

Me₆-TREN/TREN Mixed-Ligand Effect During SET-LRP in the Catalytically Active DMSO Revitalizes TREN into an Excellent Ligand

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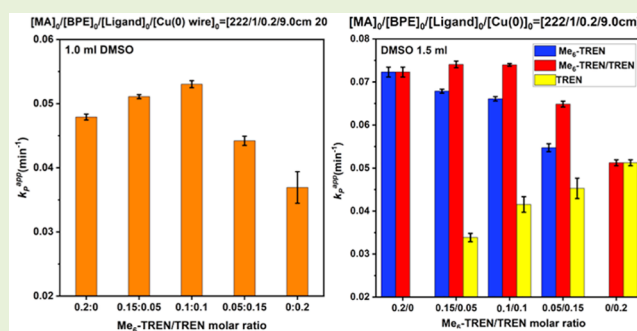


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ABSTRACT: A mixed-ligand effect was observed for mixtures of tris(2-dimethylaminoethyl)amine (Me₆-TREN) with tris(2-aminoethyl)amine (TREN) ligands during Cu(0) wire-catalyzed, single-electron transfer-living radical polymerization (SET-LRP) of methyl acrylate (MA) initiated with bis(2-bromopropionyl)ethane (BPE) in DMSO. The external order of reaction of SET-LRP both in the presence of Me₆-TREN, TREN and of the mixed-ligand Me₆-TREN/TREN, in DMSO, demonstrated a catalytic activity for DMSO similar to that reported in the presence of Cu(0) powder. The catalytic activity of DMSO, with close to 100% chain-end functionality, facilitates the much less expensive TREN to act as a very efficient ligand that is competitive with Me₆-TREN and with the mixed-ligand and revitalizes TREN into an excellent ligand. The highest activity of the mixed-ligand at 1/1 ratio between ligands suggests that in addition to a fast exchange between these two ligands, a new single dynamic ligand stabilized by hydrogen-bonding, may generate these results.



INTRODUCTION

The mixed-ligand concept represents an inexpensive but extremely efficient methodology to design new catalytic systems without synthetic efforts.¹ Almost simultaneously with its development, Feringa reported heterocombinations of chiral monodentate ligands as more efficient than homocombinations in Rh-catalyzed C–C cross-coupling.² At the same time the mixed-ligand strategy was expanded to Pd-catalyzed C–N^{3,4} and C–S⁵ cross-coupling and to Ni-mediated Suzuki cross-coupling and borylation.⁶ The advantages of the mixed-ligand catalytic systems have been observed only in several polymerization reactions.^{7–9}

A suitable solvent/N-ligand mixture is demanded for Cu(0)-catalyzed single electron transfer-living radical polymerization (SET-LRP)^{10–17} in order to facilitate the disproportionation of Cu(I)X into Cu(0) and Cu(II)X₂.^{18,19} Tris(2-dimethylaminoethyl)amine (Me₆-TREN) is a common ligand used in SET-LRP,^{10,11,14} since it favors the disproportionation by preferentially binding Cu(II)X₂ rather than Cu(I)X.²⁰ Nevertheless, the precursor of Me₆-TREN, tris(2-aminoethyl)amine (TREN)^{11,21–23} that is about 80× less expensive than Me₆-TREN, and poly(ethylene imine) (PEI)¹⁰ was also used for SET-LRP of vinyl chloride (VC), acrylates, and methacrylates during the first days of SET-LRP. Likewise, TREN^{24–26} and N,N,N',N'-pentamethyldiethylenetriamine (PMDETA)^{10,27,28} were also employed in SET-LRP.

The replacement of Me₆-TREN with TREN was not very successful in biphasic SET-LRP complex systems catalyzed by Cu(0) wire that we call “programmed,”^{29–33} although TREN is known for its efficiency in single-phase SET-LRP. Biphasic organic solvent–water SET-LRP complex systems demand the addition of Cu(II)Br₂ in order to retain the living character when TREN is used as a ligand. In this particular case, SET-LRP is an interfacial process that was discussed in more details in previous publications.³⁴ The Cu(0)-mediated SET-LRP in bi(multi)phasic mixtures of organic solvents with water is very important and opens new methodologies since the organic solvent does not have to facilitate the disproportionation of Cu(I)X/N-ligand, as in the classic SET-LRP.^{35–39} The first mixed-ligand effect in a SET-LRP system was observed in the water–organic solvent “programmed” biphasic systems when Me₆-TREN was successfully employed to replace the externally added Cu(II)X₂ with Me₆-TREN.^{10b}

In this publication, we first report experiments that demonstrate the catalytic activity of DMSO solvent in both Me₆-TREN and TREN and in the mixed-ligand Me₆-TREN/TREN-mediated SET-LRP of MA initiated with BPE at 25 °C

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Scheme 1. SET-LRP of MA Initiated with BPE and Catalyzed with Nonactivated Cu(0) Wire by Employing Various Ratios of Me₆-TREN and TREN in the Catalytically Active DMSO at 25 °C

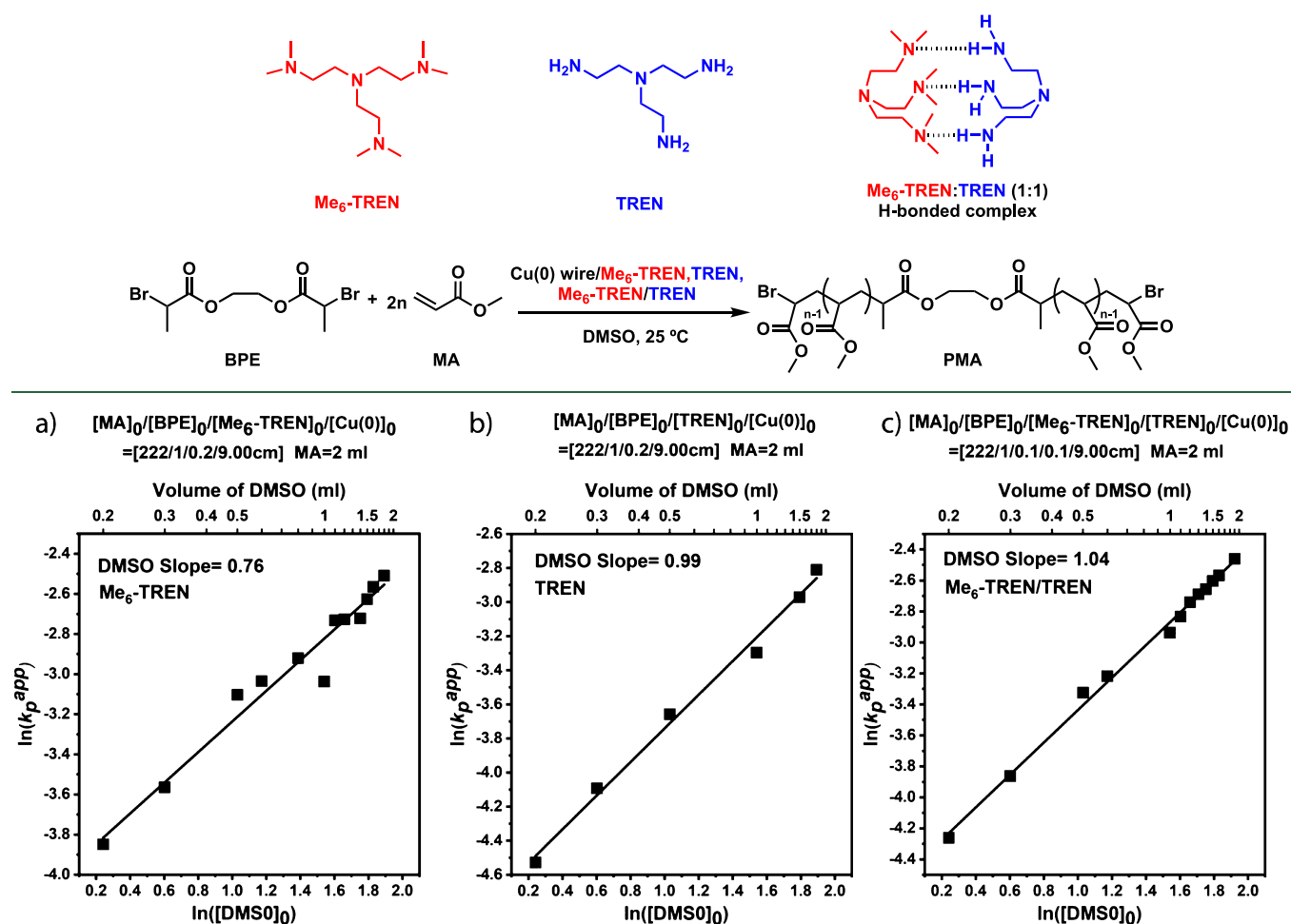


Figure 1. Determination of the external order of reaction in [DMSO]₀ for the Cu(0) wire/ligand-catalyzed polymerization of methyl acrylate (MA) in DMSO at 25 °C, initiated with BPE. $\ln(k_p^{app})$ vs $\ln([DMSO]_0)$ with DMSO varied from 0.2 to 1.9 mL, with 2 mL of MA for (a) $[MA]_0/[BPE]_0/[Me_6-TREN]_0/[Cu(0)]_0 = 222/1/0.2/9$ cm; (b) $[MA]_0/[BPE]_0/[TREN]_0/[Cu(0)]_0 = 222/1/0.2/9$ cm; (c) $[MA]_0/[BPE]_0/[Me_6-TREN]_0/[TREN]_0/[Cu(0)]_0 = 222/1/0.1/0.1/9$ cm.

and catalyzed with nonactivated Cu(0) wire. The catalytic activity of DMSO was discovered previously when Cu(0) powder was employed as catalyst,^{11a} but was not used to improve the synthetic capabilities of SET-LRP. Subsequently, the mixed-ligand effect of Me₆-TREN/TREN was investigated at two different concentrations of the DMSO solvent. Statistical analysis of the kinetics and of the control experiments together with the determination of the chain-end functionality of the resulting polymers by a combination of NMR and MALDI-TOF before and after thio-bromo “click” reaction demonstrated that the catalytic activity of DMSO can be employed to improve the efficiency of the inexpensive TREN ligand. Therefore, we can conclude that the catalytic activity of DMSO was employed to revitalize the long-neglected TREN and transform it into an excellent ligand. Since TREN is 80× less-expensive than Me₆-TREN, numerous new applications, including in the field of biomacromolecules, will evolve from the series of experiments reported here.

EXPERIMENTAL SECTION

Materials. Methyl acrylate (MA; 99%, Acros) was passed over a short column of basic Al₂O₃ to remove its radical inhibitor.

