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

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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 the two ligands, a new single dynamic ligand generated by hydrogen-bonding may be responsible for the result observed.

Keywords: mixed-ligand, SET-LRP, catalytically active DMSO, living polymerization

INTRODUCTION

The mixed-ligand effect emerged as an efficient and simple methodology to design superior catalytic activity without synthetic efforts in transition-metal-catalyzed enantioselective reactions.¹ Almost at the

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3 same time, Feringa's laboratory reported that hetero-combinations of chiral monodentate ligands were
4 more effective than homo-combinations for Rh-catalyzed C–C cross-coupling reactions.² This concept
5 was expanded to Pd-catalyzed C–N^{3,4} and C–S⁵ cross-coupling reactions as well as to Ni-catalyzed Suzuki-
6 cross-coupling and borylation reactions.⁶ However, the benefits of using mixed-ligand systems have only
7 been noted in very few metal-catalyzed polymerization experiments.⁷⁻⁹

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10 The use of an appropriate solvent/N-ligand combination is important in Cu(0)-mediated single electron
11 transfer-living radical polymerization (SET-LRP),¹⁰⁻¹⁷ since it can either promote or disfavor the
12 mechanistically fundamental disproportionation reaction of Cu(I)X into Cu(0) atomic species and
13 Cu(II)X₂.^{18,19} Tris(2-dimethylaminoethyl)amine (Me₆-TREN) is frequently employed as ligand in SET-
14 LRP,^{10,11,14} because it favors the disproportionation process by preferentially binding Cu(II)X₂ rather than
15 Cu(I)X.²⁰ However, the use of its precursor, tris(2-aminoethyl)amine (TREN),^{11,21-23} which is about 80
16 times less expensive, and poly(ethylene imine) (PEI)¹⁰ also proved very successful for SET-LRP of vinyl
17 chloride (VC) and of acrylates during the first days of SET-LRP. Likewise, TREN²⁴⁻²⁶ and N,N,N',N'',N'-
18 pentamethyldiethylenetriamine (PMDETA)^{10,27,28} are also alternative ligands to Me₆-TREN for the Cu(0)
19 wire-catalyzed SET-LRP of acrylates and methacrylates in homogeneous SET-LRP.

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22 Unfortunately, the replacement of Me₆-TREN with TREN was not so successful in aqueous-organic
23 “programmed” biphasic systems using Cu(0) wire catalyst,^{29,30-33} although TREN is very efficient in single
24 phase SET-LRP experiments. In biphasic organic solvent-water systems, the external addition of Cu(II)Br₂
25 was necessary to complement the performance of TREN and retain the living character. In this complex
26 system, SET-LRP is an interfacial process in which disproportionation and activation events take place
27 independently in the aqueous and organic compartments, respectively, whereas the “self-controlled”
28 reversible deactivation occurs at the interface.³⁴ The Cu(0)-mediated polymerization in “programmed”
29 bi(multi)phasic mixtures of organic solvents with water has been proven to be valuable in various organic
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3 solvents regardless of their ability to mediate or not disproportionation of Cu(I)X/N-ligand.³⁵⁻³⁹ Thus,
4 these designed biphasic organic solvent-H₂O “programmed” biphasic systems resolved the
5 incompatibility of SET-LRP with polar non-disproportionating solvents and non-polar non-
6 disproportionating solvents, thus expanding the library of accessible solvents. The first mixed-ligand
7 effect in a SET-LRP system was observed in the water-organic solvent “programmed” biphasic systems
8 when Me₆-TREN was employed to replace Cu(II)X₂ with Me₆-TREN.^{10b}

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10 In this publication, we first report experiments that demonstrate the catalytic activity of DMSO solvent in
11 both Me₆-TREN, TREN and in the mixed-ligand Me₆-TREN/TREN mediated SET-LRP of MA initiated
12 with BPE at 25°C and catalyzed with non-activated Cu(0) wire. The catalytic activity of DMSO was
13 discovered previously when Cu(0) powder was employed as catalyst^{11a} but was not used to improve the
14 synthetic capabilities of SET-LRP. Subsequently, the mixed-ligand effect of Me₆-TREN/TREN was
15 investigated at two different concentrations of the DMSO solvent. Statistical analysis of the kinetics and
16 of the control experiments together with the determination of the chain-end functionality of the resulting
17 polymers by a combination of NMR and MALDI-TOF before and after thio-bromo “click” reaction
18 demonstrated that the catalytic activity of DMSO can be employed to improve the efficiency of the
19 inexpensive TREN ligand. Therefore, we can conclude that the catalytic activity of DMSO was employed
20 to revitalize the long time neglected TREN and transform it into an excellent ligand. Since TREN is 80
21 times less expensive than Me₆-TREN numerous new applications including in the field of
22 biomacromolecules will evolve from the series of experiments reported here.

23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 **EXPERIMENTAL SECTION**

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51 **Materials.** Methyl acrylate (MA) (99%, Acros) was passed over a short column of basic Al₂O₃ before use
52 in order to remove the radical inhibitor. Tris(2-aminoethyl)amine (TREN) (99%, Acros), Cu(0) wire (20
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3 gauge wire, 0.812 mm diameter from Fisher) and dimethyl sulfoxide (DMSO) (99.8%, Sigma Aldrich)
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5 were used as received. Triethylamine (NEt_3) (>99.5% Chemimpex) was distilled under N_2 over CaH_2 .
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7 Bis(2-bromopropionyl)ethane (BPE) was synthesized by esterification of ethylene glycol with 2-
8
9 bromopropionyl bromide in the presence pyridine according to our previously reported metho.⁴⁰
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11 Hexamethylated tris(2-aminoethyl)amine ($\text{Me}_6\text{-TREN}$) was synthesized according to a literature
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13 procedure.⁴¹
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17 **Techniques.** 400 MHz $^1\text{H-NMR}$ spectra were recorded on a Bruker AVANCE NEO 400 NMR instrument
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19 at 27 °C in CDCl_3 containing tetramethylsilane (TMS) as internal standard. Gel permeation
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21 chromatography (GPC) analysis of the polymer samples was performed using a Shimadzu LC-20AD high-
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23 performance liquid chromatograph pump, a PE Nelson Analytical 900 Series integration data station, a
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25 Shimadzu RID-10A refractive index (RI) detector, and three AM gel columns (a guard column, 500 Å, 10
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27 μm and 104 Å, 10 μm). THF (Fisher, HPLC grade) was used as eluent at a flow rate of 1 mL min^{-1} . The
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29 number-average (M_n) and weight-average (M_w) molecular weights of PMA samples were determined with
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31 poly(methyl methacrylate) (PMMA) standards purchased from American Polymer Standards. MALDI-
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33 TOF spectra were obtained on a Voyager DE (Applied Biosystems) instrument with a 337 nm nitrogen
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35 laser (3 ns pulse width). For all polymers, the accelerating potential was 25 kV, the grid was 92.5, the
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37 laser power was 2200-2500, and a positive ionization mode was used. The sample analysis was performed
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39 with 2-(4-hydroxyphenylazo) benzoic acid as the matrix. Solutions of the matrix (25 mg/mL in THF),
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41 NaCl (2 mg/mL in deionized H_2O), and polymer (10 mg/mL) were prepared separately. The solution for
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43 MALDI-TOF analysis was obtained by mixing the matrix, polymer, and salt solutions in a 5/1/1
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45 volumetric ratio. Then 0.5 μL portions of the mixture were deposited onto three wells of sample plate and
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47 dried in air at room temperature before subjected to MALDI- TOF analysis.
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3 **Typical Procedure for SET-LRP of MA in DMSO using Me₆-TREN, TREN and the Mixed-Ligand**
4 **Me₆-TREN/TREN Systems.** Stock solutions with different ligand ratios (Me₆-TREN/TREN as 0.02 M/0
5 M, 0.015 M/0.005 M, 0.01 M/0.01 M, 0.005 M/0.015 M, 0 M/0.02 M) in DMSO were prepared. The
6 monomer (MA, 22.2 mmol, 2.00 mL), organic solvent (DMSO if necessary), DMSO stock solution (0.02
7 mmol Ligand, 1 mL), and initiator (BPE, 0.1 mmol, 33.2 mg) were added to a 25 mL Schlenk tube. The
8 reaction mixture was then deoxygenated by six freeze–pump–thaw cycles. After these cycles, the Schlenk
9 tube was opened under a positive flow of nitrogen to add the Cu(0) wire wrapped around a Teflon-coated
10 stir bar. Two more freeze–pump–thaw cycles were carried out while holding the stir bar above the reaction
11 mixture using an external magnet. After that, the Schlenk tube was filled with N₂, and the reaction mixture
12 was placed in a water bath at 25 °C. Then, the stir bar wrapped with the Cu(0) wire was dropped gently
13 into the reaction mixture. The introduction of the Cu(0) wire defines $t = 0$. Samples were taken at different
14 reaction times by purging the side arm of the Schlenk tube with nitrogen for 2 min using a deoxygenated
15 syringe and stainless steel needles. The collected samples were dissolved in CDCl₃ and quenched by air
16 bubbling. After that, the monomer conversion was measured by ¹H NMR spectroscopy. In order to
17 determine the molecular weight and polydispersity of the samples, the solvent and the residual monomer
18 were removed under vacuum. Finally, samples were dissolved in THF and passed through a short and
19 small basic Al₂O₃ chromatographic column to remove any residual copper and subsequently were
20 analyzed by GPC. The resulting PMA was precipitated in cold methanol and dried under vacuum until
21 constant weight to perform chain end analysis by ¹H NMR spectroscopy, before and after the
22 thioetherification reaction.
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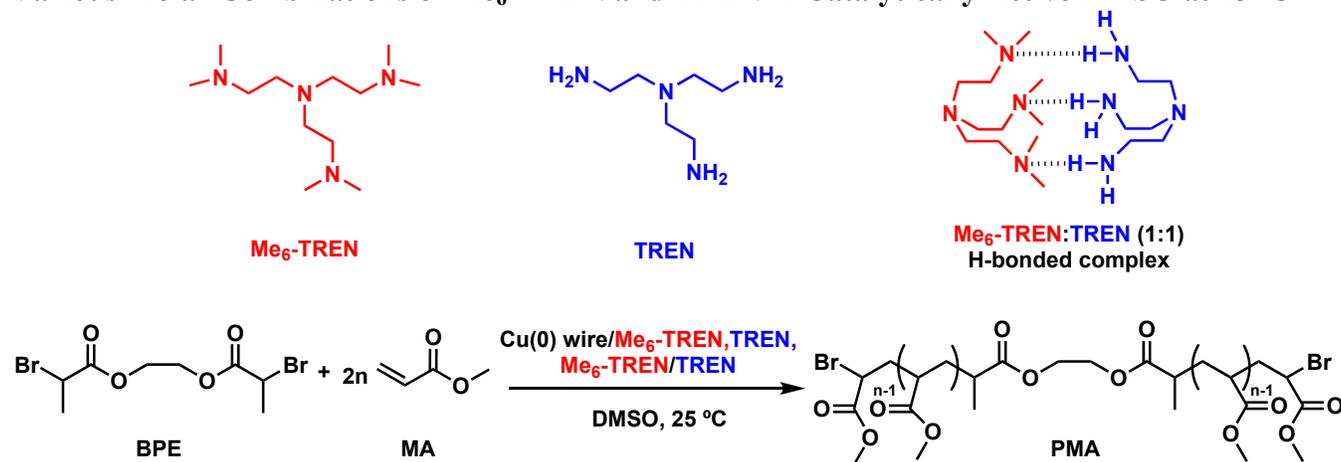
49 **General Procedure for the Chain End Modification of PMA via Thio-Bromo “Click” Reaction.** In a
50 10 mL test tube sealed with a rubber septum, thiophenol (0.05 equiv.) and distilled triethylamine (NEt₃,
51 0.05 equiv.) were added into a solution of the corresponding polymer (0.01 equiv.) in acetonitrile (1 mL)
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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 polymer was dried under vacuum until constant weight.

