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Replacing Cu(II)Br_2 with Me_6-TREN in Biphasic Cu(0)/TREN Catalyzed SET-LRP Reveals the Mixed-Ligand Effect

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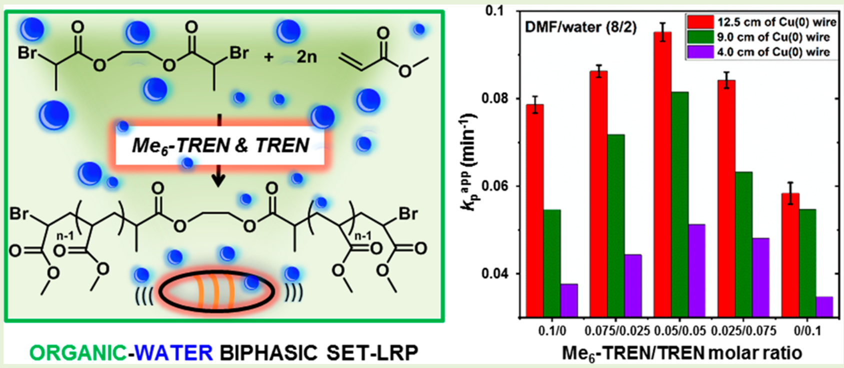
S *Supporting Information*



ABSTRACT: The mixed-ligand system consisting of tris(2-aminoethyl)amine (TREN) and tris(2-dimethylaminoethyl)amine (Me_6-TREN) during the Cu(0) wire-catalyzed single electron transfer-living radical polymerization (SET-LRP) of methyl acrylate (MA) in "programmed" biphasic mixtures of the dipolar aprotic solvents NMP, DMF, and DMAc with H_2O is reported. Kinetic and chain end analysis studies by NMR and MALDI-TOF before and after thio-bromo "click" reaction demonstrated that Me_6-TREN complements and makes the less expensive TREN a very efficient ligand in the absence of externally added Cu(II)Br_2. Statistical analysis of the kinetic data together with control experiments demonstrated that this mixed-ligand effect enhanced the apparent rate constant of propagation, monomer conversion, and molecular weight control. The most efficient effect was observed at a 1/1 molar ratio between these two ligands, suggesting that in addition to a fast exchange between the two ligands, a new single dynamic ligand generated by hydrogen bonding may be responsible for the mixed ligand observed.

INTRODUCTION

The concept of mixed-ligand systems emerged as an efficient and simple methodology to obtain superior catalytic activity in transition-metal-catalyzed enantioselective reactions.[1] Nearly at the same time, Feringa's laboratory reported that heterocombinations of chiral monodentate ligands were more effective than homocombinations for Rh-catalyzed C−C cross-coupling reactions.[2] This concept was also employed for Pd-catalyzed C−N[3,4] and C−S[5] cross-coupling reactions as well as for Ni-catalyzed Suzuki-type cross-coupling and borylation reactions.[6] However, the benefits of using mixed-ligand catalysts have only been noted so far in few metal-catalyzed polymerization experiments.[7−9]

The use of an appropriate solvent/N-ligand combination is important in Cu(0)-mediated single electron transfer-living radical polymerization (SET-LRP),[10−17] since it can either promote or disfavor the mechanistically fundamental disproportionation reaction of Cu(I)X into Cu(0) atomic species and Cu(II)X_2.[18,19] Tris(2-dimethylaminoethyl)amine (Me_6-TREN) is frequently employed as a ligand in SET-LRP,[10,11,14]

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because it favors the disproportionation process by preferentially binding $Cu(II)X_2$ rather than $Cu(I)X$.[20] However, the use of its precursor, tris(2-aminoethyl)amine (TREN),[11,21−23] which is about 80 times less expensive, and poly(ethylene imine) (PEI)[10] also proved successful for the polymerization of vinyl chloride (VC) during the first days of SET-LRP. Likewise, TREN[24−26] and *N*,*N*,*N*′,*N*″,*N*′-pentamethyldiethylenetriamine (PMDETA)[10,27,28] are also alternative ligands to Me_6-TREN for the Cu(0) wire-catalyzed SET-LRP of acrylates and methacrylates in homogeneous SET-LRP.

Unfortunately, the replacement of Me_6-TREN with TREN was not so successful in aqueous−organic "programmed" biphasic systems using Cu(0) wire catalyst,[29−33] although it is very efficient in single phase SET-LRP experiments. In biphasic organic solvent−water systems, the external addition of $Cu(II)Br_2$ was necessary to complement the performance of TREN and retain living character. In this complex system, SET-LRP is an interfacial process in which disproportionation and activation events take place independently in the aqueous and organic compartments, respectively, whereas the "self-controlled" reversible deactivation occurs at the interface.[34] The Cu(0)-mediated polymerization in "programmed" bi-(multi)phasic mixtures of organic solvents with water has been proven to be valuable in various organic solvents regardless of their ability to mediate or not disproportionation of Cu(I)X/N-ligand.[35−39] Thus, this designed biphasic organic solvent-H_2O programmed biphasic systems resolved the incompatibility of SET-LRP with polar nondisproportionating solvents and nonpolar nondisproportionating solvents, thus expanding the library of accessible solvents.

In this publication, we report that replacing $Cu(II)Br_2$ additive with Me_6-TREN in "programmed" biphasic Cu(0)-mediated SET-LRP using TREN revealed a mixed-ligand effect which increased the rate of polymerization, monomer conversion, and molecular weight control. This preliminary study demonstrates the systematic occurrence of this unexpected synergic effect between Me_6-TREN and TREN during the nonactivated Cu(0) wire-mediated SET-LRP of MA in various "programmed" biphasic systems based on mixtures of NMP, DMF, and DMAc with H_2O. The experiments reported here demonstrate for the first time the superior activity of mixed-ligand systems of these two N-ligands that are widely used in SET-LRP.

■ EXPERIMENTAL SECTION

Materials. Methyl acrylate (MA) (99%, Acros) was passed over a short column of basic Al_2O_3 before use in order to remove the radical inhibitor. Tris(2-aminoethyl)amine (TREN) (99%, Acros), Cu(0) wire (20 gauge wire, 0.812 mm diameter from Fisher), and dimethylformamide (DMF) (99.8%, Sigma-Aldrich) were used as received. *N*,*N*-Dimethylacetamide anhydrous (DMAc) (99.8%, Sigma-Aldrich) and *N*-methylpyrrolidone (NMP) (99%, Sigma-Aldrich) were distilled before use. Deionized water was used in all SET-LRP experiments. Triethylamine (NEt_3) (>99.5% Chemimpex) was distilled under N_2 over CaH_2. Bis(2-bromopropionyl)ethane (BPE) was synthesized by esterification of ethylene glycol with 2-bromopropionyl bromide in the presence pyridine according to our previously reported method.[40] Hexamethylated tris(2-aminoethyl)-amine (Me_6-TREN) was synthesized according to a literature procedure.[41]

Techniques. 400 MHz ^1H NMR spectra were recorded on a Bruker AVANCE NEO 400 NMR instrument at 27 °C in $CDCl_3$ containing tetramethylsilane (TMS) as internal standard. 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 104 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 samples were determined with poly(methyl methacrylate) (PMMA) standards purchased from American Polymer Standards. MALDI-TOF spectra were obtained on a Voyager DE (Applied Biosystems) instrument with a 337 nm nitrogen laser (3 ns pulse width). For all polymers, the accelerating potential was 25 kV, the grid was 92.5, the laser power was 2200−2500, and a positive ionization mode was used. The sample analysis was performed with 2-(4-hydroxyphenylazo) benzoic acid as the matrix. Solutions of the matrix (25 mg/mL in THF), NaCl (2 mg/mL in deionized H_2O), and polymer (10 mg/mL) 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 sample plate and dried in air at room temperature before subjected to MALDI- TOF analysis.

