. V. Mendonça, A. C. Serra, A. V. Popov and J. F. J. Coelho, *Chem. Eur. J.*, 2012, **18**, 4607-4612.
6. F. di Lena and K. Matyjaszewski, *Prog. Polym. Sci.*, 2010, **35**, 959-1021.
7. K. Matyjaszewski, *Macromolecules*, 2012, **45**, 4015-4039.
8. W. Jakubowski and K. Matyjaszewski, *Angew. Chem., Int. Ed.*, 2006, **45**, 4482-4486.
9. A. J. D. Magenau, N. C. Strandwitz, A. Gennaro and K. Matyjaszewski, *Science*, 2011, **332**, 81-84.
10. K. Matyjaszewski, W. Jakubowski, K. Min, W. Tang, J. Huang, W. A. Braunecker and N. V. Tsarevsky, *Proc. Natl. Acad. Sci. U.*, 2006, **103**, 15309-15314.
11. Y. Zhang, Y. Wang and K. Matyjaszewski, *Macromolecules*, 2011, **44**, 683-685.
12. C. M. R. Abreu, P. V. Mendonca, A. C. Serra, J. F. J. Coelho, A. V. Popov and T. Guliashvili, *Macromol. Chem. Phys.*, 2012, **213**, 1677-1687.
13. R. A. Cordeiro, N. Rocha, J. P. Mendes, K. Matyjaszewski, T. Guliashvili, A. C. Serra and J. F. J. Coelho, *Polym. Chem.*, 2013, **4**, 3088-3097.
14. P. V. Mendonca, A. C. Serra, J. F. J. Coelho, A. V. Popov and T. Guliashvili, *Eur. Polym. J.*, 2011, **47**, 1460-1466.
15. N. Rocha, P. V. Mendonca, J. P. Mendes, P. N. Simoes, A. V. Popov, T. Guliashvili, A. C. Serra and J. F. J. Coelho, *Macromol. Chem. Phys.*, 2013, **214**, 76-84.
16. C. M. R. Abreu, P. V. Mendonca, A. C. Serra, A. V. Popov, K. Matyjaszewski, T. Guliashvili and J. F. J. Coelho, *ACS Macro Lett.*, 2012, **1**, 1308-1311.
17. C. M. R. Abreu, A. C. Serra, A. V. Popov, K. Matyjaszewski, T. Guliashvili and J. F. J. Coelho, *Polym. Chem.*, 2013, **4**, 5629-5636.
18. D. Konkolewicz, P. Krys, J. R. Góis, P. V. Mendonça, M. Zhong, Y. Wang, A. Gennaro, A. A. Isse, M. Fantin and K. Matyjaszewski, *Macromolecules*, 2014, **47**, 560–570.
19. S. B. Lee, R. R. Koepsel, S. W. Morley, K. Matyjaszewski, Y. Sun and A. J. Russell, *Biomacromolecules*, 2004, **5**, 877-882.
20. S. K. Samal, M. Dash, S. Van Vlierberghe, D. L. Kaplan, E. Chiellini, C. van Blitterswijk, L. Moroni and P. Dubruel, *Chem. Soc. Rev.*, 2012, **41**, 7147-7194.
21. R. Fu and G.-D. Fu, *Polym. Chem.*, 2011, **2**, 465-475.
22. P. L. Golas and K. Matyjaszewski, *QSAR Comb. Sci.*, 2007, **26**, 1116-1134.
23. V. Ladmiral, G. Mantovani, G. J. Clarkson, S. Cauet, J. L. Irwin and D. M. Haddleton, *J. Am. Chem. Soc.*, 2006, **128**, 4823-4830.
24. S. Bayati, K. Zhu, L. T. T. Trinh, A.-L. Kjoniksen and B. Nystrom, *J. Phys. Chem. B*, 2012, **116**, 11386-11395.
25. A. Dedinaite, E. Thormann, G. Olanya, P. M. Claesson, B. Nystrom, A.-L. Kjoniksen and K. Zhu, *Soft Matter*, 2010, **6**, 2489-2498.
26. A. Shovsky, S. Knohl, A. Dedinaite, K. Zhu, A.-L. Kjoniksen, B. Nystrom, P. Linse and P. M. Claesson, *Langmuir*, 2012, **28**, 14028-14038.
