Ultrafast SET-LRP with Peptoid Cytostatic Drugs as Monofunctional and Bifunctional Initiators

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ABSTRACT

To continue expanding the use of Single Electron Transfer-Living Radical Polymerization (SET-LRP) in applications at the interface between macromolecular science, biomacromolecules, biology and medicine, it is essential to develop novel initiators that do not compromise the structural stability of synthesized polymers in biological environments. Here, we report that stable 2-bromopropionyl peptoid-type initiators such as 1,4-*bis*(2-bromopropionyl)piperazine and 4-(2-bromopropionyl)morpholine are an alternative that meets the standards reached by the well-known secondary and tertiary α-haloester-type initiators in terms of excellent control over molecular weight evolution and distribution as well as polymer chain ends. SET-LRP methodologies in organic, aqueous and biphasic organic-aqueous media were evaluated for this purpose.

Keywords: living radical polymerization, SET-LRP, peptoid-type initiators, hydrolytically stable

INTRODUCTION

Vinyl polymers containing neutral,[1,2,3] cationic,[4] anionic,[5] zwitterionic[6,7] and hydrophilic[8-13] functionality with both narrow molecular weight distribution and quantitative or near quantitative chain-end functionality are only within the reach of Cu(0)-catalyzed single-electron transfer living radical polymerization (SET-LRP).[14,15] Since its conception in the late 1990s[16] and early 2000s,[17-20] SET-LRP has gradually exceeded the limits of other LRP techniques and has been placed at the interface between polymer science and biology and medicine.[21-24] From a mechanistic viewpoint, one of the crucial traits of SET-LRP is the solvent-dependent disproportionation of the *in situ* generated Cu(I)X, in the presence of ligands that stabilize $Cu(II)X_2$ such as tris(2-amino-ethyl)amine (TREN),[14,18,19,25-28] branched poly(ethylene imine),[14,29] and tris(2-dimethylaminoethyl)amine (Me_6-TREN),[14,26-28] to regenerate the Cu(0) activator as well as $Cu(II)X_2$ that acts as deactivator.[14,15] Most monomers and solvents also disproportionate Cu(I)X into Cu(0) and $Cu(II)X_2$ but do not dissolve $Cu(II)X_2$ and therefore provide an inefficient reversible termination process.[30-32] Although a priori the requirement of polar disproportionation solvents such as water,[18,33-35] DMSO[8,14,30,34,36-39] fluorinated[40-42] and non-fluorinated[37,43,44] alcohols, dimethylformamide (DMF),[45] dimethyl acetamide (DMAC)[45] and ionic liquids[14,46] or binary mixtures of organic solvents with water[36,45,47,48] or DMSO[49] could be considered an insurmountable limitation for an optimum SET-LRP, our recently developed programmed biphasic systems in which the first phase consists of a water soluble or insoluble

disproportionating[50] or non-disproportionating solvent[51-53] or a mixture of disproportionating and non-disproportionating solvents[54] containing Cu(0), the initiator, the monomer, and the polymer and a second phase containing the disproportionating solvent, water, Cu(II)X_2 together with Me_6-TREN have faded any doubt. Nowadays, the Cu(0)-catalyzed SET-LRP is already feasible in polar non-disproportionating and non-polar non-disproportionating solvents, expanding in this way the scope of SET-LRP to a larger diversity of monomers and polymers.[50,51,54] For example, poly(butyl acrylate) of number-average molecular weight (M_n) of about 30,000 Da, narrow dispersity (M_w/M_n~1.2), and near perfect chain-end functionality can be prepared via SET-LRP in both biphasic acetone-water[51] and acetonitrile-water[51,53] reaction media. Note that acetone and acetonitrile are solvents with low equilibrium constant for the disproportionation of Cu(I)X into Cu(0) and Cu(II)X_2.[45,51-53,55]

The other characteristic feature of this LRP technique is the activation of an initiator or dormant polymer chains by Cu(0) acting as electron donor *via* a heterogeneous SET.[14,15,18,19,56] Although conceived initially using commercial copper powder as catalyst,[14,43,57-60] colloidal Cu(0) generated externally by disproportionation, isolated and reused[26,34,61] or used *in situ*,[33,47] and most recently generated *in situ* by the reduction of Cu(II)X_2 with $NaBH_4$,[50-52,54,62] together with other miscellaneous Cu(0) forms including activated[42,63,64] and non-activated Cu(0) wire,[55,65] coins,[66] and copper tubing in continuous flow reactors[67,68] have been employed in SET-LRP.

As far as the initiators are concerned, hydrolytically labile secondary and tertiary α-haloesters, mimicking the dormant polymeric species, have been widely demonstrated as effective initiators for a great variety of vinyl monomers e.g. (meth)-acrylates, (meth)-acrylamides, and vinyl chloride, leading to a precise synthesis of polymers with well-defined compositions,

architectures, and perfect structural fidelity following Cu(0)-catalyzed SET-LRP guidelines.[15,21-24] This has been achieved from a wide range of monofunctional, bifunctional, multifunctional as well as macroinitiators, prepared *via* the straightforward O-acylation of the corresponding hydroxylated compound. [21] This approach was used, for instance, in the preparation of graft copolymers and brush-like structures from a variety of naturally occurring polysaccharides.[69-71] Moreover, the alkoxide moiety of the ester group can also be easily tuned to prepare initiators suitable for aqueous SET-LRP,[34] to design polymersomes with asymmetric membranes[72] or to carry functional groups allowing subsequent post-synthetic transformations such as polymer-peptide conjugations[73] or decoration with nanoparticles.[74] However, the hydrolytically labile ester linkages in the above mentioned initiators compromise the integrity of the resulting polymer architectures in biological environments, where the conditions for hydrolytic degradation, transesterification, and transamidation are readily met.[40-42]

So far, hydrolytically stable initiators for SET-LRP involve sulfonyl halides[75-84] and carbochain alkyl halides.[85] Synthetic methods for the preparation of monofunctional, difunctional and multifunctional including "masked" initiators from both classes were elaborated.[74-83] However, they involve multiple reaction steps, and therefore simple and straightforward approaches to hydrolytically stable and at the same time biocompatible and efficient initiators are desirable. In this context, amide linkages, being roughly 100 times more stable toward catalytic hydrolysis under acidic and basic conditions than esters, are an appealing alternative. Haddleton, Sawamoto and other laboratories demonstrated that aliphatic and aromatic 2-bromoisobutyryl secondary amide initiators can also be successfully used in Cu(0)-catalyzed SET-LRP[86] and atom transfer radical polymerization (ATRP).[87,88,89,90] More recently, SET-LRP initiators containing peptide-type linkages were also used in certain bioapplications.[91-93] However, although less

prone to chemical hydrolysis than esters, the gut and the bloodstream, to mention only two biological milieus, provide unfavorable environments for peptide linkages owing to the various classes of proteases present in these physiological compartments. Thus, the development of stable and efficient SET-LRP initiators is still necessary, especially in certain applications e.g. self-assembly, polymer-ligand recognition, and intracellular imaging, where the stability and biocompatibility of the polymer main chain is crucial because of prolonged exposure to biological environments.

Tertiary amides, or peptoid-type linkages in a wider sense, not only provide biocompatibility and hydrolytic stability in both acidic and basic conditions but are also unobserved to degrade enzymatically as compared to primary and secondary amides.[94,95,96] Although tertiary amide-type initiators have not been considered previously for SET-LRP and other LRP, we hypothesized that they have potential value to replace other stable initiators such as sulfonyl halides[75-84] and carbochain alkyl halides[85] that involve tedious preparations. Here, as a proof of concept, we explore peptoid cytostatic drugs based on piperazine and morpholine as hydrolytically and enzymatically stable tertiary amide-type initiators for SET-LRP in organic, aqueous and biphasic organic-aqueous media using activated and non-activated Cu(0) wire, colloidal Cu(0) generated by disproportionation of CuBr in water and used *in situ*, and generated *in situ* by the reduction of $CuBr_2$ with $NaBH_4$. Besides being easy to prepare via N-acylation, the 2-haloacylpiperazine and morpholine-derived initiators reported here produce polyacrylates with high chain end functionality possessing these well-known excellent pharmacophore functions[97-103] located in the middle or at the polymer terminus.

