DEVELOPMENT OF HIGHLY ACTIVE AND SELECTIVE COPPER CATALYSTS FOR NEW ATRP INITIATING SYSTEMS

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Abstract

Reversible deactivation radical polymerization (RDRP) techniques have revolutionized polymer chemistry for the controlled synthesis of functional polymers with predefined molecular weights, narrow molecular weight distributions and with high chain-end functionality. One of these techniques, atom transfer radical polymerization (ATRP), makes use of a catalytic system, most commonly copper complexed by a nitrogen-based ligand, in which the L/Cu^I activator species cleaves a (macro)alkyl halide bond generating a carbon-centered radical and the oxidized L/Cu^{II}-X deactivator species. The radical propagates by adding to a few monomer units before being quickly deactivated by the L/Cu^{II}-X complex. As with any radical process, irreversible termination reactions are unavoidable and thus a gradual buildup of L/Cu^{II}-X is observed according to the persistent radical effect (PRE), leading to a suppressed rate of polymerization. Various systems with activator regeneration, also known as "low ppm Cu ATRP," have been developed to overcome the PRE, but these require the use of highly active catalysts. At the forefront of ATRP research has been the development of new externally regulated systems as well as mechanistic understanding of the processes in order to select the best catalytic system. My contribution to the field was primarily focused on: (1) the development and understanding of new initiating systems for low ppm ATRP using light and zero-valent metals such as Ag⁰ and Cu⁰, (2) the synthesis and characterization the highly active catalysts based on ligand design and (3) quantification and mechanistic understanding of radical termination processes in both conventional free radical polymerization and ATRP with highly active catalysts.

Chapter 1 overviews the progressive development of catalytic systems in ATRP. Since ATRP's discovery in 1995, various kinetic and thermodynamic parameters have been quantified in order to better understand this system. The first catalysts involved the use of relatively simple bidentate bipyridine (bpy)-based ligand and required catalyst loadings of greater than 10,000 ppm. Through rational ligand design, structure vs. reactivity relationships between activity and N-atom donor type, denticity, geometry were understood. This allowed the synthesis of more complex and robust ligands which greatly increased the efficiency of ATRP.

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The activity of catalysts in ATRP has now increased over 1,000,000,000 times compared to seminal bpy-based catalysts and allow for ATRP to be conducted using catalyst loadings as low as 5 ppm. This chapter encompasses almost 25 years of ATRP catalytic systems and discusses potential opportunities for future development.

Chapter 2 discusses mechanistic studies for the newly developed photochemically mediated ATRP. Photochemical control over ATRP with ppm amounts of copper was first achieved in 2012, however, there was significant mechanistic debate over how the polymerization operated, namely the mechanism of photochemical reduction of L/Cu^{II}-X. Using both experimental and simulation techniques, the mechanism of *photo*ATRP was elucidated. It was found that the main method of radical (re)generation occurs via a reductive quenching process between excited state deactivator complex, [L/Cu^{II}-X]* and excess amines acting as electron donors. By using model studies and kinetic simulations, other photochemical processes were studied and quantified. The effect of light irradiation on other methods of low ppm ATRP such as initiators for continuous activator regeneration (ICAR) ATRP was also quantified.

Chapter 3 discusses ATRP in the presence of zero-valent metals. This is an attractive method because the reactions are easy to operate and it opens up the possibility for catalyst recycling. ATRP was first conducted in the presence of Cu^0 in 1997, however, a vigorous mechanistic debate was ongoing for over a decade. Specifically, two mechanisms, supplemental activator and reducing agent (SARA) ATRP and single electron transfer living radical polymerization (SET-LRP), both using the same species, were debated. It was found that the SARA mechanism holds true in both aqueous and organic media. Both activation of alkyl halides by Cu^0 , k_{a0} , and comproportionation between Cu^0 and L/Cu^{II}, k_{comp} , were quantified in a variety of solvents for different ligands and alkyl halides. In-depth mechanistic studies attempted to elucidate the surface reactions occurring in SARA ATRP. Finally, a new system employing the use of Ag^0 wire as a reducing agent for L/Cu^{II}-X was used in ATRP and exhibited one of the highest degrees of "living" control in any ATRP system reported thus far.

Chapter 4 overviews in-depth kinetics of both normal and low ppm ATRP systems such as ICAR ATRP and SARA ATRP. Recent reports have made inaccurate claims about reaction

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mechanisms due to the misunderstanding that the rate of polymerization in ATRP is *not* directly related to the rate of alkyl halide activation. This chapter aims to rectify the claims made by others and to present a much clearer and accurate picture of the kinetics of ATRP.

Chapter 5 discusses the recent advancements in catalytic design in ATRP. Specifically, the tetradentate tripodal ligand tris(2-pyridylmethyl)amine (TPMA) was systematically modified to include methyl (-Me) and methoxy (-OMe) electron donating groups to decrease the redox potential, $E_{1/2}$, of the L/Cu^{1/II} couple. Substitution of each pyridine arm lead to a catalyst that was 10, 100 and 1000 times more active than the unsubstituted ligand. Structural studies of both the L/Cu^I and L/Cu^{II}-X species were also conducted. The catalysts were characterized in solution using UV-Vis, electrochemistry and low-temperature ¹H NMR spectroscopy and also used as catalysts in activators regenerated by electron transfer (ARGET) ATRP. In order to increase the activity further, the TPMA scaffold was substituted with even more electron donating dimethylamino (-NMe₂) groups. Characterization of this complex,

[Cu^{II}(TPMA^{NMe2})Br][Br], revealed the most active ATRP catalyst to date with rates of activation approaching diffusion controlled-limits ($k_a > 10^6 \text{ M}^{-1}\text{s}^{-1}$) and K_{ATRP} values approaching unity for ethyl α -bromoisobutyrate (EBiB) in acetonitrile (MeCN) at ambient temperatures. ICAR and Ag⁰-mediated ARGET ATRP exhibited a well-controlled polymerization with >99% chain-end functionality using as little as 10 ppm of catalyst.

Chapter 6 discusses the recent research efforts to understand how acrylate radicals terminate in both conventional radical polymerization (RP) and ATRP. It is known that active L/Cu^I catalysts can catalyze the termination of acrylate radicals, the mechanism, however, remains elusive. It has been concluded that un-catalyzed radical termination of acrylates occurs predominately *via* combination while CRT gives saturated chain-ends. We aimed to determine the effects that ligand geometry and electronics has on this reaction as well as elucidate the mechanism of non-catalyzed radical termination. The intimate mechanism of the CRT reaction is currently being studied. Throughout the process, a novel reaction between organotellanyl radicals (*TeR) and propagating carbon-based radicals was discovered. Finally, Chapter 7 provides a summary with an emphasis on future directions.