RESULTS AND DISCUSSION

Determination of the External Order of Reaction in DMSO During SET-LRP Catalyzed with Non-Activated Cu(0) Wire in DMSO. A closed 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, 42,43,44,45,46,47} 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 with non-activated Cu(0) wire as catalyst, MA as monomer, Me₆-TREN, TREN and mixtures of Me₆-TREN/TREN, in different concentrations of DMSO at 25°C. BPE was used as initiator in both cases.

Scheme 1. SET-LRP of MA Initiated from BPE and Catalyzed with Nonactivated Cu(0) Wire Using Various Molar Combinations of Me₆-TREN and TREN in Catalytically Active DMSO at 25 °C



The structures of both ligands and an illustration for the Cu(0) wire-catalyzed SET-LRP of MA initiated from the bifunctional initiator bis(2-bromopropionyl)ethane (BPE) are outlined in Scheme 1. Duplicate and triplicate kinetics were performed under the following reaction conditions: [MA]₀/[BPE]₀/[L]₀ = 222/1/0.2 using 9.0 cm of nonactivated Cu(0) wire.

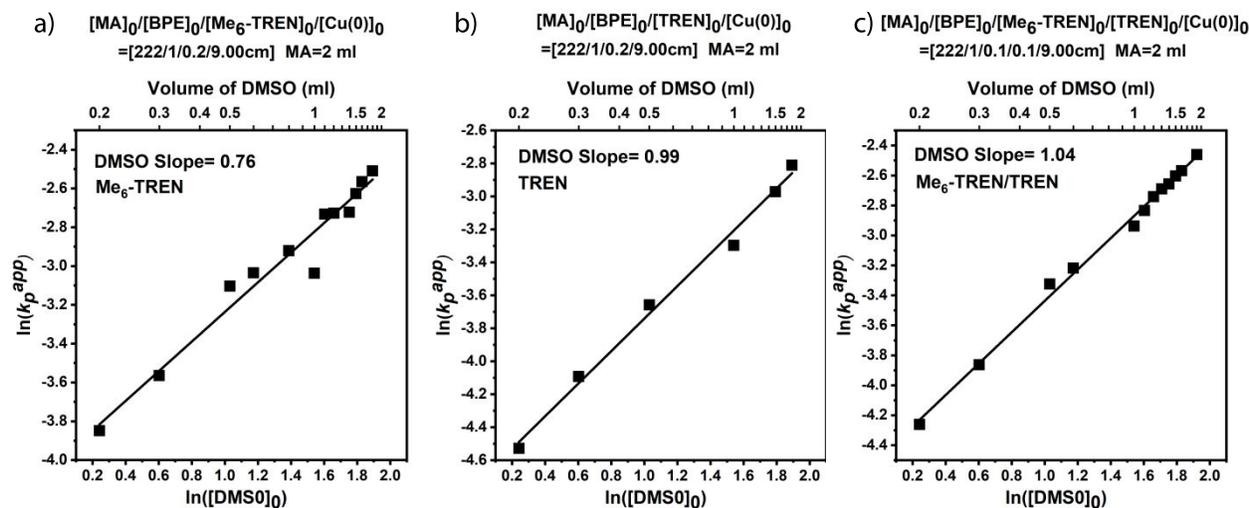


Figure 1. Determination of the external order of reaction in $[DMSO]_0$ for the Cu(0) wire/Ligand-catalyzed polymerization of methyl acrylate (MA) in DMSO at 25 °C initiated with BPE. a) $\ln(k_p^{app})$ vs $\ln([DMSO]_0)$ with DMSO varied from 0.2 to 1.9 mL with 2 mL of MA for: a) $[MA]_0/[BPE]_0/[Me_6-TREN]_0/[Cu(0)]_0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

Figure 1a reports the kinetic data for the experiments performed with Me₆-TREN as ligand, Figure 1b shows the data obtained with TREN, while Figure 1c with the mixed-ligand system Me₆-TREN/TREN. Selected kinetic experiments from which these external order of reaction in DMSO were obtained for Me₆-TREN (Figure 2a,c,e) and TREN (Figure 2b,d,f) as ligands are reported in Figures 2 when DMSO concentration was varied from 1.0 to 1.5 and to 1.8 mL DMSO with 2 mL of MA. Kinetic experiments with all other DMSO concentrations employed in Figure 1a,b,c are shown in Supporting Figures S1 to S5. First order reaction kinetics in monomer were observed for all DMSO concentrations from Figures 2 and Supporting 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 Figures S1-S5).

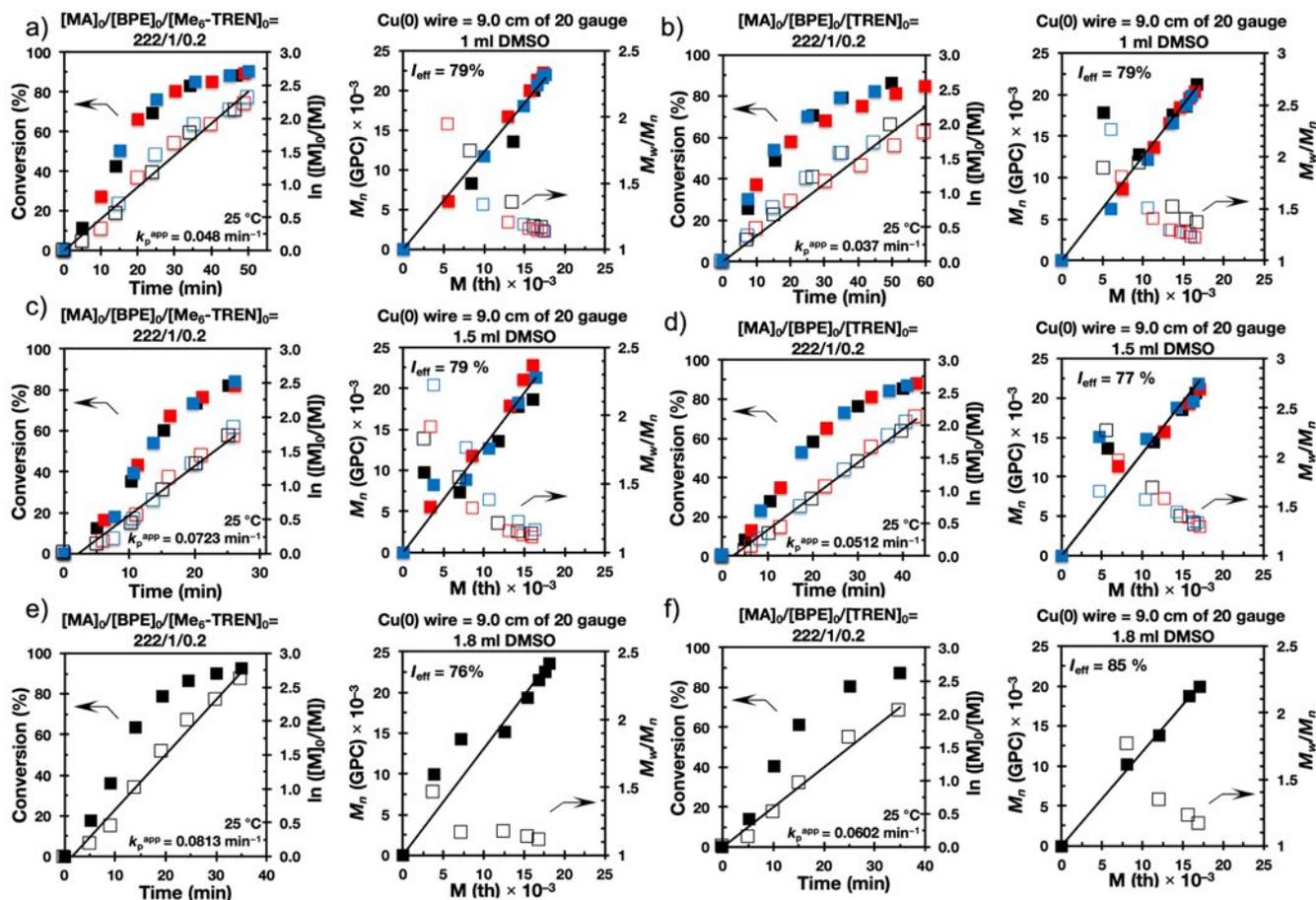


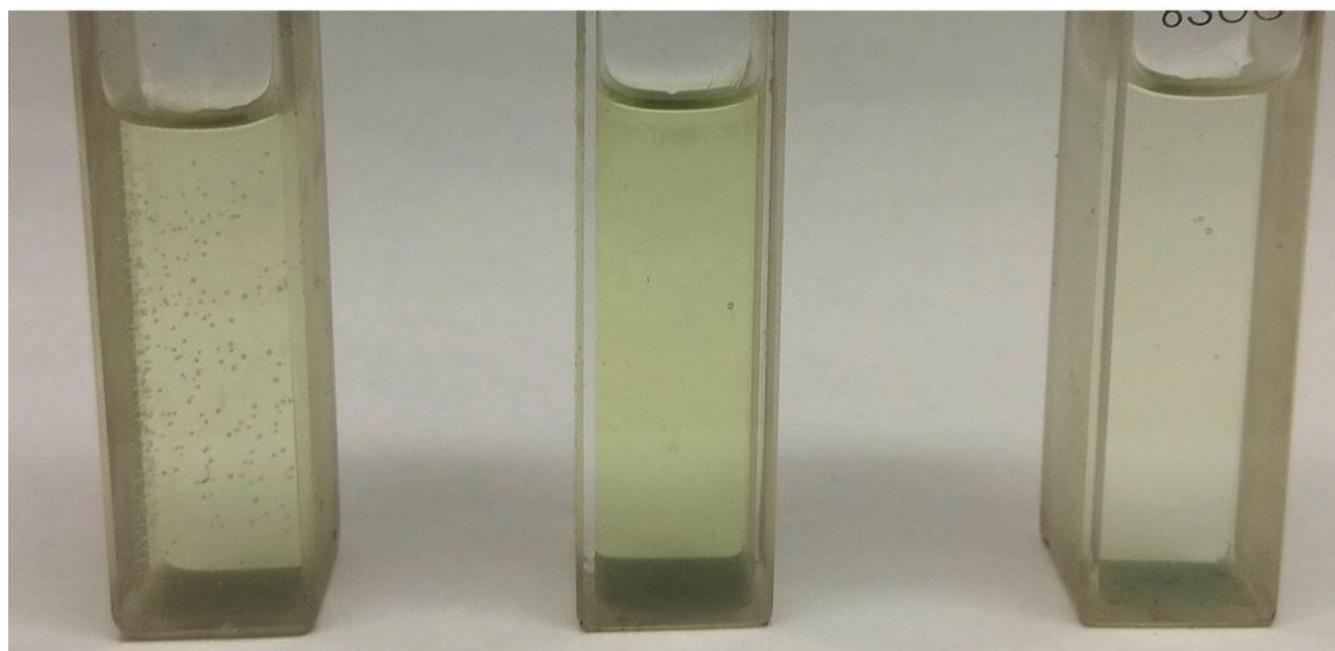
Figure 2. Kinetic plots, molecular weight and dispersity evolutions for the SET-LRP of MA in DMSO initiated with BPE and catalyzed with 9.0 cm non-activated Cu(0) wire at 25 °C. Experimental data in different colors were obtained from different kinetics experiments, sometimes performed by different researchers. k_p^{app} and I_{eff} are the average values of three experiments. k_p^{app} vs $[\text{DMSO}]_0$ with DMSO varied from 1.0 mL (a) to 1.5 mL (c) to 1.8 mL (e) with 2 mL of MA for $[\text{MA}]_0/[\text{BPE}]_0/[\text{Me}_6\text{-TREN}]_0/[\text{Cu}(0)]_0 = 222/1/0.2/9\text{cm}$. Identical experiments in which Me₆-TREN was replaced with TREN are in (b), (d), (f).