Tris(2-aminoethyl)amine (TREN; 99%, Acros), Cu(0) wire (20 gauge wire, 0.812 mm diameter from Fisher), and dimethyl sulfoxide (DMSO; 99.8%, Sigma-Aldrich) were used as received. Triethylamine (NEt₃; >99.5% Chemimpex) was distilled under N₂ from CaH₂. Bis(2-bromopropionyl)ethane (BPE) was synthesized by esterification of ethylene glycol with 2-bromopropionyl bromide in the presence of pyridine.⁴⁰ Hexamethylated tris(2-aminoethyl)amine (Me₆-TREN) was synthesized by a literature procedure.⁴¹

Techniques. ¹H NMR (400 MHz) spectra were recorded on a Bruker AVANCE NEO 400 NMR instrument at 27 °C in CDCl₃ 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 were determined with poly(methyl methacrylate) (PMMA) standards 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). 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

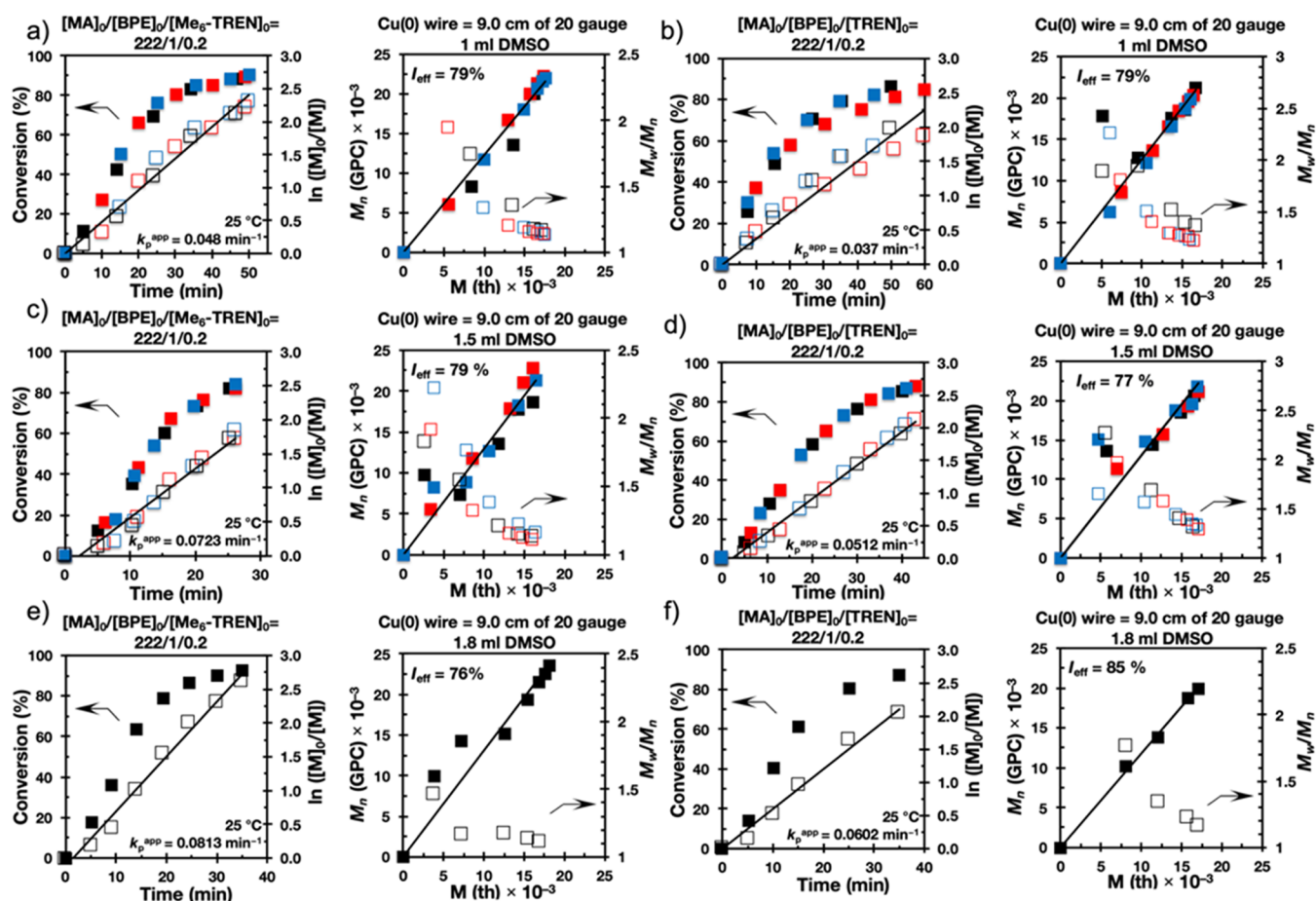


Figure 2. Kinetic plots, molecular weight and dispersity evolutions for the SET-LRP of MA in DMSO initiated with BPE and catalyzed with 9.0 cm nonactivated Cu(0) wire at 25 °C. Data in different colors were obtained from different kinetics, performed by different researchers. k_p^{app} and I_{eff} are the average values of three experiments. k_p^{app} vs [DMSO]₀ with DMSO varied from 1.0 mL (a) to 1.5 mL (c) to 1.8 mL (e) with 2 mL of MA for [MA]₀/[BPE]₀/[Me₆-TREN]₀/[Cu(0)]₀ = 222/1/0.2/9 cm. Identical experiments in which Me₆-TREN was replaced with TREN are in (b), (d), and (f).

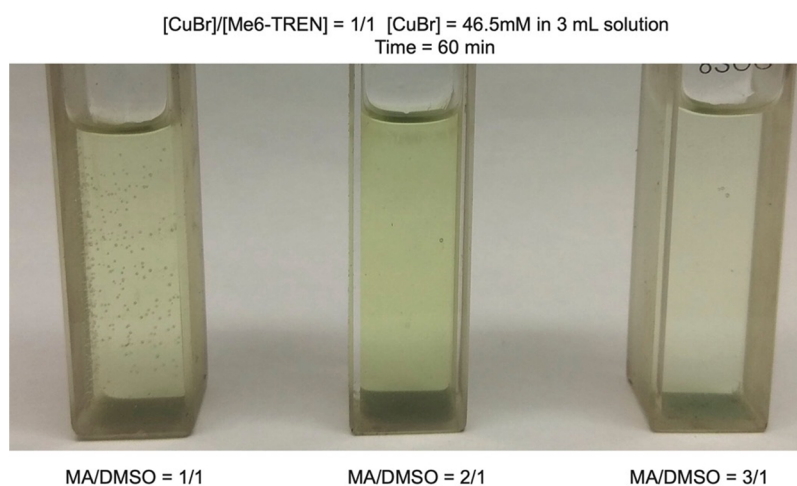


Figure 3. Visual observation of CuBr/Me₆-TREN complex dissolved in DMSO/MA. Conditions: [CuBr] = 46.5 mM, solvent = 3.0 mL, [CuBr]₀/[Me₆-TREN]₀ = 1/1. Pictures were taken 60 min after mixing the reagents.

2-(4-hydroxyphenylazo) benzoic acid as the matrix. Solutions of the matrix (25 mg/mL in THF), NaCl (2 mg/mL in deionized H₂O), and polymer (10 mg/mL) were prepared independently. The solution for MALDI-TOF analysis was obtained by mixing the matrix, polymer, and salt solutions in a 5/1/1 volumetric ratio. Subsequently, 0.5 μ L portions of the mixture were deposited onto three wells of

sample plate and dried in air at room temperature before being subjected to MALDI-TOF analysis.

Standard Procedure for SET-LRP of MA in DMSO Using Me₆-TREN, TREN, and the Mixed-Ligand Me₆-TREN/TREN Methodology. Stock solutions prepared with different ratios of Me₆-TREN to TREN such as 0.02/0 M, 0.015/0.005 M, 0.01/0.01 M,

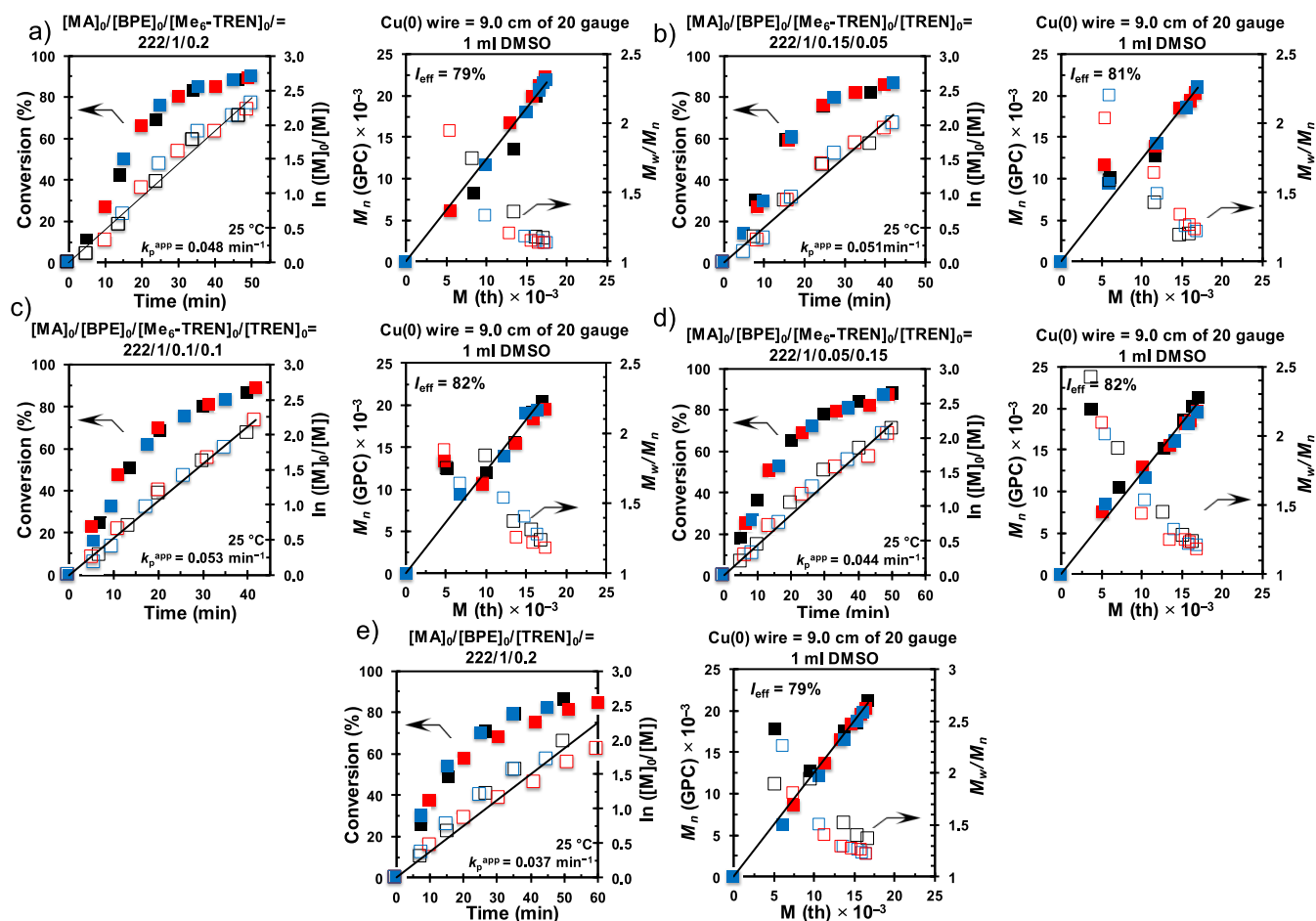


Figure 4. Kinetic plots, molecular weight, and dispersity evolutions for the SET-LRP of MA in DMSO initiated with BPE and catalyzed by the 9.0 cm nonactivated Cu(0) wire at 25 °C in the presence of (a) Me₆-TREN and (b–d) different ratios of Me₆-TREN/TREN and (e) TREN. Experimental data in different colors were obtained from different kinetics experiments, sometimes performed by different researchers. k_p^{app} and I_{eff} are the average values of three experiments. [MA]₀/[BPE]₀/[ligand]₀/[Cu(0)]₀ = 222/1/0.2/9 cm.