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Chapter 1. Progressive Development of Catalytic Systems in ATRP

1.1 Preface

This chapter encompasses the progressive development of both atom transfer radical polymerization (ATRP) catalysts but also various initiation systems that have been devised since ATRP's inception in 1995.

ATRP has its roots in the Kharasch addition of alkyl halides to alkenes resulting in carbon-carbon bond formation. Significant strides in the selectively and yield of the monoadduct were achieved in the 1950's using metal-catalyzed systems, a process which is now known as transition metal catalyzed atom transfer radical addition (ATRA). The main difference between ATRA and ATRP is that, in ATRP, the monoadduct is reactivated and allowed to propagate with monomer resulting in the controlled growth of polymeric chains.

The fundamentals of the kinetics of ATRP will be briefly discussed as well as criteria for highly active catalysts. Initially, normal ATRP started from stoichiometric amounts of alkyl halide and air-sensitive L/Cu^I catalyst under quasi-heterogeneous conditions. The synthesis of highly active catalysts has allowed the use of the air-stable L/Cu^{II}-X complex which can be slowly and continuously reduced *in situ* to the L/Cu^I activator species. This has made possible catalyst loadings to be decreased from >10,000 ppm to as little as 1 ppm under certain conditions and has significantly increased the robustness of ATRP. Various techniques for catalyst characterization and future opportunities are also briefly discussed. A tremendous acknowledgement to Dr. Francesca Lorandi for helping with the section on dispersed media in ATRP.

1.2 Background and Introduction

Living polymerizations were first introduced in 1956 by Michael Szwarc in which anionic active species were effectively able to be controlled for the polymerization of styrene and dienes.¹⁻⁴ Living anionic polymerization benefitted from the fact that, in the absence of impurities, there is no termination between polymer chains. Unfortunately, due to the highly

reactive nature of the carbanionic propagating species, great efforts are required to ensure a pure and dry system. In 1974, living cationic polymerization was developed for ring-opening⁵⁻⁸ and vinyl⁹⁻¹² polymerization of alkyl vinyl ethers¹³⁻¹⁴ and isobutene¹⁵⁻¹⁶. Similar to anionic polymerization, extensive purification and setup methods needed to be taken in order to ensure chain termination and transfer were limited. Other living polymerizations have also been developed for coordination polymerization¹⁷⁻²⁰ and ring opening metathesis polymerization (ROMP).²¹⁻²²

Compared to other polymerization systems, radical polymerization (RP) benefits from a much higher tolerance to functional groups in that almost any species with a vinyl group can be polymerized. However, unlike anionic polymerization, radical polymerization is prone to bimolecular radical terminations which are unavoidable, irreversible chain-terminating events. This minimizes the control over polymeric architecture and molecular weights while exhibiting relatively broad molecular weight distributions (MWDs). Control over the radical species was first reported in 1967 by Borsig²³⁻²⁴ and later by Otsu²⁵⁻²⁶ and Rizzardo.²⁷⁻²⁸ However, this process only gained traction in 1993 when Georges reported the synthesis of polystyrene (PS) with relatively low dispersity when conducted in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO).²⁹ This was quickly followed by a report from Wayland in which cobalt(II) porphyrin was used to reversibly trap acrylate radicals and exhibited the characteristics of a "living" radical polymerization, i.e. increasing molecular weights with conversion and relatively narrow molecular weights distributions (MWDs).³⁰ These systems set the precedence for nitroxide mediated polymerization (NMP)³¹⁻³³ and organometallic mediated radical polymerization (OMRP),³⁴⁻³⁶ respectively.

Within the past three decades, the ever-expanding toolbox of controlled radical polymerization (CRP) has revolutionized polymer chemistry because it allows for the control of polymeric architectures and thus has enabled the synthesis of a variety of commercially important polymeric products for advanced applications. CRP, more accurately known as reversible deactivation radical polymerization (RDRP),³⁷ allows for the control of living ionic polymerization, but with the versatility and scope of conventional radical polymerization (RP). In particular, atom transfer radical polymerization³⁸⁻⁴¹ (ATRP) and reversible addition

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fragmentation chain-transfer (RAFT) polymerization⁴²⁻⁴⁶ have garnered the most success of all RDRP systems. This comes in part from their ability to "tune" reaction conditions depending on the monomer chosen.

In RAFT polymerization, the choice of chain-transfer agent (CTA), also known as RAFT agent, must be correctly selected in order to effectively equilibrate polymeric radicals between dormant and active species. ATRP, on the other hand, is catalytic in nature and thus the choice of catalyst is paramount to gain sufficient control. Over the past 20 years, an extensive number of catalysts have been implemented in copper catalyzed ATRP. Through the use of rational catalyst design, catalyst loadings in ATRP have been diminished from >10,000 ppm to less than 10 ppm in some polymerization systems while concurrently expanding the monomer scope.

1.2.1 Mechanisms of Reversible Deactivation Radical Polymerization (RDRP)

Processes

RDRP methods gain control over the radical polymerization by effectively extending the lifetime of the propagating radical. For instance, in conventional radical polymerization (RP), a chain is initiated, allowed to propagate for \approx 1 second before quickly terminating with a second radical. In RDRP, a radical is only able to add a few monomers before being reversibly deactivated, thus effectively extending the lifetime of the radical from seconds to days or even months. The nature of the reversible deactivation can take on one of three forms: i) reversible termination (or deactivation) ii) catalytic reversible termination (deactivation) and iii) degenerative transfer.