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 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 $\ln(k_p^{\text{app}})$ vs $\ln([\text{DMSO}]_0)$ (Figure 1a,b,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 Me₆-TREN

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3 while in the presence of TREN and the mixed-ligand Me₆-TREN/TREN (1/1 molar ratio) the external
4 orders of reaction in DMSO were 0.99 and 1.04 respectively.
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7 **The Potential Mechanism for the Catalytic Activity of DMSO.** In order to address the catalytic activity
8 of DMSO, first it must be considered that SET-LRP experiments were performed in a mixture of two
9 solvents, DMSO and the monomer, MA. Both DMSO and MA are good solvents that mediate the
10 disproportionation of Cu(I)Br into Cu(0) and Cu(II)Br₂.^{19a}
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17 [CuBr]/[Me₆-TREN] = 1/1 [CuBr] = 46.5mM in 3 mL solution
18 Time = 60 min
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41 MA/DMSO = 1/1

42 MA/DMSO = 2/1

43 MA/DMSO = 3/1

44 **Figure 3.** Visual observation of CuBr/Me₆-TREN complex dissolved in DMSO/MA. Conditions:
45 [CuBr] = 46.5 mM, solvent = 5.0 mL, [CuBr]₀/[Me₆-TREN]₀ = 1/1. Pictures were taken 60 min after
46 mixing the reagents.

47 While both solvents MA and DMSO mediate the disproportionation in the presence of these two ligands,
48 MA and DMSO, only DMSO is a good solvent for Cu(I)Br and Cu(II)Br₂ obtained during the activation
49 and disproportionation and is also a better solvent that mediates this disproportionation. MA mediates
50 disproportionation mostly by a surface effect. Therefore, it is expected that by increasing the ratio between
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3 DMSO and MA in the reaction mixture the extent of disproportionation will increase. At the same time it
4 has been demonstrated that DMSO stabilizes Cu(0) nanoparticles while MA does not. Figure 3 presents
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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 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 catalyst.^{19b} It is well established that faster SET-LRP is mediated in more disproportionating solvents and in their mixtures.^{19c,d,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 would increase the rate of SET-LRP.^{19f} Therefore, all these factors, the extent of disproportionation that determines the concentration of Cu(0) generated by disproportionation, the Cu(0) particle size obtained by disproportionation and reactivity, the solubility of Cu(I)Br and Cu(II)Br₂ compounds in the solvent and the quality of the solvent for SET reactions. All these factors contribute to the catalytic effect of DMSO reported here even if the most reactive Cu(0) species involved in the SET-LRP process are the atoms.⁶³

The Mixed-Ligand Effect During the SET-LRP of 2 mL MA in 1 mL 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 molar ratio between Me₆-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%. The ratio between MA and DMSO was also kept constant (2mL MA to 1 mL DMSO) (Scheme 1, Figure 4)

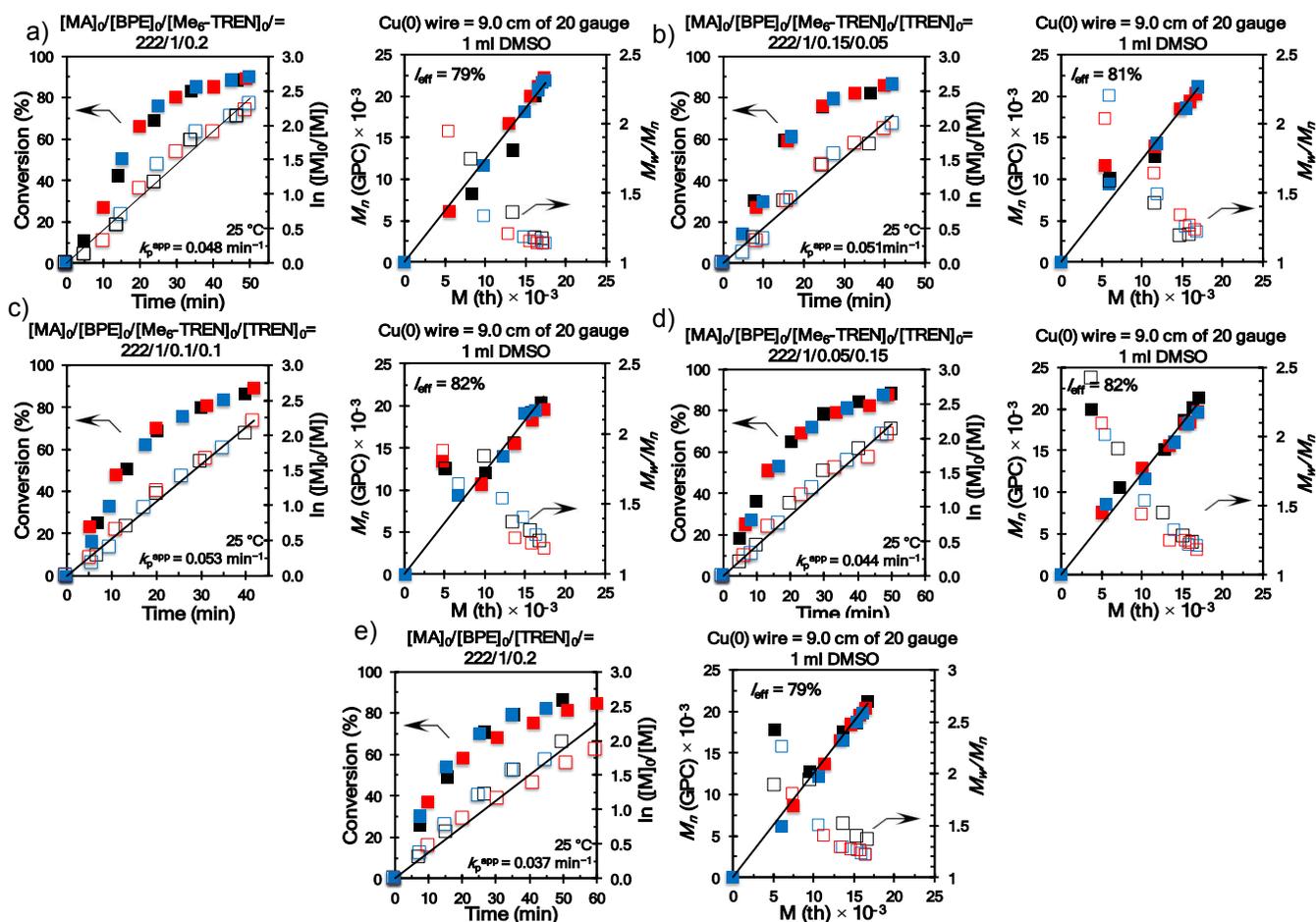


Figure 4. Kinetic plots, molecular weight and dispersity evolutions for the SET-LRP of MA in DMSO initiated with BPE and catalyzed by the 9.0 cm non-activated Cu(0) wire at 25 °C in the presence of: (a) Me₆-TREN; (b,c,d) different ratios of Me₆-TREN/TREN and (e) TREN. Experimental data in different kinetics were obtained from different kinetics experiments, sometimes performed by different researchers. k_p^{app} and I_{eff} are the average values of three experiment. $[\text{MA}]_0/[\text{BPE}]_0/[\text{Ligand}]_0/[\text{Cu}(0)]_0 = 222/1/0.2/9\text{cm}$.

Interestingly, any of the tested mixed ligand compositions provided higher k_p^{app} values than those obtained in the control experiments performed 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 most superior catalytic activity was observed at 1:1 molar combinations of both ligands (compare Figures 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 system also enabled the highest monomer

conversion and improved control over molecular weight distribution (Figures 5 and 6). The summary of all results is in Table 1.

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)	$k_p^{app}/k_p^{app}(\text{TREN})$	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.

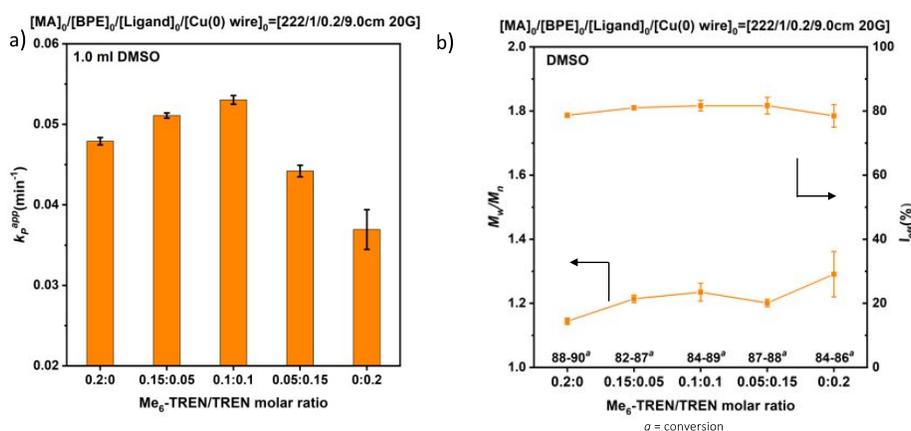


Figure 5. Evolution of k_p^{app} for the SET-LRP of MA (2 mL) initiated with BPE in DMSO (1 mL) mediated with different ratios between Me₆-TREN and TREN at 25 °C (a). Initiator efficiency ($I_{eff}(\%)$) and dispersity (M_w/M_n) as a function of the ratio between Me₆-TREN and TREN.

Representative GPC data shown in Figure 6 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. 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 80%. Overall, these results demonstrate that the mixed-ligand catalytic system consisting of nonactivated Cu(0) wire and Me₆-TREN/TREN is an effective catalyst for the SET-LRP of MA in DMSO.