EXPERIMENTAL SECTION

Materials. MA (99%, Acros) and OEOMEA (average M_n = 480, Aldrich) were passed through basic Al_2O_3 before use to remove the radical inhibitor. Cu wire (20 gauge wire, 0.812 mm diameter from Fischer), $NaBH_4$ (98%, Acros), CuBr (99.9, Aldrich), $CuBr_2$ (99%, Fluka), anhydrous piperazine (99%, Acros), morpholine (99.5% Aldrich), 2-bromopropionyl bromide (97%, Alfa Aesar), anhydrous hydrazine (98% Aldrich), thiophenol (99+%, Acros), dimethyl sulfoxide (99.9%, Certified ACS, Fisher), acetone (99.8% Certified ACS, Fisher), methanol (99.9%, Certified ACS, Fisher), hexane (99.9%, Certified ACS, Fisher), ethyl acetate (99.9%, Certified ACS, Fisher), tetrabutylammonium bromide (TBAB, 99%, Acros), sodium bicarbonate ($NaHCO_3$) (99+%, Acros) and triethylamine (NEt_3) (99.91%, Chem-impex) were used as received. Methylene chloride (99.9%, Certified ACS, Fisher) was dried over CaH_2 and freshly distilled before use. Deionized water was used for the SET-LRP experiments done in acetone/water 8/2 mixture and HPLC grade water (Fischer) was used in the SET-LRP experiments of OEOMEA. Me_6-TREN was synthesized according to a literature procedure.[104] Cu (0) wire (20 gauge wire, 0.812 mm diameter from Fischer) was activated with anhydrous hydrazine according to a procedure elaborated in our laboratory.[63,64]

Methods. 500 MHz ^{1}H-NMR spectra were recorded on a Bruker DRX500 NMR instrument at 28 °C in $CDCl_3$ containing tetramethylsilane (TMS) as internal standard. For chain end analysis of PMA and POEOMEA samples, the delay time (D1) was set at 8 s and the number of scans was set at a minimum of 100 scans. Gel permeation chromatography (GPC) analysis of the polymer samples was performed using a Shimadzu LC-20AD high-performance liquid chromatograph pump, a PE Nelson Analytical 900 Series integration data station, a Shimadzu

RID-10A refractive index (RI) detector, and three AM gel columns (a guard column, 500 Å, 10 μm, and 10^4 Å, 10 μm). THF (Fisher, HPLC grade) was used as eluent at a flow rate of 1 mL min^{-1}. The number-average (M_n) and weight-average (M_w) molecular weights of PMA and POEOMEA samples were determined with poly(methyl methacrylate) (PMMA) standards purchased from American Polymer Standards. MALDI-TOF analysis was performed on a Voyager DE (Applied Biosystems) instrument with a 337-nm nitrogen laser (3 ns pulse width). The accelerating potential was 25 kV, the grid was 90%, the laser power was 1950 arbitrary units, and a positive ionization mode was used. The sample analysis was performed with 2-(4-hydroxyphenylazo)benzoic acid as matrix. Solutions of the matrix (25 mg mL^{-1} in THF), NaCl (2 mg mL^{-1} in deionized H_2O), polymer (10 mg mL^{-1}) were prepared separately. The solution for MALDI-TOF analysis was obtained by mixing the matrix, polymer and salt solutions in a 5/1/1 volumetric ratio. Then 0.5 μL portions of the mixture were deposited onto three wells of a sample plate and dried in air at room temperature before being subjected to MALDI-TOF analysis.

Synthesis of 1,4-*bis*(2-Bromopropionyl)piperazine (BPP). Piperazine (0.78g, 9.1 mmol), triethylamine (2.53mL, 18.2 mmol), and 35 mL anhydrous DCM were placed in a 100-mL round-bottom flask. A solution of 2-bromopropionyl bromide (2mL, 19.10 mmol) in 10 mL anhydrous pyridine was added dropwise at 0-5ºC during 2h and the reaction mixture was stirred overnight. The solution was filtered and washed with 5% HCl, diluted $NaHCO_3$, brine, and water and dried with $MgSO_4$. After removal of the drying agent by filtration and the solvent under reduced pressure, BPP was obtained as a white powder after recrystallization using warm

methanol (2.18g, 65% yield). mp 162ºC (lit. mp 162ºC[105] and 163-164ºC[97]). ^{1}H NMR (500 MHz, chloroform-d) δ = 4.50 (q, 2H, C<u>H</u>-CH_3), 4.20-3.20 (m, 8H, CH_2-N), 1.85 (d, 6H, CH-C<u>H</u>$_3$).

Synthesis of 4-(2-Bromopropionyl)morpholine (BPM). Morpholine (6.00g, 68.7 mmol), triethylamine (8.00mL, 57.3 mmol), and 90 mL anhydrous DCM were placed in a 250-mL round-bottom flask. A solution of 2-bromopropionyl bromide (6mL, 57.3 mmol) in 10 mL anhydrous pyridine was added dropwise at 0-5ºC during 2h and the reaction mixture was stirred overnight. The solution was filtered and washed with 5% HCl, diluted $NaHCO_3$, brine, and water and dried with $MgSO_4$. After concentration, the resulting product was purified by column chromatography (hexane: ethyl acetate 2:1) to give a pale orange liquid (11,43g, 75% yield).

^{1}H NMR (500 MHz, chloroform-d) δ = 4.50 (q, 2H, C<u>H</u>-CH_3), 3.85-3.40 (m, 8H, CH_2-N and CH_2-O), 1.83 (d, 6H, CH-C<u>H</u>$_3$)

General Procedure for SET-LRP of MA Initiated with BPP or BPM and Catalyzed with Inactivated and Hydrazine Activated Cu(0) Wire in DMSO. Cu(0) wire (12.5 cm or 4.5 cm of 20 gauge wire) was measured and cleaned using a paper towel soaked with acetone. Then it was wrapped around a Teflon-coated magnetic stir bar, rinsed one more time with acetone and added to a 25 mL Schlenk flask. The flask was sealed with a rubber septum, placed under vacuum and backfilled with nitrogen. Optionally, the Cu(0) wire was activated with anhydrous hydrazine according to a procedure elaborated in our laboratory.[63,64] The monomer (MA, 1 mL), solvent (DMSO, 500 μL), initiator (BPP, 8.97 mg or BPM 11.1 mg), and ligand (Me_6-TREN, 1.4 μL) were added to the Schlenk flask in the following order: monomer, solvent, ligand, and initiator. The reaction mixture was then deoxygenated by seven freeze-pump-thaw cycles using

an acetone/dry ice bath as a freezing mixture. After the deoxygenation protocol, the catalyst was transferred under a positive flow of nitrogen to the Schlenk flask containing all the reactants and held above the reaction mixture using a small magnet. After two additional deoxygenation cycles, the flask was placed in a water bath thermostated at 25 ± 0.5 ºC and the Cu(0) wire wrapped around the stir bar was introduced into the reaction mixture to start the SET-LRP. To determine the monomer conversion during the reaction, after purging the side arm of the flask with nitrogen, samples of approximately one or two drops were taken at predetermined times using a nitrogen flushed gas tight syringe and dissolved immediately in oxygenated $CDCl_3$ for ^{1}H-NMR analysis. In order to measure the molecular weight and dispersity values, the polymerization samples were dissolved in THF and passed through basic Al_2O_3 to remove any residual copper. The volatiles were removed under vacuum and samples were dissolved in THF for GPC analysis. The PMA was precipitated in cold methanol, collected and dried under vacuum until constant weight before 500 MHz ^{1}H NMR analysis. In specific cases, bromine PMA chain-ends were modified using thio-bromo "click" modification with thiophenol following the previously reported method developed in our laboratory.

General Procedure for SET-LRP of MA Initiated with BPP Catalyzed with Cu(0) Generated by "Prereduction" of $CuBr_2$/Me_6-TREN with $NaBH_4$ in Acetone-Water Mixture. $NaBH_4$ was removed from the glove box just before being used and weighed into an oven-dried test tube (20×150 mm), using a balance with ±0.01 mg error. The tube was charged with a magnetic stir bar, fitted with a rubber septum and placed under a low flow of nitrogen. Next, TBAB was weighed using weighing paper and transferred to a second test tube (15×130 mm). Then, as received acetone was added to dissolve TBAB followed by the addition of monomer

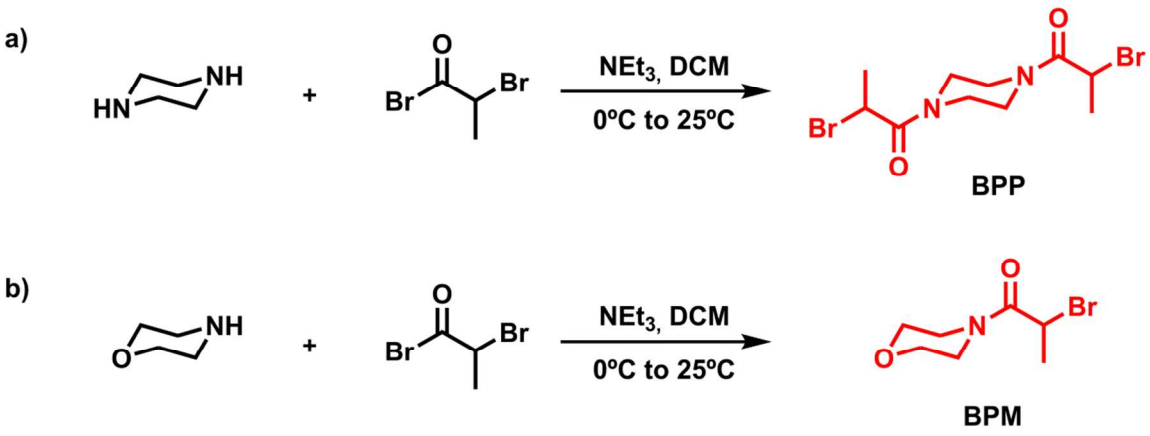
and initiator (added in the order mentioned), and sealed with a rubber septum. In a third test tube (15×85 mm) water and ligand were mixed (added in the order mentioned), and sealed with a rubber septum. Both test tubes were degassed by bubbling nitrogen for 30 min at 0 °C. 20 gauge needles were used and the sparging rate was approximately 15 bubbles per second. Meanwhile, $CuBr_2$ was weighed into the test tube (15×85 mm) and placed under positive nitrogen flow to remove oxygen. After degassing, the solution of water with ligand was transferred under nitrogen to a test tube containing $CuBr_2$ and was stirred for about one min at 25 °C until complete dissolution of $CuBr_2$. Then, this mixture was added quickly to the $NaBH_4$ using an N_2 flushed gas tight syringe. A strong stirring (stir rate setting 10 = 1200 RPM on this particular IKA Ceramag Midi hot plate) was applied during the reduction of $CuBr_2$ to Cu(0). After the reduction period, the second degassed solution of monomer, initiator, acetone, and TBAB was added to the test tube containing the mixture of Cu(0) and Cu(II) colloids and the tube was placed in a water bath thermostated at 25 ± 0.5 ºC. This addition was considered as time zero. A strong stirring (stir rate setting 10 = 1200 RPM on this particular IKA Ceramag Midi hot plate) was used at the beginning, which was then gradually decreased (to stir rate setting 4 = 480 RPM) to maintain smooth stirring as the viscosity of the reaction medium increased. To determine the monomer conversion during the reaction, samples of approximately one or two drops were taken at predetermined times using a nitrogen flushed gas tight syringe and dissolved immediately in oxygenated $CDCl_3$ for ^{1}H-NMR analysis. In order to measure the molecular weight and dispersity values, the polymerization samples were dissolved in THF and passed through basic Al_2O_3 to remove any residual copper. The volatiles were removed under vacuum and samples were dissolved in THF for GPC analysis.