Historically, reversible termination mechanisms employing the use of stable free radicals such as TEMPO, were used in nitroxide mediated polymerization (NMP) (**Scheme 1.2.1A**).^{29, 33} In NMP, the dormant species is thermally activated by homolysis of the C-Y (Y = stable free radical) bond. Other successful reversible termination systems employed the use of transition metal complexes as radical trapping agents in organometallic mediated radical polymerization via reversible termination (OMRP-RT)^{34, 47-49} and were successful with Co, Fe, Mo, Os, Ti, although cobalt-based systems have shown the largest versatility with respect to monomer scope and conditions.^{34, 50-56} Under certain conditions, OMRP can also proceed via a degenerative transfer

mechanism (OMRP-DT),⁵⁷ a mechanism which has been most widely exploited in reversible addition fragmentation chain-transfer (RAFT) polymerization (**Scheme 1.2.1C**).^{43, 58-59}

Atom transfer radical polymerization (ATRP) operates similarly to NMP and OMRP-RT. However, unlike NMP or OMRP-RT which involves relatively weak, thermally unstable bonds, alkyl bromides and chlorides are relatively more thermally stable. Therefore, ATRP takes use of a transition metal complex catalytically activating alkyl halide chain-ends and deactivating radicals, thus rendering the process catalytic (**Scheme 1.2.1B**). ATRP is intrinsically different from metal-based redox initiated free radical polymerization. In ATRP, the metal complex has two purposes: i) activation of chains from alkyl halide species and ii) deactivation of propagating radicals generated in the activation process. Without both activator and deactivator, control over the polymerization would not be possible. Various transition metals have been used in ATRP such as Cu, Ru,⁶⁰ Fe,⁶¹ Ni,⁶² Os,⁵⁴ Re,⁶³ Rh,⁶⁴ Pd,⁶⁵ Co,⁶⁶ Ti,⁶⁷ and Mo,^{52, ⁶⁸ although copper has been the most widely used and studied.⁶⁹}

RAFT polymerization utilizes thiocarbonylthio compounds⁷⁰ to shuttle propagating radicals between active and dormant states (**Scheme 1.2.1C**). Other RDRP processes operating via DT have employed the use of I- (iodine transfer polymerization, ITP),⁷¹⁻⁷⁶ Te- (tellurium radical polymerization, TERP),⁷⁷⁻⁷⁸ Bi-,⁷⁹ and Sb-based⁸⁰⁻⁸¹ CTA's. Unfortunately, most DT methods require every chain to be capped by an expensive and usually colored reagent.

A) Reversible Termination





B) Catalytic Reversible Termination

$$P_n$$
-Y + L/Mtⁿ $\xrightarrow{k_a}$ P_n^{\bullet} + L/Mtⁿ⁺¹-Y $Y = CI, Br, etc$
Mt = Cu, Ru, etc - ATRF

C) Degenerative Transfer

$$P_n \cdot Y + P_m^{\bullet} \xrightarrow{k_{tr}} P_n^{\bullet} + P_m \cdot Y$$

$$V = \sum_{Z} R, SR, OR, NR_2$$
- RAFT
- TERP
- ITP

Scheme 1.2.1 Mechanisms of various RDRP processes operating by reversible termination / deactivation, catalytic reversible termination / deactivation or degenerative transfer. For clarity, other reactions such as termination, transfer and propagation are omitted, although they occur in all RDRP systems.

1.2.2 Development of ATRP

ATRP is rooted in the Kharasch reaction. The Kharasch reaction was discovered in 1945 and used light irradiation or free radical initiators such as peroxides to catalyze the addition of haloalkanes such as H-CCl₃, CCl₄ or CBr₄ to alkenes in an anti-Markovnikov fashion, as shown in **Scheme 1.2.2**.⁸²⁻⁸³ This process was limited due to the extensive amount of radical side reactions such as termination and oligomerization/polymerization.

Transition metal species were accidentally added to a reaction mixture by corrosion of a steel autoclave by Minisci in 1956.⁸⁴ Notably, for chloroform, a higher selectively of alkene addition between C-Cl was observed while under Kharasch conditions the alkene was added between the C-H bond. This was later extended in 1961 using Fe^{III} or Cu^{II} salts which dramatically, and purposely, increased the yield and selectively of the monoadduct.⁸⁵ In the presence of Cu^{II} halide complexes, after addition of the initiating radical to the alkene, the subsequent radical was quickly trapped by the oxidized metal complex to form the monoadduct. Although the selectively of the process significantly increased, relatively large fractions of copper catalysts were required, typically from 10 to 30 mol%. This new metal catalyzed radical addition was coined the term transition metal catalyzed atom transfer radical addition (ATRA).⁸⁶⁻⁸⁸

Kharasch (1945)



Scheme 1.2.2 Transition metal catalyzed atom transfer radical addition (ATRA) of haloalkanes to alkenes in the presence of (top) radical initiators or (bottom) metal complexes.

In 1995, the Matyjaszewski group took the roots of ATRA and developed a system for the controlled polymerization of styrene using as little as 1 mol% of copper catalyst. Contrary to ATRA which uses a monomer to alkyl halide ratio of [M]:[RX] = 1:1, ATRP uses a much larger ratio which is equal to targeted degree of polymerization (DP).

Around the same time, Sawamoto *et al* took a similar approach using a rutheniumbased catalyst which was also shown to effectively catalyze ATRA.⁸⁹ Indeed, the [Ru^{II}(PPh₃)₃Cl₂] complex catalyzed the RDRP of MMA in the presence of additives such as aluminum isopropoxide or amines. Since this seminal report, a number of Ru-based catalysts based on dichlorides,⁹⁰⁻⁹¹ half-metallocenes,⁹²⁻⁹³ *p*-cymene⁹⁴ and alkylidene⁹⁵⁻⁹⁶ complexes have all been shown to be effective catalysts for well-controlled polymerizations.⁹⁷ Ru-based catalysts will be discussed in **Section 1.3.10.1**.

1.2.3 Mechanistic Aspects of ATRP

ATRP relies on both the L/Cu^I activator and the L/Cu^{II}-X deactivator complexes to effectively mediate the polymerization. The activator species must be sufficiently reactive to homolytically cleave the C-X bond in the (macro)alkyl halide initiator (X = Cl or Br). Likewise, the L/Cu^{II}-X deactivator complex must be able to quickly trap propagating radicals to regenerate the P_n-X (macro)alkyl halide dormant species.⁹⁸

Over the course of two decades, various parameters regarding catalyst speciation were studied. As shown in **Scheme 1.2.3**, large stability constants, β^n (n = I, II) in both oxidation states, are required to ensure that the copper ion is sufficiently coordinated by ligand. ATRP requires large values of both β^I and β^{II} , however β^{II} should be sufficiently larger than β^I to give a thermodynamic driving force for activation.⁹⁹ Thus, K_{ATRP} can be related to β^{II}/β^I .¹⁰⁰ It has been shown that with tetradentate ligands, the L/Cu^I-X complex is an inefficient catalyst in ATRP, thus low values of K_X^I are preferred to ensure a larger fraction of "true" activator, [L/Cu^I]⁺.¹⁰¹ Contrary to L/Cu^I, it is *required* that halide is associated to L/Cu^{II}-X since L/Cu^{II} itself does not deactivate radicals and will not allow for sufficient control. Therefore, K_X^{II} should be large.^{69, 101}

In organic media, this is generally not an issue ($K^{II}_X \approx 10^5 \text{ M}^{-1}$).¹⁰² However, in aqueous systems, significant halide dissociation from L/Cu^{II}-X is observed such that $K_X^{II} = 4.4 \text{ M}^{-1}$ for the [Cu^{II}(Me₆TREN)Br]⁺ complex.¹⁰³ To circumvent this, excess halide salts are typically added to shift the equilibrium back to the L/Cu^{II}-X deactivator species.¹⁰⁴ Generally, values of β^{II}_X increase¹⁰⁵ in the order I < Br < Cl < F although iodide⁷²⁻⁷³ and fluoride¹⁰⁵ are inefficient halides in ATRP because of a too weak and too strongly bound ion to L/Cu^{II}, respectively.



