SET-LRP of the Hydrophobic Biobased Menthyl Acrylate

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ABSTRACT: Cu(0) wire-catalyzed single electron transfer-living radical polymerization (SET-LRP) of (-)-menthyl acrylate, a biobased hydrophobic monomer, was investigated at 25 ºC in ethanol, *iso*-propanol, ethyl lactate, 2,2,2-trifluoroethanol (TFE) and 2,2,3,3-tetrafluoropropanol (TFP). All solvents are known to promote, in the presence of N-ligands, the mechanistically required self-regulated disproportionation of Cu(I)Br into Cu(0) and Cu(II)Br_2. Both fluorinated alcohols brought out their characteristics of universal SET-LRP solvents and showed the proper polarity balance to mediate an efficient polymerization of this bulky and hydrophobic monomer. Together with the secondary alkyl halide initiator, methyl 2-bromopropionate (MBP) and the tris(2-dimethylaminoethyl)amine (Me_6-TREN) ligand, TFE and TPF mediated an efficient SET-LRP of MnA at room temperature that proceeds through a self-generated biphasic system. The results presented here demonstrate that Cu(0) wire-catalyzed SET-LRP can be used to target polyMnA with different block lengths and narrow molecular weight distribution at room temperature. Indeed, the use of a combination of techniques that includes GPC, ^{1}H NMR, MALDI-TOF MS performed before and after thioetherification of bromine terminus *via* "thio-bromo" click chemistry, and *in situ* reinitiation copolymerization experiments supports the near perfect chain end functionality of the synthesized biobased hydrophobic polymers. These results expand the possibilities of SET-LRP into the area of renewable resources where hydrophobic compounds are widespread.

Keywords: living radical polymerization, SET-LRP, renewable resources, well-defined polymers

INTRODUCTION

During the past decade, many methodologies to practice single-electron transfer living radical polymerization (SET-LRP) have been developed because of intensive research efforts undertaken in different laboratories.[1,2,3,4,5,6,7] The continuous evolution of this technique, which evolved from studies on the metal-catalyzed LRP of vinyl chloride,[8,9,10] has made available today a diversity of methodologies that differ in the way to present Cu(0) catalyst to the rest of reagents (i.e. monomer, initiator, ligand, an solvent).[1] Nowadays, SET-LRP practitioners not only can use almost any form of Cu(0) (e.g. powder,[11] nanopowder,[12] activated[13,14] and non-activated[15] wire,[16] coins,[17] and bars[18]), but also Cu(0) nanoparticles prepared *via* disproportionation of Cu(I)Br and used *ex situ* and *in situ*.[19,20,21,22,23] Cu(0) nanoparticles can also be prepared *in situ* from the reduction of $Cu(II)Br_2$ by sodium borohydride ($NaBH_4$)[24,25] or alternative reducing agents.[26]

Studies and developments on the key-role of solvent on SET-LRP have also constituted an indisputable step forward.[27,28,29,30,31,32,33,34] SET-LRP requires the use of solvents favoring the disproportionation of Cu(I)X into Cu(0) and $Cu(II)X_2$. Originally, the success of this LRP technique was thought to be contingent upon the solubility of targeted monomers and polymers in polar solvents (e.g. DMSO, DMF, alcohols, and water). Such solvents in the presence of ligands such as tris(2-dimethylaminoethyl)amine (Me_6-TREN), tris(2-aminoethyl)amine (TREN) and branched poly(ethyleneimine) (PEI), that destabilize Cu(I)X *via* preferentially binding to $Cu(II)X_2$,[35,36] promote the mechanistically required disproportionation of Cu(I)X into Cu(0) activator and $Cu(II)X_2$ deactivator.[29] In fact, in the presence of polar and non-polar non-disproportionating solvents such as CH_3CN and specially toluene, in which both Cu(I)X and $Cu(II)X_2$ are not sufficiently soluble, a significant loss of chain-end functionality is observed as the conversion increases.[27] However, good molecular weight control, high-level retention of chain end functionality and high monomer conversions has been observed in "self-generated" SET-LRP systems in which polymer phase-separates from the homogeneous reaction mixture above or after reaching a certain molecular weight.[37,38,39,40,41,42,43] The first "self-generated" biphasic system was first observed during the synthesis of poly(methyl acrylate) (PMA) with M_n = 1,600,000 g/mol in DMSO.[42]

The same phenomenon was also observed during the polymerization of butyl acrylate (BA) in the same solvent.[43] Later, polymers with highly hydrophobic character such as poly(lauryl acrylate), and poly(stearyl acrylate) could be obtained with high level of control via "self-generated" biphasic systems in *iso*-propanol (^{i}PrOH).[37,39] A biphasic system also evolved from the SET-LRP of 2-ethylhexyl acrylate in 2,2,2-trifluoroethanol (TFE).[38] All these reports inspired the elaboration organic solvent/water "programmed" biphasic systems that relies on the unexpected immiscibility between a solution of water containing Cu(II)Br_2 and a ligand with organic solvents, including water miscible organic solvents, containing monomer and polymer.[44,45,46,47,48,49,50] Of particular interest are combinations of polar and/or non-polar non-disproportionating solvents with water because they overcome the inherent SET-LRP requirements to use polar disproportionating solvents.[45,47]

Since its invention, SET-LRP has been widely used by researchers working at the interface of polymer science with biology and medicine.[3,7] The derivation of renewable resources to well-defined polymers has recently experienced a remarkable resurgence to meet contemporary sustainability challenges.[51,52] In this context, SET-LRP has been demonstrated as a very efficient LRP technique to produce well-defined glycopolymers[53,54,55] as well as to prepare graft-copolymers from natural polysaccharides[56,57] and polymer-protein conjugates.[58,59,60] As mentioned above, it has also been used to deliver well-defined polymers up to 10,000 g/mol from biobased lauryl and stearyl acrylates.[37,39] However, the polymerization of highly hydrophobic and bulky monomers derived from terpenes, terpenoids and rosin has not been investigated so far.[61] In this publication, we report the SET-LRP of the hydrophobic and biobased (-)-menthyl acrylate (MnA) in a series of alcohols, i.e. ethanol (EtOH),[31,44,50,62] ^{i}PrOH,[37,39,63] ethyl lactate (EtLa),[64] TFE,[38,65,66,67,68] and 2,2,3,3-tetrafluoropropanol (TFP)[65,66,67,68,69]) that previously demonstrated promising properties SET-LRP solvents. Among them, the two fluorinated alcohols demonstrated the best performance using hydrazine-activated Cu(0) wire as catalyst, the secondary alkyl halide initiator, methyl 2-bromopropionate (MBP) and the tris(2-dimethylaminoethyl)amine (Me_6-TREN) ligand. The polymerization of this terpenoid-derived monomer proceeds through a self-

generated biphasic reaction mixture without compromising the creation of well-defined polymers with near perfect chain end functionality.