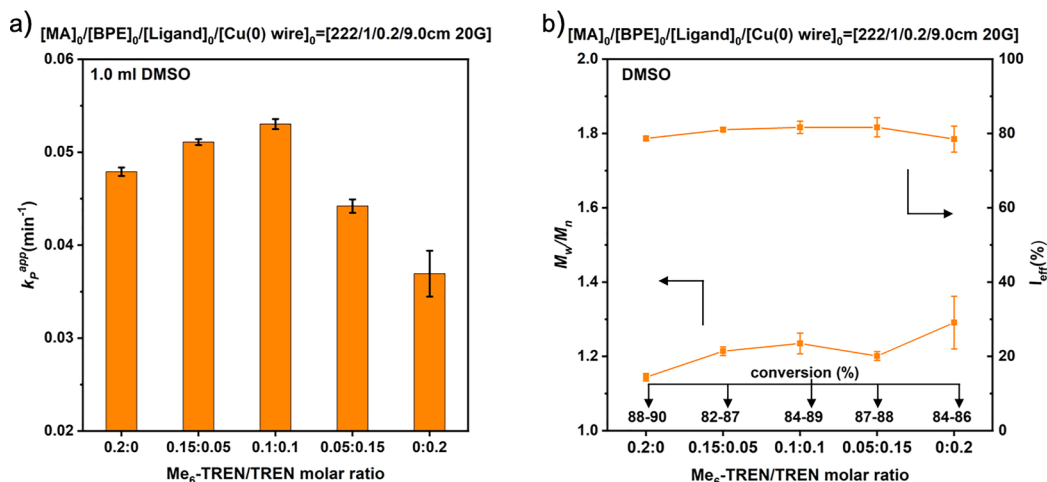


Figure 5. Evolution of k_p^{app} for the SET-LRP of MA (2 mL) initiated with BPE in DMSO (1 mL) mediated with different ratios between Me₆-TREN and TREN at 25 °C (a). Initiator efficiency (I_{eff} (%)) and dispersity (M_w/M_n) as a function of the ratio between Me₆-TREN and TREN.

0.005/0.015 M, and 0/0.02 M in DMSO were first made. The monomer (MA, 22.2 mmol, 2.00 mL), organic solvent (DMSO if necessary), DMSO stock solution (0.02 mmol ligand, 1 mL), and initiator (BPE, 0.1 mmol, 33.2 mg) were added in this order to a 25 mL Schlenk tube. The mixture was deoxygenated by six

freeze–pump–thaw cycles. Subsequently, 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 with the help of an external magnet. The Schlenk

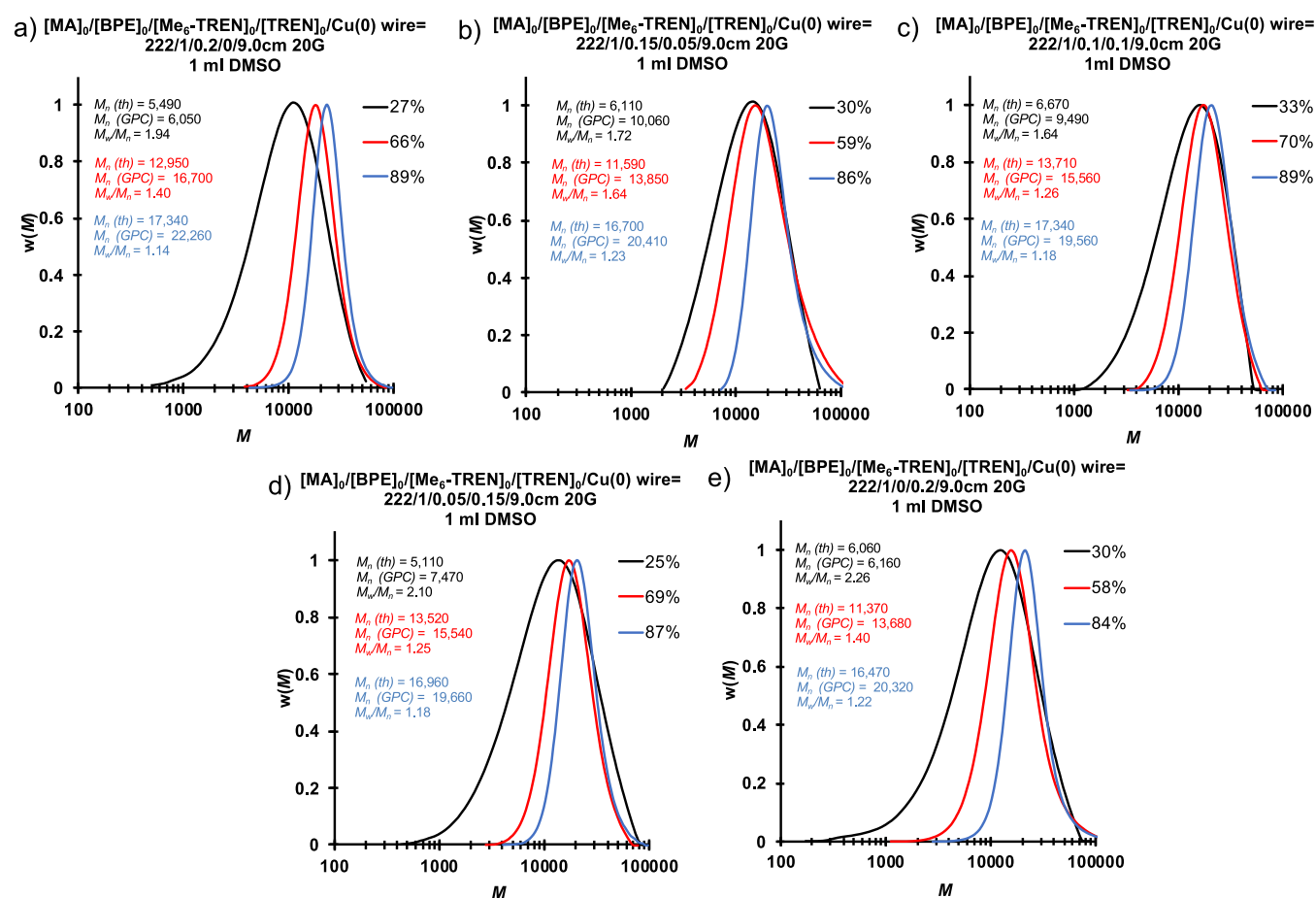


Figure 6. Representative GPC traces of the evolution of molecular weight as a function of conversion for the SET-LRP of MA in a mixture of 2 mL MA with 1 mL DMSO catalyzed by 9.0 cm nonactivated Cu(0) wire at 25 °C in the presence of various ligand compositions, as mentioned on top of the GPC curves. Reaction conditions: MA = 2 mL, DMSO = 1 mL, [MA]₀/[BPE]₀/[L]₀ = 222/1/0.2.

Table 1. Dependence of k_p^{app} on the Dimension of the Cu(0) Wire in the SET-LRP of MA Initiated with BPE in DMSO at 25 °C^a

entry	wire length (cm) 20G	reaction condition	k_p^{app} (min ⁻¹)	k_p^{app}/k_p^{app} (TREN)	M_w/M_n	I_{eff} (%)
1	9.0	[MA]/[BPE]/[Me ₆ -TREN] 222/1/0.2	0.048	1.3	1.14	79
2	9.0	[MA]/[BPE]/[Me ₆ -TREN]/[TREN] 222/1/0.15/0.05	0.051	1.4	1.21	81
3	9.0	[MA]/[BPE]/[Me ₆ -TREN]/[TREN] 222/1/0.1/0.1	0.053	1.4	1.23	82
4	9.0	[MA]/[BPE]/[Me ₆ -TREN]/[TREN] 222/1/0.05/0.15	0.044	1.2	1.20	82
5	9.0	[[MA]/[BPE]/[TREN] 222/1/0.2	0.037	1.0	1.23	79

^aReaction conditions: monomer = 2 mL; solvent = 1 mL.

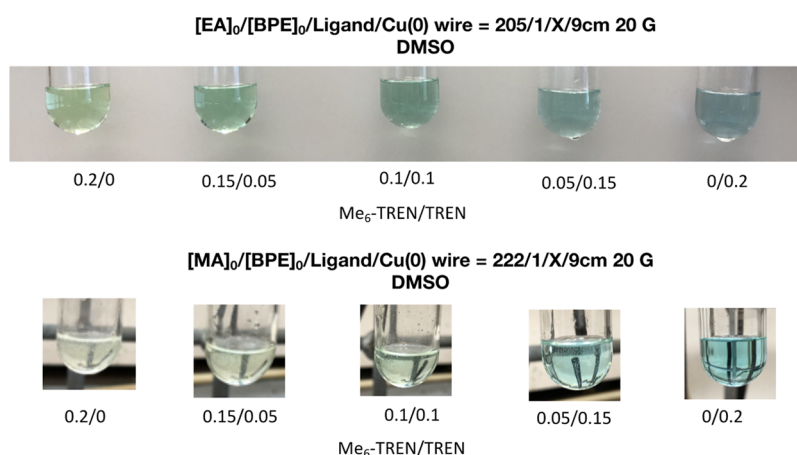


Figure 7. Visualization of the reaction mixture of SET-LRP of MA initiated with BPE in DMSO using various ligand ratios (X) shown under the Schlenk tube. Reaction conditions are on top of each series of experiments.