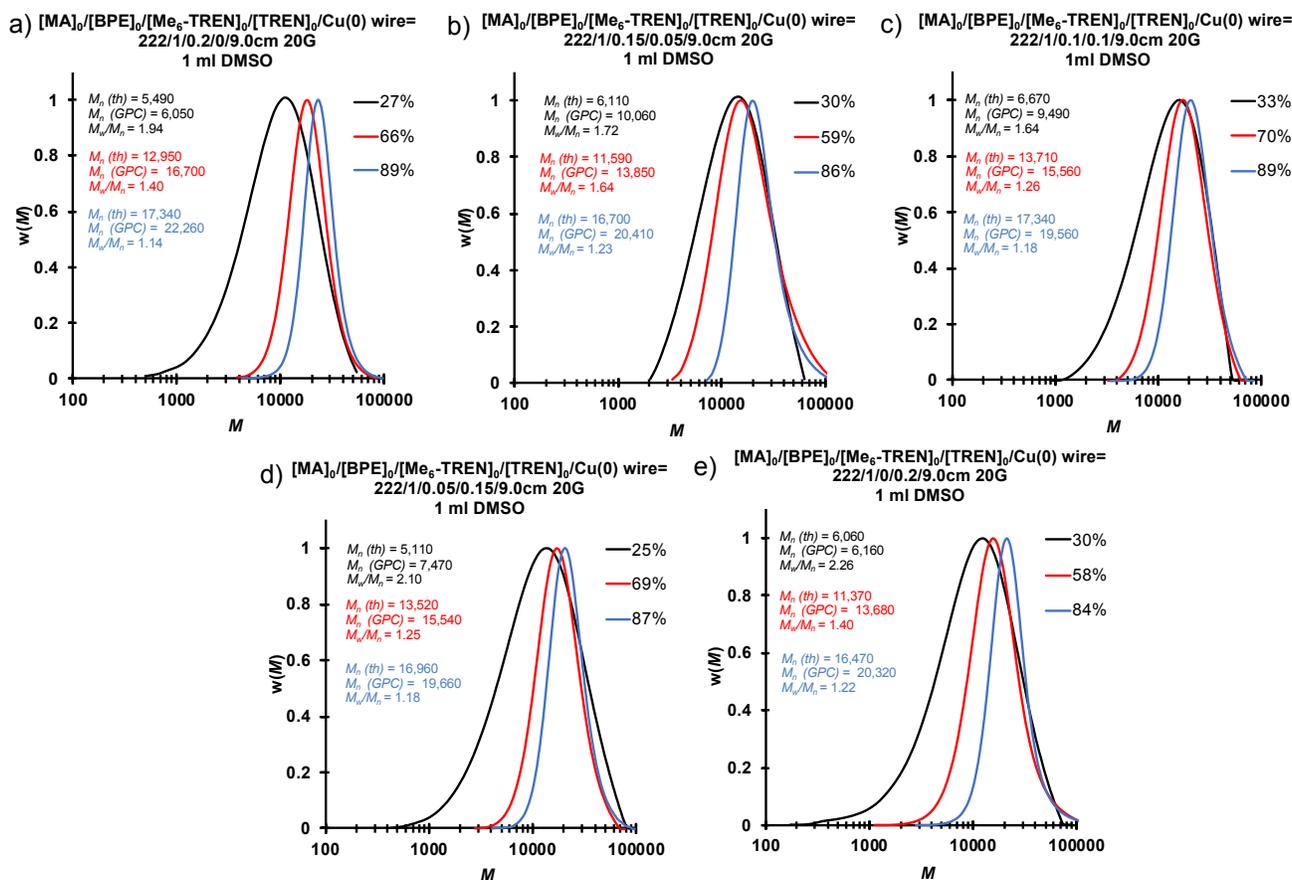
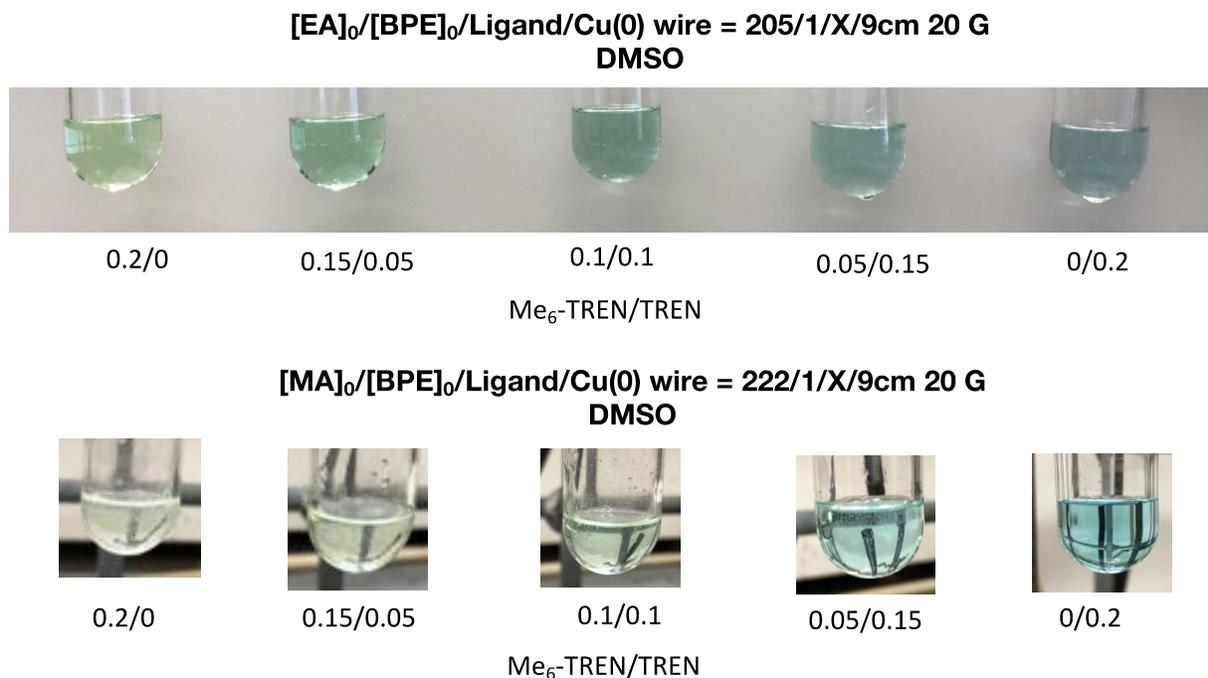


Figure 6. Representative GPC traces of the evolution of molecular weight as a function of conversion for the SET-LRP of MA in a mixture of 2 mL MA with 1 mL DMSO catalyzed by 9.0 cm nonactivated Cu(0) wire at 25 °C in the presence of various ligand compositions as mentioned on top of the GPC curves. Reaction conditions: MA = 2 mL, DMSO = 1 mL, $[MA]_0/[BPE]_0/[L]_0 = 222/1/0.2$.

Visualization of the Reaction Mixtures at the End of the Polymerization. The images in Figure 7 reveal a slight increase in the blue color of the reaction mixture 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. A similar effect was observed during the mixed-ligand effect observed in biphasic water-organic solvent reaction mixtures.^{10b}



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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.

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Structural Analysis of PMA Before and After Thio-Bromo “Click” Functionalization. A combination 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 living character of SET-LRP performed at various molar ratios between Me₆-TREN and TREN and compare them with Me₆-TREN and TREN. Lower molar mass polymers were prepared for these investigations. Figures 8 and 9 show representative ¹H NMR spectra of PMA samples isolated at high conversion after biphasic SET-LRP in DMSO in the presence of Me₆-TREN (Figures 8a, 9a), Me₆-TREN/TREN (Figures 8b, 9b) and TREN (Figures 8c, 9c) before and after thio-bromo “click” reaction. Within experimental error the chain end functionality (F^{Br} , F^{SPH} %) of all PMA samples is 100%.

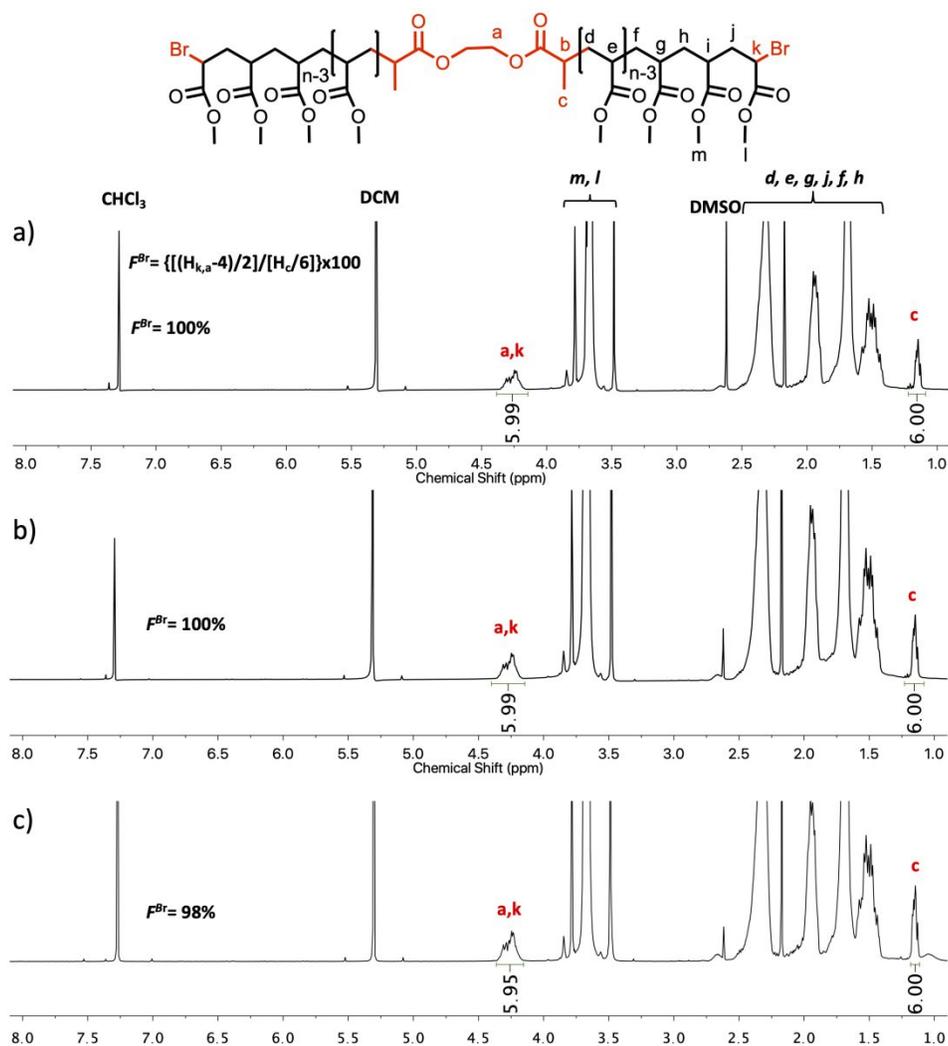


Figure 8. ^1H NMR spectra at 400 MHz of α,ω -di(bromo)PMA at: (a) 94% conversion ($M_n = 8,620$ and $M_w/M_n = 1.22$) ($[\text{MA}]_0/[\text{BPE}]_0/[\text{Me}_6\text{-TREN}]_0 = 60/1/0.2$); (b) 90% conversion ($M_n = 9,090$ and $M_w/M_n = 1.41$) ($[\text{MA}]_0/[\text{BPE}]_0/[\text{Me}_6\text{-TREN}]_0/[\text{TREN}]_0 = 60/1/0.1/0.1$); (c) 96% conversion ($M_n = 7,3840$ 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 non-activated 9 cm Cu(0) wire of 20 gauge. The signals at 7.26 ppm 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 (%).