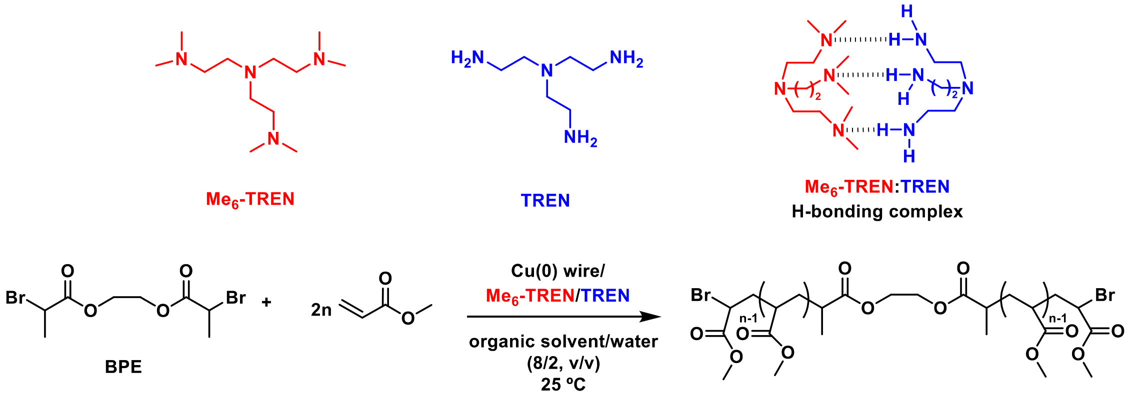
Typical Procedure for SET-LRP of MA in "Programmed" Biphasic Mixtures using Mixed-Ligand Systems. Stock solutions with different ligand ratios (Me_6-TREN/TREN as 0.05 M/0 M, 0.0375 M/0.0125 M, 0.025 M/0.025 M, 0.0125 M/0.0375 M, 0 M/0.05 M) in water were prepared. The monomer (MA, 11.1 mmol, 1.00 mL), organic solvent (DMF, DMAc, or NMP, 0.4 mL), water stock solution (0.005 mmol Ligand, 0.1 mL), and initiator (BPE, 0.05 mmol, 16.6 mg) were added to a 25 mL Schlenk tube. The reaction mixture was then deoxygenated by six freeze−pump−thaw cycles. After these cycles, the Schlenk tube was opened under a positive flow of nitrogen to add the Cu(0) wire wrapped around a Teflon-coated stir bar. Two more freeze−pump−thaw cycles were carried out while holding the stir bar above the reaction mixture using an external magnet. After that, the Schlenk tube was filled with N_2, and the reaction mixture was placed in a water bath at 25 °C. Then, the stir bar wrapped with the Cu(0) wire was dropped gently into the reaction mixture. The introduction of the Cu(0) wire defines $t = 0$. Samples were taken at different reaction times by purging the side arm of the Schlenk tube with nitrogen for 2 min using a deoxygenated syringe and stainles steel needles. The collected samples were dissolved in $CDCl_3$ and quenched by air bubbling. After that, the monomer conversion was measured by ^1H NMR spectroscopy. In order to determine the molecular weight and polydispersity of the samples, the solvent and the residual monomer were removed under vacuum. Finally, samples were dissolved in THF and passed through a short and small basic Al_2O_3 chromatographic column to remove any residual copper and subsequently were analyzed by GPC. The resulting PMA was precipitated in cold methanol and dried under vacuum until constant weight to perform chain end analysis by ^1H NMR spectroscopy, before and after the thioetherification reaction.

General Procedure for the Chain End Modification of PMA via Thio-Bromo "Click" Reaction. In a 10 mL test tube sealed with a rubber septum, thiophenol (0.05 equiv) and distilled triethylamine (NEt_3, 0.05 equiv) were added into a solution of the corresponding polymer (0.01 equiv) in acetonitrile (1 mL) under a nitrogen flow. The reaction mixture was stirred at room temperature for 3 h. Then, the resulting modified PMA was precipitated in cold methanol and washed with methanol several times. The resulting modified polymers were dried under vacuum until constant weight.

■ RESULTS AND DISCUSSION

The Mixed-Ligand Effect During the Biphasic SET-LRP of MA in NMP−Water Mixture using Me_6-TREN and TREN as Ligands. To the best of our knowledge, the use of mixed-ligand systems of Me_6-TREN and TREN was not employed before in SET-LRP or any other metal-catalyzed LRP technique. Hence, in the first series of experiments reported here, we sought to investigate their performance by mediating the "programmed" biphasic SET-LRP of MA in NMP-water mixtures (8/2, v/v). This dipolar aprotic solvent is

Scheme 1. Biphasic SET-LRP of MA Initiated from BPE and Catalyzed with Nonactivated Cu(0) Wire Using Various Molar Combinations of Me_6-TREN and TREN[a]



[a]Organic solvents investigated herein are NMP, DMF, and DMAc.