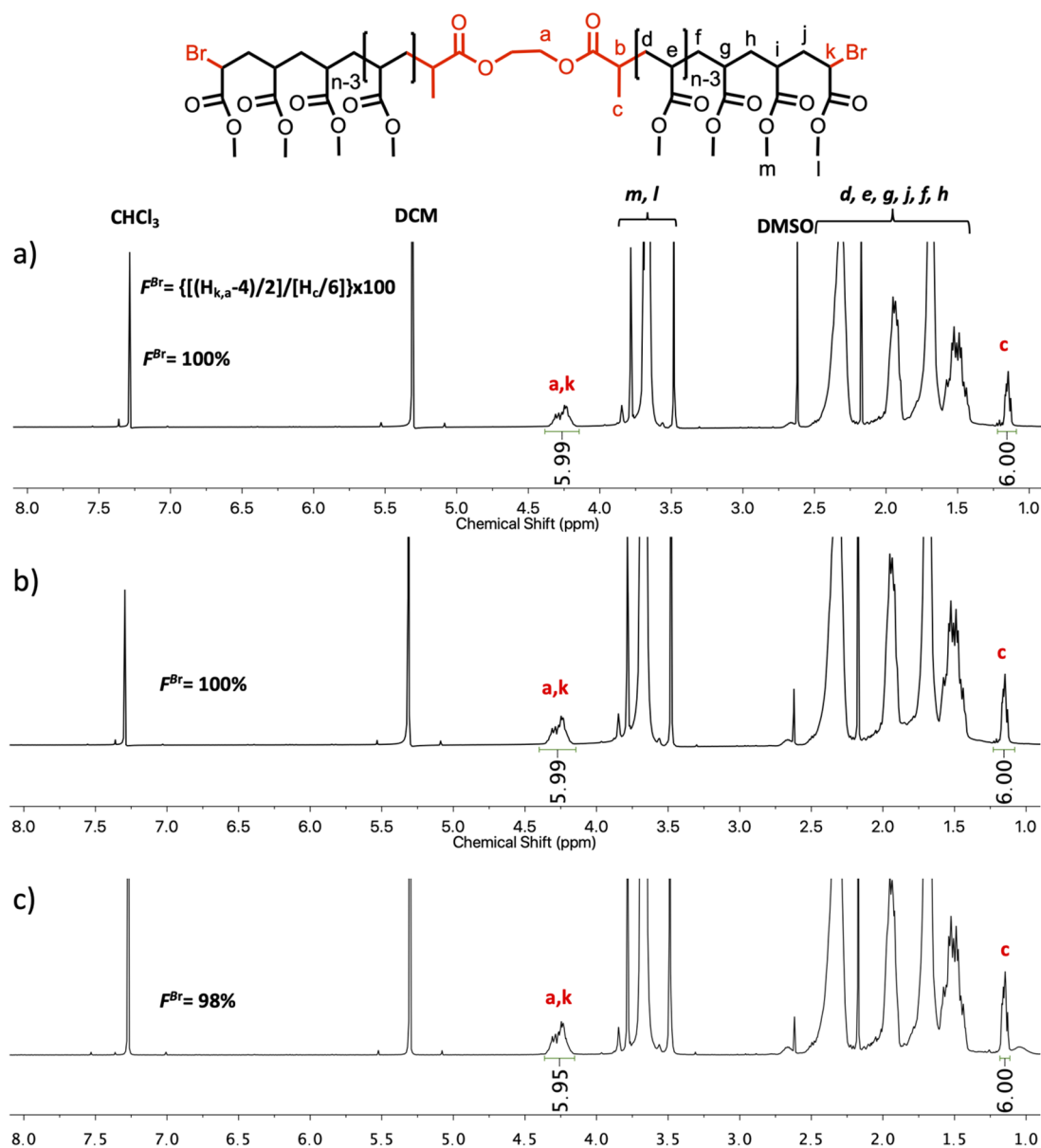


Figure 8. ^1H NMR spectra at 400 MHz of α,ω -di(bromo)PMA at (a) 94% conversion ($M_n = 8620$ and $M_w/M_n = 1.22$; $[\text{MA}]_0/[\text{BPE}]_0/[\text{Me}_6\text{-TREN}]_0 = 60/1/0.2$); (b) 90% conversion ($M_n = 9090$ and $M_w/M_n = 1.41$; $[\text{MA}]_0/[\text{BPE}]_0/[\text{Me}_6\text{-TREN}]_0/[\text{TREN}]_0 = 60/1/0.1/0.1$); (c) 96% conversion ($M_n = 7384$ and $M_w/M_n = 1.23$; $[\text{MA}]_0/[\text{BPE}]_0/[\text{TREN}]_0 = 60/1/0.2$); Polymerization conditions: MA = 2 mL, DMSO = 1.0 mL, and nonactivated 9 cm Cu(0) wire of 20 gauge. The signals at 7.26 and 5.30 ppm are due to partially nondeuterated residue of CDCl_3 and dichloromethane, respectively. F^{Br} values refer to chain-end functionality of PMA before thio-bromo “click” reaction (%).

tube was filled with N_2 , and the reaction was placed in a water bath at 25 $^\circ\text{C}$. Then, the stir bar wrapped with the Cu(0) wire was dropped gently into the reaction. The introduction of the Cu(0) wire defines $t = 0$. Samples were taken at different times by purging the side arm of the Schlenk tube with nitrogen for 2 min using a deoxygenated syringe and stainless steel needles. 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 small basic Al_2O_3 chromatographic column to remove any residual copper and 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 of the chain ends.

General Method for the Chain-End Thioetherification 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 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 polymer was dried under vacuum to a constant weight.

RESULTS AND DISCUSSION

Determination of the External Order of Reaction in DMSO During SET-LRP Catalyzed with Nonactivated Cu(0) Wire in DMSO. A close to first order external order of reaction in the DMSO used as solvent was observed when Cu(0) powder was employed as catalyst in SET-LRP.^{11a,42–47}

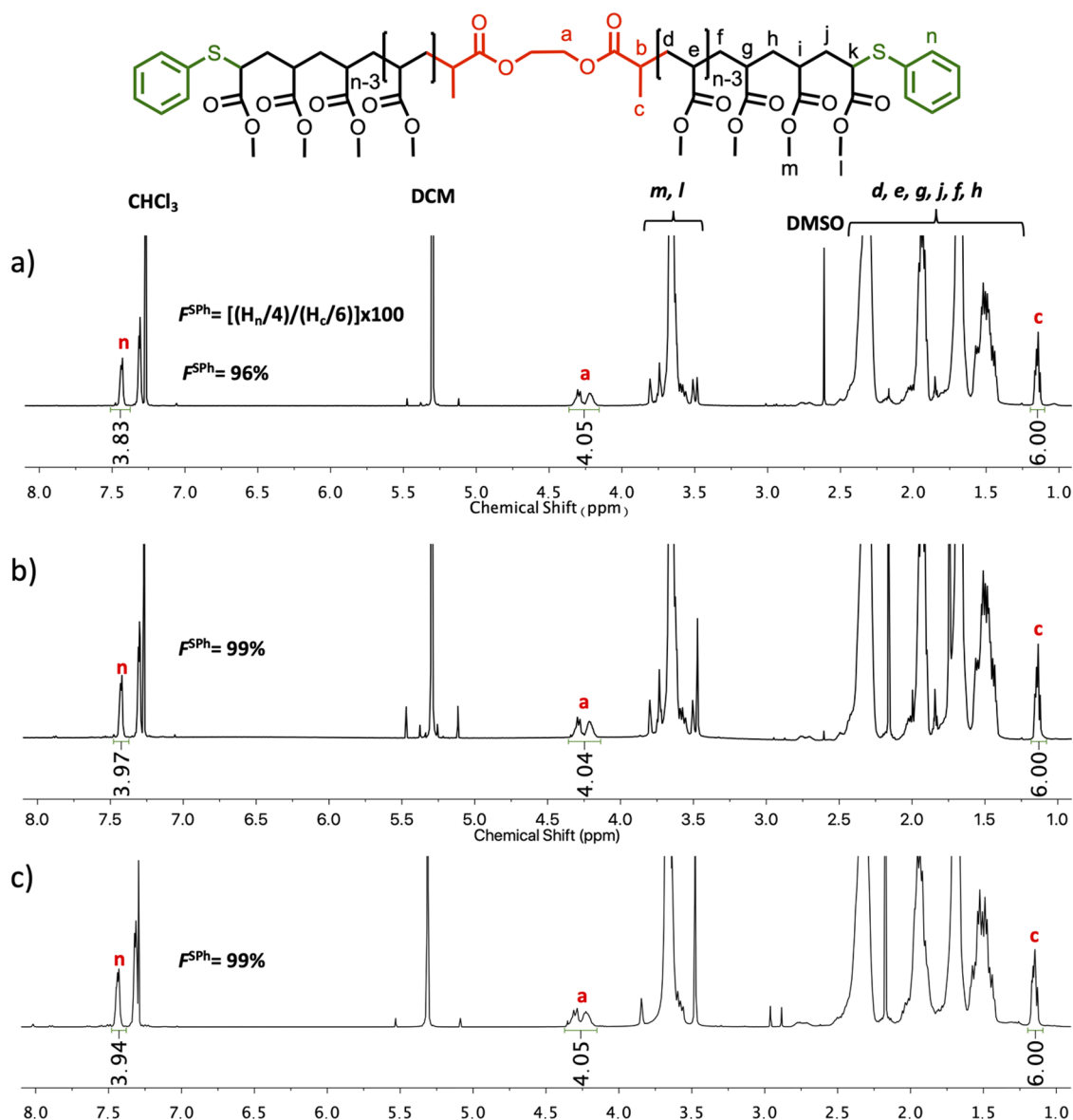


Figure 9. ^1H NMR spectra at 400 MHz of α,ω -di(phenylthio)PMA at (a) 94% conversion ($M_n = 8620$ and $M_w/M_n = 1.22$; $[\text{MA}]_0/[\text{BPE}]_0/[\text{Me}_6\text{-TREN}]_0 = 60/1/0.2$); (b) 90% conversion ($M_n = 9090$ and $M_w/M_n = 1.41$; $[\text{MA}]_0/[\text{BPE}]_0/[\text{Me}_6\text{-TREN}]_0/[\text{TREN}]_0 = 60/1/0.1/0.1$); (c) 96% conversion ($M_n = 7380$ and $M_w/M_n = 1.23$; $[\text{MA}]_0/[\text{BPE}]_0/[\text{TREN}]_0 = 60/1/0.2$); Conditions: MA = 2 mL, DMSO = 1.0 mL, and nonactivated 9 cm Cu(0) wire of 20 gauge wire. The signals at 7.26 and 5.30 ppm are due to a partially nondeuterated residue of CDCl_3 and dichloromethane, respectively. F^{SPH} values refer to chain-end functionality of PMA after a thio-bromo “click” reaction (%).

This external first order of reaction in DMSO demonstrated the catalytic activity of DMSO when SET-LRP was performed in DMSO as solvent. Three series of experiments were carried out with nonactivated Cu(0) wire as catalyst, MA as monomer, and $\text{Me}_6\text{-TREN}$, TREN, and mixtures of $\text{Me}_6\text{-TREN}$ /TREN in different concentrations of DMSO at 25 °C. BPE was used as initiator in all cases.

The structures of the two ligands and an equation of the Cu(0) wire-catalyzed SET-LRP of MA initiated with bis(2-bromopropionyl)ethane (BPE) are outlined in Scheme 1. Duplicate and triplicate kinetics were carried out under the following conditions: $[\text{MA}]_0/[\text{BPE}]_0/[\text{L}]_0 = 222/1/0.2$ using 9.0 cm of nonactivated Cu(0) wire.

Figure 1a reports the kinetic data for the experiments performed with $\text{Me}_6\text{-TREN}$ as ligand, Figure 1b shows the data obtained with TREN, while Figure 1c shows the data obtained with the mixed-ligand system $\text{Me}_6\text{-TREN}$ /TREN. Selected

kinetic experiments from which these external orders of reaction in DMSO were obtained for $\text{Me}_6\text{-TREN}$ (Figure 2a,c,e) and TREN (Figure 2b,d,f) as ligands are reported in Figures 2 when the DMSO concentration was varied from 1.0 to 1.5 and to 1.8 mL of DMSO with 2 mL of MA. Kinetic experiments with all other DMSO concentrations employed in Figure 1a–c are shown in Supporting Information, Figures S1–S5. First order reaction kinetics in monomer were observed for all DMSO concentrations from Figures 2 and Supporting Information Figures S1–S5. A continuous increase in the rate of polymerization and of the corresponding apparent rate constant, k_p^{app} , as the concentration of the DMSO increased or the overall concentration of the MA decreased was observed in all cases (Figures 2 and Supporting Information, Figures S1–S5).