General Procedure for SET-LRP of OEOMEA Initiated with BPM Catalyzed with Cu(0) Generated by Disproportionation of CuBr in Water. To a 25 mL Schlenk flask fitted with a magnetic stir bar, a mixture of H_2O (HPLC, 0.55 mL), and Me_6-TREN (11.2 μL) was added and fitted with a rubber septum. The mixture was degassed by purging nitrogen through the solution for 30 min. After CuBr (5.98 mg) was carefully added under slight positive pressure of N_2. The solution was stirred for 30 min at 25 °C to generate a bluish green solution of $CuBr_2$/Me_6-TREN and the brown suspension of Cu(0) powder. Meanwhile, a vial was charged with a magnetic stir bar, H_2O (0.55 mL), BPM (23.13 mg) and OEOMEA (1 g), sealed with a rubber septum. This mixture was purged with nitrogen for 30 min. After that, the degassed water/initiator/monomer solution was transferred via a degassed syringe equipped with a long needle through the septum to the bottom of the Schlenk flask containing Cu(0)/$CuBr_2$/Me_6-TREN, previously placed in a water bath thermostated at 25 ± 0.5 ºC, to start SET-LRP. To determine the monomer conversion during the reaction, samples of approximately one or two drops were taken at predetermined times using a nitrogen flushed gas tight syringe and dissolved immediately in oxygenated D_2O for ^{1}H-NMR analysis In order to measure the molecular weight and dispersity values, the polymerization samples were dissolved in THF and passed through basic Al_2O_3 to remove any residual copper. The volatiles were removed under vacuum and samples were dissolved in THF for GPC analysis. The POEOMEA was precipitated in cold diethyl ether, collected and dried under vacuum until constant weight before 500 MHz ^{1}H NMR analysis. In specific cases, ω-bromo PMA chain-ends were modified using thio-bromo "click" modification with thiophenol following the previously reported method developed in our laboratory.

General Procedure for SET-LRP of OEOMEA Initiated with BPM and Catalyzed with Cu(0) Generated by Reduction of $CuBr_2$ with $NaBH_4$ in Water. According to a previously reported method,[62] a 25 mL Schlenk flask was charged with a magnetic stir bar, $CuBr_2$ (4.65 mg) and $NaBH_4$ (0.40 mg) and sealed with a rubber septum. $NaBH_4$ was removed from the glove box just before being used and weighed on a balance with ±0.01 mg error. The flask was purged with nitrogen for 30 min. Meanwhile, H_2O (0.55 mL) and Me_6-TREN (5.6 μL) were introduced into a test tube (15×85 mm), the tube was sealed with a rubber septum, and the mixture was deoxygenated by bubbling nitrogen for 30 min. Then, the degassed mixture was transferred via a degassed syringe to the bottom of the Schlenk tube with $CuBr_2$ and $NaBH_4$ where the reduction of $CuBr_2$ to Cu(0) was allowed to proceed for 30 min. Immediately after, a deoxygenated mixture containing H_2O (0.55 mL), BPM (23.13 mg) and OEOMEA (1 g) was introduced to start SET-LRP that was conducted at 25 ± 0.5 ºC. To determine the monomer conversion during the reaction, samples of approximately one or two drops were taken at predetermined times using a nitrogen flushed gas tight syringe and dissolved immediately in oxygenated D_2O for ^{1}H-NMR analysis. In order to measure the molecular weight and dispersity values, the polymerization samples were dissolved in THF and passed through basic Al_2O_3 to remove any residual copper. The volatiles were removed under vacuum and samples were dissolved in THF for GPC analysis. The POEOMEA was precipitated in cold diethyl ether, collected and dried under vacuum until constant weight before 500 MHz ^{1}H NMR analysis. In specific cases, ω-bromo PMA chain-ends were modified using thio-bromo "click" modification with thiophenol following the previously reported method developed in our laboratory.

RESULTS AND DISCUSSION

Monofunctional and Bifunctional Water Insoluble and Water Soluble SET-LRP Initiators from Piperazine and Morpholine. Piperazines and morpholines are widespread structural templates in drug discovery with a high number of positive hits encountered in biological applications.[103] Several disubstituted haloacylpiperazines were previously synthesized and investigated as cytostatic alkylating drugs.[97,106] Regardless of their anticancer activity, 2-haloacylpiperazine and morpholine derivatives and other initiators containing tertiary amide linkages are of interest for SET-LRP and other LRP as they will confer high stability in biological environments to the synthesized polymers.[94] The synthesis of bifunctional and monofunctional SET-LRP initiators 1,4-bis(2-bromopropionyl)piperazine (BPP) and 4-(2-bromopropionyl)morpholine (MBP) from piperazine and morpholine is outlined in Scheme 1. Note that BPP is the α-isomer of 1,4-*bis*(3-bromopropionyl)piperazine (Vercyte®), a cytostatic drug manufactured by Abbot laboratories.



Scheme 1. Synthesis of bifunctional and monofunctional initiators BPP and BPM.

BPP and BPM were prepared in one-step, according to modified literature methods, *via* the N-acylation of piperazine and morpholine, with a slight excess of 2-bromopropionyl bromide in dry dichloromethane (DCM) in the presence of triethylamine or $NaHCO_3$.[97-100,107] The pure

bifunctional initiator BPP was obtained as a white crystalline solid [mp 162ºC (lit. mp 162ºC[105] and 163-164ºC[97])] in higher than 65% yield after recrystallization in MeOH, whereas BPM was isolated as a pale orange liquid (75% yield) after purification by silica flash column chromatography eluting with hexane/ethyl acetate (2:1). ^{1}H NMR analysis confirmed the purity and chemical structure of both initiators.

Interestingly, ^{1}H NMR analysis of the symmetric initiator BPP in $CDCl_3$ measured at room temperature showed that the signals of the methylene protons of the piperazine ring appear between 3.3 and 4.2 ppm as a complex spectroscopic pattern, arising from slow conformation changes (Figure 1a).