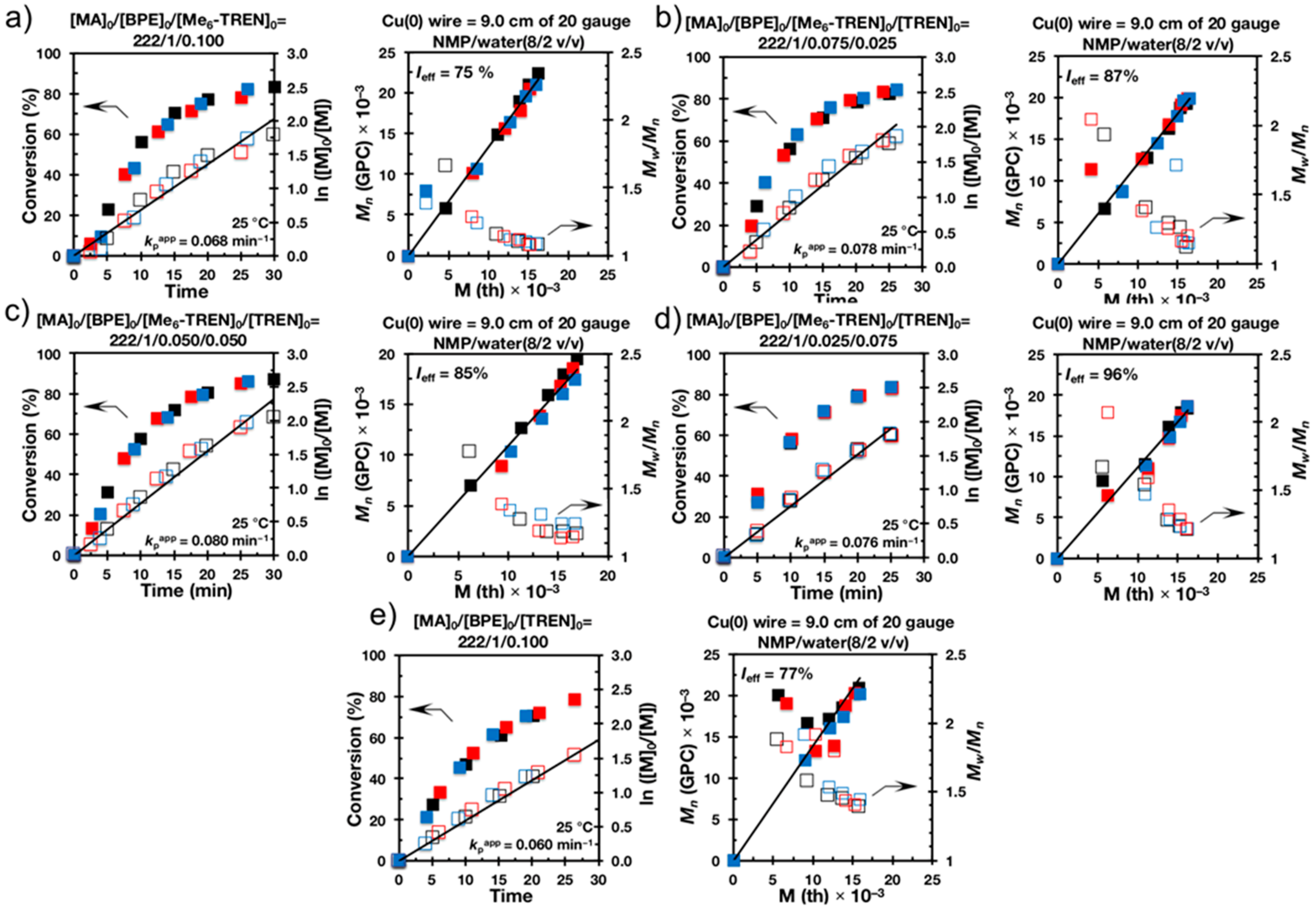


Figure 1. Kinetic plots, molecular weight, and polydispersity evolution for the SET-LRP of MA in NMP/water mixture (8/2, v/v) initiated with BPE and catalyzed by the 9.0 cm nonactivated Cu(0) wire at 25 °C. Experimental data in different colors were obtained from different kinetics experiments sometimes performed by different researches. k_p^{app} and I_{eff} are the average values of three experiments. Reaction conditions: MA = 1 mL, NMP = 0.4 mL, water = 0.1 mL, $[MA]_0/[BPE]_0/[L]_0$ = 222/1/0.1.

not one of the most efficient SET-LRP solvents in homogeneous solution[42] but becomes excellent in biphasic systems with water.[29,39] The chemical structure of both ligands and a schematic illustration for the Cu(0) wire-catalyzed SET-LRP of MA initiated from the bifunctional initiator bis(2-bromopropnionyl)ethane (BPE) are depicted in Scheme 1. Triplicate kinetic experiments were performed under the following reaction conditions: $[MA]_0/[BPE]_0/[L]_0$ = 222/1/0.1 using 9.0 cm of nonactivated Cu(0) wire. The molar ratio between Me_6-TREN and TREN was varied from 1:0 to 0:1 while maintaining the total amount of ligand, relative to initiator, constant at 10 mol %.

Interestingly, any of the tested mixed ligand compositions provided higher k_p^{app} values than those obtained in the control

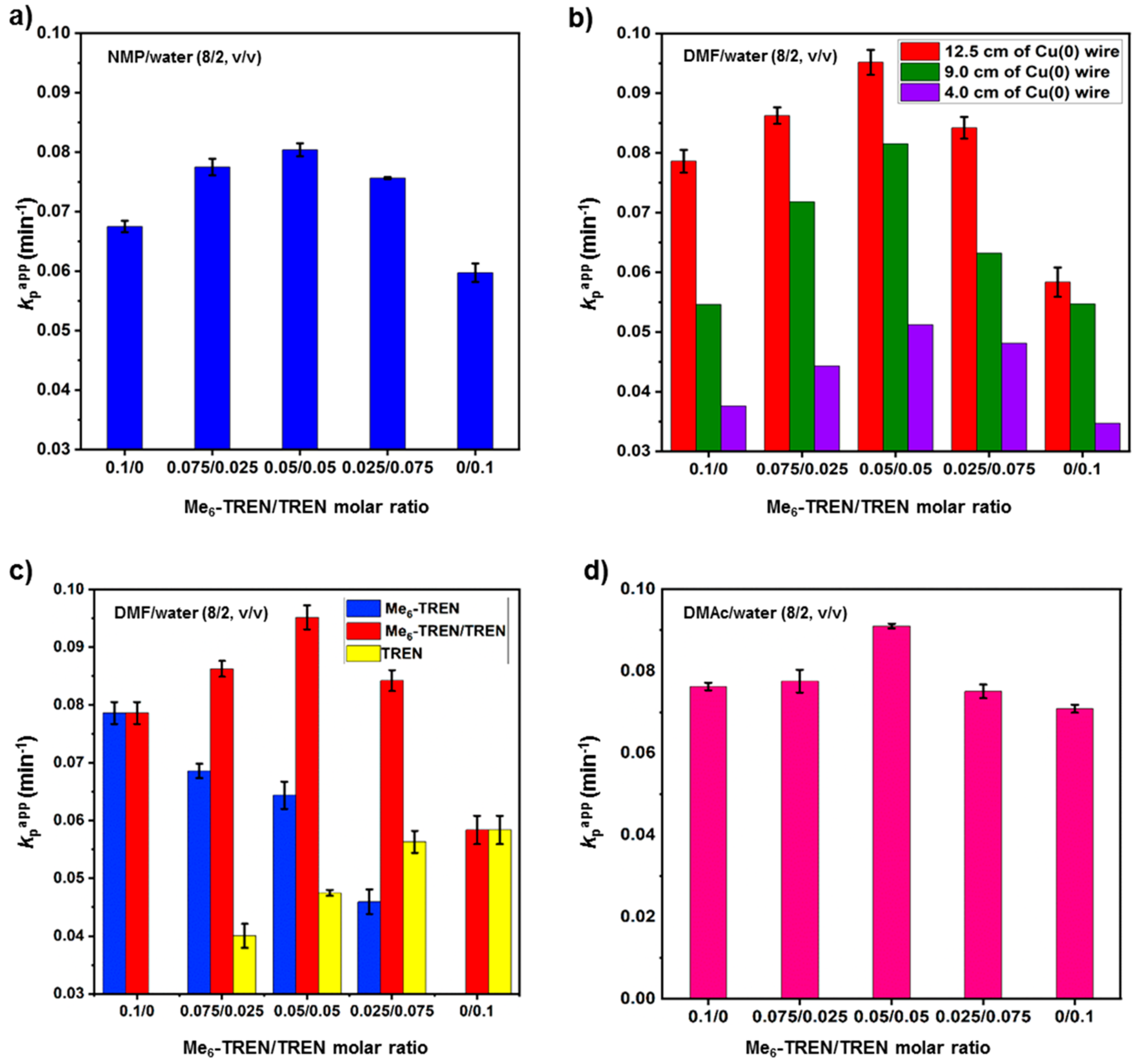


Figure 2. Evolution of k_p^{app} for the SET-LRP of MA initiated with BPE in various "programmed" biphasic reaction mixtures at 25 °C. (a) NMP/water mixture (8/2, v/v) using 9.0 cm nonactivated Cu(0) wire as catalyst. (b) DMF/water mixture (8/2, v/v) using 12.5, 9.0, and 4.0 cm of nonactivated Cu(0) wire as catalyst. (c) DMF/water mixture (8/2, v/v) using 12.5 cm of nonactivated Cu(0) wire as catalyst and (d) DMAc/water mixture (8/2, v/v) using 9.0 cm of nonactivated Cu(0) wire as catalyst. Reaction conditions: MA = 1 mL, organic solvent = 0.4 mL, water = 0.1 mL, and $[MA]_0/[BPE]_0/[L]_0$ = 222/1/0.1 (a,b, and d) $[MA]_0/[BPE]_0/[L]_0$ = 222/1/0.1−0.0 (c).