In any organic or polymerization reaction the decrease in the reactants concentration generated by increasing the solvent concentration results in a decrease of the rate of reaction. This

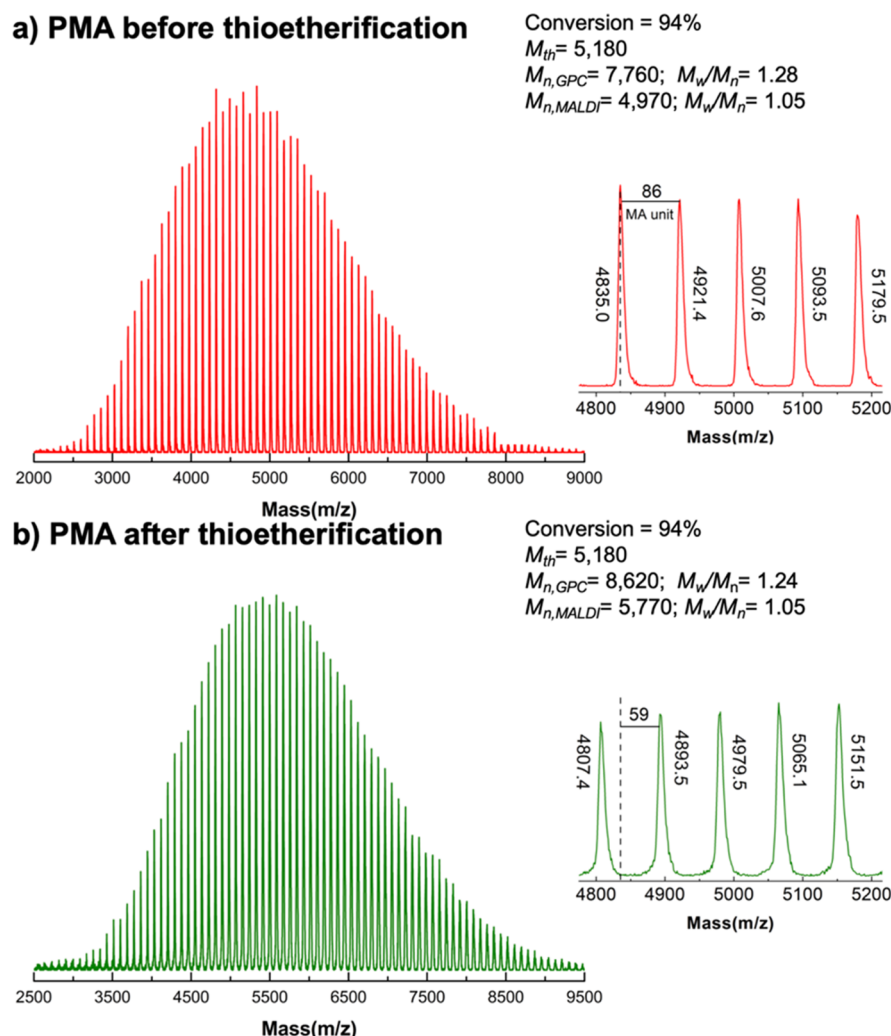


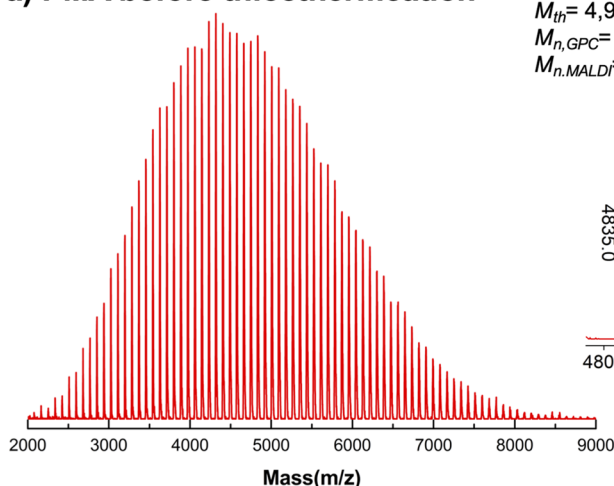
Figure 10. MALDI-TOF of PMA-Br isolated at 94% from SET-LRP of MA in DMSO solution initiated with BPE and catalyzed by nonactivated Cu(0) wire at 25 °C. (a) Before “thio-bromo click” reaction. (b) After “thio-bromo click” reaction. Reaction conditions: MA = 2 mL, DMSO = 1.0 mL, $[MA]_0/[BPE]_0/[Me_6-TREN]_0 = 60/1/0.2$, 9.0 cm of 20 gauge Cu(0) wire. The dotted line in expansion after thioetherification shows the original peak from before thioetherification, while 59 represents the increase in molar mass after thioetherification, that is, $2 \times [SC_6H_5 (109, 2) - Br (79, 9)] = 58.57$ for each chain-end.

unexpected trend that consists of the increase in rate of polymerization with the decrease of the monomer concentration demonstrates the catalytic activity of DMSO in SET-LRP. This result is in agreement with the experiments reported with Cu(0) powder as catalyst.^{11a} The determination of the external order of reaction in DMSO was calculated by plotting the $\ln(k_p^{app})$ vs $\ln([DMSO]_0)$ (Figure 1a–c). The slope of these dependencies provided the external order of reaction in DMSO for the different ligands used in these SET-LRP experiments. An external order of reaction in DMSO of 0.76 was obtained in the presence of Me_6 -TREN, while in the presence of TREN and the mixed-ligand Me_6 -TREN/TREN (1/1 molar ratio), the external orders of reaction in DMSO were 0.99 and 1.04, respectively.

Potential Mechanism for the Catalytic Activity of DMSO. In order to address the catalytic activity of DMSO, first it must be considered that SET-LRP experiments were performed in a mixture of two solvents, DMSO and the monomer, MA. Both DMSO and MA are good solvents that mediate the disproportionation of Cu(I)Br into Cu(0) and Cu(II)-Br₂.^{19a}

While both solvents MA and DMSO mediate the disproportionation in the presence of these two ligands, MA and DMSO, only DMSO is a good solvent for Cu(I)Br and Cu(II)Br₂ obtained during the activation and disproportionation and is also a better solvent that mediates this disproportionation. MA mediates disproportionation mostly by a surface effect. Therefore, it is expected that by increasing the ratio between DMSO and MA in the reaction mixture, the extent of disproportionation will increase. At the same time it has been demonstrated that DMSO stabilizes Cu(0) nanoparticles, while MA does not. Figure 3 presents disproportionation experiments that support this hypothesis. An increase in the amount of Cu(0) obtained by disproportionation is observed at the transition from MA/DMSO = 3/1 to 2/1. This increase continues to the transition to MA/DMSO = 1/1. However, in addition to this trend, at a 1/1 ratio, the stabilization of Cu(0) nanoparticles by the higher concentration of DMSO is also visible (see left vial in Figure 3). Increasing the stability of nanoparticles decreases the crystallization process and provides smaller but more active Cu(0) nanoparticles of the catalyst.^{19b} It is well established that faster SET-LRP is mediated in more

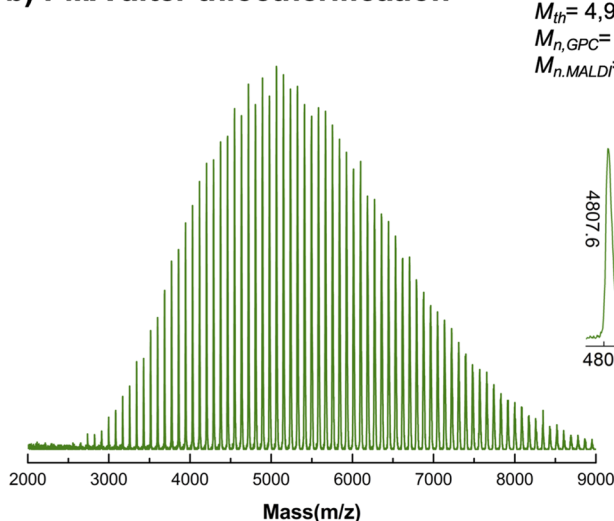
a) PMA before thioetherification



Conversion = 90%

 $M_{th} = 4,980$ $M_{n,GPC} = 8,310$; $M_w/M_n = 1.44$ $M_{n,MALDI} = 4,790$; $M_w/M_n = 1.06$

b) PMA after thioetherification



Conversion = 90%

 $M_{th} = 4,980$ $M_{n,GPC} = 9,090$; $M_w/M_n = 1.41$ $M_{n,MALDI} = 5,470$; $M_w/M_n = 1.05$

Figure 11. MALDI-TOF of PMA-Br isolated at 90% from SET-LRP of MA in DMSO solution initiated with BPE and catalyzed by a nonactivated Cu(0) wire at 25 °C: (a) Before the “thio-bromo click” reaction; (b) After the “thio-bromo click” reaction. Reaction conditions: MA = 2 mL, DMSO = 1.0 mL, $[MA]_0/[BPE]_0/[Me_6-TREN]_0/[TREN]_0 = 60/1/0.1/0.1$, 9.0 cm of 20 gauge Cu(0) wire. The dotted line in expansion after thioetherification shows the original peak from before thioetherification, while 59 represents the increase in molar mass after thioetherification, that is, $2 \times [SC_6H_5 (109, 2)-Br (79, 9)] = 58.57$ for each chain end.

disproportionating solvents and in their mixtures.^{19c–e} In addition, mixtures of solvents can display also a cooperative and synergistic effect that was not yet investigated for the case of MA/DMSO.^{19e} Last but not least, since DMSO is one of the best solvents for SET processes, an increased concentration of DMSO also is expected to increase the rate of SET-LRP.^{19f} Therefore, all these factors, the extent of disproportionation that determines the concentration of Cu(0) produced by disproportionation, the Cu(0) particle size generated by disproportionation and their different reactivities, the solubility of Cu(I)Br and Cu(II)Br₂ compounds in the MA/DMSO solvent, and the quality of the MA/DMSO solvent for SET reactions, contribute to the catalytic effect of DMSO reported here, even if the most reactive Cu(0) species employed in the SET-LRP are atoms.⁴⁸

Mixed-Ligand Methodology During the SET-LRP of 2 mL of MA in 1 mL of DMSO Using Me₆-TREN, Me₆-TREN/TREN, and TREN as Ligands. The detection of the mixed-ligand effect for Me₆-TREN/TREN was first observed and reported for SET-LRP performed in water/organic

solvents biphasic systems.^{10b} In the current series of experiments, the ratio between Me₆-TREN and TREN was changed from 1:0 to 0:1 while keeping the ratio of ligand to initiator constant at 10 mol %. The ratio between MA and DMSO was also kept constant (2 mL of MA to 1 mL of DMSO; Scheme 1 and Figure 4)

Interestingly, all tested mixed-ligand compositions generated higher k_p^{app} values than those obtained in control experiments carried out in the presence of either Me₆-TREN or TREN. These results will be discussed later. The partial replacement of Me₆-TREN with TREN increased the k_p^{app} while retaining first-order kinetics (Figure 4). The best catalytic activity was observed at a 1:1 molar ratio of the two ligands (compare Figure 4a, b, and c), suggesting the H-bonded new ligand from Scheme 1. Under these conditions, the SET-LRP of MA proceeded faster than control experiments with Me₆-TREN (Figure 4a) and TREN (Figure 4e), respectively. This mixed-ligand methodology also provided the highest conversion and an improved control over molecular weight distribution (Figures 5 and 6). The summary of results is in Table 1.