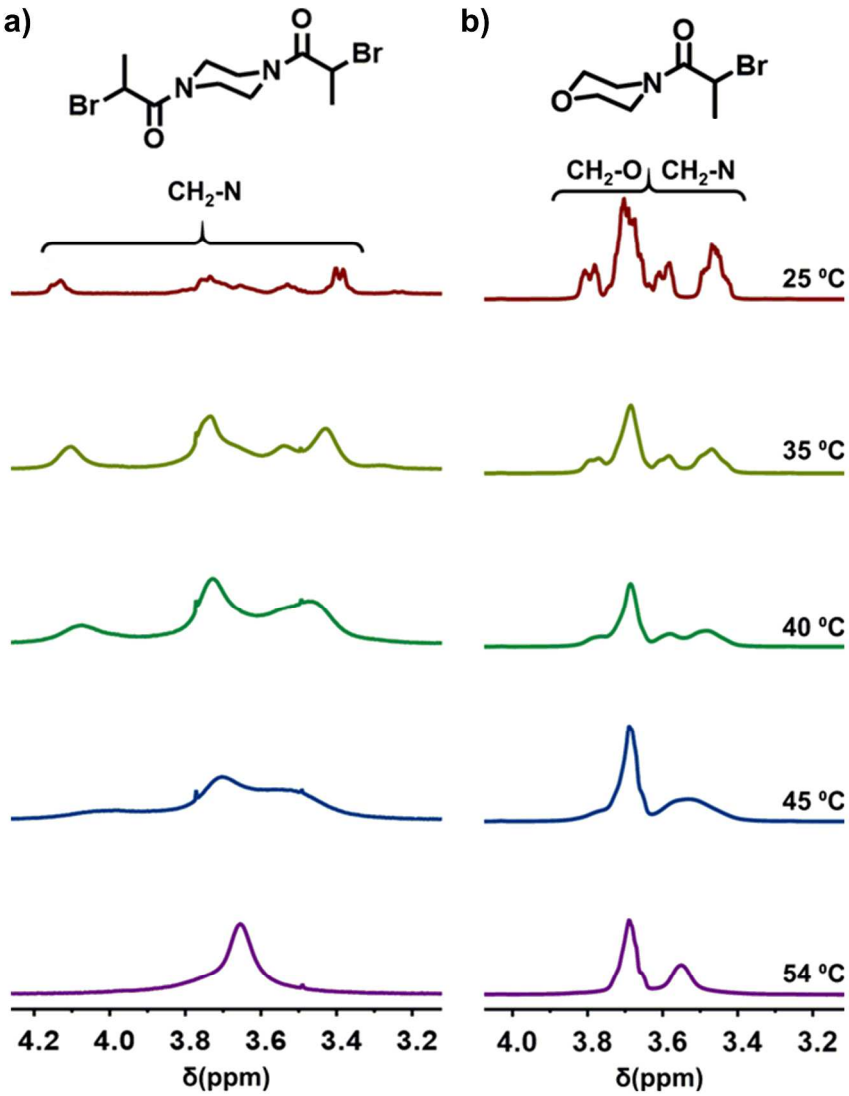
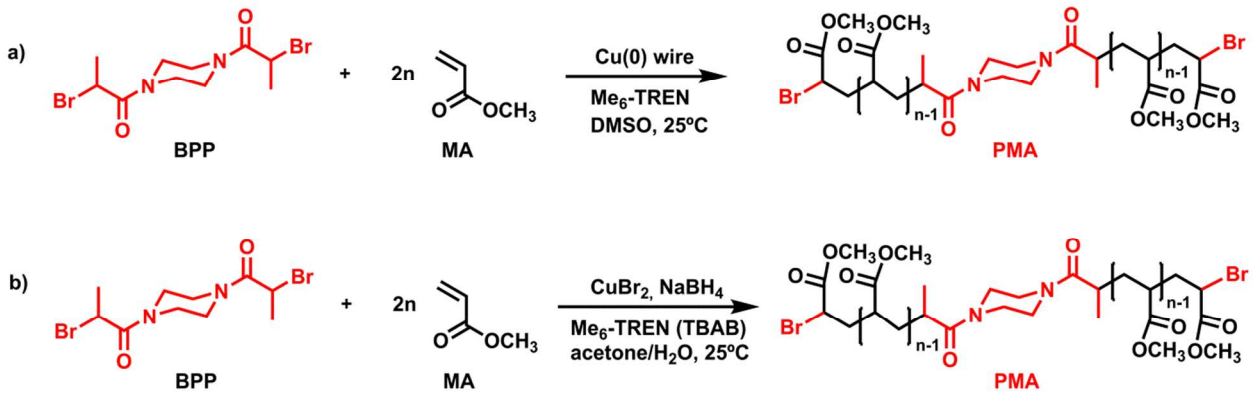


Figure 1. Temperature-dependent 500 MHz ^{1}H NMR spectra of a) bifunctional BPP and b) monofunctional BPM initiators measured in $CDCl_3$.

Such behavior is related to the existence of *syn* and *anti* conformers resulting from the partial double bond character of N, N-dialkylated amides. However, the complexity of the signals for the N-CH_2 groups suggests that the presence of 2-bromoacyl substituents in BPP also reduces the flipping of the piperazine ring conformations. As can be seen in Figure 1a, temperature-dependent ^{1}H NMR analysis of BPP confirmed the limited stereo dynamic nature of BPP at room

temperature. On gradual heating, signals of the N-CH_2 protons of the piperazine ring became narrower and coalesced at 54ºC into a singlet centered at 3.7 ppm. Also in the case of haloacyl substituted morpholine initiator (BPM), the ^{1}H NMR analysis suggests the presence of rotational conformers. At room temperature, the ring protons of the morpholine moiety (-NCH_3 and –OCH_2) appeared as four signals (ratio 1:4:1:2) in the ^{1}H NMR spectra measured in $CDCl_3$ at 25ºC. Normally, under these conditions only three signals are expected for acylated morpholines arising from the presence of two different conformers (rotamers). As expected, when monitoring ^{1}H NMR spectrum of BPM over a minimum range of 30ºC, the four signals gradually disappear and merge into the two expected signals at increased temperatures (>50 ºC) (Figure 1b).

Cu(0) Wire-Catalyzed SET-LRP of MA Initiated with BPP in DMSO. The polymerization of methyl acrylate (MA) using the bifunctional initiator BPP was first investigated in DMSO using Cu(0) wire/Me_6-TREN-catalyzed SET-LRP. As can be seen in Scheme 2a, BPP produces a telechelic PMA with a very strong piperazine dipeptoid-type core but is much easier to prepare than other stable carbochain SET-LRP bifunctional initiators recently used by our laboratory[63] i.e. the synthesis of 2,5-dibromohexanedionate from adipic acid implies a three-step synthesis.[85]



Scheme 2. SET-LRP of MA initiated with BPP catalyzed by a) 12.5 cm of a 20 gauge Cu(0) wire/Me_6-TREN in DMSO and b) Cu(0) generated by the prereduction of $CuBr_2$ with $NaBH_4$ in the presence of TBAB in acetone/water mixture at 25ºC.

The polymerizations following this methodology were performed under the following conditions: [MA]/[BPP]/[Me_6-TREN] = 444/1/0.2 in 50% (v/v) DMSO at 25ºC. This system was investigated using both inactivated[55,65] and hydrazine activated Cu(0) wire[42,63,64] (Figure 1a and b, respectively). The kinetic plots of SET-LRP initiated with bis(2-bromopropionyloxy)ethane (BPE), under the same experimental conditions, and the evolution of the number-average molecular weight (M_n) and the dispersity (M_w/M_n) with theoretical molar mass (M_n^{th}) calculated for a LRP process are shown in Figure 1c for comparison. In all cases, a linear dependence of $\ln[M]_0/[M]$ with time, which is characteristic of an LRP process with first order rate of polymerization in growing radical species, is observed. As expected, the polymerization in the presence of activated Cu(0) wire/Me_6-TREN is remarkably faster compared to the polymerization catalyzed with non-treated Cu(0) wire.[40,63,64] The activation protocol that involves washing the wire with acetone and stirring in anhydrous hydrazine solution increases the k_p^{app} by 57% (from 0.053 min^{-1} to 0.092 min^{-1}, Fig. 1a and b). The greater k_p^{app} for the hydrazine activated Cu(0) wire experiment is attributed to the removal of the less reactive Cu_2O layer on the commercial Cu(0) surface, in combination with surface roughness morphology changes that produce an enhancement in the available surface area.[63,108]

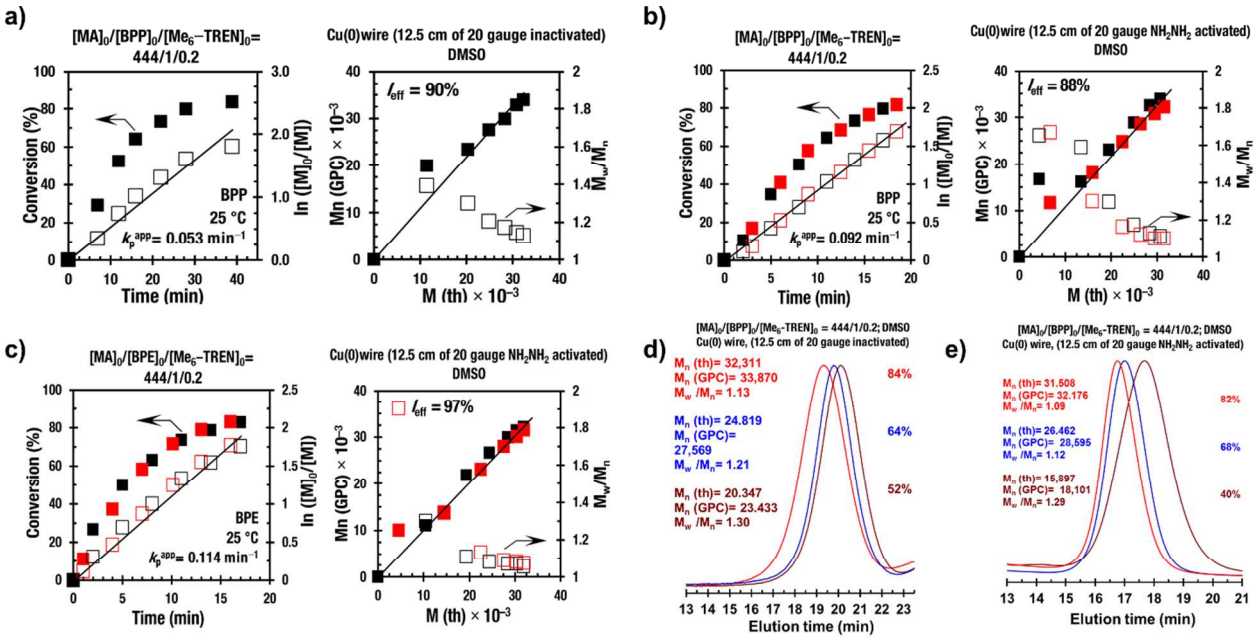


Figure 2. Kinetic plots and molecular weight and dispersity evolutions for the SET-LRP of MA in DMSO initiated with BPP (a, b, d, e) and BPE (c), catalyzed by Cu(0) wire at 25 ^{0}C. Reaction conditions: MA = 1 ml, DMSO = 0.5 ml; (a) $[MA]_0/[BPP]_0/[Me_6\text{-}TREN]_0$ = 444/1/0.2 using inactivated Cu (0) wire; (b) $[MA]_0/[BPP]_0/[Me_6\text{-}TREN]_0$ = 444/1/0.2 using NH_2NH_2 activated Cu(0) wire; (c) $[MA]_0/[BPE]_0/[Me_6\text{-}TREN]_0$ = 444/1/0.2 using NH_2NH_2 activated Cu (0) wire; (d) GPC traces of PMA obtained in (a); (e) GPC traces of PMA obtained in (b). Cu(0) wire = 12.5 cm of 20 gauge wire. Experimental data in different colors were obtained from different kinetic experiments.