27. L. Oddo, G. Masci, C. Di Meo, D. Capitani, L. Mannina, R. Lamanna, S. De Santis, F. Alhaique, T. Coviello and P. Matricardi, *Acta Biomater.*, 2010, **6**, 3657-3664.
28. A. Tamura, M. Nishi, J. Kobayashi, K. Nagase, H. Yajima, M. Yamato and T. Okano, *Biomacromolecules*, 2012, **13**, 1765-1773.
29. M. L. Patrizi, M. Diociaiuti, D. Capitani and G. Masci, *Polymer*, 2009, **50**, 467-474.
30. S. Utsel, E. E. Malmstrom, A. Carlmark and L. Wagberg, *Soft Matter*, 2010, **6**, 342-352.
31. Y. Zhang, Y. Wang, C.-h. Peng, M. Zhong, W. Zhu, D. Konkolewicz and K. Matyjaszewski, *Macromolecules*, 2011, **45**, 78-86.
32. G. J. P. Britovsek, J. England and A. J. P. White, *Inorg. Chem.*, 2005, **44**, 8125-8134.
33. K. Sivakumar, F. Xie, B. M. Cash, S. Long, H. N. Barnhill and Q. Wang, *Org. Lett.*, 2004, **6**, 4603-4606.
34. Q. Zhang, P. Wilson, Z. Li, R. McHale, J. Godfrey, A. Anastasaki, C. Waldron and D. M. Haddleton, *J. Am. Chem. Soc.*, 2013, **135**, 7355-7363.
35. D. Konkolewicz, Y. Wang, M. Zhong, P. Krys, A. A. Isse, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 8749-8772.
36. K. Matyjaszewski, S. Coca, S. G. Gaynor, M. Wei and B. E. Woodworth, *Macromolecules*, 1997, **30**, 7348-7350.
37. N. V. Tsarevsky, T. Pintauer and K. Matyjaszewski, *Macromolecules*, 2004, **37**, 9768-9778.
38. S. Averick, A. Simakova, S. Park, D. Konkolewicz, A. J. D. Magenau, R. A. Mehl and K. Matyjaszewski, *ACS Macro Lett.*, 2011, **1**, 6-10.
39. D. Konkolewicz, A. J. D. Magenau, S. E. Averick, A. Simakova, H. He and K. Matyjaszewski, *Macromolecules*, 2012, **45**, 4461-4468.
40. A. Simakova, S. E. Averick, D. Konkolewicz and K. Matyjaszewski, *Macromolecules*, 2012, **45**, 6371-6379.
41. N. V. Tsarevsky, W. A. Braunecker and K. Matyjaszewski, *J. Organomet. Chem.*, 2007, **692**, 3212-3222.
42. A. Anastasaki, C. Waldron, P. Wilson, R. McHale and D. M. Haddleton, *Polym. Chem.*, 2013, **4**, 2672-2675.
43. T. Pintauer and K. Matyjaszewski, *Chem. Soc. Rev.*, 2008, **37**, 1087-1097.
44. Y. Wang, M. Zhong, W. Zhu, C.-H. Peng, Y. Zhang, D. Konkolewicz, N. Bortolamei, A. A. Isse, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 3793-3802.

45. N. Chan, M. F. Cunningham and R. A. Hutchinson, *Polym. Chem.*, 2012, **3**, 486-497.
46. S. Harrisson, P. Couvreur and J. Nicolas, *Macromolecules*, 2012, **45**, 7388-7396.
47. M. Zhong, Y. Wang, P. Krys, D. Konkolewicz and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 3816-3827.
48. S. R. Trenor, A. R. Shultz, B. J. Love and T. E. Long, *Chem. Rev.*, 2004, **104**, 3059-3078.
49. S. Martwiset, O. Yavuzcetin, M. Thorn, C. Versek, M. Tuominen and E. B. Coughlin, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 188-196.



Supplemental activator and reducing agent atom transfer radical polymerization (SARA ATRP) of the cationic monomer (3-acrylamidopropyl)trimethylammonium chloride (AMPTMA) was successfully performed for the first time in ecofriendly conditions.
82x43mm (150 x 150 DPI)