experiments performed in the presence of either Me$_6$-TREN or TREN (Figure 1 and 2a). For example, the replacement of 2.5 mol % of Me$_6$-TREN with TREN increased the k_p^{app} from 0.068 min^{-1} (Figure 1a) to 0.078 min^{-1} (Figure 1b), while retaining first-order kinetics. Similar trends were observed using the inverse ligand composition (Figure 1d). Moreover, in both cases a slight increase in monomer conversion was also noted (Figure S1a). Nevertheless, the superior catalytic activity was observed wherein 1:1 molar combinations of both ligands. Under these conditions, the SET-LRP of MA proceeded approximately 1.2 and 1.3-fold faster than control experiments with Me$_6$-TREN and TREN, respectively. This particular mixed-ligand system also enabled the highest monomer conversion (Figure S1a). In addition, the synergistic effect between both ligands also improved the control over molecular weight distribution attained by SET-LRP.

Representative GPC data shown in Figure 3 illustrate the evolution of molecular weight as a function of conversion during these experiments. GPC chromatograms revealed monomodal polymer peak distributions shifting to higher molecular weight while increasing conversion. However, significantly higher than expected M_n^{GPC} values were obtained at low conversion for the control experiment using TREN without Me$_6$-TREN (Figure 3e). Accordingly, using the 0:1 molar combination of ligands a nonlinear evolution of molecular weight was detected during the early stages of the polymerization (right panel of Figure 1e). Likewise, the broadest PMA at ultimate monomer conversion was obtained under these conditions (M_w/M_n = 1.39 at 81% conversion). In previous publications, the addition of Cu(II)Br$_2$ additive was used to significantly improve molecular weight control under these conditions.[29−33] In this case, GPC analysis revealed that Me$_6$-TREN was complementary and made TREN a very efficient ligand without using the externally added Cu(II)Br$_2$. As can be seen in Figure S1a, replacing only 2.5 mol % of TREN with Me$_6$-TREN improved significantly the molecular weight distribution evolution throughout polymerization (compare panels e and d of Figure 1). As expected, increasing

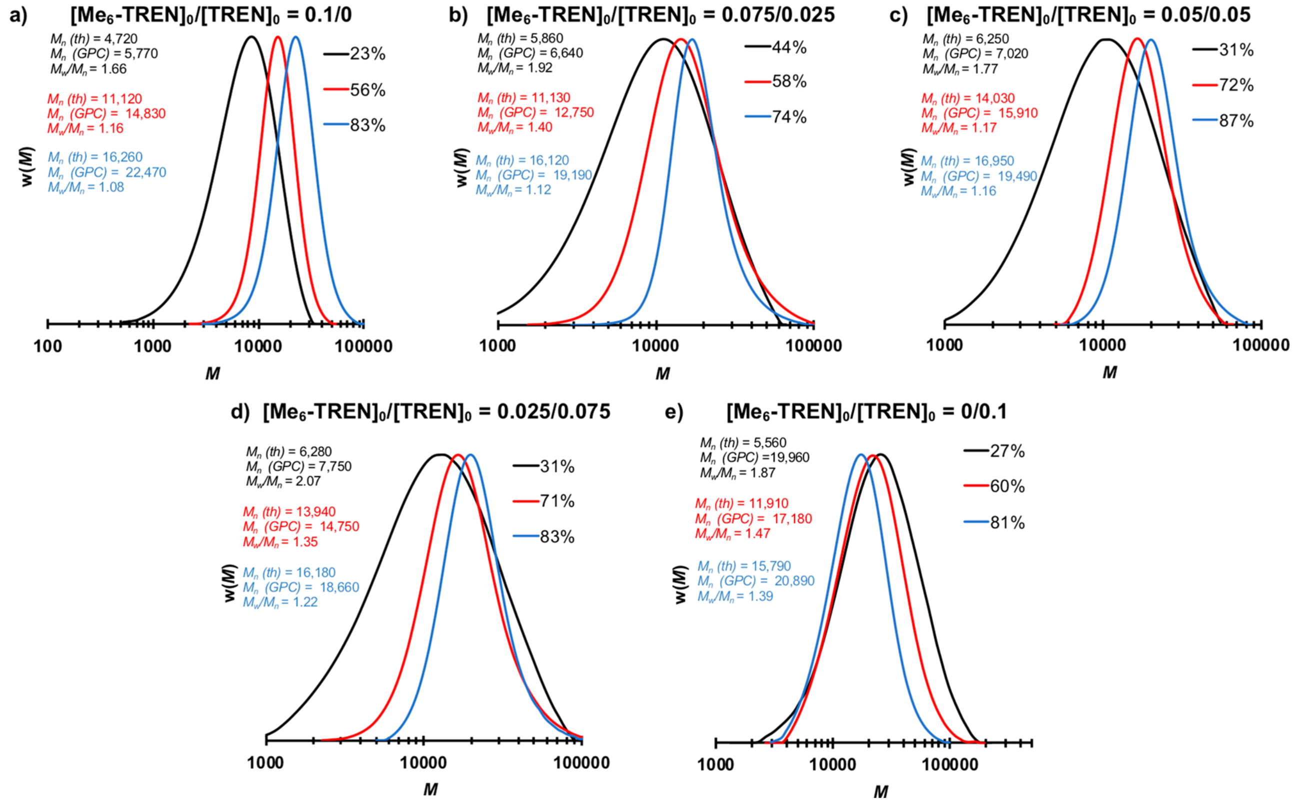


Figure 3. Representative GPC traces of the evolution of molecular weight as a function of conversion for the SET-LRP of MA in a mixture of NMP/water (8/2, v/v) and catalyzed by the 9.0 cm nonactivated Cu(0) wire at 25 °C in the presence of various ligand compositions. Reaction conditions: MA = 1 mL, NMP = 0.4 mL, water = 0.1 mL, $[\mathrm{MA}]_0/[\mathrm{BPE}]_0/[\mathrm{L}]_0 = 222/1/0.1$.

further the amount of hexamethylated ligand resulted in a better defined polymer (Figure S1a). Note that the average M_w/M_n was below 1.2 using the equimolar combination of ligands. Meanwhile, whereas initiator efficiency (I_{eff}) was around 75% for both control experiments, the use of mixed-ligand systems significantly enhanced this value. Again, the most important effect was observed at 1:1 molar ratio between ligands. In this case, the I_{eff} was determined to be above 90%. Overall, these results demonstrate that the mixed-ligand catalytic system consisting of nonactivated Cu(0) wire and Me_6-TREN/TREN is an effective catalyst for the SET-LRP of MA under biphasic reaction conditions.