In both cases, the experimental number-average molecular weight (M_n), determined by size exclusion chromatography (SEC), of the resulting PMA exhibits a linear evolution that is close to theoretical values. The polymerization using activated Cu(0) reached ~80% conversion in less than 20 min, achieving PMA with M_n 32,176 Da and slightly narrower dispersity (M_w/M_n=1.09) than that obtained from the non-treated catalyst (M_w/M_n = 1.13).[63,109] It is important to highlight that the SET-LRP of MA initiated by BPP is comparable to that initiated with BPE, the typical ester-based bifunctional initiator used by our laboratory,[36,43,63,110] although a slightly lower I_{eff}

can be observed (see Figure b and c). This result suggests a lower rate of initiator from the peptoid-type initiator. In fact, BPP is expected to possess less active C-Br bonds than the corresponding PMA propagating chains as a result of the more-electron-donating nitrogen atom.

500 MHz ^{1}H NMR spectra of PMA samples isolated at 84% (M_n =33,870, M_w/M_n=1.13) and 82% (M_n =32,176, M_w/M_n=1.09) monomer conversion from inactivated and hydrazine-activated Cu(0) wire-catalyzed experiments using BPP as initiator, together with their proton assignments, are presented in Figure 3. Due to the bifunctional structure of BPP initiator, the chain end functionality of the prepared PMAs is 100% since the only termination occurring during the radical polymerization of acrylates is by bimolecular termination.[14] Interestingly, after growing PMA chains from BPP initiator, the piperazine-derived heterocyclic nucleus of the corresponding polymer does not show the above-mentioned reduced stereo dynamic nature observed at room temperature for BPP. As can be seen in Figure 3, N-CH_2 protons appear in this case as a broad signal at 3.6 ppm suggesting enhanced mobility. The degree of termination in both PMA samples can be accurately and directly calculated from the ^{1}H NMR spectra by integrating the peaks corresponding to the initiator derived –CH(C$\underline{H}_3$) (δ = 1.10 ppm) with the α-bromo chain end –C$\underline{H}$(CO_2CH_3)Br (δ = 4.25 ppm) without the need to modify the polymer chain ends *via* thio-bromo click methodology.[15,21,36,111,112,113]

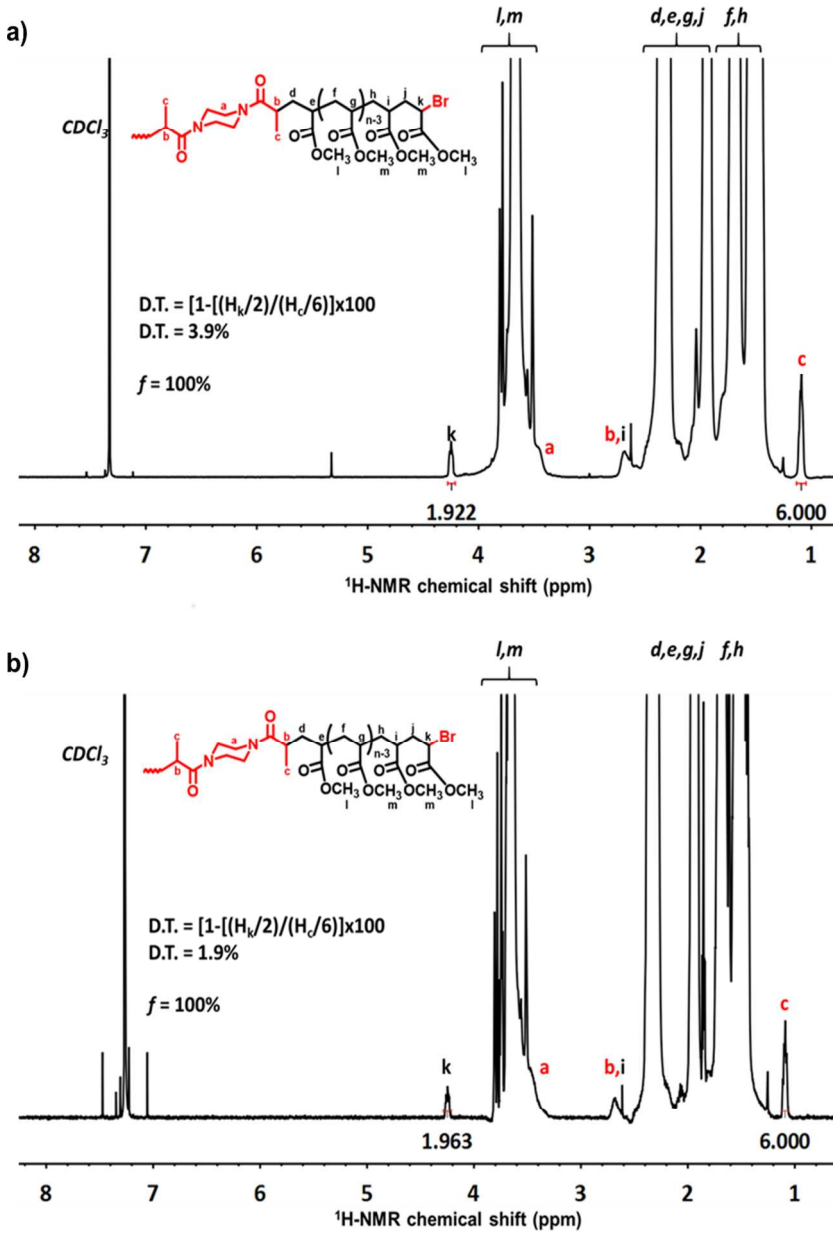


Figure 3. 500 MHz ^{1}H-NMR spectra recorded in $CDCl_3$ along with the assignments of the various protons of Br-PMA-Br isolated at (a) 84% and (b) 82% monomer conversion from SET-LRP of MA in DMSO initiated with BPP, catalyzed by non-treated Cu (0) wire (a) and NH_2NH_2 activated Cu(0) wire (b). Reaction conditions: $[MA]_0/[BPP]_0/[Me_6\text{-TREN}]_0$ = 444/1/0.2. Cu (0) wire = 12.5 cm of 20 gauge wire.

In accordance to previous results reported by our laboratory, SET-LRP does not require high levels of bimolecular termination during the early stages of the polymerization that is demanded by other metal-catalyzed LRP techniques to generate the persistent radical effect.[114] This is because the disproportionation of the *in situ* generated Cu(I)X/L, regenerating the Cu(0) activator and Cu(II)X_2, allows for accumulation of sufficient levels of Cu(II)X_2 deactivator. In this case, SET-LRP showed slightly higher levels of termination when performed with inactivated Cu(0) wire, although in both cases the degree of bimolecular termination can still be considered low considering the ultrafast rate of polymerization (PMA with M_n 35,000 Da and M_w/M_n=1.40 is achieved in less than 20 min).

To further verify the chain end functionality of the PMA prepared from BPP, the polymer isolated from an experiment under conditions $[MA]_0/[BPP]_0/[Me_6\text{-TREN}]_0$ = 111/1/0.2 at 80% monomer conversion (M_n = 10,300, M_w/M_n=1.40) was treated with thiophenol in the presence of triethylamine. This "thio-bromo" click reaction results in a complete nucleophilic displacement of active α-bromo chain ends into the corresponding thioether derivatives. Figure 4 shows that the original molecular weight peaks, corresponding to PMA with bromine terminals, are completely missing after nucleophilic displacement of the secondary alkyl bromide with thiophenol and a new series of peaks, spaced by 86 mass units, appears at about 60 molar mass units above the previous one. This value corresponds to two times the molar mass difference between –S-Ph and –Br. The minor peaks in the spectrum of the modified PMA, at 22 mass units below the main peaks, correspond to those of the polymeric chains associated with H^+. The combination of 500-MHz ^{1}H-NMR, GPC, and MALDI-TOF analysis demonstrated that the use of the peptoid-type initiator BPP does not compromise the appealing characteristics of SET-LRP initiated from α-haloester-type initiators in polar disproportionation solvents such as DMSO, and

allows the ultrafast preparation of telechelic PMA with both narrow molecular weight distribution and quantitative chain-end functionality.