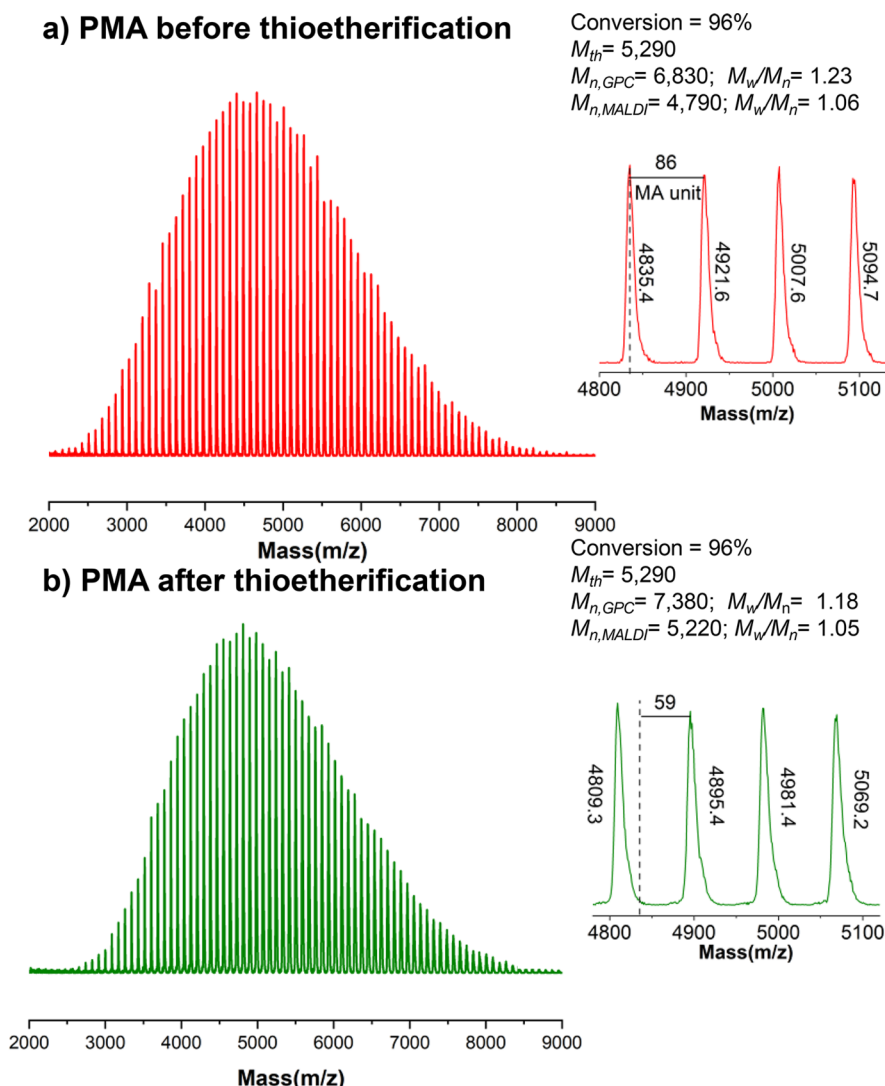


Figure 12. MALDI-TOF of PMA-Br isolated at 96% from SET-LRP of MA in DMSO solution initiated with BPE and catalyzed by nonactivated Cu(0) wire at 25 °C: (a) Before the “thio-bromo click” reaction; (b) After the “thio-bromo click” reaction. Reaction conditions: MA = 2 mL, DMSO = 1.0 mL, $[MA]_0/[BPE]_0/[TREN]_0 = 60/1/0.2$, 9.0 cm of 20 gauge Cu(0) wire. The dotted line in expansion after thioetherification shows the original peak from before thioetherification, while 59 represents the increase in molar mass after thioetherification, that is, $2^* [SC_6H_5(109, 2)-Br(79, 9)] = 58.57$ for each chain end.

Representative GPC data plotted in Figure 6 illustrate the dependence of molecular weight vs conversion. GPC data show monomodal peak distributions shifting to higher molar mass at high conversion. The most relevant result was observed at the 1:1 molar ratio between the two ligands. In this case, the I_{eff} was found to be above 80%. These data demonstrate that the mixed-ligand catalyst consisting of nonactivated Cu(0) wire and Me₆-TREN/TREN is an effective new catalytic system for the SET-LRP of MA in DMSO.

Visualization of the Polymerization Reaction at High Conversion. The images in Figure 7 reveal an almost undetectable increase in the blue color of the reaction mixture as the concentration of TREN increased. This trend most probably indicates a negligible increase in the extent of bimolecular termination that is too low to be detected by NMR and MALDI-TOF. A similar result was observed during the mixed-ligand effect observed in biphasic water–organic solvent systems.^{10b}

Structural Analysis of PMA Before and After Thio-Bromo “Click”. A combination 400 MHz ¹H NMR and

MALDI-TOF methods before and after reacting the -Br end-groups of PMA with thiophenol via thio-bromo “click” reaction⁴⁹ were employed to estimate the living character of SET-LRP performed at various molar ratios between Me₆-TREN and TREN and compare them with Me₆-TREN and TREN. Low molecular weight polymers were synthesized for these investigations. Figures 8 and 9 show representative ¹H NMR spectra of PMA isolated at high conversion of SET-LRP in DMSO in the presence of Me₆-TREN (Figures 8a and 9a), Me₆-TREN/TREN (Figures 8b and 9b), and TREN (Figures 8c, 9b) before and after thio-bromo “click” reaction. Within experimental error, the chain end functionality (F^{Br} , $F^{SPH_{0\%}}$) of all PMA samples is 100%.

This is a remarkable result that demonstrates that the catalytic activity of DMSO increases the ligand activity of TREN and transforms it into an excellent ligand.

Structural Analysis by MALDI-TOF Before and After Thio-Bromo “Click” Reaction. Representative MALDI-TOF spectra of PMA synthesized using Me₆-TREN, TREN, and equimolar amounts of Me₆-TREN and TREN isolated in between

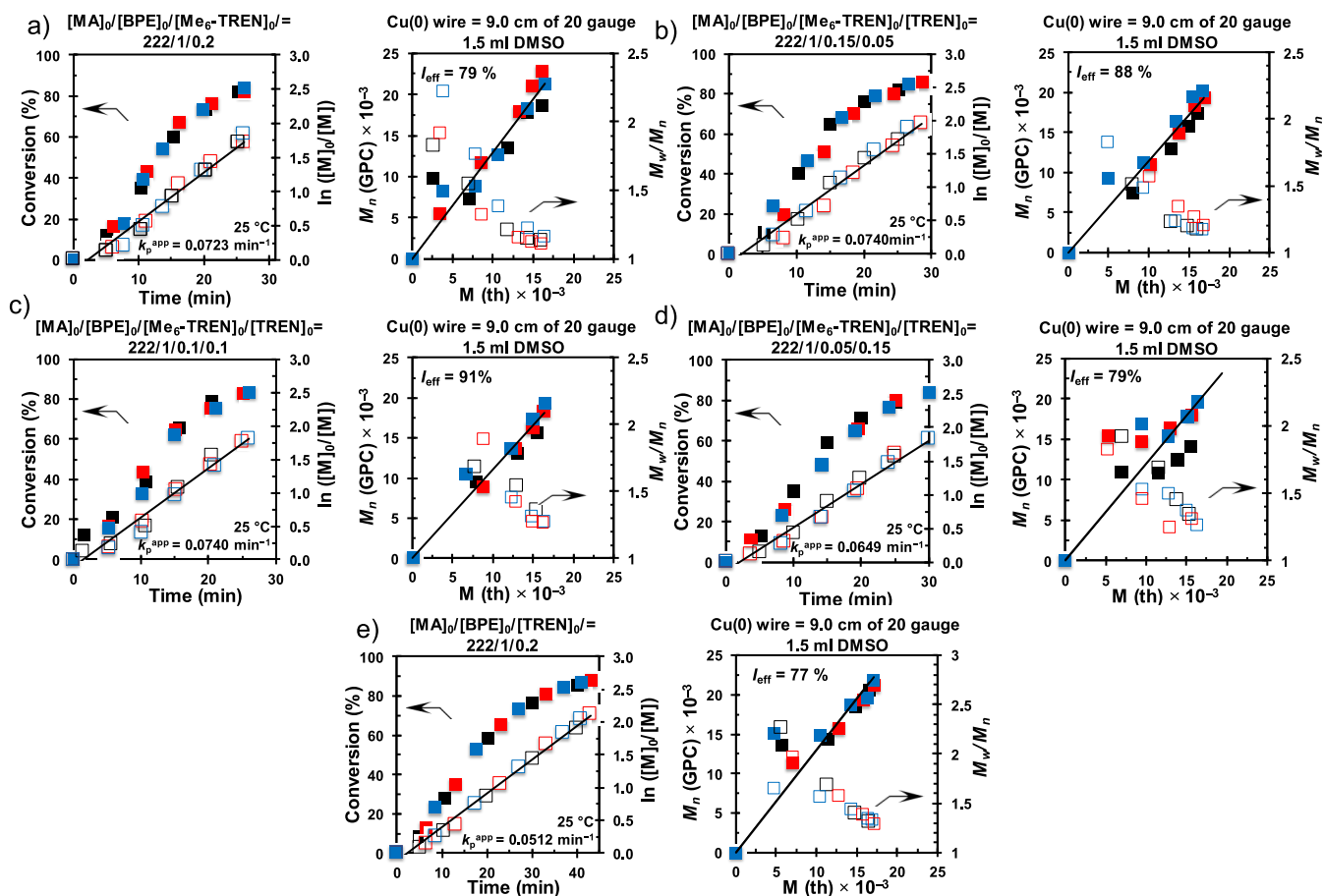


Figure 13. Kinetic plots, molecular weight, and dispersity evolutions for the SET-LRP of MA in DMSO, initiated with BPE and catalyzed by the 9.0 cm nonactivated Cu(0) wire at 25 °C. Experimental data in different colors were obtained from different kinetics experiments, carried out by different research. k_p^{app} and I_{eff} are the average values of three experiments ($[MA]_0/[BPE]_0/[ligand]_0/[Cu(0)]_0 = 222/1/0.2/9$ cm); MA = 2 mL; DMSO = 1.5 mL.

90% and 96% conversion were analyzed before and after thioetherification (Figures 10, 11, and 12). The polymers isolated after SET-LRP at very high conversions showed one molecular weight distribution that was assigned to the bromine-terminated PMA ionized with Na^+ .

After thioetherification, the original peaks disappeared and reappeared at 59 mass units higher mass values. This is the expected mass difference value for the 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 (Figures 10, 11, and 12, respectively). This demonstrates again the role of the catalytic activity of DMSO in transforming the neglected TREN into an excellent ligand for SET-LRP.

Mixed-Ligand Effect Observed During SET-LRP of 2 mL of MA in 1.5 mL of DMSO Using Me_6 -TREN, Me_6 -TREN/TREN, and TREN as Ligands. Kinetic experiments for the SET-LRP of 2 mL of MA in 1.5 mL of DMSO performed with the mixed-ligand Me_6 -TREN/TREN under similar reaction conditions to the experiments performed with 2 mL of MA in 1 mL of DMSO from Figure 4 are reported in Figure 13.

The freeze-though process was identical in both series of experiments, and therefore, due to the larger scale of the experiments reported in Figure 13, a small induction period was

observed in a few cases. All experiments from Figure 13 were performed as triplicates. A comparison of the k_p^{app} values from Figure 4 with the data from Figure 13 indicates an increase in the k_p^{app} values by increasing the concentration of DMSO. An increase in the concentration of DMSO corresponds to a decrease in the concentration of MA and is expected to provide, under normal kinetic conditions, a decrease in the rate of polymerization. Therefore, the increased k_p^{app} values correspond to the catalytic effect of DMSO. Representative GPC experiments for the kinetics from Figure 13 are reported in Figure 14.

The GPC traces from Figure 14 provide the same trend with the corresponding data from Figure 6. Control experiments for the kinetic data reported in Figure 13 are reported in Figure 15.

Their GPC data are shown in Figure 16, while the summary of all results is reported in Table 2.