EXPERIMENTAL SECTION

Materials. (-)-Menthol (Mn, ≥ 99 %, Sigma Aldrich), acryloyl chloride (96%, Sigma Aldrich), methyl 2-bromopropionate (MBP, 98%, Sigma Aldrich), tris[2-(dimethylamino)ethyl]amine (Me_6-TREN, 97%, Sigma Aldrich), hydrazine hydrate (60%, hydrazine, Sigma Aldrich), *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitril (DCTB, ≥ 98%, Sigma Aldrich, 98%), potassium trifluoroacetate (KTFA, Sigma Aldrich), 2,2,2-trifluoroethanol (TFE, ≥ 99%, Merck), 2,2,3,3-tetrafluoropropanol (TFP, 99%, Molekula), dimethylsulfoxide (DMSO, ≥ 99.7%, Sigma Aldrich) and methanol (MeOH, HPLC grade Scharlab) were used as received. Butyl acrylate (BA, 99%, Sigma Aldrich) was passed through a short column of basic Al_2O_3 prior to use in order to remove the radical inhibitor. EtLa (ethyl 2-hydroxypropionate, natural >98%, Sigma Aldrich) was passed through a short column of basic Al_2O_3 before to use in order to remove the peroxide residues.[70] Triethylamine (≥ 99% , Scharlab), was distilled before to use under calcium hydride. Other solvents were purchased from Panreac and used as received except dichloromethane (DCM) that was freshly distilled on calcium hydride. Copper(0) wire 99.9% pure of 20 gauge, purchased from Creating Unkamen, was activated using a deoxygenated solution of hydrazine hydrate in DMSO following a previously reported procedure.[13] Menthyl acrylate (MnA) was synthesized by esterification of the corresponding alcohol with acryloyl chloride in the presence of trimethylamine following a reported procedure (Scheme 1a).[71]

Methods. 400 MHz ^{1}H-NMR spectra were recorded on a Varian VNMR-S400 NMR instrument at 25 ºC in $CDCl_3$ with tetramethylsilane as an internal standard. For chain end analysis of low molecular weight polyMnA by ^{1}H-NMR a delay time (D1) of 10 s and a minimum number of 150 scans (nt) were used. Gel permeation chromatography (GPC) analysis was carried out with an Agilent 1200 series system equipped with three columns (PLgel 3 μm MIXED-E, PLgel 5 μm MIXED-D and PLgel 20 μm) from Polymer Laboratories) and an Agilent 1100 series refractive-index detector. THF (Panreac, HPLC grade) was used as eluents at a flow rate of 1.0 mL/min. The calibration curves for GPC analysis were

obtained using PSS ReadyCal poly(methyl methacrylate) (PMMA) standards. MALDI-TOF analysis was performed on a Voyager DE (Applied Biosystems) instrument with a 337-nm nitrogen laser (3-ns pulse width) using the following parameters in a linear ionization mode: accelerating potential = 25 kV, grid voltage = 93.5% and laser power = 1500 units. The analysis was performed using DCTB as matrix and KTFA as cationization agent. Samples for MALDI-TOF analysis were prepared as follows: THF solutions of DCTB (30 mg/mL), KTFA (10 mg/mL), and polyMnA (10 mg/mL) were prepared separately. The solution for MALDI-TOF analysis was obtained by mixing the matrix, polymer and salt solutions in a 9/1/1 volumetric ratio. Then five 2 μL drops of the mixture were spotted onto a MALDI plate and dried at room temperature before being subjected to analysis. Calorimetric studies were carried out on a Mettler DSC3+ thermal analyzers using N_2 as a purge gas (100 mL/min at scanning rate 20 °C/min in the -80 to 120 °C temperature range. Calibration was made using an indium standard (heat flow calibration) and an indium-lead-zinc standard (temperature calibration).

General Procedure for the SET-LRP of MnA in TFE. A solution of MnA (1 mL, 4.5 mmol), TFE (0.5 mL), Me_6-TREN (10.1 μL, 0.090 mol) and MBP (2.4 μL, 0.0090 mmol) was prepared in a 25 mL Schlenk flask. Then the removal of oxygen was accomplished by applying 4 freeze-pump (~1 min)-thraw cycles. After that, 4.5 cm of hydrazine-activated Cu(0) wire of 20 gauge wrapped around a Teflon-coated stirring bar was loaded under positive argon pressure. An additional freeze-pump (~1 min)-thraw cycle was applied before placing the flask in a water bath thermostated at 25 ºC with stirring. To monitor the monomer conversion, the side arm of the tube was purged with argon before it was opened to remove two drops of sample using an airtight syringe. Samples were dissolved in $CDCl_3$ to determine the monomer conversion by ^{1}H NMR spectroscopy. The M_n and M_w/M_n values were determined by GPC with polystyrene standards. Finally, to stop the reaction the Schlenk flask was opened to air and the polymerization mixture was dissolved in 2 mL of CH_2Cl_2. Then, the resulting solution was precipitated twice in 100 mL MeOH with vigorous stirring. Solvent was removed by filtration, and the final glassy white polymer was dried under vacuum until constant weight.

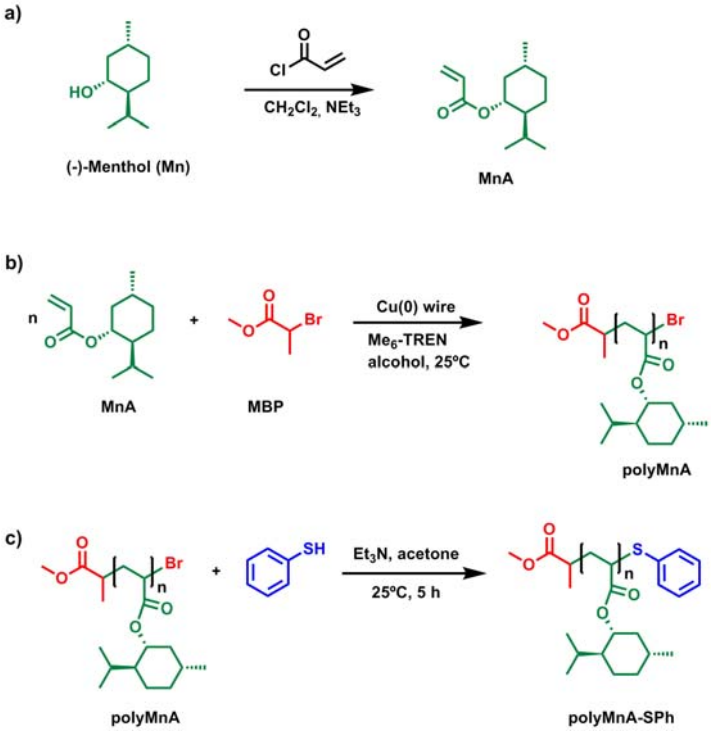
General Procedure for the Chain-End Modification of polyMnA *via* "Thio-Bromo" Click Reaction. A solution of polyMnA (0.2 g, M_n^{th} = 4841 g/mol) in acetone (1 mL) was prepared in a 10 mL vial equipped with a rubber septum. Next, thiophenol (12.5 μL, 0,123 mmol) and triethylamine (NEt_3, 17.1 μL, 0,123 mol) were added and the reaction mixture was stirred at room temperature over 5 h at. Finally, polyMnA-SPh was isolated by precipitation into 10 mL of MeOH with vigorous stirring and washed twice with fresh solvent. The final polymer was died under vacuum until constant weight before MALDI-TOF analysis.

General Procedure for the *in-situ* Chain Extension of PolyMnA with BA. A solution of the monomer (MnA, 1 mL, 4.5 mmol), solvent (0.5 mL), Me_6-TREN (4.81 μL, 0.018 mmol) and initiator (MBP, 20.10 μL, 0.18 mmol) was prepared in a 25 mL Schlenk tube. The reaction mixture was deoxygenated as described above by 4 freeze-pump (~1 min)-thaw cycles. Hydrazine-activated Cu(0) wire (4.5 cm of 20 gauge wire) wrapped around a Teflon-coated stirring bar was added under positive pressure of argon. After an additional freeze-pump (~1 min)-thaw cycle, the flask was placed in a water bath thermostated at 25 ºC with stirring. The SET-LRP was left to proceed for 5 h and then the monomer conversion was determined by ^{1}H NMR after sampling the reaction with an airtight syringe. Next, a deoxygenated solution containing 2.58 mL BA (0.018 mol) and 4.8 μl Me_6-TREN (0.018 mmol) in 1.3 mL TFE was injected. After 24 h, the conversion of BA was determined and the polymerization mixture was dissolved in 2 mL of CH_2Cl_2 before precipitating the final copolymer in 100 mL MeOH with vigorous stirring. The solvent was decanted off and the final sticky polymer was dried under vacuum until constant weight.

RESULTS AND DISCUSSION

Selection of solvent for SET-LRP of MnA. Finding a solvent with a proper polarity balance to both promote disproportionation of Cu(I)X, whilst retaining high solubility/swelling properties with respect to poly(menthyl acrylate) (polyMnA) was anticipated to be a key-point to succeed with the SET-LRP of

MnA. The monomer was synthesized by esterification of the corresponding alcohol with acryloyl chloride in the presence of triethylamine (Scheme 1a).[71]



Scheme 1. SET-LRP of the hydrophobic MnA: (a) synthesis of MnA, (b) SET-LRP of MnA initiated with MBP and catalyzed by Cu(0) wire/Me_6-TREN in alcohols, (c) "thio-bromo click" thioetherification of polyMnA using thiophenol.