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.

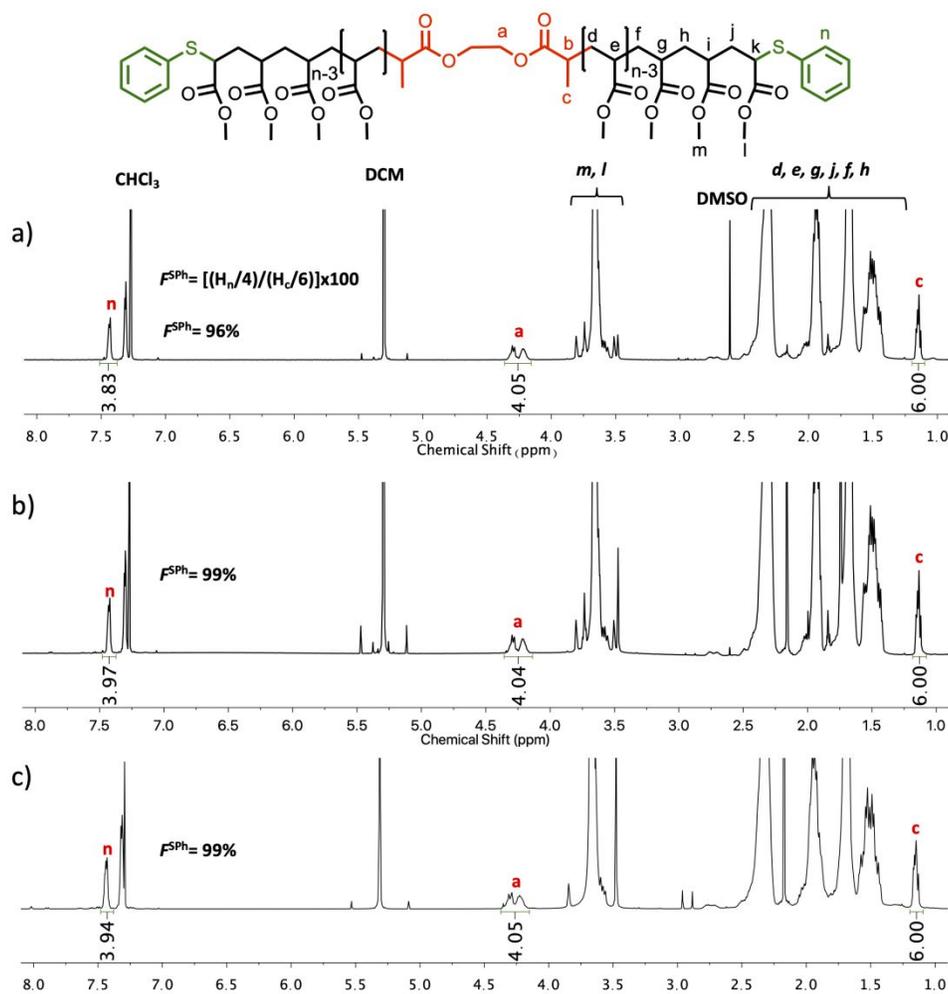


Figure 9. ^1H NMR spectra at 400 MHz of α,ω -di(phenylthio)PMA at: (a) 94% conversion ($M_n = 8,620$ and $M_w/M_n = 1.22$) ($[\text{MA}]_0/[\text{BPE}]_0/[\text{Me}_6\text{-TREN}]_0 = 60/1/0.2$); (b) 90% conversion ($M_n = 9,090$ and $M_w/M_n = 1.41$) ($[\text{MA}]_0/[\text{BPE}]_0/[\text{Me}_6\text{-TREN}]_0/[\text{TREN}]_0 = 60/1/0.1/0.1$); (c) 96% conversion ($M_n = 7,380$ 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 non-activated 9 cm Cu(0) wire of 20 gauge wire. The signals at 7.26 ppm and 5.30 ppm are due to partially nondeuterated residue of CDCl_3 and dichloromethane, respectively. F^{SPH} values refer to chain end functionality of PMA after thio-bromo “click” reaction (%).

Structural Analysis by MALDI-TOF Before and After Thio-Bromo “Click” Reaction.

Representative MALDI-TOF spectra of PMA synthesized using $\text{Me}_6\text{-TREN}$, TREN and equimolar amounts of $\text{Me}_6\text{-TREN}$ and TREN isolated in between 90% and 96% conversion were analyzed before and after the thioetherification reaction (Figures 10, 11, 12). The polymers isolated after SET-LRP at very

high conversions showed one distribution which can be assigned to the corresponding bromine-terminated polyacrylate chains ionized with Na^+ .

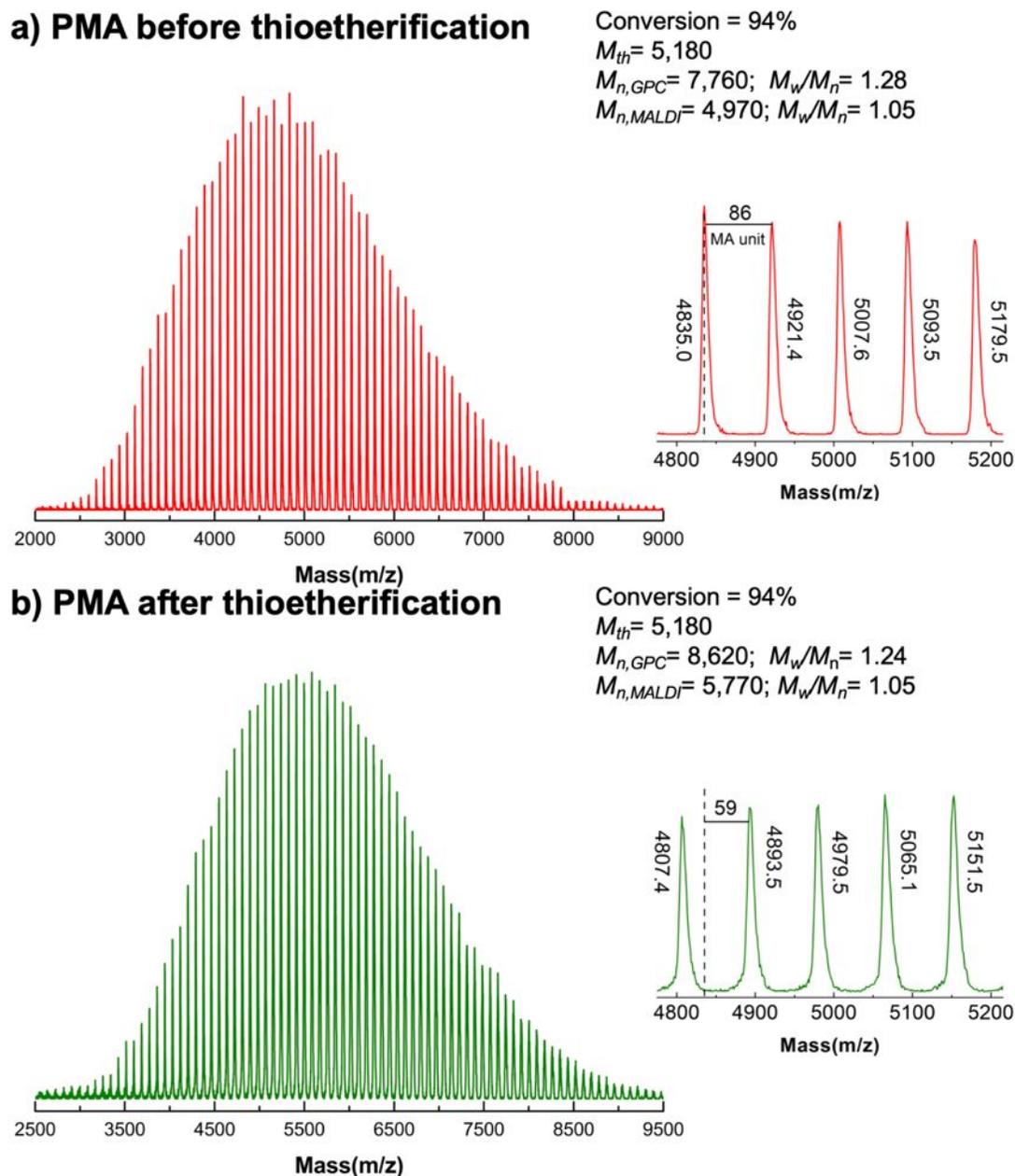


Figure 10. MALDI-TOF of PMA-Br isolated at 94% from SET-LRP of MA in DMSO solution initiated with BPE and catalyzed by non-activated Cu(0) wire at 25 °C. (a) Before “thio-bromo click” reaction. (b) After “thio-bromo click” reaction. Reaction conditions: MA = 2 mL, DMSO = 1.0 mL, $[\text{MA}]_0/[\text{BPE}]_0/[\text{Me}_6\text{-TREN}]_0 = 60/1/0.2$, 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 i.e., $2 * [\text{SC}_6\text{H}_5 (109, 2)\text{-Br} (79, 9)] = 58.57$ for each chain end.

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 replacement of -Br atoms (2×79.9) by -SPh moieties (2×109.2) at both polymer chain-ends.