Figure 17 illustrates the results of the mixed-ligand effect performed with 2 mL of MA and 1.5 mL of DMSO. The control experiment data are also included in Figure 17 to support the mixed-ligand effect. The most remarkable series of results comes from the comparison of the data from the mixed-ligand effect carried out with 2.0 mL of MA and 1.0 mL of DMSO versus 2.0 mL of MA and 1.5 mL of DMSO (compare Figure 4 with Figure 13 and Figure 5a with Figure 17). This comparison is also made in Table 3. The most representative result

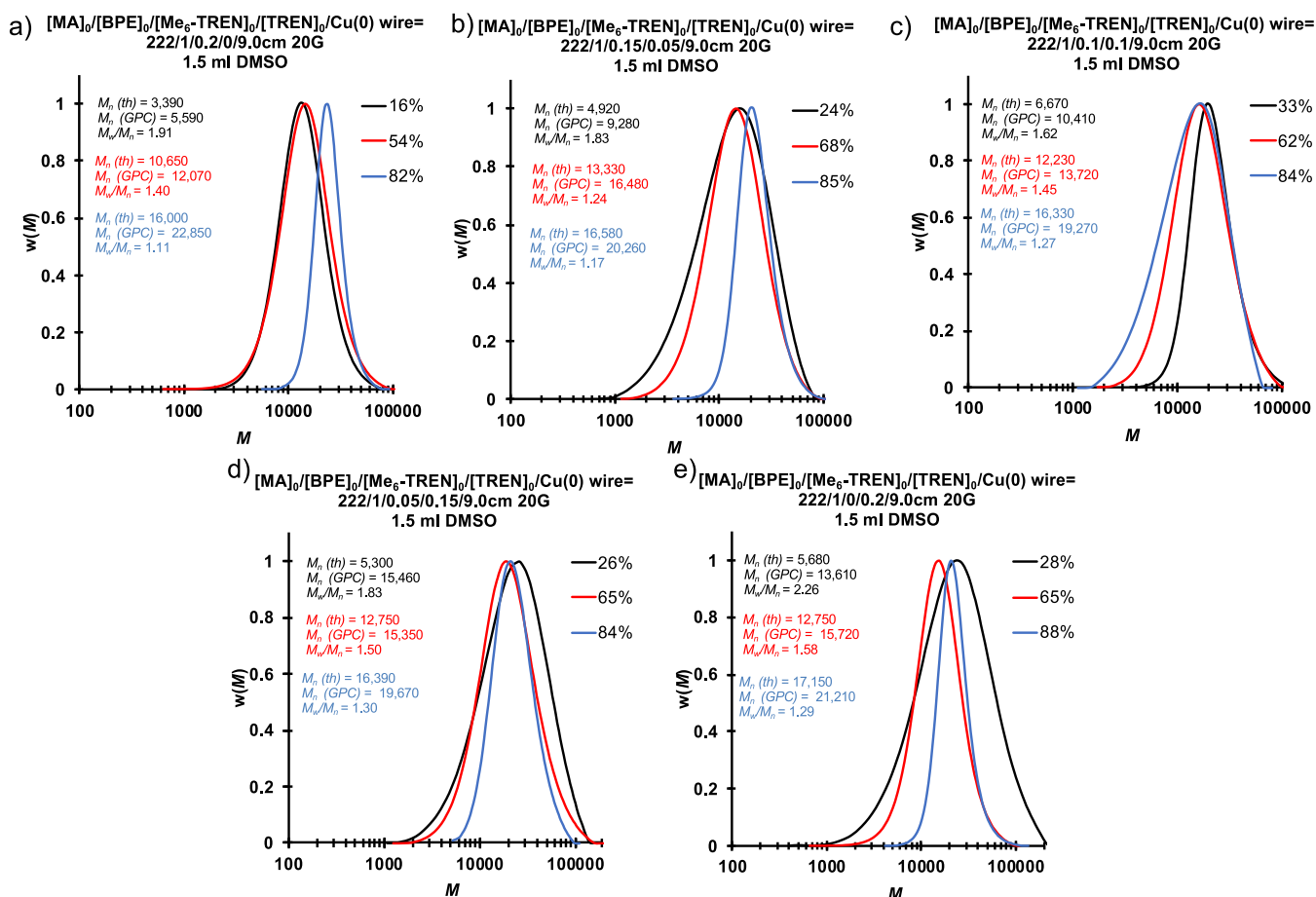


Figure 14. Representative GPC traces of the evolution of molecular weight as a function of conversion for the SET-LRP of MA in a mixture of 1 mL of DMSO and catalyzed by the 9.0 cm nonactivated Cu(0) wire at 25 °C in the presence of various ligand compositions. Reaction conditions: MA = 2 mL, DMSO = 1.5 mL, $[MA]_0/[BPE]_0/[L]_0 = 222/1/0.2$.

from this comparison is that, while the k_p^{app} value for Me_6 -TREN at 1 mL of DMSO is 1.30, the value of k_p^{app} for TREN at 1.5 mL of DMSO is 1.38. Therefore, TREN becomes at 1.5 mL of DMSO more efficient than Me_6 -TREN at 1 mL of DMSO. This result explains the revitalization of TREN and its transformation into an excellent ligand by the catalytic effect of DMSO.

Structural Analysis of PMA Before and After Thio-Bromo “Click” Reaction. Structural analysis was performed by a combination of 1H NMR and MALDI-TOF before and after thio-bromo “click” reaction (Figures S6–S10). The chain-end functionality of the PMA is 97% before thio-bromo “click” reaction and 98%, respectively, after thio-bromo “click” reaction, regardless of the structure of the ligand employed during SET-LRP (Figures S7 and S8). These excellent results are confirmed by the MALDI-TOF analysis performed before and after thio-bromo “click” reactions (Figures S6, S9, and S10).

Brief Comments on the Significance of These Results for the Area of Biomacromolecules. SET-LRP catalyzed by Cu(0) wire, powder, coins, and other objects occurs in disproportionating solvents and generates polyacrylates with very high chain-end functionality.^{26,50} Within the limits of the instrumental analysis, this includes also 100% chain-end functionality for PMA.^{26,50} In nondisproportionating solvents, including polar, like acetonitrile,⁴³ and nonpolar, like toluene,⁵⁰ the chain-end functionality of the macromolecules is much

lower. The highest chain-end functionality was always obtained in the absence Cu(II) X_2 both with TREN or Me_6 -TREN²⁶ or in the presence of a negligible amount of Cu(II) X_2 .^{26,50} Larger quantities of added Cu(II) X_2 lower the chain-end functionality of the polymers, although SET-LRP provides the highest chain-end functionality of any LRP.^{26,50,51} Detailed discussions of chain-end functionality as a function of the concentration of the externally added Cu(II) X_2 are available.²⁶ In the presence of externally added Cu(II)Br₂, the lower chain-end functionality values can be explained by the Cu(II)Br₂ mediated oxidation of the propagating radicals to carbocations and subsequent proton transfer to generate the chain-end double bonds.^{52,53,54} Double bonds at chain-ends have been observed in polyacrylates made by SET-LRP in the presence of externally added Cu(II) X_2 .^{51a} In this respect, TREN is a less basic ligand than Me_6 -TREN, and therefore, TREN is a more-efficient ligand than Me_6 -TREN in attempts to provide perfectly functional PMA chain-ends. The very high chain-end functionality obtained under SET-LRP conditions was explained by the polymer adsorption on the surface of Cu(0) that is accompanied by a decreased reactivity of the growing radicals in bimolecular termination but not in the propagation reaction.^{55,56} This high-end functionality contrasts the much lower 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) occurs by the most active site of their face centered crystal (FCC) that is

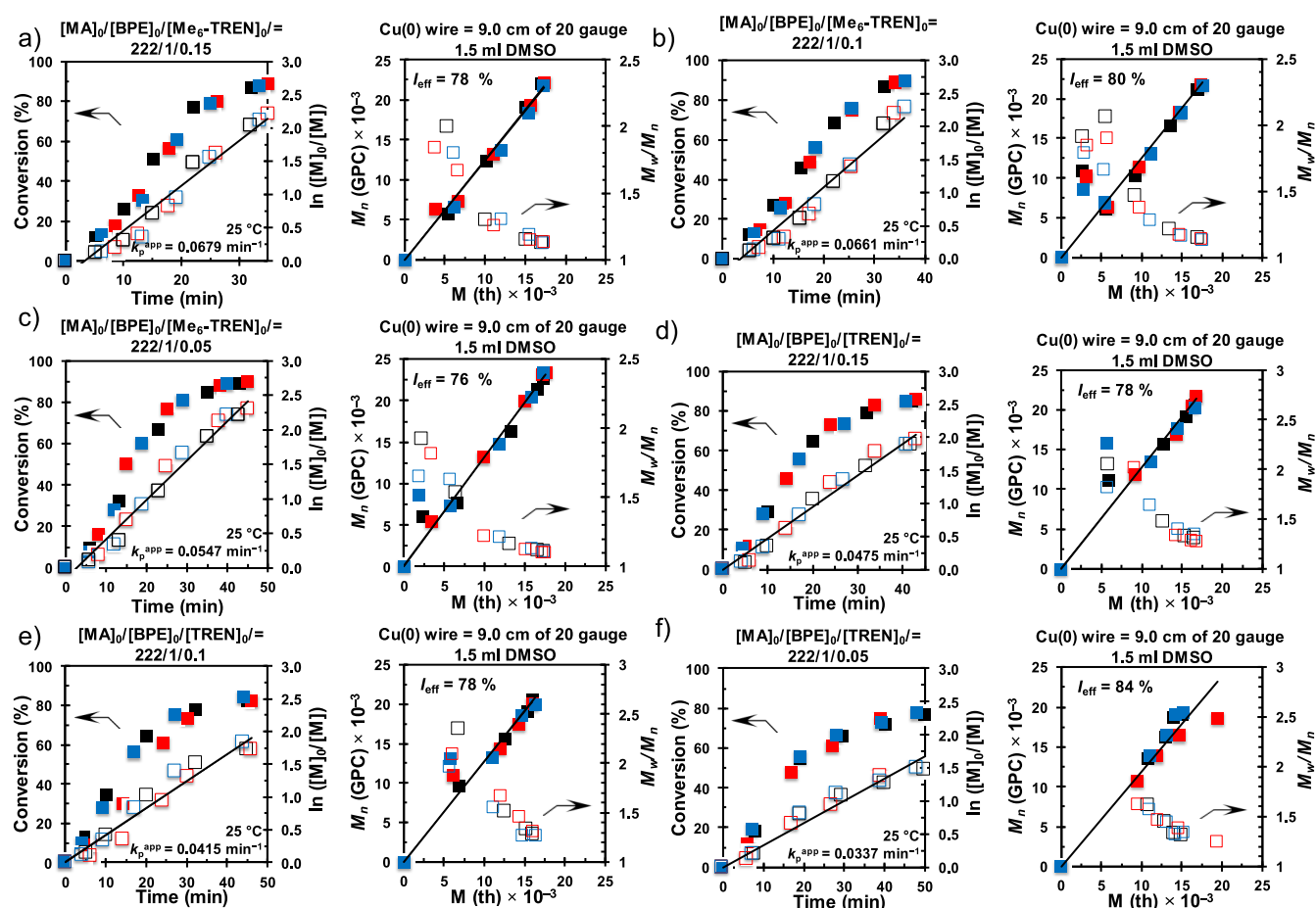


Figure 15. Control experiments: Kinetic plots, molecular weight, and dispersity evolutions for the SET-LRP of MA in DMSO, initiated with BPE and catalyzed by the 9.0 cm nonactivated Cu(0) wire at 25 °C. Experimental data in different colors were obtained from different kinetics experiments and generated by different research. K_p^{app} and I_{eff} is the average value of three experiment ($[MA]_0/[BPE]_0/[ligand]_0/[Cu(0)]_0 = 222/1/0.15$ to $0.05/9$ cm); MA = 2 mL.