The Mixed-Ligand Effect During the Biphasic SET-LRP of MA in DMF−Water Mixture using Me_6-TREN and TREN as Ligands and Various Cu(0) Wire Lengths. The accuracy of the trend disclosed above was tested with an additional set of control experiments using different Cu(0) wire lengths in a DMF-water mixture (8/2, v/v). Thus, the SET-LRP of MA was investigated using wire lengths of 12.5, 9.0, and 4.0 cm while maintaining the rest of the polymerization conditions unchanged. Figures S2−4 show the corresponding kinetic plots and evolution of experimental M_n and M_w/M_n versus theoretical M_{th}. Kinetic experiments using 9.0 cm of nonactivated Cu(0) wire showed the same trend (Figure 2b, green columns) as in the case of Figure 2a. The biphasic SET-LRP of MA in a DMF/water (8/2, v/v) mixture was faster using mixed-ligand systems. However, again, the highest k_p^{app} and I_{eff} values were observed at 1:1 molar ratio of Me_6-TREN and TREN. Under these conditions, SET-LRP was approximately 1.5-fold faster than the control experiment with either Me_6-TREN or TREN. Indeed, monomer conversion was also slightly improved when the mixed-ligand systems 0.075/0.025 (82%) and 0.05/0.05 (87%) were used. Mixed-ligand effects were also noted for the polymerization using 12.5 and 4.0 cm of Cu(0) wire. Previous reports demonstrated that SET-LRP catalysts utilize a surface-mediated activation.[43,44] Accordingly, the use of 12.5 cm of Cu(0) wire provided the faster series of polymerizations, whereas with the shortest wire length reactions were slower (Figure 2b, red and purple columns, respectively). For example, at the 1:1 molar ratio between ligands, the k_p^{app} values decrease as follows, 0.095 min^{-1} (12.5 cm), 0.082 min^{-1} (9.0 cm), and 0.051 min^{-1} (4.0 cm). Nevertheless, the evolution of k_p^{app} values as a function of ligand ratio reiterates again the benefit of employing a combination of both ligands. These results suggest the existence of an optimum molar ratio between ligands. Accordingly, both monomer conversion and I_{eff} also showed higher values in the mixed-ligand systems for the polymerization using 4.0 cm of Cu(0) wire. However, the highest amount of catalyst did not provide a clear trend (compare Figure S1b,c with S1d).

An additional set of control experiments were performed to highlight the occurrence of fast exchange between the two ligands at all compositions (Figure 2c). The SET-LRP of MA was investigated using decreasing ligand loading using either Me_6-TREN or TREN and no coligand. The corresponding kinetic plots are shown in Figure S5, panels a-c (Me_6-TREN) and Figure S5, panels d-f (TREN). The control experiments from Figure 2c demonstrate both for the case of TREN (yellow colored experiments) and of Me_6-TREN (blue colored experiments) a continuous decrease of the rate of polymerization as the concentration of the ligand decreases. These experiments contrast the experiments in which mixed-ligand with identical compositions as the single ligands are used (see red colored experiments). In these series of experiments an increase in rate is obtained as the ratio between the two ligands tends to approach the 1/1 ratio. This trend demonstrates the mixed-ligand effect. The fact that the most important effects have been systematically observed at a 1/1 molar ratio suggests that in addition to a fast exchange between the two ligands, a new single dynamic ligand generated by H-bonding should be considered in future mechanistic investigations (Scheme 1).

The interaction between both ligands was confirmed by ^{1}H NMR analysis of their equimolar mixture prepared in $CDCl_3$. Figure 4 shows that signal corresponding to amine protons of TREN shifts downfield (0.15 ppm) and becomes broader in the presence of Me$_6$-TREN, suggesting the formation of a more rigid complex than TREN or Me$_6$-TREN.

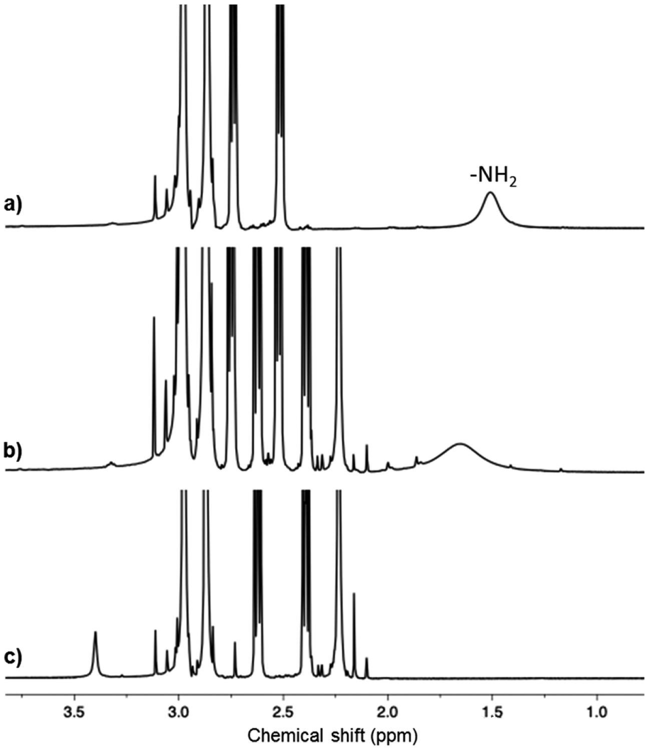


Figure 4. ^{1}H NMR spectra at 400 MHz of (a) TREN, (b) 1:1 molar ratio mixture of TREN and Me$_6$-TREN, and (c) Me$_6$-TREN in $CDCl_3$ at 25 °C.

The Mixed-Ligand Effect During the Biphasic SET-LRP of MA in DMAc−Water Mixture using Me$_6$-TREN and TREN as Ligands. In the last series of kinetics, we examined the solvent screening with a DMAc-water mixture also at 8/2 (v/v). The SET-LRP of MA was investigated using only 9.0 cm of nonactivated Cu(0) wire. In this case, all the tested compositions showed two first-order kinetic regimes with a slower second domain (Figure S6). The same behavior was previously observed during the homogeneous SET-LRP of MA in DMAc with lower loadings of water.[42] On the basis of previous reports, this result may be attributed to rapid activation combined with insufficient disproportionation, which favors bimolecular termination events between growing chains. Nevertheless, even under these conditions, the 1:1 molar ratio of Me$_6$-TREN and TREN provided the fastest polymerization (Figure 2d). Moreover, I_{eff} values also were higher for mixed-ligand systems, but no clear trend was observed on monomer conversion (Figure S1e). As in all previously tested systems, with the transition from TREN to Me$_6$-TREN, the resulting PMA showed narrower molecular weight distribution.

Visualization of the Reaction Mixtures at the End of the Polymerization: How Biphasic SET-LRP Takes Place? NMP, DMF, and DMAc are dipolar aprotic solvents miscible with water. However, irrespective of the ligand or mixture of ligands used, the SET-LRP of MA in aqueous mixtures of these solvents containing 20% water proceeds under biphasic reaction conditions as can be seen in the series of digital images recorded at the end of the polymerizations (Figure 5).