This Mn-derived monomer is highly hydrophobic, and thus classic polar SET-LRP solvents are not expected to be a good choice to deliver an efficient SET-LRP process at 25ºC. After discarding dipolar aprotic solvents such as DMSO and DMF because of their undesirable health, safety, environmental problems and high price, we focused our attention to alcohols because are the most attractive SET-LRP solvents from a sustainability viewpoint.[62] Besides being most of them non-toxic, they have lower boiling points than dipolar aprotic solvents and are miscible with water at any composition and therefore can evolve into either homogeneous[38,63,72] or biphasic SET-LRP systems.[44,50] MeOH, the least expensive commercially available organic solvent, was unfortunately unable to solubilize MnA at room temperature. However, the good solubility of this biobased monomer in EtOH (MnA:EtOH = 2/1, v/v) encouraged us to first test the SET-LRP in this alcohol. Using methyl 2-bromopropionate (MBP) as monofunctional initiator, the polymerization was held over 8 h at room temperature under the following

conditions: $[MnA]_0/[MBP]_0/[Me_6\text{-}TREN]_0$ = 50/1/0.1, MnA = 1 mL, EtOH = 0.5 mL and 4.5 cm of hydrazine-activated Cu(0) wire of 20 gauge (Scheme 1b, Table 1 entry 1). Polymerization of MnA occurred, as indicated by a high monomer conversion (92%). However, despite the low targeted $[M]_0/[I]_0$, EtOH was not able to either solubilize or swell polyMnA. As can be seen in the image shown in Figure 1a, the polymer separated as a white solid from a green ethanolic solution, containing residual monomer and catalyst. GPC analysis revealed poor control of the molecular weight distribution (M_w/M_n = 3.40) and brought out clear evidences of radical bimolecular coupling processes (see shoulder peak at higher molecular weight position in Figure 1a, bottom). Inspired by previous reports from our laboratory and others, EtLa[64] and ^{i}PrOH[37,39,63] were tested as solvents for the SET-LRP of MnA under identical conditions.

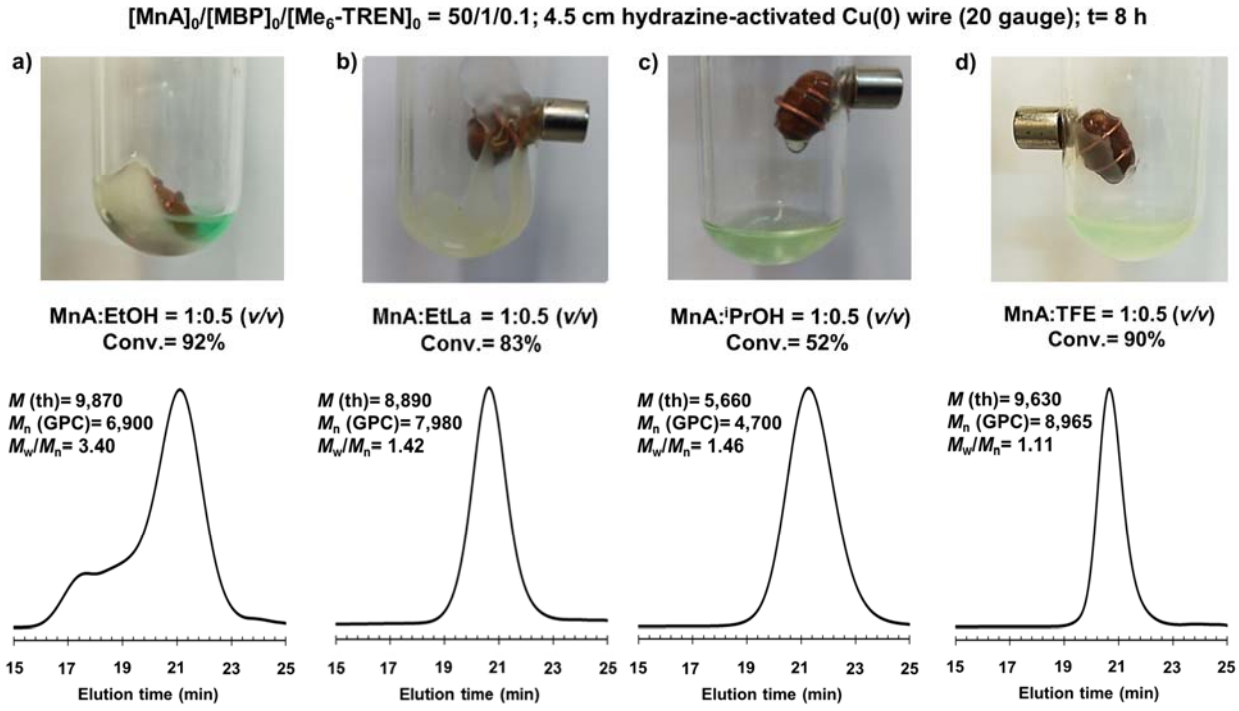


Figure 1. Visualization of the reaction mixture, monomer conversion and GPC chromatograms after the SET-LRP of MnA initiated with MBP in (a) EtOH, (b) EtLa, (c) ^{i}PrOH, and (d) TFE. Reaction conditions: MnA = 1 mL, solvent = 0.5 mL, $[MnA]_0/[MBP]_0/[Me_6\text{-}TREN]$ = 50/1/0.1 using 4.5 cm of hydrazine-activated Cu(0) wire (20 gauge), reaction time = 8 h.

Table 1 SET-LRP of MnA initiated with MBP using 4.5 cm of hydrazine-activated Cu(0) wire (20 gauge) in various alcohols at 25º C. Reaction conditions: MnA = 1 mL, solvent = 0.5 mL.

Entry	Solvent	$[M]_0/[I]_0/[L]_0$	k_p^{app} (min^{-1})	Time (min)	Conv. (%)	M (th) (g mol^{-1})	M_n (NMR)[c] (g mol^{-1})	M_n (GPC) (g mol^{-1})	M_w/M_n (GPC)
1	EtOH	50/1/0.1	-	480	92	9,870	-	6,900	3.40
2	EtLa	50/1/0.1	-	480	83	8,890	-	7,980	1.42
3	^{i}PrOH	50/1/0.1	-	480	52	5,660	-	4,700	1.46
4	TFE	50/1/0.1	-	480	90	9,630	-	8,965	1.11
5[a,b]	TFE	50/1/0.1	0.0058	400	82	8,680	-	7,312	1.13
6[b]	TFE	50/1/0.1	0.0052	310	80	8,580	9,246	7,880	1.10
7	TFE	100/1/0.1	0.0031	400	67	14,280	-	13,530	1.23
8	TFE	100/1/0.2	0.0042	300	73	15,600		14,325	1.15
9	TFE	100/1/0.5	0.0060	327	88	18,590	18,901	17,930	1.14
10	TFE	200/1/1	0.0037	410	78	32,980	33,850	32,220	1.17
11	TFE	25/1/0.1	0.0089	270	90	4,900	4,934	4,690	1.14
12	TFP	50/1/0.1	0.0071	276	84	9,000	-	8,900	1.14

[a] Non-activated Cu(0) wire (20 gauge) was used. [b] MnA:TFE = 1:1, v/v was used. [c] From end group analysis.