Scheme 1.2.3 ATRP equilibrium showing preferred speciation and relative ligand, β^n and halide $\beta^n x$ association, or stability, constants for both the Cu^I and Cu^{II} ions.

As noted above, in the vast majority of organic solvents, the largest fraction of Cu^I species is in the form of the true L/Cu^I activator while the largest fraction of Cu^{II} is in the form of the deactivator, L/Cu^{II}-X. Thus, it becomes possible to formally express the equilibrium constant, K_{ATRP} , thermodynamically as four contributing reactions i) bond homolysis of the R-X alkyl halide, K_{BH} ii) electron affinity of the halogen radical, K_{EA} iii) oxidation of the L/Cu^{II} complex, K_{ET} and iv) association of the halide to the L/Cu^{II} complex, K_X . While these elementary reactions only take place formally and not in practice, one can express the overall equilibrium constant of $K_{ATRP} = K_{BH}K_{EA}K_{ET}K_X$ as shown in **Scheme 1.2.4**.¹⁰⁶ Reactions (i) and (ii) are dependent only on the alkyl halide while reaction (iii) is dependent on the copper catalyst. Reaction (iv) is dependent on the complex, halide species and solvent. The effect of temperature and solvent

has also been studied. More polar solvents¹⁰⁷⁻¹⁰⁹ and higher temperature¹¹⁰⁻¹¹¹ both results in larger values of K_{ATRP} .

$$\mathbf{R} \cdot \mathbf{X} \stackrel{\mathbf{K}_{\mathsf{BH}}}{\longleftarrow} \mathbf{R}^{\bullet} + \mathbf{X}^{\bullet} \qquad (i)$$

$$X^{\bullet} + e^{-} \stackrel{K_{EA}}{\longrightarrow} X^{-}$$
 (ii)

$$\begin{bmatrix} \mathbf{Cu}^{\mathsf{I}}(\mathsf{L}) \end{bmatrix}^{+} \stackrel{\mathsf{K}_{\mathsf{ET}}}{=} \begin{bmatrix} \mathbf{Cu}^{\mathsf{II}}(\mathsf{L}) \end{bmatrix}^{2+} + e^{-} \quad \text{(iii)}$$

$$[Cu^{II}(L)]^{2+} + X^{-} \xrightarrow{K_{X}} [X-Cu^{II}(L)]^{+}$$
(iv)
R-X +
$$[Cu^{I}(L)]^{+} \xrightarrow{K_{ATRP}} R^{\bullet} + [X-Cu^{II}(L)]^{+}$$

Scheme 1.2.4 Thermodynamic representation of the elementary reactions of the ATRP equilibrium. *Reprinted with permission from* ⁹⁹. *Copyright 2007 Elsevier.*

1.2.3.1 Effect of (Macro)Alkyl Halide on KATRP

The structures of (macro)alkyl halides affect *K*_{ATRP} due to different values of *K*_{BH}, more commonly known as the bond dissociation energy (BDE). This is the enthalpy required to homolytically cleave the carbon halogen bond to generate a carbon centered radical and a halogen radical (**Scheme 1.2.4**).¹¹² Generally, the BDE depends on the relative stability of the resulting radical i.e. more stabilized radical results in a smaller BDE.¹¹³ Radicals can be stabilized by either steric, polar and/or resonance effects.¹¹⁴ For example, ethyl α -bromopropionate (EtBriB; **Figure 1.2.1**) has a lower BDFE than methyl α -bromopropionate (MBrP; **Figure 1.2.1**) because the resulting tertiary radical is more stabilized than the secondary radical while both species are stabilized by the ester group via resonance. Ethyl α -bromophenylacetate (EBPA; **Figure 1.2.1**), on the other hand, is a secondary alkyl halide but has both ester and aromatic resonating groups and thus is approximately 10⁴ times more active than EtBriB. Alkyl bromides are "more active" than alkyl chlorides by a factor of 30 due to approximately 10 kcal/mol larger Δ H°. Alkyl iodides have even lower BDFE, however, overall activity in ATRP is related not only to BDFE but also to affinity for the L/Cu^{II} center. Since iodide

coordinates very weakly to L/Cu^{II}, its activity in ATRP is limited.^{112-113, 115} Fluoride, on the other hand, coordinates very strongly to L/Cu^{II} but has significantly larger BFE of the alkyl fluoride making bond homolysis difficult.¹⁰⁵ Values of K_{ATRP} for the tris(2-pyridylmethyl)amine TPMA/Cu^{II} catalytic system in MeCN at 22°C are shown in **Figure 1.2.1**.¹⁰⁶ DFT calculated BDFE's (ΔG°), and enthalpies (ΔH°) at room temperature are shown in **Table 1.2.1**, for comparison.¹¹² Generally, values of K_{ATRP} and BDFE follow the same trend i.e. smaller BDFE results in larger values of K_{ATRP} . Throughout this chapter, larger values of K_{ATRP} typically indicate "more active" system.



Figure 1.2.1 Values of K_{ATRP} for various small molecule alkyl halide initiators for the TPMA/Cu¹ system in acetonitrile (MeCN) at 22°C from ¹⁰⁶. Copyright 2008 American Chemical Society.

Table 1.2.1 Comparison Between KATRP a	nd Thermodynamic !	Parameters of Bond	Homolysis and
Alkyl Halide Reduction.			