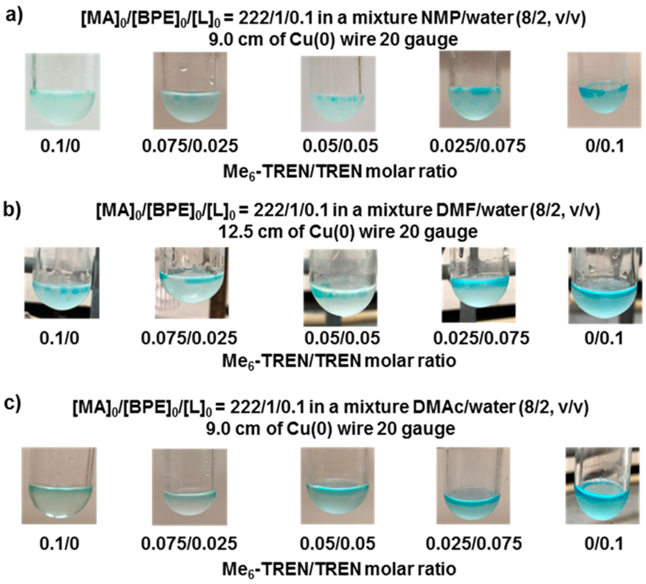
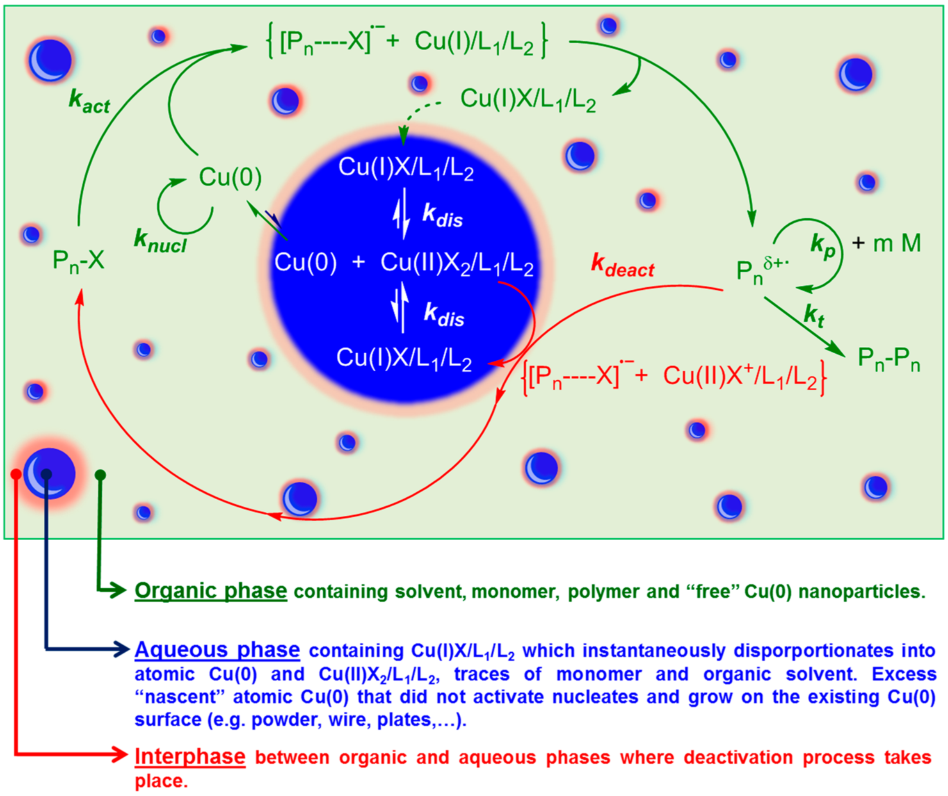


Figure 5. Visualization of the reaction mixture after the biphasic SET-LRP of MA initiated with BPE using various ligand compositions. (a) NMP/water (8/2, v/v), (b) DMF/water (8/2, v/v), and (c) DMAc/water (8/2, v/v). Reaction conditions: MA = 1 mL, organic solvent = 0.4 mL, water = 0.1 mL, $[MA]_0/[BPE]_0/[L]_0$ = 222/1/0.1.

Note that these biphasic reaction mixtures are "programmed" by the partition of the Cu(I)Br/mixed-ligand generated during the activation step in the organic phase, to the water phase, where it disproportionates into atomic Cu(0) and Cu(II)Br$_2$. Under these conditions, dissociation of I-X and P$_n$-X is achieved in the organic phase through a heterolytic outer-sphere SET-process wherein the outer sphere electron donor Cu(0) transfers an electron to I-X/P$_n$-X resulting, depending of the structure of the initiator, in a radical anion $[P_n/P\text{-}X]^{\bullet -}$, which degrades in a stepwise or concerted pathway to $P_n^{\bullet\delta+}$ and X^- (Scheme 2).[12−14] Detailed mechanism and definitions by both IUPAC Organic and Electrochemistry Divisions were discussed in previous reviews.[12−14]

Subsequently, Cu(I)X species generated during or after the SET event, are partitioned from the organic phase into the aqueous phase associated with an N-ligand. This process is determined by the much higher solubility of Cu(I)X/L in the aqueous phase rather than in organic phase. In the water phase, the Cu(I)X/L species quantitatively disproportionate (equilibrium constant for disproportionation, $K_{disp} = 0.89 \times 10^6 - 5.8 \times 10^7$)[45,46] to generate the atomic Cu(0) activator and Cu(II)X$_2$/L deactivator. While water is miscible with dipolar

Scheme 2. Schematic Representation of Cu(0)-Catalyzed SET-LRP in Organic-Water "Programmed" Biphasic Reaction Mixtures[a]



Organic phase containing solvent, monomer, polymer and "free" Cu(0) nanoparticles.

Aqueous phase containing $Cu(I)X/L_1/L_2$ which instantaneously disporportionates into atomic Cu(0) and $Cu(II)X_2/L_1/L_2$, traces of monomer and organic solvent. Excess "nascent" atomic Cu(0) that did not activate nucleates and grow on the existing Cu(0) surface (e.g. powder, wire, plates,...).

Interphase between organic and aqueous phases where deactivation process takes place.

[a] Color code: organic phase, green; aqueous phase, blue; interphase, red.

aprotic solvents, the solution of $Cu(II)Br_2/L$ in water is not miscible with the solution of the dipolar aprotic solvent containing MA. This immiscibility is responsible for the transition from a single-phase reaction mixture to a biphasic reaction mixture. Cu(0) atomic species activate the dormant species, and the excess of Cu(0) nucleates and grows on the existing Cu(0) surface (e.g., powder, wire, plates, etc.),[47] increasing its area and therefore the reactivity of the original Cu(0) surface. Propagation takes place in the organic phase via the addition of the monomer to the growing radicals. However, the $Cu(II)X_2$-mediated deactivation of the propagating macroradicals is thought to occur at the interphase between organic and aqueous phase via reverse outer-sphere oxidation of $P_n^\bullet$ to P_n-X (Scheme 2). Accordingly, after SET-LRP, the organic phase consisting mainly of PMA and residual monomer dissolved in the organic solvent was almost colorless, whereas the water droplets were bluish because they contain $Cu(II)Br_2/L$ complexes with only some traces of organic solvent and monomer (Figure 5). The images in Figure 5 also revealed a slight increase in the blue color of the water phase as the concentration of TREN increases. This trend may indicate a negligible increase in the extent of bimolecular termination that is too low to be detected by NMR and MALDI-TOF analysis experiments. This effect will be investigated in more detail, and it will be reported elsewhere. A similar color change going from Me_6-TREN to TREN was observed during the control experiments using ethyl acetate instead of MA (Figure S7). $[EA]_0$ in Figure S7 refers to ethyl acetate that has been used as a nonreactive model for methyl acrylate.