We recently reported that EtLa is an attractive environmentally friendly solvent for the SET-LRP of both hydrophilic and hydrophobic monomers.[64] ^{i}PrOH has also been widely used to practice the SET-LRP of a variety of vinyl monomers under homogeneous conditions as well as challenging long chain hydrophobic monomers such as lauryl and stearyl acrylates through "self-generated" biphasic systems.[37,39,63] On one hand, Cu(0) wire-catalyzed SET-LRP in EtLa reached 83% conversion in 8 h (Table 1 entry 2). The GPC analysis of the resulting polymer was symmetric with no tailing or shoulder peak (Figure 1b, bottom). However, M_w/M_n was quite far from the expected value for a well-defined polymer (M_w/M_n = 1.42). PolyMnA did not precipitate in this agrochemical solvent but the reaction mixture showed slight opaqueness at the end of the process (Figure 1b, up). Nevertheless, EtLa was able to swell polyMnA and no sign of precipitation was observed. On the other hand, the reaction mixture in ^{i}PrOH was a green one-phase solution with no visual sign of insolubility (Figure 1c, up). Unfortunately, the polymerization of MnA in this alcohol achieved only 52% conversion after 8 h under these conditions (Table 1 entry 3). GPC analysis revealed the formation of polyMnA with M_n = 4,700 g/mol and M_w/M_n = 1.46 (Figure 1c, bottom).

Fluorinated alcohols such as TFE and TFP have been coined "universal solvents" for SET-LRP, as they open the possibility of polymerizing a broad polarity spectrum of monomers.[38,65,66,67,68,69] In fact, the SET-LRP of MnA in TFE provided encouraging results (Figure 1d). The polymerization of MnA in TFE resulted in polyMnA with M_n = 8,964 g/mol at 90% conversion (Table 1 entry 4). The final polymer was well-defined as indicated by a perfectly symmetric GPC peak (M_w/M_n = 1.11) regardless the reaction mixture was greenish with some turbidity at the end of the SET-LRP process. This aspect will be discussed in detail later in this manuscript. These solvent screening experiments provided an initial starting point to study on the SET-LRP of MnA in TFE.

SET-LRP of MnA in TFE catalyzed by Cu(0) wire. Both TFE and TFP are unique SET-LRP solvents because activate *in situ* commercial Cu(0) wire by themselves.[68] It is well-known that Cu(0) wire is more reactive without its characteristic oxide layer and different activation protocols are usually applied to practice with this SET-LRP methodology.[1] The Cu_2O/CuO layer on the surface of any commercial Cu(0) wire is responsible, in most of the cases, of the induction periods reported for SET-LRP reactions. Hence, the first kinetic experiments to study in-depth the SET-LRP of MnA in TFE was carried out using commercially available non-activated Cu(0) wire (4.5 cm of 20 gauge wire) under the following conditions $[MnA]_0/[MBP]_0/[Me_6\text{-TREN}]_0$ = 50/1/0.1. Despite using MnA:TFE =1:1, v/v, the SET-LRP showed an induction period of approximately 90 min with no reaction after which, the polymerization proceeded fulfilling all the expected characteristics for a LRP process (Figure 2a). Thus, the $\ln[M]_0/[M]$ increases linearly up to approximately 80% conversion suggesting that concentration of propagating radicals remains constant throughout the entire process. Moreover, a linear evolution of molecular weight with conversion and the formation of a polyMnA with narrow molecular weight was also observed. Consistently with the results presented in the previous subchapter, well-defined polyMnA with M_n = 7,312 g/mol and M_w/M_n = 1.13 was obtained at 82% conversion (Table 1, entry 5).

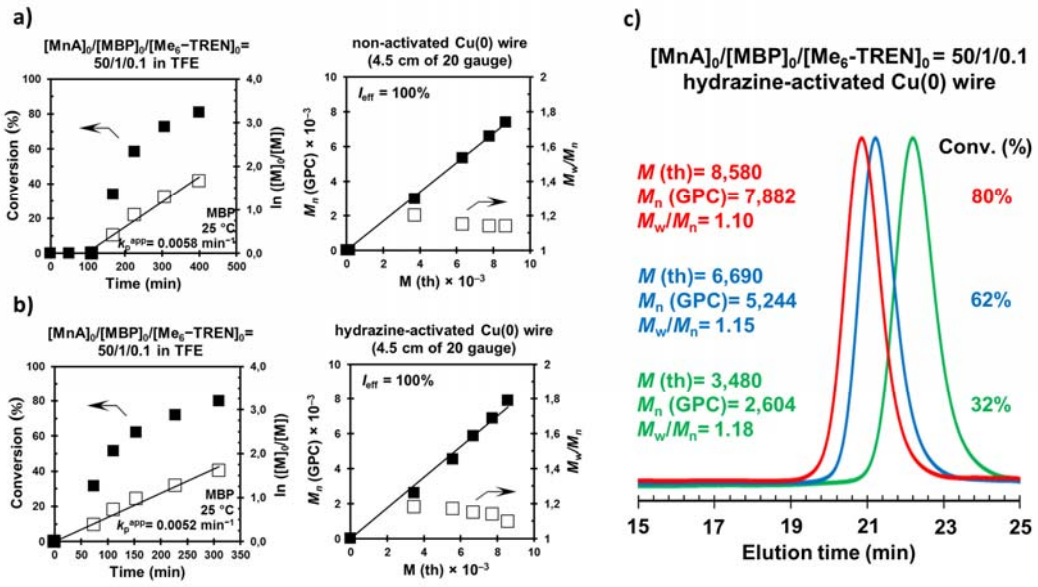


Figure 2. Conversion and ln([M]$_0$/[M]) *vs* time kinetic plots and experimental M_n (GPC) and M_w/M_n *vs* theoretical M(th) in SET-LRP of MnA in TFE initiated with MBP and catalyzed by (a) non-activated Cu(0) wire and (b) hydrazine-activated Cu(0) wire. (c) Representative GPC chromatograms of polyMnA obtained from kinetic experiment shown in (b). Reaction conditions: MnA = 1 mL, TFE = 1 mL, [MnA]$_0$/[MBP]$_0$/[Me$_6$-TREN] = 50/1/0.1 using 4.5 cm of Cu(0) wire (20 gauge).

Upon switching to hydrazine-activated Cu(0) wire the long induction period disappeared (Figure 2b). It is important to note that polymerization proceeded over 80% conversion in 300 min with strictly the same k_p^{app} (k_p^{app} = 0.052 min^{-1}) to the experiment with the non-activated Cu(0) counterpart (k_p^{app} = 0.058 min^{-1}) (Table 1, entries 5 and 6). We do not know the reason for this induction period although this result may suggest that the activation of Cu(0) wire by TFE is not effective in highly hydrophobic reaction mixtures. Again, the kinetic and molecular weight/dispersity evolution plots together with chain end analysis, that will be discussed in another subchapter, are consistent with a LRP process. As previously noted, the reaction mixture was turbid and opaque at the end of the polymerization. As can be seen in Figure 3a-d, turbidity progressively appeared with increasing conversion, suggesting that phase separation occurs during polymerization of MnA in TFE. SET-LRP systems in which growing polymer chains precipitate out of the initially homogeneous mixture to generate a biphasic system consisting of a solvent swollen polymer-rich phase and a second organic phase containing the solvent, monomer and soluble Cu(II)X$_2$ species were named "self-generated" biphasic systems by Whittaker and

Haddleton laboratories.[41] Our group and others observed this phenomenon during the polymerization of various hydrophobic monomers (i.e. butyl acrylate, 2-ethylhexyl acrylate, lauryl acrylate) in various solvents such as DMSO,[37,41,43] TFE,[38] ^{i}PrOH,[37,39] ethyl lactate,[64] and dimethyl lactamide.[40] Here, after centrifugation in air, the biphasic nature of the reaction mixture is clearly visible with an upper layer containing polyMnA swelled in TFE and a lower layer containing the residual monomer, ligand and Cu(II)Br_2 dissolved in the remaining TFE. Despite the formation of a biphasic system, GPC analysis during the polymerization of MnA in TFE revealed the formation of polyMnA with narrow molecular weight distribution at all conversions, as indicated by low dispersity values (M_w/M_n = 1.2 – 1.10) (Figure 1c). Experimental molecular weight values (M_n (GPC)), as determined by GPC analysis with against PMMA standards, and theoretical values (M_n (th)) were in good agreement.