		ΔH°	ΔG°	$E^{\Theta}_{RX/R+X-}$
RX (X = Cl, Br)	$K_{\rm ATRP}^{\rm a}$	(kcal/mol) ^b	(kcal/mol)	(V vs. SCE) ^e
MCIP	3.8 x 10 ⁻⁸	69.9	60.4	-0.85
BzCl	4.5 x 10 ⁻⁷	69.4	60.8	-0.73
MBrP	3.2 x 10 ⁻⁷	61.4	51.8	-0.68

BzBr	6.8 x 10 ⁻⁷	60.2	52.5	-0.51
PECI	8.8 x 10 ⁻⁷	68.5	58.8	-0.55
PEBr	4.6 x 10 ⁻⁶	59.9	50.3	-0.49
EBiB	1.0 x 10 ⁻⁵	58.9	49.4	-0.64
AllBr	1.7 x 10 ⁻⁵	56.4	46.9	-
BrPN	1.1 x 10 ⁻⁴	57.2	47.2	-0.49
EBPA	9.2 x 10 ⁻²	С	d	-
VOAc	-	69.5	59.5	-

^aValues of K_{ATRP} were determined experimentally at 22°C in MeCN using the TPMA/Cu^I catalyst, from ¹⁰⁶. ^bCalculated using the 6-31G** basis set, from ¹¹². ^cThe BDFE of ethyl bromophenylacetate (EBPA) was not calculated in the study. ^dValues of K_{ATRP} for 1-bromoethyl acetate (vinyl acetate mimic) have not been measured. ^eExperimentally determined values of $E^{\Theta}_{RX/R+X-}$ at 25°C in MeCN from ¹¹⁶.

Unlike with copper complexes, the redox potentials of alkyl halides cannot be directly measured via cyclic voltammetry (CV). The primary reason is because the electrochemical reduction of R-X is an irreversible process accompanied by a single cathodic peak in CV. However, $E^{\Theta}_{RX/R+X-}$ can be estimated using the thermodynamic cycle shown in **Scheme 1.2.5**. Thus, the first two elementary equilibria in **Scheme 1.2.4** can be combined and represented by the overall redox potential of the alkyl halide, $E^{\Theta}_{RX/R+X-}$. These values are typically in the range of -0.4 V to -1.0 V for alkyl bromides and -0.5 V to -1.2 V for alkyl chlorides which reflects the lower activity of alkyl chlorides in ATRP.

$$\begin{array}{c} \mathsf{RX}_{(\mathrm{s})} & \stackrel{\Delta G_{\mathsf{BH}}}{\longrightarrow} \; \mathsf{R}^{\bullet}_{(\mathrm{s})} \, + \, \mathsf{X}^{\bullet}_{(\mathrm{s})} \\ \\ \hline \\ X_{(\mathrm{s})} \, + \, \mathrm{e}^{-}_{(\mathrm{g})} & \stackrel{\overline{E_{X \cdot / X \cdot}}}{\longrightarrow} \; X^{-}_{(\mathrm{s})} \\ \hline \\ \mathsf{RX}_{(\mathrm{s})} \, + \, \mathrm{e}^{-}_{(\mathrm{g})} & \stackrel{\overline{E_{\mathsf{RX} / \mathsf{R}^{\circ} + X \cdot}}}{\longrightarrow} \; \mathsf{R}^{\bullet}_{(\mathrm{s})} \, + \, \mathsf{X}^{-}_{(\mathrm{s})} \end{array}$$

Scheme 1.2.5 Thermodynamic cycle for the estimation of redox potential of alkyl halides

1.2.3.2 Redox Properties of Halogen Radicals (*K*_{EA})

As shown in **Figures 1.2.4 and 1.2.5**, reduction of halogen radical to the halide anion (K_{EA} or $E^{\Theta}_{X^{\bullet}/X^{-}}$) affects values of K_{ATRP} . In water, these values can be calculated using a thermodynamic cycle in which the overall process is $\frac{1}{2} H_{2(g)} + X^{\bullet}_{(aq)} \leftrightarrow H^{+}_{(aq)} + X^{-}_{(aq)}$.¹¹⁶ This

process can also be extended towards organic systems more commonly employed in ATRP by taking into consideration the free energy of transfer of the respective halide anion from aqueous to organic solvent. These values can be found in the literature for many different organic solvents.¹¹⁷⁻¹¹⁸ Values for $E^{\Theta}_{X^{\bullet}/X^{-}}$ were estimated to be 3.06, 2.03, 1.60 and 1.06 V vs. SCE in MeCN. In DMF, these values were 0.06 to 0.15 V more positive than in MeCN. In aqueous media, values were > +0.3 V compared to MeCN.

1.2.3.3 Redox Properties of Organic Radicals

Redox properties of propagating radicals are important in order to gain a deeper insight into the mechanistic picture of the ATRP catalytic cycle, as well as assess potential side reactions that may occur during the polymerization. Redox potentials have been previously measured using homogeneous redox catalysis according to **Scheme 1.2.6**.¹¹⁹ A precursor, D, is electrochemically reduced to the radical anion, D[•], which can undergo dissociative electron transfer with an alkyl halide resulting in the organic radical, R[•], halide anion, X⁻, with regeneration of the precursor, D. Residual D[•] can then react with the radical either in a coupling reaction to form RD⁻ or in a reduction reaction to form R⁻. The latter is dependent on the redox potential of both D/D[•] and R[•]/R⁻ for which analysis of the competition between coupling and reduction can be used to measure the standard reduction potential or R[•]. These experiments yielded values of $E^{\Theta_{R^\bullet/R^-}}$ for acetonitrile (*CH₂CN), acetate (*CH₂COOEt) and acrylate (CH₃*CHCOOMe) radicals equal to -0.72, -0.63, and -0.66 V vs. SCE, respectively in MeCN. $E^{\Theta_{R^\bullet/R^-}}$ for a wider variety of alkyl radicals was explored using DFT methods in MeCN and DMF.¹²⁰ Although these values varied significantly for *CH₂CN ($E^{\Theta_{R^\bullet/R^-} = -0.42$ V vs. SCE), they matched relatively well for the acrylate radical ($E^{\Theta_{R^\bullet/R^-} = -0.71$ V vs. SCE) and followed a noticeable trend.

$$D + e^{-} \iff D^{+}$$

$$D^{+} + RX \longrightarrow R^{+} + X^{-} + D$$

$$R^{+} + D^{+} \longrightarrow RD^{-}$$

$$R^{+} + D^{+} \iff R^{-} + D$$

Scheme 1.2.6 Contributing reactions used to estimate standard reduction potentials of organic radicals.

In some instances, it is thermodynamically possible that the L/Cu¹ is reducing enough to reduce alkyl radicals to the carbanion which will quickly undergo a chain-breaking process. However, it is important to also consider the kinetics of the reaction in which cases such reducing L/Cu¹ complexes are also attributed with high values of K_{ATRP} which means a relatively low fraction of L/Cu¹. Together with the low concentration of radicals ([R[•]] < 10⁻⁸ M), the overall impact of radical reduction should be small. Nevertheless, in certain systems it should be carefully considered.