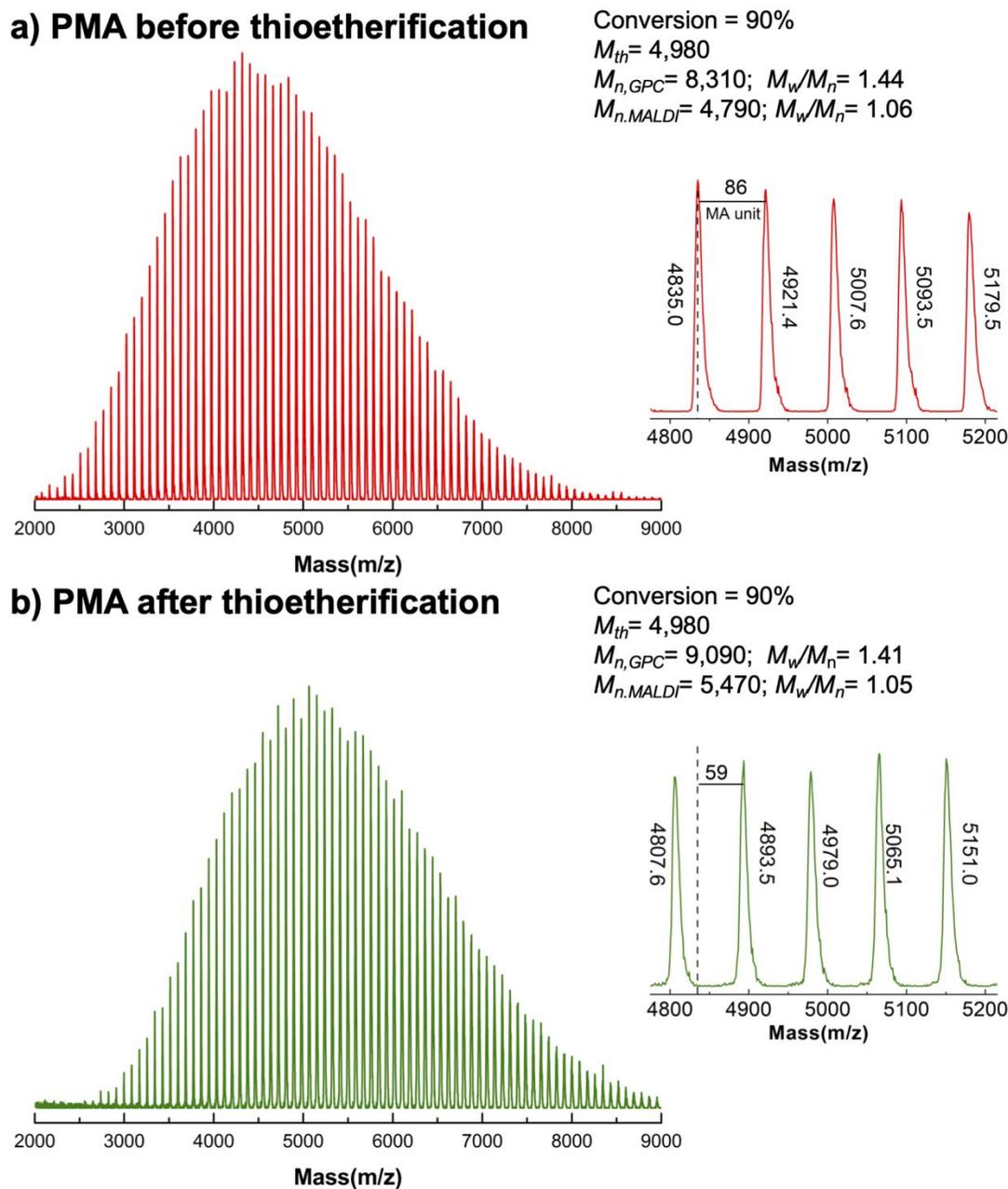


Figure 11. MALDI-TOF of PMA-Br isolated at 90% from SET-LRP of MA in DMSO solution initiated with BPE and catalyzed by non-activated Cu(0) wire at 25 °C. (a) Before “thio-bromo click” reaction. (b) After “thio-bromo click” reaction. Reaction conditions: MA = 2 mL, DMSO = 1.0 mL, $[MA]_0/[BPE]_0/[Me_6-TREN]_0/[TREN]_0 = 60/1/0.1/0.1$, 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 i.e., $2 * [\text{SC}_6\text{H}_5 (109, 2) - \text{Br} (79, 9)] = 58.57$ for each chain end.

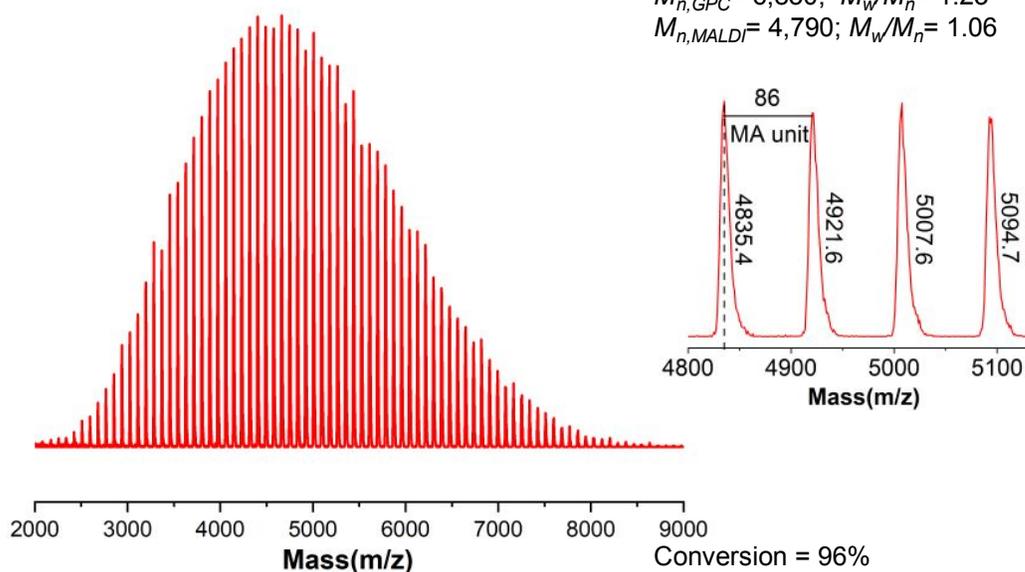
a) PMA before thioetherification

Conversion = 96%

$M_{th} = 5,290$

$M_{n,GPC} = 6,830$; $M_w/M_n = 1.23$

$M_{n,MALDI} = 4,790$; $M_w/M_n = 1.06$



b) PMA after thioetherification

Conversion = 96%

$M_{th} = 5,290$

$M_{n,GPC} = 7,380$; $M_w/M_n = 1.18$

$M_{n,MALDI} = 5,220$; $M_w/M_n = 1.05$

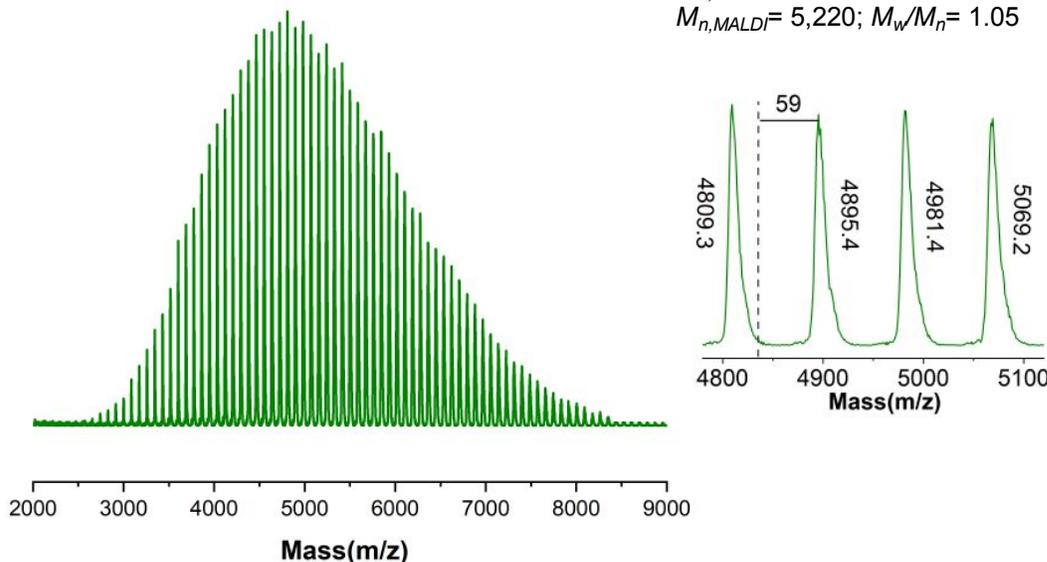


Figure 12. MALDI-TOF of PMA-Br isolated at 96% from SET-LRP of MA in DMSO solution initiated with BPE and catalyzed by non-activated Cu(0) wire at 25 °C. (a) Before “thio-bromo click” reaction. (b) After “thio-bromo click” reaction. Reaction conditions: MA = 2 mL, DMSO = 1.0 mL, $[\text{MA}]_0/[\text{BPE}]_0/[\text{TREN}]_0 = 60/1/0.2$, 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 i.e., $2 * [\text{SC}_6\text{H}_5 (109, 2) - \text{Br} (79, 9)] = 58.57$ for each chain end.

MALDI-TOF analysis of PMA prepared using Me₆-TREN and TREN showed also high levels of chain end functionality (Figures 10, 11, 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.

The Mixed-Ligand Effect During SET-LRP of 2 mL MA in 1.5 mL DMSO Using Me₆-TREN, Me₆-TREN/TREN and TREN as Ligands. Kinetic experiments for the SET-LRP of 2 mL MA in 1.5 mL DMSO performed with the mixed-ligand Me₆-TREN/TREN under similar reactions conditions to the experiments performed with 2 mL MA in 1 mL DMSO from Figure 4 are reported in Figure 13.

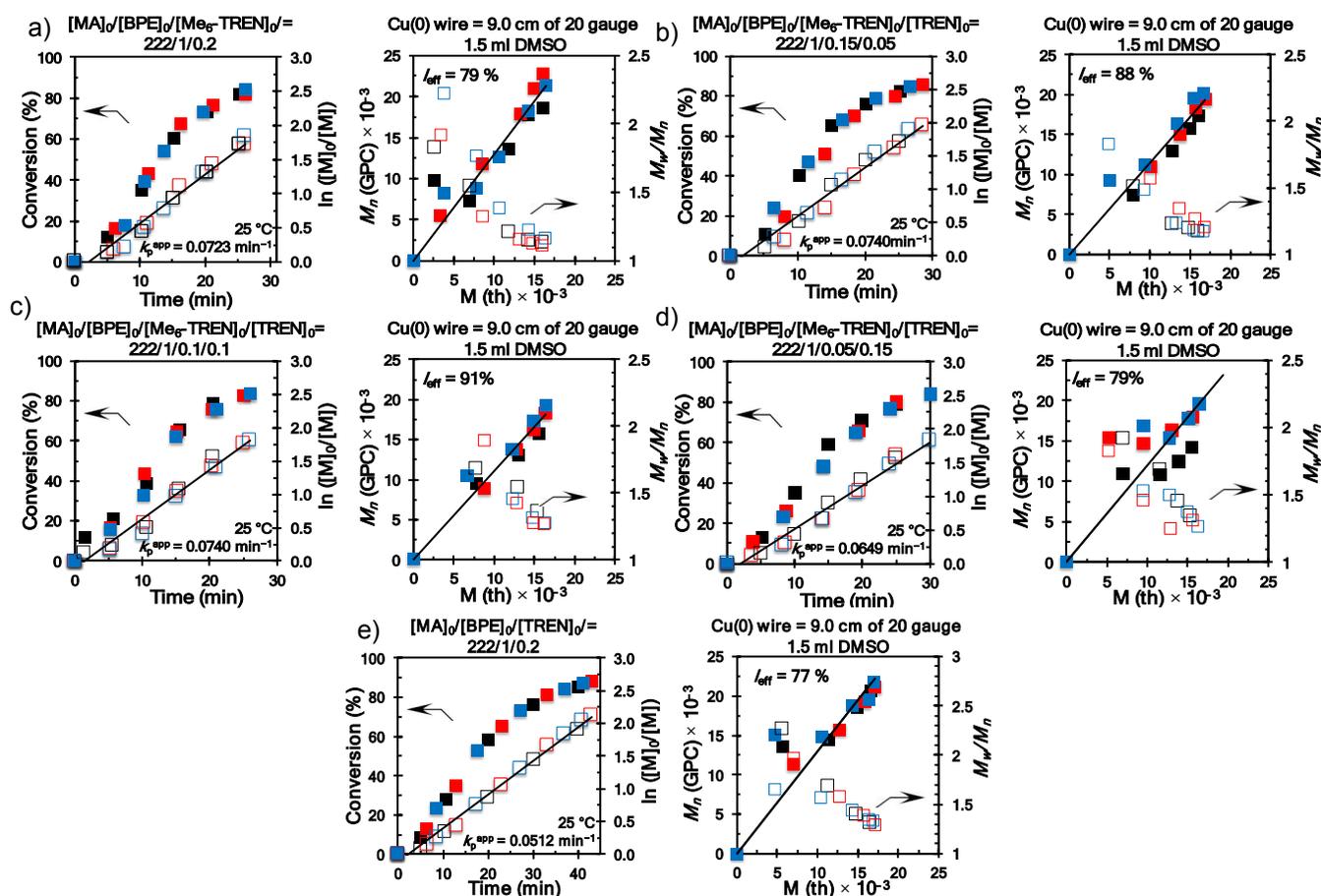


Figure 13. Kinetic plots, molecular weight and dispersity evolutions for the SET-LRP of MA in DMSO, initiated with BPE and catalyzed by the 9.0 cm non-activated Cu(0) wire at 25 °C. Experimental data in different colors were obtained from different kinetics experiments, sometimes performed by different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

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 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.