Structural Analysis of PMA before and after Thio-Bromo "Click" Functionalization. A combination of 400 MHz ^1H NMR and MALDI-TOF measurements before and after reacting -Br end-groups of PMA with thiophenol via thio-bromo "click" reaction[48,49] were used to assess the livingness of polymers prepared using various molar ratios between Me_6-TREN and TREN. Low molar mass polymers were prepared using the three above investigated "programmed" biphasic mixtures targeting SET-LRP of MA at a $[MA]_0/[BPE]_0 = 60$. Figure 6 shows representative ^1H NMR spectra of PMA samples isolated at high conversion after biphasic SET-LRP in DMF/water mixture (8/2, v/v) using 1:0, 1:1, and 0:1 molar ratios of Me_6-TREN and TREN.

Within the experimental error, the integral of signal *c*, corresponding to the CH_3- groups of the middle-chain initiator residue, and signal *a,k*, corresponding to the middle-chain CH_2 groups and CH-Br end-groups, did not provide any evidence of termination events. Irrespective of the ligand composition, the bromine chain-end functionality was in all cases >98% at monomer conversion >90%.

The chain-end functionality of PMA calculated after thio-bromo "click" reaction with thiophenol also supports the near perfect functionality of the synthesized PMA (Figure S8). The MALDI-TOF analysis of the prepared samples was also consistent with these results. Figure 7 depicts representative MALDI-TOF spectra of PMA synthesized using equimolar amounts of Me_6-TREN and TREN analyzed before and after the thioetherification reaction. The polymer isolated after SET-LRP showed one distribution which can be assigned to the corresponding bromine-terminated polyacrylate chains ionized with Na^+. After thioetherification with thiophenol, the original series of peaks vanished and appeared 59 mass units above. This is the expected mass difference value considering the

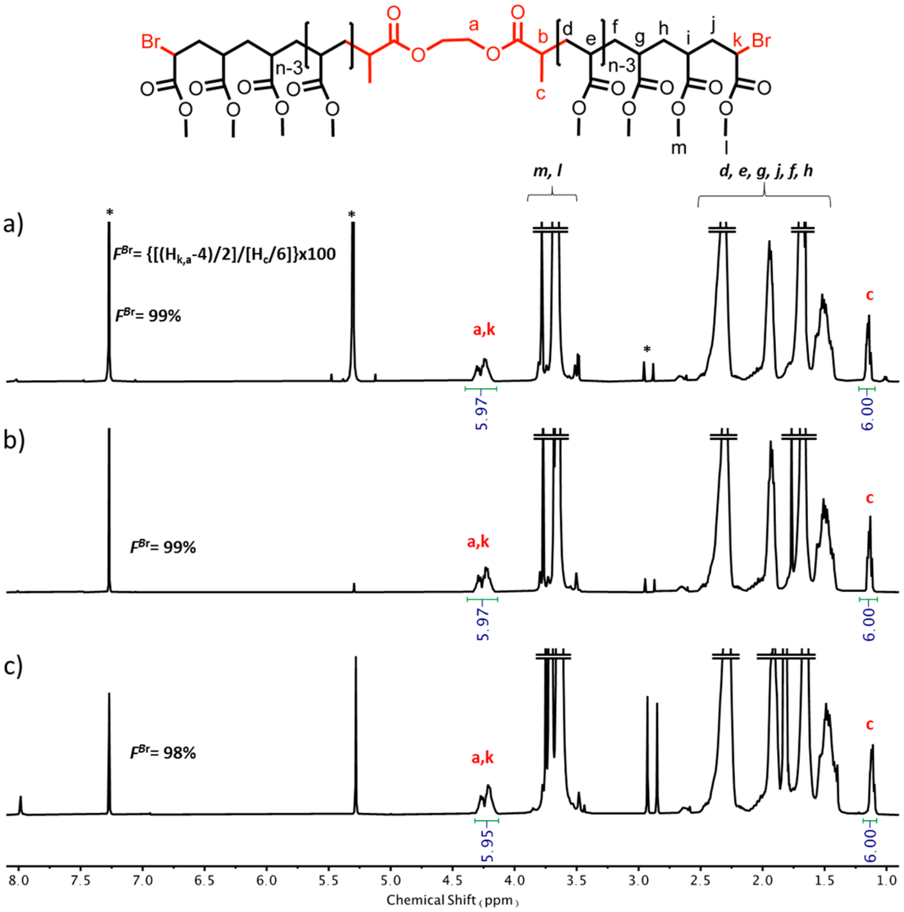
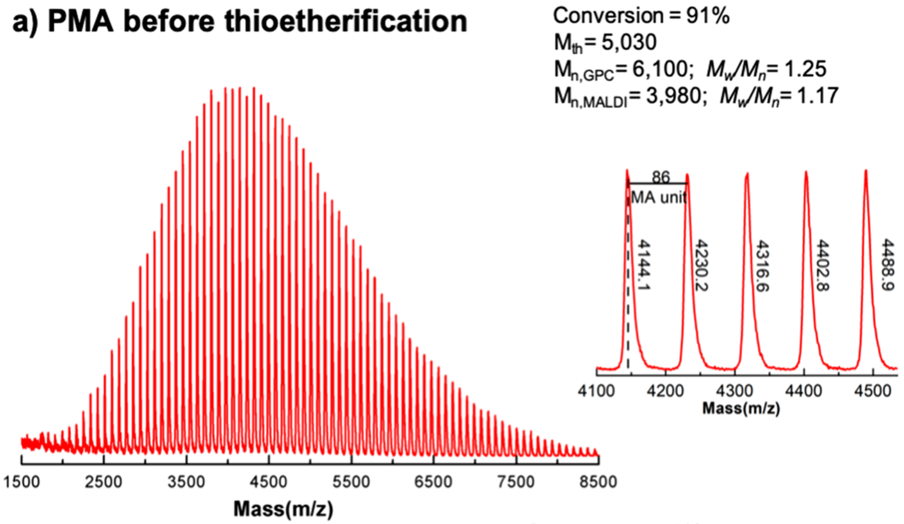


Figure 6. ^{1}H NMR spectra at 400 MHz of α,ω-di(bromo)PMA at (a) 93% monomer conversion (M_n = 6480 and M_w/M_n = 1.14) ($[MA]_0/[BPE]_0/[Me_6\text{-TREN}]_0$ = 60/1/0.1); (b) 91% monomer conversion (M_n = 6100 and M_w/M_n = 1.25) ($[MA]_0/[BPE]_0/[Me_6\text{-TREN}]_0/[TREN]_0$ = 60/1/0.05/0.05); (c) 94% monomer conversion (M_n = 5990 and M_w/M_n = 1.25) ($[MA]_0/[BPE]_0/[TREN]_0$ = 60/1/0.1). Polymerization conditions: MA = 1 mL, DMF = 0.4 mL, water = 0.1 mL using 12.5 cm of nonactivated Cu(0) wire 20-gauge wire. ^{1}H NMR resonances from residual solvents are indicated with *.

replacement of -Br atoms (2 × 79.9) by -SPh moieties (2 × 109.2) at both polymer chain-ends. MALDI-TOF analysis of PMA prepared using Me$_6$-TREN and TREN showed also high levels of chain end functionality (Figure S9 and S10, respectively). Likewise, equivalent samples prepared in NMP/water and DMAc/water (8/2, v/v) mixtures provided also evidence of chain-end functionality close to 100% in all cases (see Figures S11−S20).