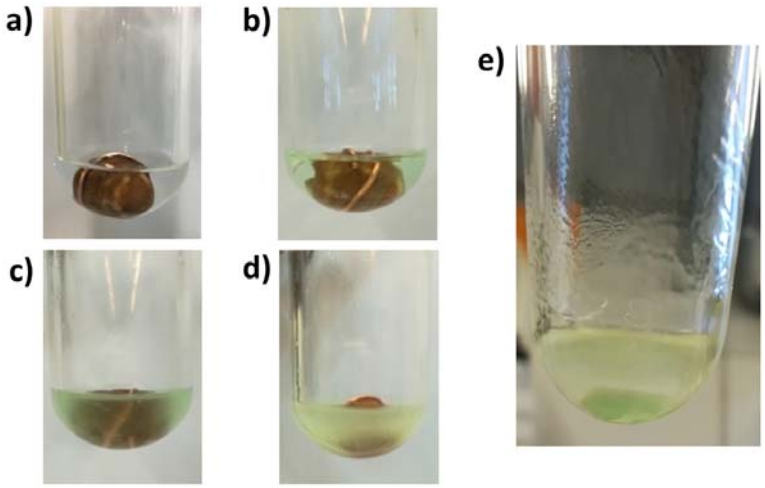


Figure 3. (a-d) Visualization of the progressive formation of a biphasic reaction mixture thorough the SET-LRP of MnA in TFE. Digital images were captured at 0% conv. (0 min), 40% conv. (100 min), 75% conv. (200 min) and 90% conv. (300 min). Reaction conditions: MnA = 1 mL, TFE = 0.5 mL, $[MnA]_0/[MBP]_0/[Me_6\text{-TREN}]$ = 50/1/0.1 using 4.5 cm of hydrazine-activated Cu(0) wire (20 gauge). (e) Digital image of the "self-generated" biphasic system at 94% conv. captured after centrifugation in air.

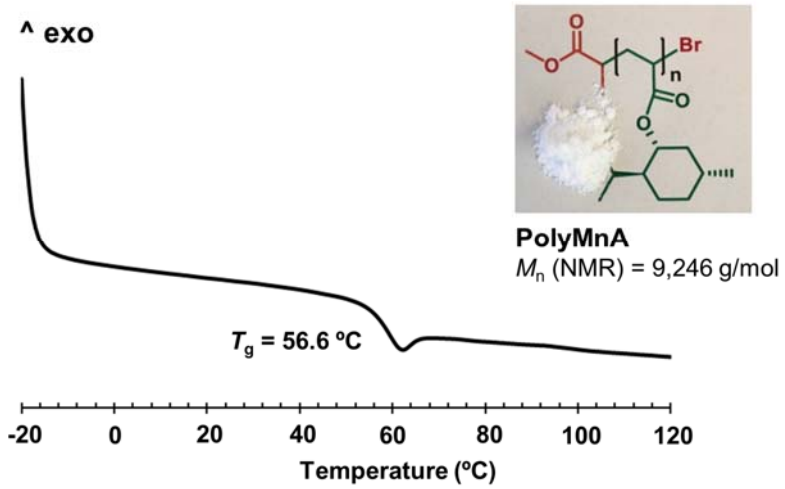


Figure 4. DSC analysis of PolyMnA with M_n (NMR) = 9,246 g/mol isolated after precipitation in MeOH (inset: digital image of the polymer).

PolyMnA with M_n (NMR) = 9,246 g/mol, isolated after precipitation in MeOH, is a glassy white solid (Figure 4). This polymer is soluble in THF, CH_2Cl_2, and acetone but insoluble in DMSO, acetonitrile, and EtOH. Because the glass transition temperature (T_g) of polyMnA is at around 55 ºC, this biobased polymer could be used as biocompatible glassy minority end-block in sustainable ABA thermoplastic elastomers.[73,74,75,76,77,78,79,80] The relatively high T_g of polyMnA is attributed to reduced polymer flexibility caused by structural rigidity and limited "free volume" of the pendant menthyl groups. Thermoplastic elastomers with hard-block T_g as low as 50 ºC are appealing for biomedical applications because the upper service temperatures of these materials is well above the body temperature.

Synthesis of high molecular weight polyMnA. We were interested in pushing the limits of this polymerization system by targeting higher molecular weight polymers. First, SET-LRP of MnA at $[M]_0/[I]_0$ = 100 was performed under the following conditions: $[MA]_0/[MBP]_0/[Me_6\text{-TREN}]_0$ = 100/1/0.1, MnA = 1mL, TFE = 0.5 mL using 4.5 cm of hydrazine-activated wire. However, using 10 mol% with respect to the initiator, the polymerization reached a plateau below 70% conversion (Table 1 entry 7).

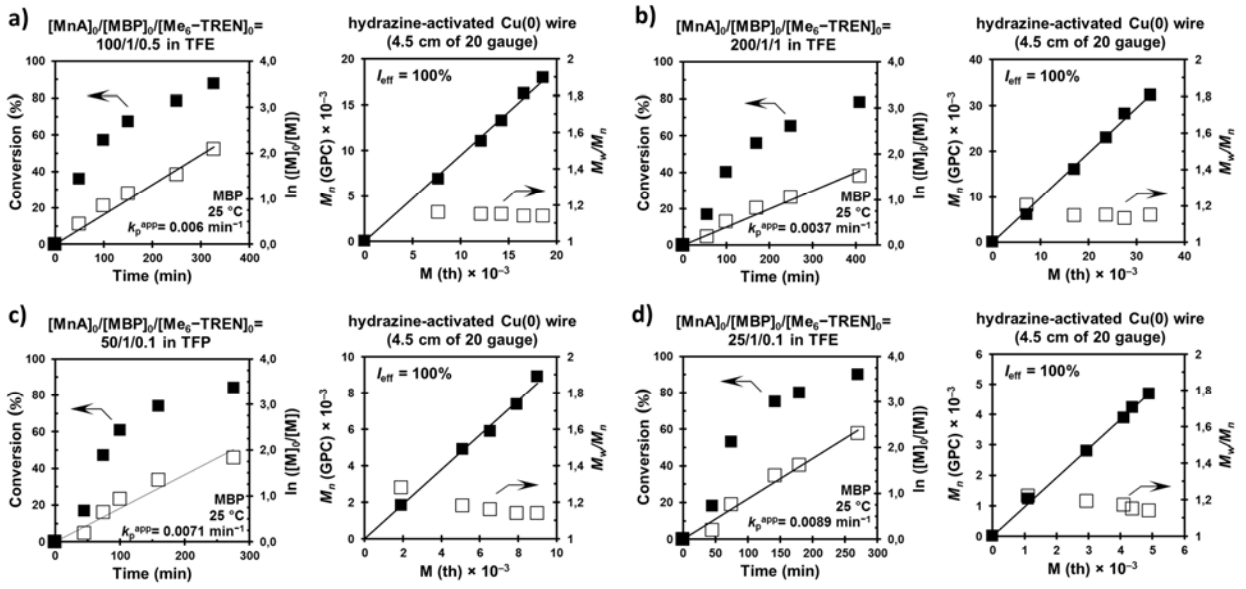


Figure 5. Conversion and ln([M]$_0$/[M]) *vs* time kinetic plots and experimental M_n (GPC) and M_w/M_n *vs* theoretical M(th) in SET-LRP of MnA in TFE or TFP initiated with MBP and catalyzed by hydrazine-activated Cu(0) wire. (a) [MnA]$_0$/[MBP]$_0$/[Me$_6$-TREN] = 100/1/0.5 in TFE, (b) [MnA]$_0$/[MBP]$_0$/[Me$_6$-TREN] = 200/1/1 in TFE, (c) [MnA]$_0$/[MBP]$_0$/[Me$_6$-TREN] = 50/1/0.1 in TFP, and (d) [MnA]$_0$/[MBP]$_0$/[Me$_6$-TREN] = 25/1/0.1 in TFE. Reaction conditions: MnA = 1 mL, solvent = 0.5 mL, 4.5 cm of Cu(0) wire (20 gauge).