1.2.3.4 Effect of Catalyst on KATRP

The catalyst plays a crucial role not only for generation of radicals but also deactivation of radicals. Looking back to **Scheme 1.2.4**, the bottom two elementary equilibria, K_{ET} and K_X , depend on the nature of the catalyst, although solvent has been shown to play a drastic role on K_X . K_{ET} can be conveniently estimated via cyclic voltammetry (CV) in which the redox potential, $E_{1/2}$, of the L/Cu^{1/II} couple can be measured. Theoretically, the more negative $E_{1/2}$, the larger the resulting value of K_{ATRP} . This is because more negative values result in a more stabilized L/Cu^{II} species relative to L/Cu^I and thus will shift the ATRP equilibrium to the right.

The crucial role of the catalyst is demonstrated in the kinetics of ATRP. While a brief introduction will be discussed here, the reader is referred to a recent contribution from our group exploring the in-depth kinetics of ATRP.¹²¹

1.2.4 Analysis of ATRP Catalytic Activity

As will be discussed in-depth throughout this review, the activity of an ATRP catalyst is paramount to not only the choice of initiation system but also the control that is achieved throughout the polymerization. The three main parameters are used to determine the potential effectiveness of a catalyst in ATRP (**Scheme 1.2.3**): the rate coefficient of activation, k_a , the rate coefficient of deactivation, k_d , and the ATRP equilibrium constant, K_{ATRP} which is equal to k_a/k_d .⁶⁹

1.2.4.1 Quantification of KATRP

Perhaps, the most facile way to measure K_{ATRP} is by simultaneous measurement of monomer conversion and [L/Cu^{II}-X] concentration with time.^{106, 122} The rate of polymerization is expressed in **Eq. 1.2.1** for which [R•] is equal to slope of the (ln[M]₀/[M] vs. time) plot divided by k_p . The radical concentration in ATRP can be expressed by rearrangement of the ATRP equilibrium expression (**Eq. 1.2.2**). Thus, K_{ATRP} can be calculated according to **Eq. 1.2.3** since propagation rate coefficients, k_p , are well-known in literature.¹²³⁻¹³⁰ The increase in [L/Cu^{II}-X] is related to the amount of termination and will give the error in the calculated values of K_{ATRP} , which is typically less than 5%.

$$Rate_p = -\frac{d[M]}{dt} = k_p[M][R \cdot]$$
 (Eq. 1.2.1)

$$[R \cdot] = \frac{[L/Cu^{I}]}{[L/Cu^{II} - X]} [RX] K_{ATRP}$$
(Eq. 1.2.2)

$$K_{ATRP} = -\frac{[L/Cu^{II} - X]}{k_p [RX] [L/Cu^{I}]} \frac{d \ln[M]}{dt}$$
(Eq. 1.2.3)

Quantification of K_{ATRP} can also be conducted using either UV-Vis-NIR absorption spectroscopy, stopped-flow techniques or a rotating disk electrode (RDE) to measure the concentration of L/Cu^{II}-X with time which accumulates due to the persistent radical effect (PRE; **Section 1.2.5.1**).¹³¹⁻¹³³ Fitting [L/Cu^{II}-X] vs. time to **Eq. 1.2.4** allows one to linearize the data for which the slope is equal to $2k_t K_{ATRP}^2$, where k_t is the rate coefficient of conventional radical termination.¹³⁴⁻¹³⁶ UV-Vis-NIR is appropriate for less active systems i.e. $K_{ATRP} < 10^{-6}$ while the RDE or the stopped-flow method should be used for more active systems i.e. $K_{ATRP} < 10^{-4}$.

$$F(Y) = \int \frac{[L/Cu^{II} - Br]_t^2}{([RX]_0 - [L/Cu^{II} - Br]_t)^2 - ([L/Cu^{II} - Br]_t)^2} d[L/Cu^{II} - Br] = 2k_t K_{ATRP}^2 t \qquad (Eq. 1.2.4)$$

Values of K_{ATRP} can be *estimated* by conducting cyclic voltammetry (CV) on the L/Cu^{II}-X complex. Under these conditions, CV measures the stability of the L/Cu^{II}-X species relative to the L/Cu^{II}-X species. Since the ATRP equilibrium is dependent on [L/Cu^{II}-X]/[L/Cu^I], these simple experiments can provide significant insight into the activity of the complex. However, to obtain accurate values of K_{ATRP} by this method, one must compare an unknown $E_{1/2}$ to the redox potential and K_{ATRP} of a well-known complex.

1.2.4.2 Quantification of k_a

Analysis of k_a is similar to analysis of K_{ATRP} except, here, the reaction is conducted in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). TEMPO is used to isolate the deactivation reaction by effectively trapping radicals generated by R-X activation by the L/Cu¹ complex. The disappearance of R-X or the accumulation of the TEMPO adduct (R-TEMPO) can be measured via ¹H NMR, GC or HPLC.^{113, 137-142} The accumulation of L/Cu^{II}-X with time can also be measured using UV-Vis-NIR.¹¹¹ These methods are well-suited for less active systems with k_a <10¹ M⁻¹s⁻¹. To analyze more active systems, stopped-flow techniques have been successfully employed.¹⁴³⁻¹⁴⁴ Most recently, potential step chronoamperometry at a RDE can allow for the monitoring of the consumption of L/Cu^{1,145-147} For reactions using very active catalysts or in aqueous media, values of k_a are so large ($k_a > 10^5 \text{ M}^{-1}\text{s}^{-1}$; $t_{1/2} \approx 1 \text{ s}$ assuming second-order conditions) that they can't be accurately measured on the time scale of UV-Vis-NIR or RDE. Thus, CV under catalytic conditions must be employed.¹⁴⁸⁻¹⁵¹ This method involves addition of $L/Cu^{II}-X$ and RX to the reaction mixture in the presence of excess TEMPO. The $L/Cu^{II}-X$ species is electrochemically reduced to the L/Cu^I activator *in situ* which then quickly activates the alkyl halide, causing a dramatic decrease in the cathodic current, all in the diffusion later at the working electrode. Conducting these reactions at various scan rates with different [RX]₀ allows one to simulate the experimental voltammograms which can be fit to a certain value of k_{a} . However, for accurate simulation, a number of parameters such as K_X^{I} , K_X^{II} , k_t , etc. must be known. This method, although less accurate than analysis via UV-Vis-NIR or RDE, is the best method for highly reactive systems with values of $k_a > 10^3 \text{ M}^{-1}\text{s}^{-1}$.