111.⁶⁰ Both powder^{19b} and wire⁶¹ catalyzed SET-LRP demonstrated that objects produced from Cu(0) crystals exhibit surface- and morphology-dependent reactivity. Moreover, reactivity of the catalyst increases when Cu(0) atoms are produced by disproportionation, followed by nucleation and growth on the original surface of the Cu(0) wire or other object.^{19b,61} Nucleation and growth of Cu(0) have been demonstrated during SET-LRP on the surface of the wire.⁶¹ Colloidal Cu(0) particles were also observed during SET-LRP.⁴² However, the highest activity of Cu(0) is as atoms. Cu(0) atoms are more reactive than Cu(I)X and are well-known SET catalysts.⁶² This diversity of catalytic Cu(0) species is all involved in the SET-LRP process, but could not be observed to reduce Cu(II)X₂ to Cu(I)X species during the SET-LRP process,⁶³ although this reduction may occur in the absence of polymerization or activation. This short discussion indicates that the decrease in the amount of Cu(II)X₂ during SET-LRP provides a more efficient chain-end functionality and a lower amount of contamination of the resulting polymer with Cu species. The use of a TREN and Me₆-TREN mixed-ligand complex system to mediate the Cu(0) wire-catalyzed SET-LRP of MA in the catalytically active solvent DMSO provides a new methodology to control the SET-LRP process. Kinetics and end-group analysis demonstrated that Me₆-TREN complements and makes TREN a very efficient ligand in the absence of externally added Cu(II)Br₂ when the catalytically active solvent DMSO is

employed. The highest rate is observed at a 1/1 molar ratio between ligands. This indicates that, in addition to a fast exchange between ligands, a new single dynamic ligand stabilized by hydrogen-bonding should be considered in mechanistic studies (Scheme 1). Most important, SET-LRP performed at the proper concentration of DMSO does not require the activation of the Cu(0) wire. The high chain end functionality^{26,50,51,61} obtained in the absence of externally added Cu(II)Br₂ makes the SET-LRP in the presence of this mixed-ligand system and, in the presence of TREN, the method of choice for the synthesis of biomacromolecules, as already reported for many examples, including some from our laboratory.⁶⁴

CONCLUSIONS

DMSO exhibits a catalytic effect when used as solvent during SET-LRP of MA initiated with BPE and catalyzed with nonactivated Cu(0) wire both in the presence of Me₆-TREN and TREN and in mixtures of Me₆-TREN with TREN. A mixed-ligand effect was observed when mixtures of Me₆-TREN with TREN were used as ligands. The catalytic activity of DMSO can be exploited, as demonstrated here, to enhance the reactivity of TREN and of its 1/1 mixture with Me₆-TREN, while decreasing the basicity of the ligand and eliminating side reactions mediated by it. The most fundamental question related to this topic that must be addressed is the following: do

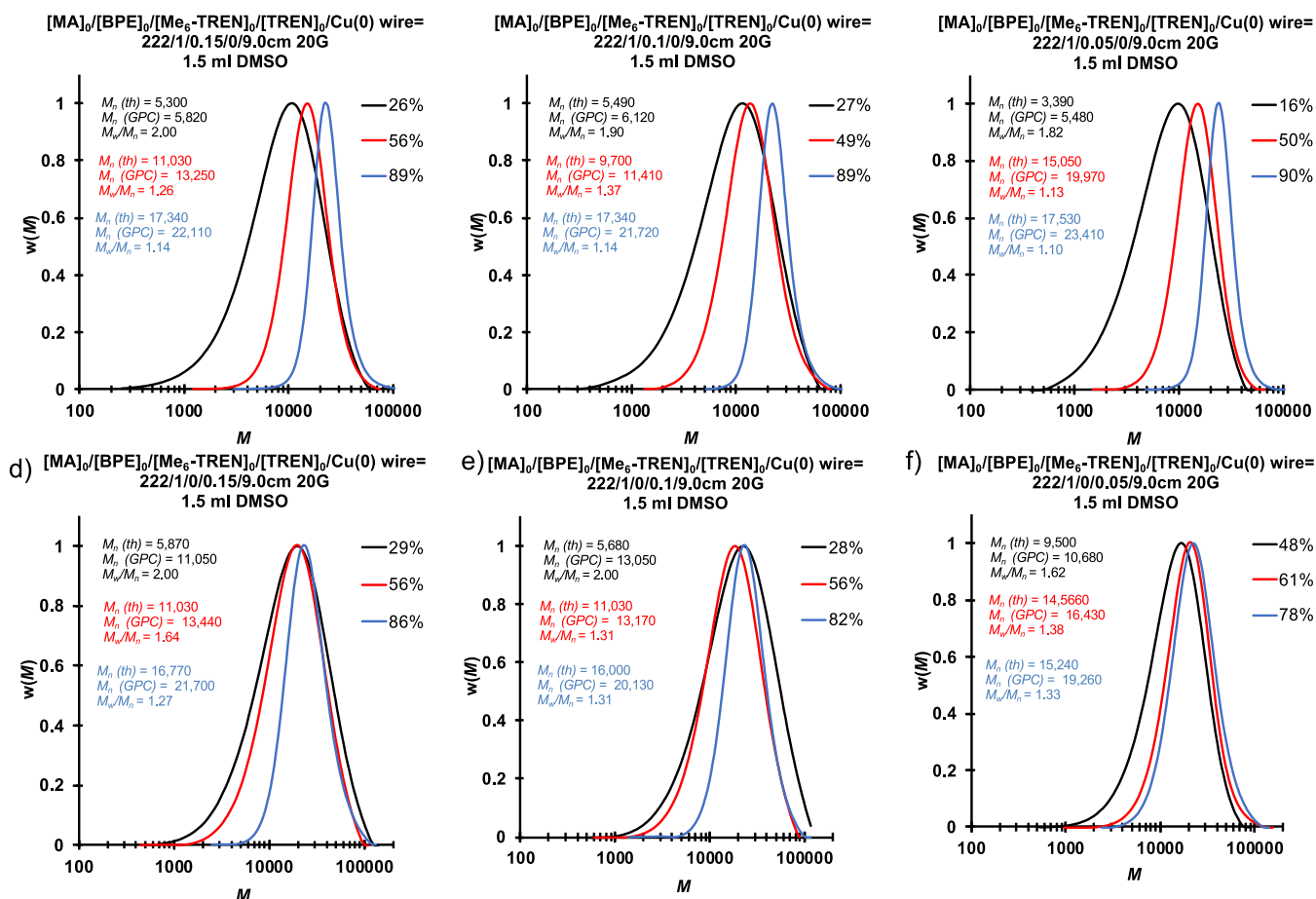


Figure 16. Representative GPC traces of the evolution of molecular weight as a function of conversion for the SET-LRP of MA in a mixture of 1 mL of DMSO and catalyzed by the 9.0 cm nonactivated Cu(0) wire at 25 °C in the presence of various ligand compositions. Conditions: MA = 2 mL, DMSO = 1.5 mL, ([MA]₀/[BPE]₀/[ligand]₀/[Cu(0)]₀ = 222/1/0.15 to 0.05/9 cm); MA = 2 mL.

Table 2. Dependence of k_p^{app} on the Dimension of the Cu(0) Wire in the SET-LRP of MA-Initiated with BPE in 1.5 mL of DMSO at 25 °C^a

entry	wire length (cm) 20G	reaction condition	k_p^{app} (min ⁻¹)	M_w/M_n	I_{eff} (%)
1	9.0	[MA]/[BPE]/[Me ₆ -TREN] 222/1/0.2	0.0723	1.11	79
2	9.0	[MA]/[BPE]/[Me ₆ -TREN]/[TREN] 222/1/0.15/0.05	0.0740	1.17	88
3	9.0	[MA]/[BPE]/[Me ₆ -TREN]/[TREN] 222/1/0.1/0.1	0.0740	1.26	91
4	9.0	[MA]/[BPE]/[Me ₆ -TREN]/[TREN] 222/1/0.05/0.15	0.0649	1.26	79
5	9.0	[MA]/[BPE]/[TREN] 222/1/0.2	0.0512	1.28	77
6	9.0	[MA]/[BPE]/[Me ₆ -TREN] 222/1/0.15	0.0679	1.13	78
7	9.0	[MA]/[BPE]/[Me ₆ -TREN] 222/1/0.10	0.0661	1.13	80
8	9.0	[MA]/[BPE]/[Me ₆ -TREN] 222/1/0.05	0.0547	1.10	76
9	9.0	[MA]/[BPE]/[TREN] 222/1/0.15	0.0475	1.27	78
10	9.0	[MA]/[BPE]/[TREN] 222/1/0.10	0.0415	1.27	78
11	9.0	[MA]/[BPE]/[TREN] 222/1/0.05	0.0337	1.24	84

^aReaction conditions: monomer = 2 mL; solvent = 1.5 mL.

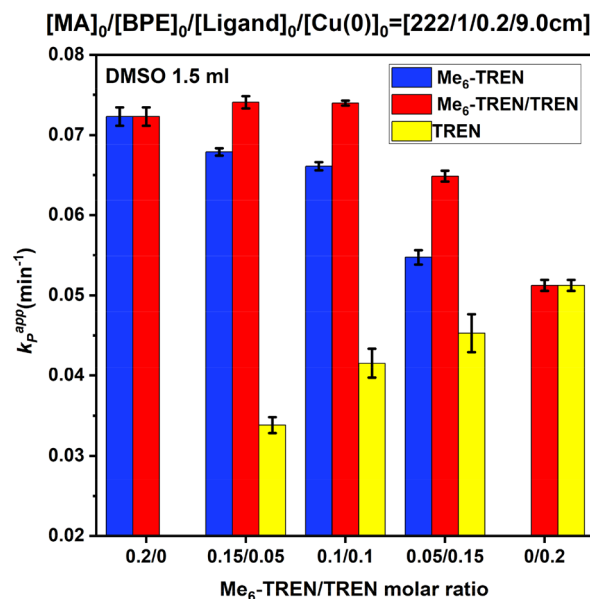


Figure 17. Evolution of k_p^{app} for the SET-LRP of MA (2 mL) initiated with BPE in DMSO (1.5 mL) mediated with different ratios between Me₆-TREN and TREN at 25 °C (in red). Control experiments performed only with Me₆-TREN (in blue) and only with TREN (in yellow) are also incorporated.

Table 3. Dependence of k_p^{app} on the 9 cm 20 G of the Cu(0) Wire in the SET-LRP of MA Initiated with BPE in DMSO at 25 °C^a

entry	vol of DMSO (mL)	reaction condition	k_p^{app} (min ⁻¹)	k_p^{app} / k_p^{app} (entry 10)	M_w/M_n	I_{eff} (%)
1	1.5	[MA]/[BPE]/[Me ₆ -TREN] 222/1/0.2	0.072	1.95	1.11	79
2	1.0	[MA]/[BPE]/[Me ₆ -TREN] 222/1/0.2	0.048	1.30	1.14	79
3	1.5	[MA]/[BPE]/[Me ₆ -TREN]/[TREN] 222/1/0.15/0.05	0.074	2.00	1.17	88
4	1.0	[MA]/[BPE]/[Me ₆ -TREN]/[TREN] 222/1/0.15/0.05	0.051	1.38	1.21	81
5	1.5	[MA]/[BPE]/[Me ₆ -TREN]/[TREN] 222/1/0.1/0.1	0.074	2.00	1.26	91
6	1.0	[MA]/[BPE]/[Me ₆ -TREN]/[TREN] 222/1/0.1/0.1	0.053	1.43	1.23	82
7	1.5	[MA]/[BPE]/[Me ₆ -TREN]/[TREN] 222/1/0.05/0.15	0.065	1.76	1.26	79
8	1.0	[MA]/[BPE]/[Me ₆ -TREN]/[TREN] 222/1/0.05/0.15	0.044	1.19	1.20	82
9	1.5	[[MA]/[BPE]/[TREN] 222/1/0.2	0.051	1.38	1.28	77
10	1.0	[[MA]/[BPE]/[TREN] 222/1/0.2	0.037	1.00	1.23	79

^aReaction conditions: MA = 2 mL.

all disproportionating solvents display a catalytic effect in SET-LRP or only DMSO? Research to address this question is in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.biomac.9b01765>.

Addition kinetic plots and characterization results, including NMR and MALDI-TOF spectra (PDF)

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Notes

The authors declare no competing financial interest.

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