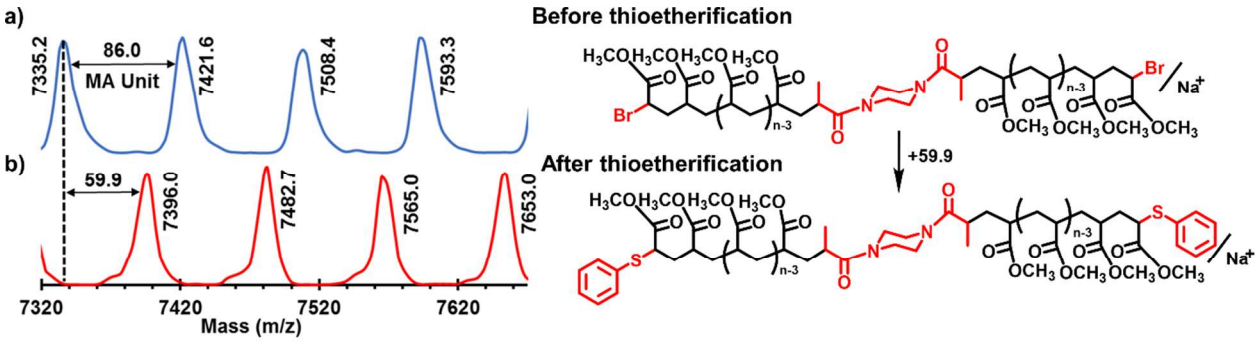


Figure 4. MALDI-TOF spectra of Br-PMA-Br isolated at 80% conversion from the SET-LRP of MA initiated with BPP and catalyzed by activated Cu (0) wire in DMSO at 25 ^{0}C before (a) and after (b) "thio-bromo click" reaction. Reaction condition: MA = 1 ml, DMSO = 0.5 ml, $[MA]_0/[BPP]_0/[Me_6\text{-TREN}]_0$ = 111/1/0.2. NH_2NH_2 activated Cu (0) wire = 12.5 cm of 20 gauge wire. Dotted line in the expansion after thioetherification shows the original peak from before thioetherification, while 59.9 represents the increase in molar mass after thioetherification *i.e.*, 2*(SC6H5 (109.2) – Br (79.9) = 59.9).

SET-LRP of MA Initiated with BPP in a Biphasic Acetone-Water Mixture Catalyzed with Cu(0) Generated by "Prereduction" of $CuBr_2/Me_6$-TREN with $NaBH_4$. In a recent publication, our group reported the development of an ultrafast SET-LRP of hydrophobic acrylates in biphasic acetone-water mixtures.[51] In spite of the fact that acetone is an excellent solvent for many polymers including polyacrylates, its low equilibrium constant for the disproportionation of Cu(I)X limited its use in SET-LRP so far.[45,55] The elaboration of this method is part of our recent efforts to eliminate the dependence of SET-LRP to polar disproportionating solvents by using biphasic SET-LRP systems in which the first phase consists

of a water soluble or insoluble disproportionating or non-disproportionating solvent or a mixture of disproportionating and non-disproportionating solvents containing the Cu(0), initiator, monomer, and polymer and a second phase containing the solvent, water, and $Cu(II)X_2$ together with Me_6-TREN.[50,51,52,54]

The SET-LRP of MA initiated with BPP was also investigated in an acetone/water mixture (8/2, v/v) in the presence of tetra-*n*-butylammonium (TBAB) (Scheme 2b). In this biphasic system, the electron-donor Cu(0) is externally generated from $CuBr_2$. As a proof of concept, we applied a methodology that involves the prereduction of $CuBr_2$ to colloidal Cu(0) by using $NaBH_4$ as reducing agent. Thus, after allowing the generation of Cu(0) particles for a predetermined period of time, the aqueous phase containing Cu(0) and Me_6-TREN is mixed with the solution containing monomer, acetone, TBAB and an initiator (Figure 5a). As can be seen in Figure 5b, the kinetic experiment yielded almost 100% monomer conversion in 45 min, exhibiting a first order linear evolution of $\ln[M]_0/[M]$ with time ($[MA]_0/[BPP]_0/[Me_6\text{-}TREN]_0/[CuBr_2]_0/[NaBH_4]_0/[TBAB]_0$ = 222/1/0.4/0.4/0.32/0.1). Figures 5b and c show that the experimental M_n increases linearly with conversion indicating a controlled radical reaction while, at the same time, the obtained PMA at high conversion shows a low M_w/M_n.

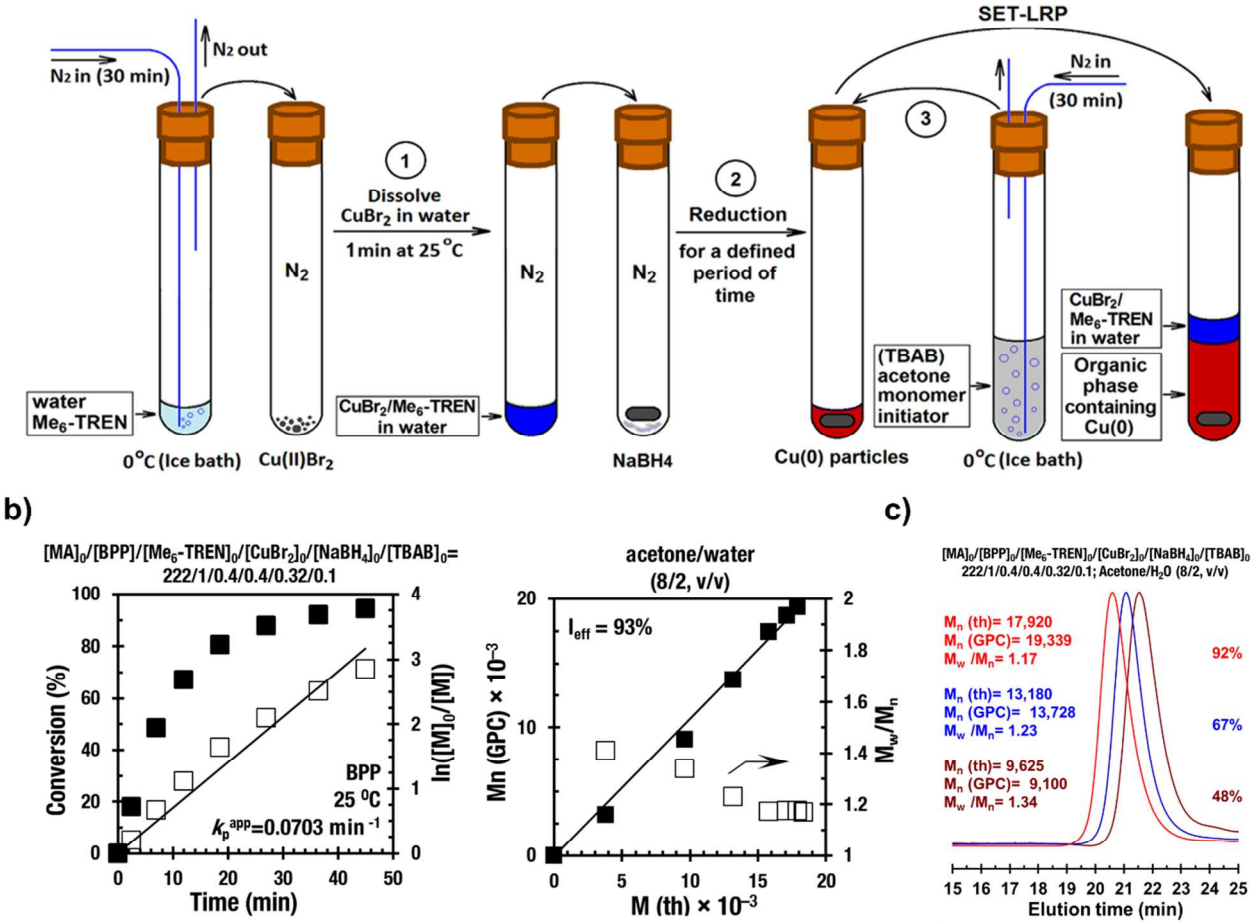
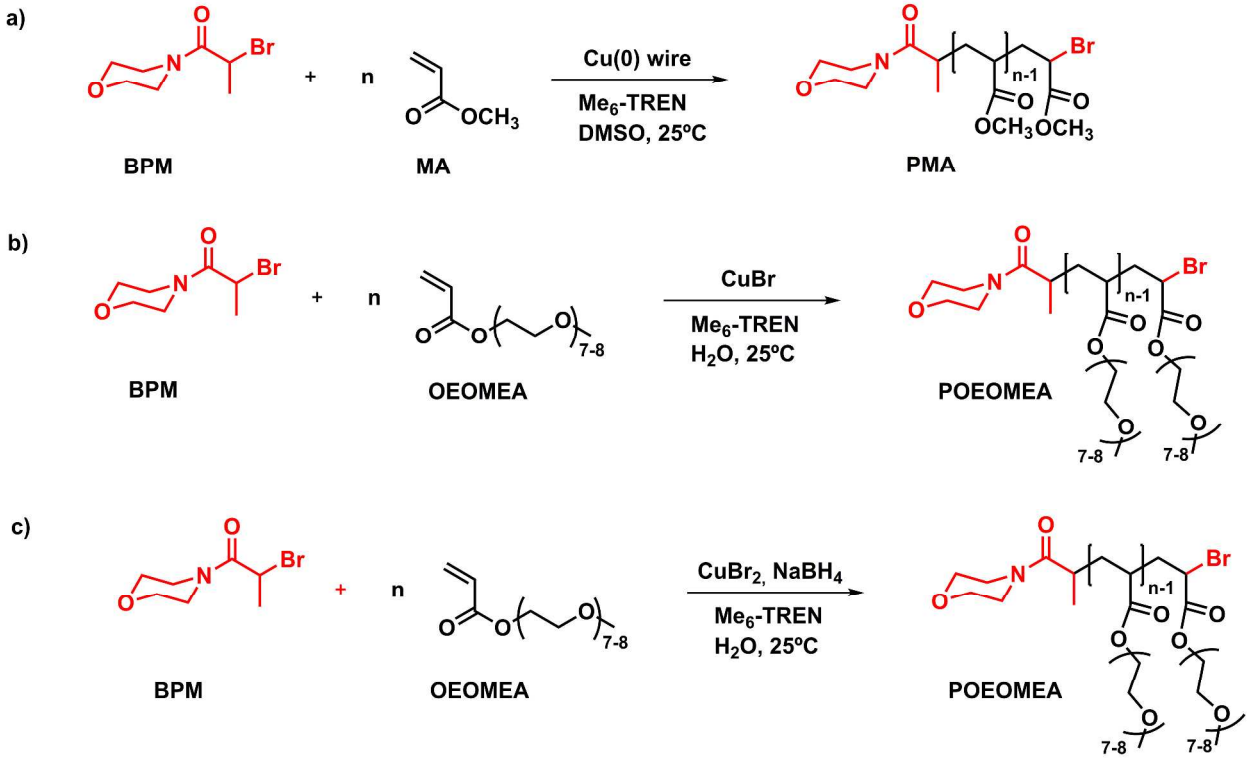