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A large number of activation rate coeficients^{106, 113, 140} are available in the literature for a wide variety of catalysts, alkyl halide, solvents^{110, 139, 152-154} and temperatures.¹¹¹ It should be stressed that many of these values are apparent values (k_a^{app}) without speciation of the L/Cu¹ complex taken into account. Namely, absolute rate constants of activation by [L/Cu¹]⁺ are sometimes larger than apparent values based on [L/Cu¹-X] and thus will also increase values of K_{ATRP} .¹⁴⁷ Nevertheless, values of k_a can range from 10⁻⁵ M⁻¹s⁻¹ to 10⁸ M⁻¹s⁻¹ for a wide variety of systems.

1.2.4.3 Quantification of k_d

Due to reaction rates that approach diffusion-controlled limits, the quantification of deactivation is much more difficult compared to K_{ATRP} or k_a . Thus, k_d is generally calculated from the ratio of k_a and K_{ATRP} ($k_d = k_a/K_{ATRP}$).

One method for estimation of k_d comes from monitoring both monomer conversion and evolution of polymer dispersity as shown in **Eq. 1.2.5a** which does not take into account termination reactions. Recently, **Eq. 1.2.5b** was derived which takes into account termination reactions.¹⁵⁵⁻¹⁵⁷ Values for k_d can be estimated if the values of dispersity (*D*) and M_n are known. Furthermore, conversion can be monitored via NMR while values of k_p are widely available in the literature. In successful ATRP reactions, termination is negligible and thus it can be assumed [RX] = [RX]_0. Finally, if one uses an active catalytic system with large values of K_{ATRP} , it can be assumed that >99% of all soluble copper is in the form of L/Cu^{II}-X and thus, [L/Cu^{II}-X] = [L/Cu^{II}-X]_0. This type of equation is limited to RDRP systems which operate via reversible termination (NMP, OMRP, ATRP, etc.) with negligible termination. It is further simplified if applied to degenerative transfer mechanisms such as RAFT, since CTA initiator also acts as deactivator, transfer agent. For reactions with significant termination, Eq. 1.2.5 should also include a term related to terminated chains.

$$\mathbf{D} = 1 + \frac{1}{M_n} + \frac{k_p [RX]_0}{k_d [L/Cu^{II} - X]} (\frac{2}{conv} - 1)$$
(Eq. 1.2.5a)

$$\mathbf{D} = 1 + \frac{1}{M_n} + \frac{k_p [RX]_0}{k_d [L/Cu^{II} - X]} \left(\frac{2}{conv} - 1\right) + \left(\frac{k_t k_a [L/Cu^{II}]_0}{4k_p k_d [L/Cu^{II} - X]_0}\right) p$$
(Eq. 1.2.5b)

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Radical clock reactions have also been used, although this method relies on accurate parameters such as competitive trapping of radicals by TEMPO, $k_{\text{comb},T}$, as shown in **Eq. 1.2.6**.¹³⁷ A novel method using single pulse-pulsed laser polymerization with electron paramagnetic resonance (SP-PLP-EPR) has been used to accurately measure k_{d} .¹⁵⁸

$$k_d = k_{comb,T} \frac{[TEMPO]}{[L/Cu^{II} - X]} \frac{d[RX]}{d[R - TEMPO]}$$
 (Eq. 1.2.6)

Electrochemical methods have recently been introduced to allow the estimation of k_d . This method makes use of CV in the presence of alkyl halides and concurrent electrochemical simulations of the resulting voltammograms. As with data analysis for k_a , this method requires accurate knowledge of many parameters throughout the catalytic cycle. This method becomes more reliable as more parameters become accurately known.¹⁵⁹

1.2.5.1 Kinetics of "Normal" ATRP

The kinetics of all radical polymerizations follow the general rate law as shown in **Eq. 1.2.1**.¹⁶⁰ In ATRP, the concentration of radicals depends on the equilibrium constant, as shown in **Scheme 1.2.3** and is expressed in **Eq. 1.2.2**.³⁹ Since for a given system (catalyst, solvent, alkyl halide, temperature, etc.) K_{ATRP} remains relatively constant, the rate depends only on the absolute [L/Cu^I]₀:[L/Cu^{II}-X]₀ ratio. Theoretically, one can diminish the concentration of total copper to very small amounts if a [L/Cu^I]₀:[L/Cu^{II}-X]₀ ratio is maintained.¹⁶⁰ In practice, however, this is not achievable and relatively high amounts are required, typically >1000 ppm and in some cases >10,000 ppm. This is because normal ATRP is subject to the persistent radical effect (PRE). ¹³¹⁻¹³²

In ATRP, each activation by L/Cu^I results in the formation of a transient propagating (macro)radical P_n^{\bullet} and the persistent radical L/Cu^{II}-X (d⁹ electron system). The propagating radical has one of two fates, either irreversibly terminates with a second transient radical (bimolecular radical termination) or deactivates with L/Cu^{II}-X (i.e. reversibly terminates). Since persistent radicals do not self-terminate, each transient radical termination event results in the

accumulation of L/Cu^{II}-X. This causes a gradual decrease in the [L/Cu^{II}:[L/Cu^{II}-X] ratio and thus, according to **Eq. 1.2.2**, decrease in propagation rate. This is the main reason if very low catalyst loadings are used in normal ATRP, only a small fraction of chains need to be terminated to effectively halt the reaction. To overcome this obstacle, stoichiometric amounts of catalyst relative to [RX]₀ were traditionally required.

Since the rate of polymerization is dependent on *K*_{ATRP}, the rate of polymerization can be increased by using a "more active" system. This could be done by increasing temperature or pressure, conducting the reaction in a more polar solvent or by using a more active catalyst. However, it is important to note that, since in normal ATRP, the reactions start from a relatively large amount of L/Cu¹ activator, the use of a very active catalyst can be severely detrimental. This is due to a very fast rate of activation of alkyl halide which causes an initially large concentration of radicals. This leads to significant amount of termination at the onset and thus, due to the PRE, the [L/Cu¹]:[L/Cu¹¹-X] ratio has been decreased to the point that limited conversions are reached.

Due to the susceptibility of normal ATRP to the PRE, only moderately active catalysts could be used. This puts a severe limitation on the monomer scope of normal ATRP since less active monomers require more active catalysts.