Next, the SET-LRP of MnA at [M]$_0$/[I]$_0$ = 100 was performed increasing the ligand concentration with respect to the MBP to 20 mol% and 50 mol%. While polymerization in the presence of 0.2 equivalents of Me$_6$-TREN did still not exceed 75% conversion, with 0.5 equivalents of Me$_6$-TREN the ln[M]$_0$/[M] kinetic plot was linear up to almost 90% conversion (k_p^{app} = 0.0060 min^{-1}) (Figure 4a, Table 1 entries 8 and 9). The reason because higher molecular weight target requires higher concentration of ligand can be related to specific interactions between soluble copper species and TFE. These interactions, which are in competition with those with Me$_6$-TREN, may lead to bimolecular termination and limited conversion due to ineffective deactivation events. In previous publications, the use of concentrations of ligand higher than 10 mol% respect to the initiator was also necessary for the SET-LRP of N-(2-hydroxypropyl)methacrylamide[81] and 2-hydroxyethyl acrylate[82] in H$_2$O and MeOH, respectively. Note that in our study, the high ionizing power and strong hydrogen bond donating ability of TFE may increase this effect. In fact, the SET-LRP of 2-ethylhexyl acrylate[38] and di(ethylene glycol) 2-ethylhexyl

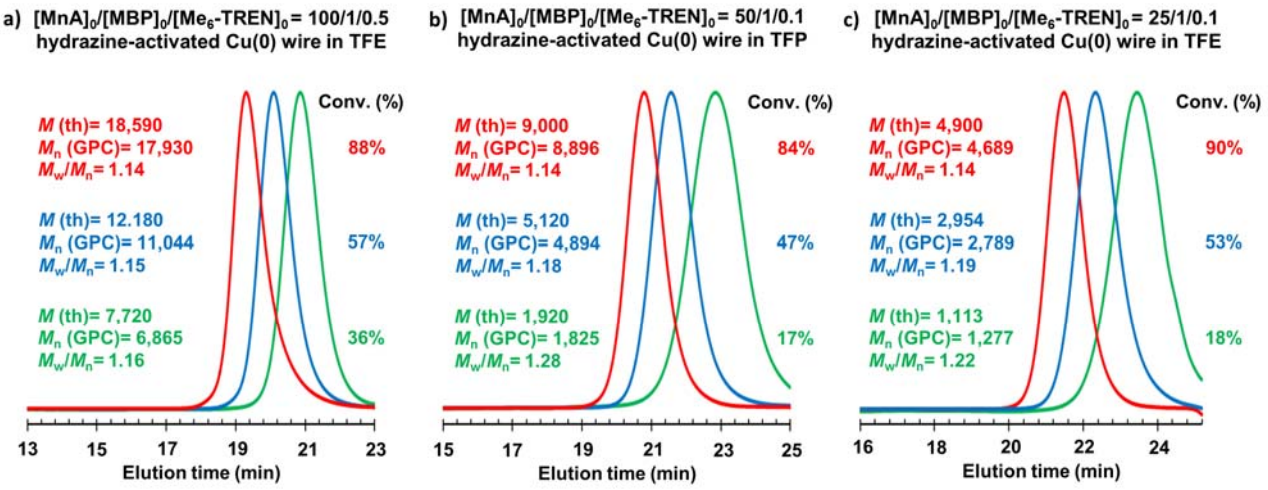


Figure 6. Representative GPC chromatograms of polyMnA from kinetic plots in SET-LRP of MnA in TFE or TFP initiated with MBP and catalyzed by hydrazine-activated Cu(0) wire. (a) $[MnA]_0/[MBP]_0/[Me_6\text{-TREN}] = 100/1/0.5$ in TFE, (b) $[MnA]_0/[MBP]_0/[Me_6\text{-TREN}] = 50/1/0.1$ in TFP, and (c) $[MnA]_0/[MBP]_0/[Me_6\text{-TREN}] = 25/1/0.1$ in TFE. Reaction conditions: MnA = 1 mL, solvent = 0.5 mL, 4.5 cm of Cu(0) wire (20 gauge).

ether acrylate[83] in TFE also required the use of higher concentration of Me_6-TREN to achieve optimum results. Thus, we were able to obtain polyMnA with M_n just below 20,000 g/mol and M_w/M_n = 1.14 (Figure 5a). At $[M]_0/[I]_0$ = 200, increasing the concentration of ligand from 0.5 to 1 equivalents with respect to the MBP, the polymerization also exhibited a linear first order kinetic plot reaching 80% conversion in less than 7 h (Figure 4b, Table 1 entry 10). These results demonstrate that molecular weight control of this system is not just limited to low target molecular weight. Higher molecular weight polyMnA isolated from these experiments were also characterized by DSC. The T_g value of polyMnA increased slightly with molecular weight. DSC analysis of the polymers with M_n (NMR) = 18,901 g/mol and M_n (NMR) = 33,850 g/mol showed T_g values at 60.1 ºC and 62.3 ºC, respectively.

SET-LRP of MnA in TFP. As mentioned above, both TFE and TFP are excellent SET-LRP solvents for the polymerization of both hydrophilic and hydrophobic acrylates.[38,65,66,67,68,69] Well-defined polyMnA could also be prepared in TFP. However, the use of TFE is more suitable because is less expensive and has a lower boiling point (73.6 ºC *vs* 107-109ºC). The polymerization of MnA in TFP using MBP as initiator and catalyzed by 4.5 cm of Cu(0) wire activated with hydrazine reached 84% conversion after 4.5 h (Figure 5c, Table 1 entry 12). The polymerization rate was similar that that

obtained using TFE as solvent (k_p^{app} = 0.0071 min^{-1} *vs* 0.0052 min^{-1}). A linear increase in M_n with conversion and narrow molecular weight distribution indicated the SET-LRP of MnA in TFP was well-controlled. The formation of a biphasic reaction micture also occurred in this case. Low, medium, and high conversion GPC chromatograms are shown in Figure 6b.

Chain-end analysis of polyMnA prepared by SET-LRP of MnA in TFE. To explore in detail the degree of control attained for the SET-LRP of MnA in TFE, polyMnA with theoretical degree of polymerization of 25 at 100% conversion was prepared to have a sample with molecular weight suitable for a precise determination of the percentage of the chain-end functionality by ^{1}H NMR analysis. At [M]/[I] = 25, kinetic and molecular weight dispersity plots were consistent with previous experiments and showed the typical features of a LRP process (Figure 5d). Despite the formation, also in this case, of a biphasic reaction mixture, GPC chromatograms at different conversions were symmetric without high/low molecular weight tailing (Figure 6c). The structural analysis of the final sample, isolated at 90% conversion by precipitation in MeOH, was carried out by ^{1}H NMR spectroscopy and MALDI-TOF MS spectrometry. The fraction of polyMnA chains that are capped with bromine atoms at the ω-terminus was determined to be 96% by the ratio between characteristic signals of both α and ω polymer terminus (see Figure 7).