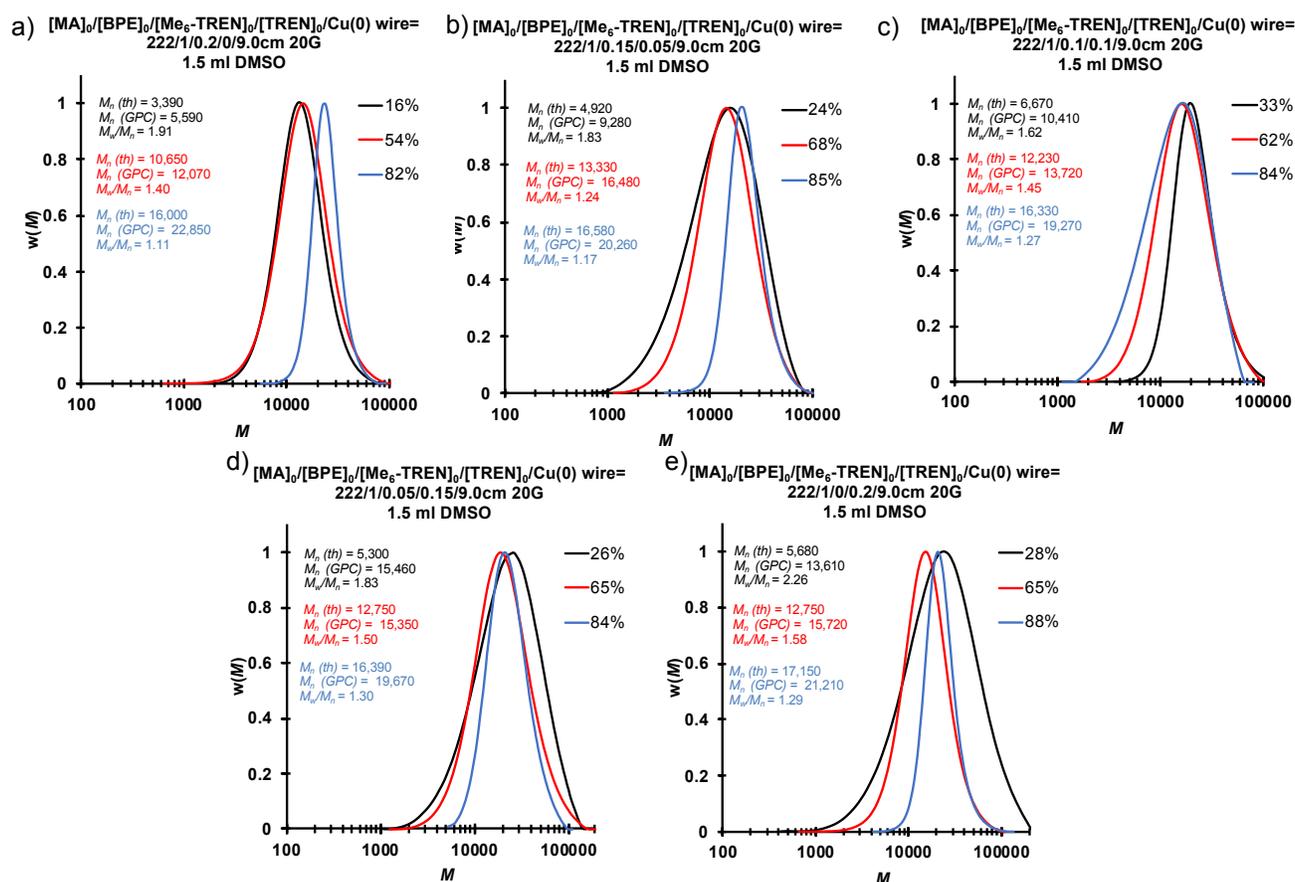


Figure 14. Representative GPC traces of the evolution of molecular weight as a function of conversion for the SET-LRP of MA in a mixture of 1 ml DMSO and catalyzed by the 9.0 cm nonactivated Cu(0) wire at 25 °C in the presence of various ligand compositions. Reaction conditions: MA = 2 mL, DMSO = 1.5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

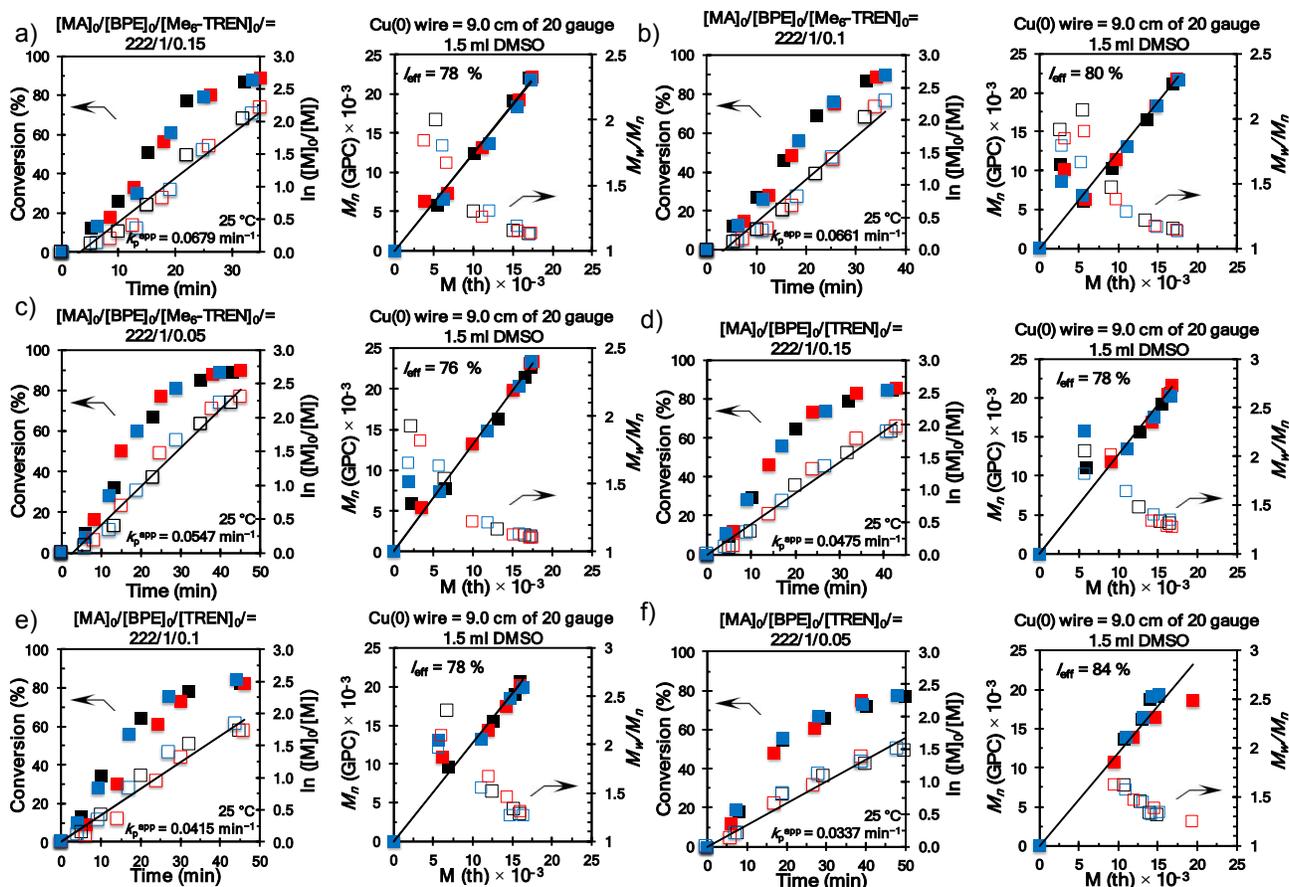


Figure 15. Control experiments. Kinetic plots, molecular weight and dispersity evolutions for the SET-LRP of MA in DMSO, initiated with BPE and catalyzed by the 9.0 cm non-activated Cu(0) wire at 25 °C. Experimental data in different colors were obtained from different kinetics experiments and sometimes performed by different researches. 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 $0.05/9\text{cm}$); 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 DMSO at 25 °C^a

entry	Wire length (cm) 20G	Reaction condition	k_p^{app} (min ⁻¹)	M_w/M_n	$I_{\text{eff}}(\%)$
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.

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.