Figure 5. (a) "Prereduction" methodology for the SET-LRP of MA catalyzed by Cu (0) generated from an aqueous solution containing $CuBr_2$, Me_6-TREN and the reductant $NaBH_4$. (b) Kinetic plot and molecular weight and dispersity evolutions for the SET-LRP of MA in acetone/water mixture = 8/2 (v/v) mixture initiated with BPP and catalyzed by Cu (0) generated by *in situ* reduction of $CuBr_2$ with $NaBH_4$ at 25 ^{0}C. The v/v ratio must be multiplied by 10 to obtain % acetone/% water. The value of v + v must be divided by 5 to obtain the total volume of solvents, 2 ml. Reaction conditions: $[MA]_0/[BPP]_0/[Me_6\text{-TREN}]_0/[CuBr_2]_0/[NaBH_4]_0/[TBAB]_0$ = 444/1/0.4/0.4/0.32/0.1. Prereduction time 28 seconds. (c) GPC traces of PMA obtained in (b).

SET-LRP Initiated with BPM in Organic and Aqueous Media. The solubility of the morpholine-derived monofunctional initiator BPM in polar organic solvents and water

encouraged us to study SET-LRP in both organic and aqueous media using: (i) hydrazine-activated Cu(0) wire in DMSO, and Cu(0) generated externally by (ii) the disproportionation of CuBr and (iii) the reduction of $CuBr_2$ with $NaBH_4$ in water (Scheme 3). Regardless of the monomer/SET-LRP methodology used, polymers synthesized using BPM initiators contain a morpholine function located at the ω-chain end. This is a biologically relevant template considered an important building block in the field of medicinal chemistry.[103]



Scheme 3. SET-LRP initiated with BPM of a) MA catalyzed by 4.5 cm of a 20 gauge Cu(0) wire/Me_6-TREN in DMSO, b) OEOMEA catalyzed by Cu(0) powder generated by disproportionation and used *in situ* and c) OEOMEA catalyzed by Cu(0) generated by the prereduction of $CuBr_2$ with $NaBH_4$ in water at 25°C.

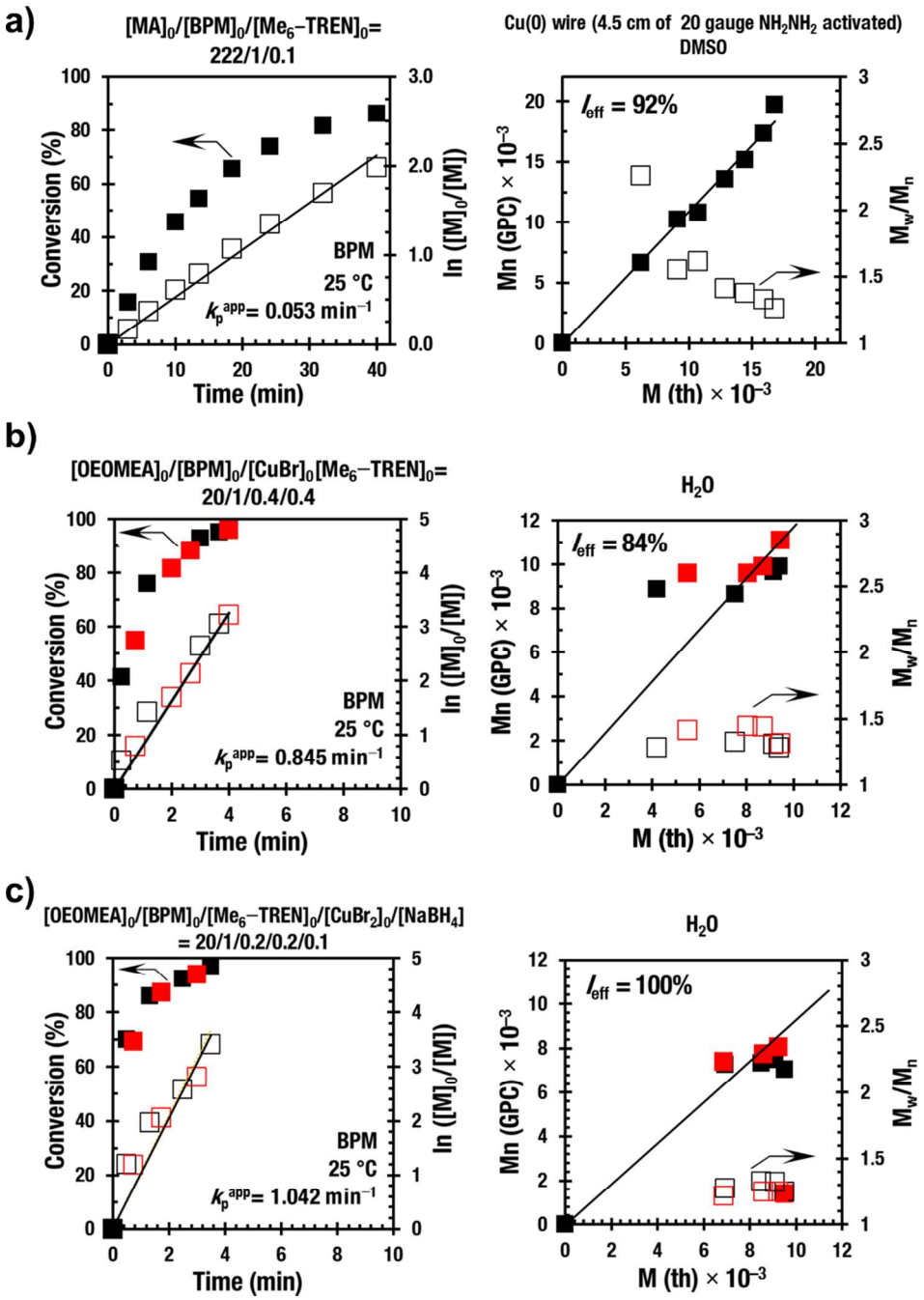


Figure 6. Kinetic plots and molecular weight and dispersity evolutions for the SET-LRP of MA (a) in DMSO and OEOMEA (b and c) in water initiated with BPM and catalyzed by Cu (0) (a) wire, (b) generated by disproportionation of CuBr in water and (c) generated by *in situ* reduction of $CuBr_2$ with $NaBH_4$ at 25 ^{0}C. Reaction conditions: MA = 1 ml, DMSO = 0.5 ml; (a) $[MA]_0/[BPM]_0/[Me_6\text{-}TREN]_0$ = 222/1/0.1 using NH_2NH_2 activated Cu (0) wire = 4.5 cm of 20 gauge wire; (b) $[MA]_0/[BPM]_0/[Me_6\text{-}TREN]_0/[CuBr]_0$ = 20/1/0.4/0.4; (c) $[MA]_0/[BPP]_0/[Me_6$-

TREN]$_0$/[$CuBr_2$]$_0$/[$NaBH_4$]$_0$ = 20/1/0.2/0.2/0.1. Experimental data in different colors were obtained from different kinetic experiments.

First, SET-LRP of MA initiated with BPM was investigated in DMSO using hydrazine-activated Cu(0) wire. As can be seen in Figure 6a, a fast polymerization took place with no induction period. The polymerization proceeded with first order kinetics to near complete conversion, showing a linear evolution of experimental M_n that remains close to the theoretical values during the whole process. In spite of the fact that BPM is a monofunctional initiator, it is important to highlight that the initiator efficiency is comparable to that obtained for the peptoid-type bifunctional initiator BPP.