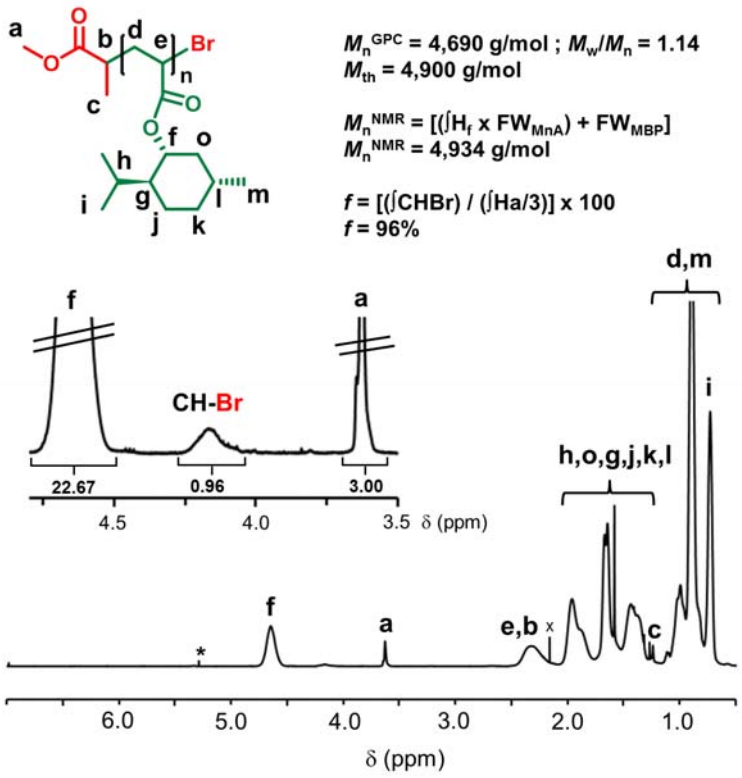


Figure 7. ^{1}H-NMR spectrum (400 MHz) of polyMnA isolated at 90% conversion (M_n^{GPC} = 4,690 Da, M_w/M_n = 1.14) from SET-LRP of MnA in TFE. Reaction conditions: MnA = 1 mL, solvent = 0.5 mL, $[MnA]_0/[MBP]_0/[Me_6\text{-TREN}]$ = 25/1/0.1 using 4.5 cm of Cu(0) wire (20 gauge). ^{1}H NMR resonances from residual CH_2Cl_2 and acetone are indicated with * and x, respectively.

Within the experimental error of the ^{1}H NMR measurement, this result supports the perfect or near perfect retention of chain end functionality achieved by this SET-LRP system. End group analysis of the final product by ^{1}H NMR was also used to determine the molecular weight M_n (NMR) (Figure 6). M_n (NMR) was also calculated for higher molecular weight samples (Table 1, entries 6, 9, and 10). In all cases, M_n (NMR) values are in reasonable agreement with theoretical values and M_n (GPC) values determined using PMMA standards. MALDI-TOF MS analysis before and after modifying the polyMnA bromine terminus with thiophenol *via* "thio-bromo" click chemistry[84,85] leaves no doubt about the outstanding degree of control attained by the SET-LRP of this bulky hydrophobic monomer in TFE (Scheme 1c and Figure 7).

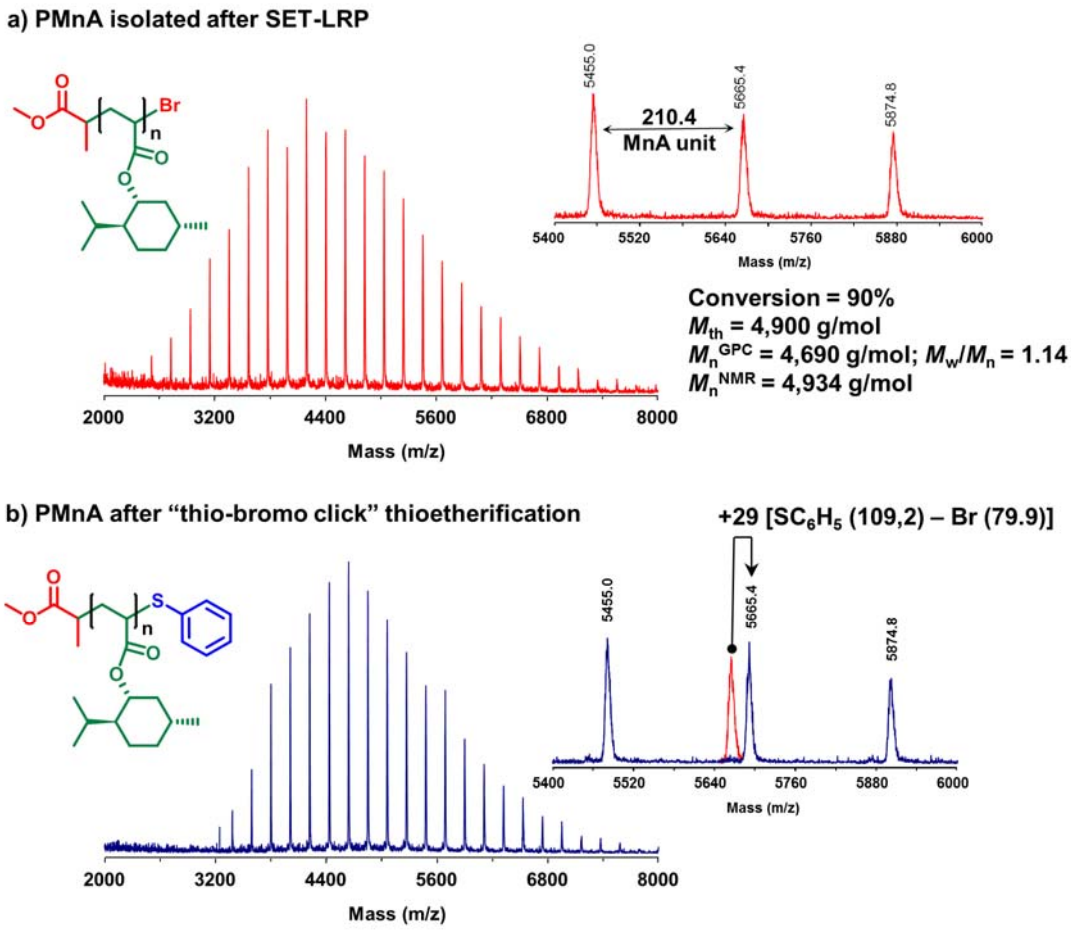


Figure 8. MALDI-TOF of polyMnA isolated at 90% conversion (M_n^{GPC} = 4,690 g/mol, M_w/M_n = 1.14) from SET-LRP of MnA in TFE (a) before and (b) after "thio-bromo click" reaction. Reaction conditions: MnA = 1 mL, solvent = 0.5 mL, $[MnA]_0/[MBP]_0/[Me_6\text{-TREN}]$ = 25/1/0.1 using 4.5 cm of Cu(0) wire (20 gauge). Red line in the expansion after modification shows the original peak corresponding to the bromo-terminated polyMnA.

PolyMnA isolated after SET-LRP shows a single distribution of peaks attributable to polyMnA-Br/K^+ species separated by 210.4 mass units (see Figure 7a, inset expansion). Delightfully, with the reaction of polyMnA with thiophenol in the presence of NEt_3 the original distribution completely vanishes and a new series of well-defined and symmetrical peaks emerges 29 units above the parent distribution (Figure 7b). This value is consistent with the increase in mass after the reaction of thiophenol at ω-polymer chain end. It should be noted that this reaction at the ω-polymer terminus was performed in acetone because polyMnA was not soluble in MeCN, the common solvent used for the "thio-bromo" click modification of conventional polyacrylates.[84,85]