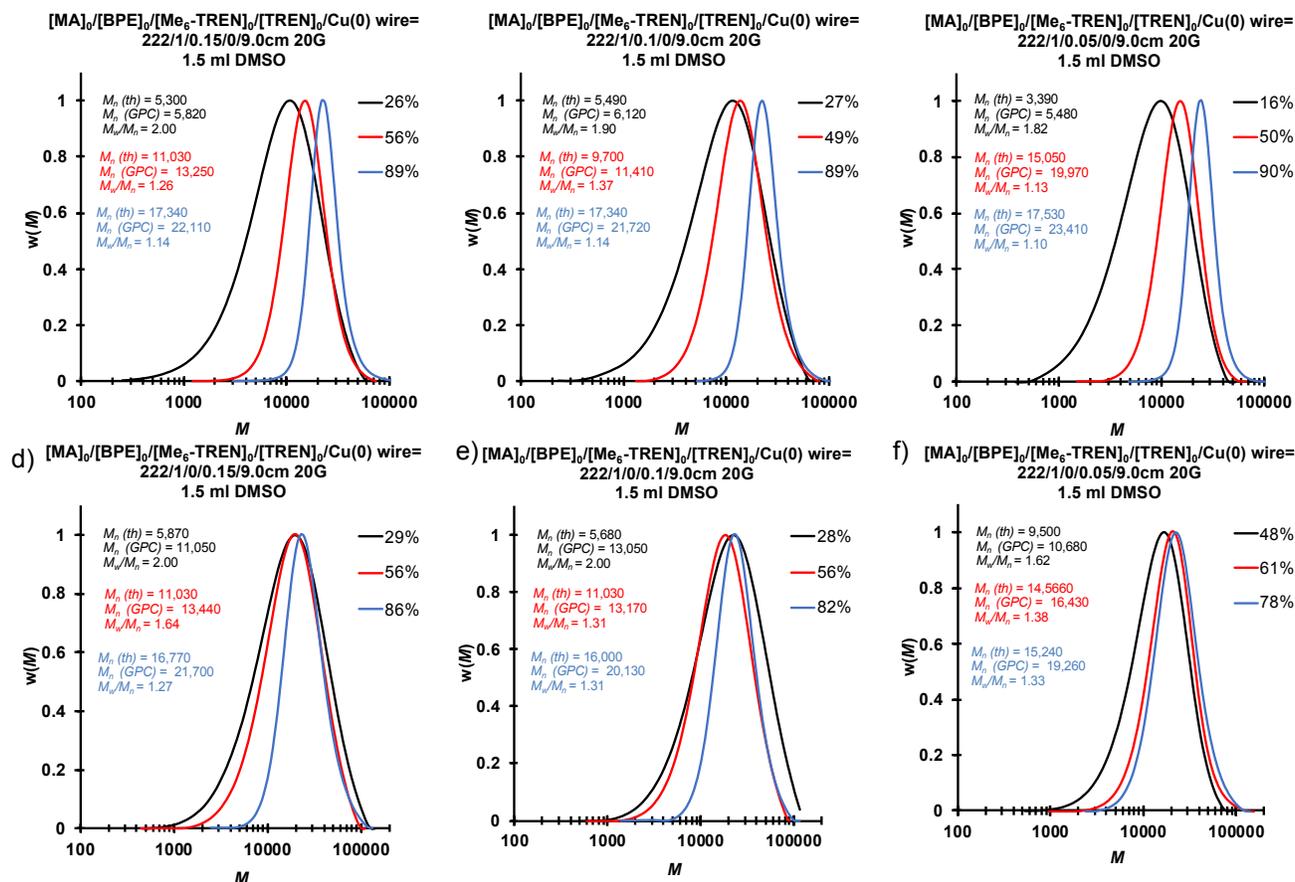


Figure 16. Representative GPC traces of the evolution of molecular weight as a function of conversion for the SET-LRP of MA in a mixture of 1 ml DMSO and catalyzed by the 9.0 cm nonactivated Cu(0) wire at 25 °C in the presence of various ligand compositions. Reaction conditions: MA = 2 mL, DMSO = 1.5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

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 MA and 1.5 mL 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 MA and 1.0 mL DMSO vs 2.0 mL MA and 1.5 mL DMSO (compare Figures 4 with 13 and Figures 5a with Figure 17a). This comparison is also made in Table 3. The most representative result from this comparison is that while k_p^{app} value for Me₆-TREN at 1 mL DMSO is 1.30, the value of k_p^{app} for

TREN at 1.5 mL DMSO is 1.38. Therefore, TREN becomes at 1.5 mL DMSO more efficient than Me₆-TREN at 1 mL DMSO. This result explains the revitalization of TREN and its transformation into an excellent ligand by the catalytic effect of DMSO.

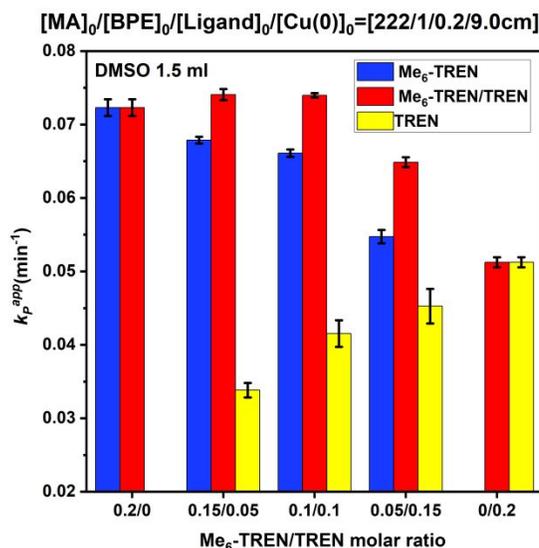


Figure 17. Evolution of k_p^{app} for the SET-LRP of MA (2 mL) initiated with BPE in DMSO (1.5 mL) mediated with different ratios between Me₆-TREN and TREN at 25 °C (in red). Control experiments performed only with Me₆-TREN (in blue) and only with TREN (in yellow) are also incorporated.

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

entry	Volume of DMSO (ml)	Reaction condition	k_p^{app} (min ⁻¹)	$k_p^{app}/k_p^{app}(\text{entry } 10)$	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

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3 **Structural Analysis of PMA Before and After Thio-Bromo “Click” Reaction by a Combination of**
4 **NMR and MALDI-TOF.** Structural analysis was performed by a combination of $^1\text{H-NMR}$ and MALDI-
5 TOF before and after thio-bromo “click” reaction (Figures S6 to S10). The chain-end functionality of the
6 PMA is 97% before thio-bromo “click” reaction and 98% respectively after thio-bromo “click” reaction
7 regardless of the structure of the ligand employed during SET-LRP (Figures S7 and S8). These excellent
8 results are confirmed by the MALDI-TOF analysis performed before and after thio-bromo “click”
9 reactions (Figures S6, S9, S10).

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12 **Brief Comments on the Significance of these Results for the Field of Biomacromolecules and**

13 **Concluding Remarks.** SET-LRP catalyzed by $\text{Cu}(0)$ wire, powder, coins and other objects occurs in
14 disproportionating solvents and provides polyacrylates with unexpectedly high chain end functionality for
15 a living radical polymerization process.^{26,50} This includes, within the limits of NMR experimental error,
16 100% chain end functionality for PMA.^{26,50} In non-disproportionating solvents including polar solvents
17 like acetonitrile,⁴³ and non-polar solvents like toluene,⁴² the chain end functionality of the resulting
18 polymers is much lower. Best chain end functionality is observed in the absence Cu(II)X_2 and could be
19 obtained either with TREN or $\text{Me}_6\text{-TREN}$ ²⁶ or in the presence of a very small amount of Cu(II)X_2 .^{26,50}
20 Larger amounts of Cu(II)X_2 additive decrease the chain end functionality of the resulting polymers
21 although SET-LRP provides the highest chain end functionality of any LRP prepared polymers.^{26,50,51}
22 Details of chain end functionality as a function of the concentration of externally added Cu(II)X_2 were
23 discussed previously.²⁶ Under these conditions, the lower chain end functionality values can be explained
24 by the Cu(II)Br_2 mediated oxidation of propagating radicals to carbocations that subsequently provide
25 chain end double bonds by proton transfer to the basic components of the reaction mixture such as $\text{Me}_6\text{-}$
26 TREN and TREN in their non-complexed forms.^{52,53,54} Terminal double bond chain ends have been
27 reported in polyacrylates obtained by SET-LRP in the presence of Cu(II)X_2 .^{51a} In this respect, TREN is a

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3 less basic ligand than Me₆-TREN, and therefore TREN is a more efficient ligand than Me₆-TREN in
4 attempts to provide perfectly functional PMA chain ends. The unusually high chain end functionality
5 observed under SET-LRP reaction conditions was attributed to the polymer adsorption on the surface of
6 Cu(0) that decreases the reactivity of the growing radicals in bimolecular termination events but not during
7 the propagation reactions.^{55,56} This high chain end functionality contrasts with the much lower chain end
8 functionality observed in ATRP, where the persistent radical effect (PRE)⁵⁷ is responsible for the
9 production of Cu(II)X₂.^{58,59} Activation of the alkyl halides by Cu(0) objects occurs by the most active site
10 of their face centered crystal (FCC) that is 111.⁶⁰ Both powder⁶¹ and wire⁶² experiments demonstrated that
11 objects produced from Cu(0) crystals have a reactivity that is surface dependent. Moreover, this reactivity
12 increases when Cu(0) atoms are produced by disproportionation followed by activation, nucleation and
13 growth on the original surface of Cu(0).^{19,63} Nucleation and growth has been demonstrated to occur during
14 SET-LRP on the surface of the wire.⁶⁴ Colloidal Cu(0) particles were also demonstrated during
15 SET-LRP.⁴³ However the highest activity of Cu(0) is as atoms. Cu(0) atoms are more reactive than Cu(I)X
16 and are classic and well-established SET catalysts.⁴⁴ This diversity of catalytic Cu(0) species is all
17 involved in the SET-LRP process but could not be observed to reduce Cu(II)X₂ to Cu(I)X species during
18 the SET-LRP process.⁴⁵ However, this reduction is not excluded to occur in the absence of activation.
19 This brief mechanistic discussion demonstrates that the reduction of the amount of Cu(II)X₂ during SET-
20 LRP can contribute to a better control of the chain ends and to a lower amount of contamination of the
21 product with Cu species. The use of TREN and Me₆-TREN mixed-ligand system to mediate the Cu(0)
22 wire-catalyzed SET-LRP MA in the catalytically active solvent DMSO provides a new methodology to
23 control the SET-LRP process. Kinetic data and chain end analysis demonstrate that Me₆-TREN can
24 complement and make TREN a very efficient ligand in the absence of externally added Cu(II)Br₂ when
25 the catalytically active solvent DMSO is employed. The fact that the most important effect is observed at
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3 1/1 molar ratio between ligands suggests that in addition to a fast exchange between the two ligands, a
4 new single dynamic ligand generated by hydrogen-bonding should be considered in future mechanistic
5 investigations. The rate of polymerization at 1/1 molar ratio between the two ligands is higher than that
6 obtained with each of the individual ligand at the same molar concentration. At the same time, SET-LRP
7 experiments performed at the proper concentration of DMSO do not require the use of the activated Cu(0)
8 wire. The high chain end functionality⁶⁵ generated in the absence of externally added Cu(II)Br₂ makes the
9 SET-LRP in the presence of the mixed-ligand and/or TREN the method of choice for the synthesis of
10 biomacromolecules as already reported for many examples, including some from our laboratory.⁶⁶
11 Therefore, the catalytic activity DMSO can be exploited, as demonstrated here, to enhance the reactivity
12 of TREN and of its 1/1 mixture with Me₆-TREN while decreasing the basicity of the ligand and eliminating
13 side-reaction mediated by it. The most fundamental question related to this topic that must be addressed
14 is the following: do all disproportionating solvents display a catalytic effect in SET-LRP or only DMSO?
15 Research to answer this question is in progress.
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34 ASSOCIATED CONTENT

35 Supporting Information

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37 The Supporting Information is available free of charge on the ACS Publications website at DOI:
38 10.1021/acs.biomac.XXXXX. Addition kinetic plots and characterization results including NMR and
39 MALDI-TOF spectra (PDF)
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