Although commercially available Cu(0) powder and Cu(0) wire may be used as a catalyst in aqueous SET-LRP, the quantitative disproportionation of CuBr to Cu(0) and $CuBr_2$ in H_2O makes it possible to use the *in situ* generated Cu(0) as a catalyst for SET-LRP.[10,15,33,35,47,115,116] Alternatively, as shown above, Cu(0) can also be generated externally taking advantage of the instantaneous reduction of $CuBr_2$ with $NaBH_4$ in water.[62] Both protocols were applied here to the SET-LRP of a water soluble monomer such as oligo(ethylene oxide) methyl ether acrylate (OEOMEA) initiated with BPM using the following conditions: [OEOMEA]$_0$/[BPM]$_0$/[Me_6-TREN]$_0$/[CuBr]$_0$ = 20/1/0.4/0.4 and [OEOMEA]$_0$/[BPM]$_0$/[Me_6-TREN]$_0$/[$CuBr_2$]$_0$/]$NaBH_4$]$_0$ = 20/1/0.2/0.2/0.1 (Figure 6a and b, respectively). Kinetic plots for both experiments reveal extremely fast polymerizations of OEOMEA reaching almost complete conversion in 4 min. Throughout the polymerization, POEOMEA chains grow extremely fast even though they show narrow M_w/M_n and experimental M_n, determined by GPC using PMMA standards, close to theoretical values.

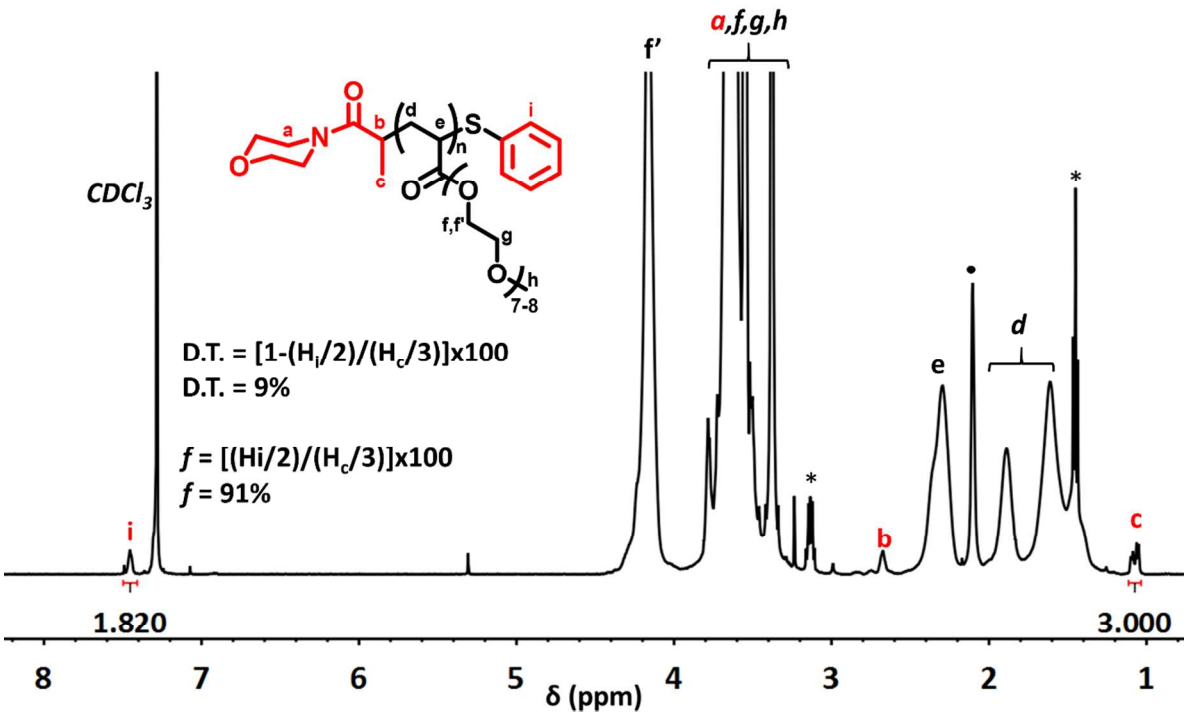


Figure 7. 500 MHz ^{1}H-NMR spectra recorded in $CDCl_3$ along with the assignment of the various protons after thioetherification of bromine chain-end by "thio-bromo" click reaction of poly(OEOMEA) isolated at 96% monomer conversion from SET-LRP of OEOMEA in water initiated with BPM and catalyzed by Cu(0) generated by disproportionation of CuBr in water. Reaction conditions: $[MA]_0/[BPM]_0/[Me_6\text{-TREN}]_0/[CuBr]_0 = 20/1/0.4/0.4$. ^{1}H-NMR resonances from residual diethyl ether and acetonitrile present with the poly(OEOMEA) is indicated with "*" and "•", respectively.

Undoubtedly, a very fast LRP using a monofunctional initiator can generate doubts about the chain end functionality of the resulting polymer. The polymer isolated from the experiment where the Cu(0) catalyst was generated externally from CuBr was characterized by 500 MHz ^{1}H-NMR spectroscopy to dispel any doubts. In this case, to assess the bromine chain-end functionality of the isolated POEOMEA at 96% conversion it was necessary to use "thio-bromo" click reaction due to the overlapping of the signal corresponding to the secondary bromine chain end (–C<u>H</u>(CO_2R)Br) with a signal of the polymeric chain (-COOC<u>H_2</u>-). Figure 7 shows the 500

MHz ^{1}H NMR spectrum of the purified polymer after thioetherification reaction from which the bromine-chain end fidelity of the parent polymer was indirectly determined by the integration of the ratio between the phenyl (Ar-H, δ = 7.42 ppm) and the pharmacophore-containing initiator (–CH(C$\underline{H}_3$) at δ = 1.10 ppm) chain ends. The high degree of functionality (f = 91% at 96% conversion) is consistent with a surface mediated activation and bimolecular termination mechanism, previously reported by our laboratory, taking place throughout the environmentally-friendly aqueous SET-LRP protocol where Cu(0) nanopowder is generated *in situ* from CuBr/Me_6-TREN *via* instantaneous disproportionation.[33]

Why Peptoid-type Initiators? Traditionally**,** Cu(0)-catalyzed SET-LRP has gone hand in hand with α-haloester-type initiators.[14,15,21] Although they are synthesized in a straightforward manner directly from the corresponding hydroxylated compound and provide efficient initiation, the labile nature of the ester groups compromise the hydrolytic stability of the resulting polymer architectures toward catalytic hydrolysis, transesterification and transamidation under acidic and basic conditions[110] as well as in enzymatic environments. Easily accessible *via* N-acylation of the corresponding secondary amines, tertiary amides, or peptoid-type linkages in a wider sense, are in the spotlight of our research not only because they are far more hydrolytically stabile than ester-type initiators but also because they are biocompatible and have not been observed to degrade enzymatically.[86-90, 94-96] Additionally, in the results presented above, we have shown that tertiary amide-type initiators can be considered efficient initiators because they provide excellent control over molecular weight evolution, distribution, and polymer chain ends of the resulting polymers. Recently piperazine-based peptoid repeat units have been demonstrated to be both hydrolytically and enzymatically stable.[96] Thus, the simple synthesis, biocompatibility, and

hydrolytic and enzymatic stability of peptoid-type initiators and their availability as both efficient monofunctional and bifunctional initiators that can be soluble or insoluble in water make them appealing for the preparation of a large diversity of stable macromolecular and biomacromolecular architectures that are suitable for numerous biological and biomedical applications.

CONCLUSIONS

SET-LRP has been using secondary and tertiary α-haloesters-type initiators indiscriminately since its origins. In spite of being easily accessible via O-acylation of hydroxylated compounds, a serious drawback of such initiators is the poor hydrolytic and enzymatic stability that is ultimately transferred to the synthesized polymer. Here, we demonstrate that 2-bromopropionyl peptoid-type initiators are an alternative in applications at the interface between macromolecular science, biomacromolecules, biology and medicine where hydrolytic stability and biocompatibility could be a serious drawback.[94-96] Regardless of its properties as a cytostatic alkylating drug, 1,4-bis(2-bromopropionyl)piperazine was successfully used to initiate the SET-LRP of MA in DMSO and in a biphasic acetone-water mixture. Whereas in DMSO Cu(0) wire was used as catalyst, Cu(0) was generated externally from $CuBr_2$ *via* instantaneous reduction with $NaBH_4$ in the biphasic methodology. A monofunctional initiator was also synthesized from morpholine by straightforward N-acylation with 2-bromopropionyl bromide. In this case, 4-(2-bromopropionyl)morpholine was used in both organic (DMSO) and aqueous SET-LRP protocols to polymerize MA and the water soluble acrylate OEOMEA. In the case of the SET-LRP in water, Cu(0) was generated externally in two different ways: (i) from $CuBr_2$ using $NaBH_4$ as a reductant and (ii) from CuBr/Me_6-TREN taking advantage of its instantaneous

disproportionation in water. In these studies we have shown that, without exception, SET-LRP initiated with the reported peptoid-type monofunctional and bifunctional initiators exhibited excellent control over molecular weight evolution and distribution as well as polymer chain ends. Although this was not the motivation of this work, the fact that the initiators reported here lead to polymers bearing well-known pharmacophore functions underscores the possibility of studying the biological properties of these and other polymers prepared from them.

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Author Contributions

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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Ultrafast SET-LRP with Peptoid Cytostatic Drugs as Monofunctional and Bifunctional Initiators

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Table of Contents Graphic