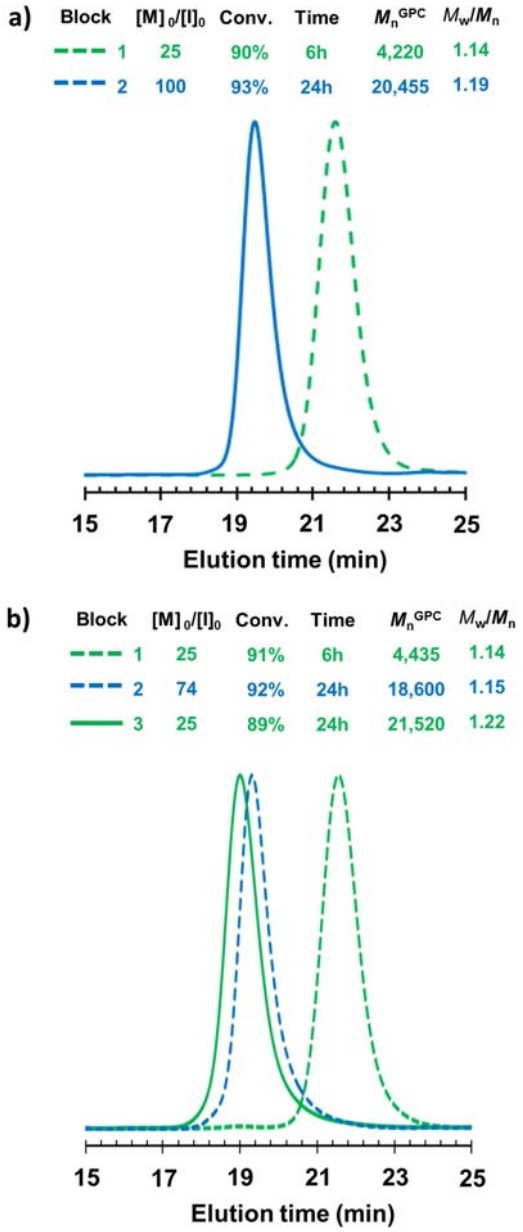


Figure 8. *In situ* chain extension from polyMnA. Initial conditions for block copolymerization: $[MnA]_0/[MBP]_0/[Me_6\text{-TREN}]$ = 25/1/0.1, MnA:TFE = 2:1 (v/v), 4.5 cm of hydrazine activated Cu(0) wire (20 gauge). Block copolymerization achieved by addition of a) BA (100 equiv.) and Me_6-TREN (0.1 equiv) in TFE (BA:TFE = 2:1 (v/v)) and b) BA (75 equiv.) and Me_6-TREN (0.1 equiv) in TFE (BA:TFE = 2:1 (v/v)) and MnA (25 equiv.) and Me_6-TREN (0.1 equiv) in TFE (MnA:TFE = 2:1 (v/v))

As an additional proof of the high chain ends fidelity of the synthesized polyMnA, *in situ* chain extension experiments from a low molecular weight polyMnA were carried out using BA. Figure 8a shows that the addition *via* cannula of a deoxygenated solution of BA and Me_6-TREN in TFE led to a clear and neat displacement of the polyMnA GPC curve while maintaining low dispersity. In another

experiment, two successive *in situ* chain extensions were carried out *via* sequential addition of two aliquots of BA and MnA to deliver multiblock poly(MnA)-*b*-poly(BA)-*b*-poly(MnA) with M_n = 21,520 g/mol and M_w/M_n = 1.23. Despite the compunds synthesized are not really strict AB or ABA block copolymers, these results open up new avenues to investigate the SET-LRP of other terpene-derived hydrophobic monomers[86,87] with the final goal to prepare innovative sustainable ABA thermoplastic elastomers from renewable resources or other multiblock structures with menthol units.[73,74,75,76,77,78,79,80] Experiments on these lines will be reported at due time.

Controlled LRP of MnA: SET-LRP *vs* ATRP

Hydrophobic and bulky compounds such as (-)-Mn are widespread in the realm of renewable resources. Although significant efforts have made in the past to create polymers from terpene-, terpenoid-, and rosin-derived monomers, the precise synthesis of well-defined polymers is receiving increasing attention. [87,88,89] In recent years, the popularity of SET-LRP has raised exponentially due to the possibility to deliver polymers with nearly 100% chain end fidelity at high conversion.[1] This is possible because only in SET-LRP, and not in atom transfer radical polymerization (ATRP), Cu(II)X_2 deactivator is produced *via* disproportionation without the need for bimolecular termination.[1,5,6,7] However, the SET-LRP of MnA was anticipated to be challenging due to its high hydrophobicity and bulkiness. In fact, hydrophobic monomers/polymers have been until recently the Achilles' heel of SET-LRP. Results reported here demonstrate that the use of fluorinated alcohols such as TFE in combination with a secondary alkyl halide initiator (MBP) and Me_6-TREN ligand allows the preparation of polyMnA with a range of targeted degrees of polymerization (DP = 25-200, M_n^{th} = 5,400-42,200) at room temperature. In spite of the appealing characteristics of MnA (e.g. optically active biomass-derived monomer) and the potential applications of the corresponding polymer,[71,90,91] according to our knowledge, the controlled LRP of this monomer received scarce attention until now. Only the Cu(I)X-mediated ATRP of MnA was previously investigated in anisole, a solvent with poor disproportionating properties, using various catalytic systems based on the air-sensitive Cu(I)Br.[92] The use of Cu(0) wire

in SET-LRP is much more convenient because offers an easier catalyst handling and recovery/recycling. In addition, Cu(0) wire-catalyzed SET-LRP tolerates oxygen from air,[93,94,95,96] because Cu(0) catalyst consumes the O_2 from the reaction mixture, and therefore can be practiced using simple N_2 sparging in a test tube[97] or even without deoxygenation protocols.[98] Best results for the ATRP of MnA were obtained using also Me_6-TREN as ligand and a secondary alkyl halide initiator (i.e. ethyl 2-bromopropionate). However, optimum ATRP polymerization conditions required much higher temperature (95ºC) than the SET-LRP system (25ºC). Unfortunately, detailed structural analysis of the polyMnA products prepared by ATRP was not reported. Conversely, the combination of ^{1}H NMR and MALDI-TOF MS before/after "thio-bromo" click chemistry as well as reinitiation copolymerization experiments presented here supports the near perfect chain end functionality of the polyMnA synthesized by SET-LRP.

Therefore, the SET-LRP system offers an environmentally friendly methodology operating at room temperature for the preparation of block, multiblock and more complex architectures based on this monomer and thus expand the already described medical applications of (-)-Mn. Moreover, they will expand the possibilities of SET-LRP into the area of renewable resources where hydrophobic compounds are widespread and will provide new opportunities for their application in the area of medicine and biomacromolecules. Although the use of fluorinated alcohols such as TFE and TFP can be questioned from an economic and sustainability viewpoint, TFE can be easily removed from reaction mixtures by distillation and recycled due to its low boiling point. Moreover, "self-generating" biphasic SET-LRP offer important advantages respect to homogeneous systems in terms of *in situ* purification of the polymer from soluble copper species and the suppression of bimolecular termination.[37,39] Finally, the use of "programmed biphasic systems based on mixtures of these alcohols and water are expected to provide faster reactions.[44,45,46,47,48,49,50,99]

CONCLUSIONS

Pushing the limits of fluorinated alcohols as solvents for SET-LRP, here we report the hydrazine-activated Cu(0) wire-mediated SET-LRP of the biobased (-)-menthyl acrylate at room temperature. TFE and TFP showed much better performance than other alcohols such as EtOH, iPrOH, and EtLa in terms of conversion and molecular weight control. The monofunctional initiator MBP and the Me_6-TREN ligand were used to initiate the polymerization and mediate the mechanistically required disproportionation of Cu(I)Br into Cu(0) and $Cu(II)Br_2$. Regardless of the bulkiness and hydrophobicity of this biobased monomer, SET-LRP successfully created polyMnA with a range of targeted degrees of polymerization (DP = 25-200, M_n^{th} = 5,400-42,200 g/mol) in moderate reaction times (<7 h). In all cases, polymerization kinetics were used to demonstrate a perfect living polymerization behavior as indicated by linear time evolution of $\ln([M]_0/[M])$ and M_n^{GPC} *vs* M_n^{th} plots. The hydrophobicity of this monomer forced SET-LRP in TFE and TFP to proceed through a self-generated biphasic system. However, this does not compromise the achievement of outstanding control of molecular weight and narrow molecular weight distribution. The high-end group fidelity of these biobased polyacrylates is supported by a combination of ^{1}H NMR, MALDI-TOF MS performed before and after modification of bromine terminus *via* "thio-bromo" click chemistry, and *in situ* reinitiation copolymerization experiments. Well-defined polyacrylates from any of eight existing stereoisomers of menthol are expected to be accessible by this methodology, so that optically active polymers and copolymers can be targeted. Moreover, the high chain end functionality of the synthesized polymers can help to expand the already described medical applications of Mn[100,101,102,103,104,105] *via* the preparation of well-defined bioconjugates. Last but not least, these results are envisioned to encourage the use of SET-LRP in the preparation of well-defined and functional polymers with complex architecture with new biomedical applications biobased on this and other hydrophobic biobased monomers.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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