Brief Comments on SET-LRP Mechanism and on Significance for the Field of Biomacromolecules. SET-LRP catalyzed by Cu(0) wire, powder, coins, and other objects occurs in disproportionating solvents and provides polymers with unexpectedly high chain end functionality for a living radical polymerization process.[26,50] This includes, within the limits of NMR experimental error, 100% chain end functionality.[26,50] In nondisproportionating solvents including polar solvents like acetonitrile[43] and nonpolar solvents like toluene,[50] the chain end functionality of the resulting polymers is much lower. Best chain end functionality is observed in the absence Cu(II)X$_2$ and could be obtained either with TREN or Me$_6$-TREN[26] or in the presence of very small amount of Cu(II)X$_2$.[26,50] Larger amounts of Cu(II)X$_2$ additive decrease the chain end functionality of the resulting polymers, although it remains the highest chain end functionality of any LRP prepared polymers.[26,50,51] Details of chain end functionality as a function of the concentration of externally added Cu(II)X$_2$ are discussed in previous publications.[26,50] Under these conditions, the lower chain end functionality values can also be explained by the Cu(II)Br$_2$-mediated oxidation of radicals to carbocations that subsequently provide chain end double bonds by proton transfer to the basic components of the reaction mixture.[52−54] Terminal double bond chain ends have been reported in polyacrylates obtained by SET-LRP in the presence of Cu(II)X$_2$.[51a] The unusually high chain end functionality observed under SET-LRP reaction conditions was attributed to the polymer adsorption on the surface of Cu(0) that decreases the reactivity of the growing radicals in bimolecular termination events but not in the propagation reactions.[55,56] This high chain end functionality contrasts with the much lower chain end functionality observed in ATRP, where the persistent radical effect (PRE)[57] is responsible for the production of Cu(II)X$_2$.[58,59] Activation of the alkyl halides by Cu(0) objects occurs by the most active site of their face centered crystal (FCC), that is, 111.[60] Both powder[43] and wire[44] experiments demonstrated that objects produced from Cu(0) crystals have a reactivity that is surface dependent. Moreover, this reactivity increases when Cu(0) atoms are produced by disproportionation followed by activation, nucleation and growth on the original surface of Cu(0).[19,61] Nucleation and growth has been demonstrated to occur during SET-LRP on the surface of the wire.[47] Colloidal Cu(0) particles were also demonstrated during SET-LRP.[62] However,



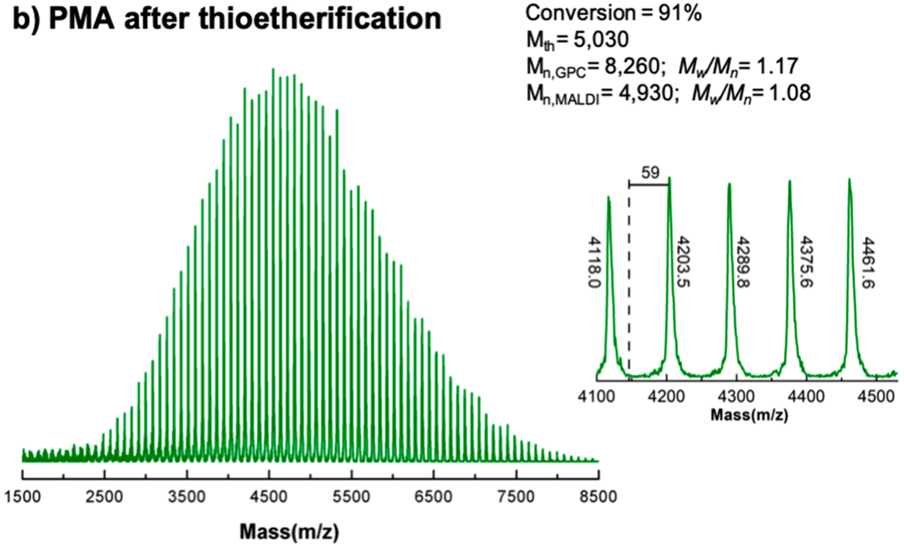


Figure 7. MALDI-TOF of α,ω-di(bromo)PMA isolated at 91% monomer conversion from SET-LRP of MA in DMF/water (8/2, v/v) mixture initiated with BPE and catalyzed by nonactivated Cu(0) wire at 25 °C: (a) before and (b) after "thio-bromo "click". Polymerization conditions: MA = 1 mL, DMF = 0.4 mL, water = 0.1 mL using 12.5 cm of nonactivated Cu(0) wire 20-gauge wire ($[MA]_0/[BPE]_0/[TREN]_0 = 60/1/0.05/0.05$). The dotted line in expansion after thioetherification shows the original peak from before thioetherification, while 58 represents the increase in molar mass after thioetherification i.e., 2x[SPh (109. 2) − Br (79.9)] = 58.57 for each chain end.

the highest activity of Cu(0) is as atoms. Cu(0) atoms are more reactive that Cu(I)X and are classic and well-established SET catalysts.[63] This diversity of catalytic Cu(0) species are all involved in the SET-LRP process but they could not be observed to reduce $Cu(II)X_2$ to Cu(I)X species during the SET-LRP process;[64] however, it cannot be excluded to occur in the absence of activation. This brief mechanistic discussion demonstrates that the reduction of the amount of $Cu(II)X_2$ during SET-LRP can contribute to a better control of the chain ends and to a lower amount of contamination of the product with Cu species. Because this polymerization proceeds in biphasic systems containing water, the mixed ligand process elaborated here is expected to impact the field of biomacromolecules at a much higher level than SET-LRP performed with externally added $Cu(II)Br_2$ or ATRP also in the presence of externally added $Cu(II)Br_2$.

■ CONCLUSIONS

The use of TREN and Me_6-TREN mixed-ligand system to mediate the Cu(0) wire-catalyzed SET-LRP MA in various "programmed" biphasic mixtures based on dipolar aprotic solvents and water is reported. Kinetic data and chain end analysis demonstrate that Me_6-TREN can complement and make TREN a very efficient ligand in the absence of externally added $Cu(II)Br_2$. During the SET-LRP of MA in 8/2 (v/v) aqueous mixtures of NMP, DMF, and DMAc with H_2O the use of the mixed-ligand system demonstrated an enhanced rate of polymerization, monomer conversion, and molecular weight control. The fact that the most important effect is observed at 1/1 molar ratio between ligands suggests that in addition to a fast exchange between the two ligands, a new single dynamic ligand generated by hydrogen-bonding should be considered in future mechanistic investigations. The rate of polymerization at 1/1 molar ratio between the two ligands is higher than that obtained with each of the individual ligand at the same molar concentration. At the same time, SET-LRP experiments performed in biphasic systems with H_2O do not require the use of the activated Cu(0) wire. The high chain end functionality generated in the absence of externally added $Cu(II)Br_2$ makes the SET-LRP in the presence of the mixed-

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ligand the method of choice for the synthesis of biomacromolecules.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.biomac.9b01282.

> Kinetic plots, molecular weight, and polydispersity evolution for the SET-LRP of MA; digital images of control experiments; ^{1}H NMR and MALDI-TOF MS of PMA after SET-LRP; and summary of SET-LRP of MA (PDF)

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Notes

The authors declare no competing financial interest.

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