1.2.5.2 Kinetics of ATRP with Activator Regeneration

ATRP with activator regeneration, also known as "low ppm" ATRP, significantly improved some fallbacks of traditional ATRP discussed above. In low ppm ATRP, the reaction mixture contains only the air-stable L/Cu^{II}-X species, thus making preparation significantly easier. Low ppm systems employ various reduction mechanisms to (re)generate the L/Cu^{II} activator from the L/Cu^{II}-X species which builds up due to the PRE (**Scheme 1.2.7**).¹⁶¹ This allows for the PRE to be compensated for and prevent rate retardation. Thus, significantly lower catalyst loadings can be used in these systems.

Because the initial reaction mixture contains no activator, many low ppm systems exhibit a short induction period. In this time, K_{ATRP} is being established until the point where

enough L/Cu^I is generated *in situ* such that the [L/Cu^I]:[L/Cu^{II}-X] allows for a steady-state of radicals to be established and polymerization to commence.



Scheme 1.2.7 Mechanism of ATRP with activator regeneration

One key difference of low ppm systems is that the kinetics follow the steady-state approximation, similar to conventional radical polymerization or RAFT,⁴⁴⁻⁴⁶ which allows for a dynamic $[L/Cu^{I}]/[L/Cu^{II}-X]$ ratio that depends on [RX], $[R^{\bullet}]$ and K_{ATRP} . The steady-state approximation assumes that the radical concentration is constant with time. In normal ATRP, this ratio is relatively fixed depending on $[L/Cu^{I}]_{0}$ and $[L/Cu^{II}-X]_{0}$. Therefore, the rate of radical generation (R_g) is equal the rate of radical termination (R_t), as shown in **Eq 1.2.7**. In most low ppm ATRP systems, the rate-determining step (RDS) of radical generation is the reduction of L/Cu^{II}-X to L/Cu^I, the latter of which quickly generates a radical via activation of alkyl halide. Each specific low ppm system employs the use of a unique reduction mechanism and thus the rate law of radical generation depends on the system used but can generally be expressed by Eq, 1.2.8 where k_{red} is the rate coefficient of reduction and [Y] is a species involved in the reduction mechanism. Since the RDS in low ppm systems is the reduction of L/Cu^{II}-X, most systems also depend on [L/Cu^{II}-X]₀. As will be discussed later, a special case arises in initiators for continuous activator regeneration (ICAR) ATRP which employs conventional radical initiators for which the rate of polymerization does not depend on [L/Cu^{II}-X]₀.^{160, 162-163} Furthermore, in supplemental activator and reducing agent (SARA) ATRP, the rate of polymerization depends on both activation of alkyl halides by Cu⁰, k_{a0} , and comproportionation of Cu⁰ with [L/Cu^{II}-X]₀,

 k_{comp} .^{145, 164-168} Bimolecular radical termination is generally assumed to be the predominate loss of radicals and is expressed by **Eq. 1.2.9** where k_t is the rate coefficient of radical termination and [R[•]] is the radical concentration at a given time. The coefficient of 2 is due to the fact that each termination event consumes two radicals. A special case arises with very active ATRP systems in the polymerization of acrylates for which a catalyzed radical termination (CRT) process is the predominate pathway of radical loss.¹⁶⁹⁻¹⁷¹ The general case of radical loss only by bimolecular radical termination will be considered at this stage.

$$\frac{d[R]}{dt} = R_g - R_t = 0$$
 (Eq. 1.2.7)

$$R_g = k_{red} [L/Cu^{II} - X][Y]$$
(Eq. 1.2.8)

$$R_t = 2k_t [R \cdot]^2$$
(Eq. 1.2.9)

$$[R \cdot] = \sqrt{\frac{k_{red}[L/Cu^{II} - X][Y]}{2k_t}}$$
(Eq. 1.2.10)

Inserting Eq. 1.2.8 and 1.2.9 into Eq. 1.2.7 and solving for [R[•]] leads to Eq. 1.2.10 which is the generalized steady-state radical concentration for ATRP with activator regeneration. As noted above, a special case is ICAR ATRP (and SARA ATRP) which does not follow this generalized expression and will be discussed later. Notice that since the rate of termination is dependent on [R[•]]², the rate of low ppm ATRP generally scales with a square-root dependence on [L/Cu^{II}-X] and [Y] and inverse square root on k_t .

At this point it is imperative to briefly discuss the importance of the dynamic equilibrium that defines the $[L/Cu^{I}]:[L/Cu^{II}-X]$ ratio that is exhibited in low ppm ATRP. The level of control in ATRP is related to the rate of deactivation, $R_d = k_d[R^\bullet][L/Cu^{II}-X]$. The faster the rate of deactivation, the more control will be exhibited in a given ATRP system. In traditional ATRP, deactivation is promoted via initially added L/Cu^{II}-X deactivator. However, in low ppm system, the [L/Cu^{II}-X] at a given point is determined by [RX], [R•] and K_{ATRP} . Specifically, larger values of K_{ATRP} will give a greater fraction of L/Cu^{II}-X deactivator and more efficient deactivation and control.

This becomes apparent when comparing three different catalysts in ICAR ATRP as shown in **Figure 1.2.2**. These three common catalytic systems span over 3000-fold differences in activities and include 2,2'-bipyridine (bpy; $K_{ATRP} = 3 \times 10^{-9}$), N,N,N',N",N" – pentamethyldiethylenetriamine (PMDETA; $K_{ATRP} = 8 \times 10^{-8}$) and tris(2-pyridylmethyl)amine (TPMA; $K_{ATRP} = 1 \times 10^{-5}$). Under low ppm ATRP conditions, bpy is an inefficient catalyst because values of K_{ATRP} are not large enough to provide a sufficient amount of deactivator. Moving towards relatively more active catalysts such as PMDETA and TPMA, the dynamic equilibrium results in a larger fraction of L/Cu^{II}-X and thus gives better control. On the other hand, bpy works well in traditional ATRP because the [L/Cu^I]:[L/Cu^{II}-X] ratio is predefined by initial setup. Under similar normal ATRP conditions, more active catalysts will fail because the activity is too large such that termination is prevalent and the reaction falls victim to the PRE.

Thus, the reaction conditions need to be carefully chosen to match not only catalyst and monomer, but also the initiation system i.e. normal initiation or activator regeneration. In order to achieve a high degree of control in traditional ATRP, less active catalysts are required. However, this presides with significantly high catalyst loadings in order to overcome the PRE. On the other hand, one can use more active catalysts in ATRP with activator regeneration which exhibits a dynamic equilibrium for which the [L/Cu^{I]}:[L/Cu^{II}-X] ratio is defined by [R[•]], [RX] and K_{ATRP} . It is therefore theoretically possible to use as active catalyst as possible under low ppm conditions and in fact, this should provide even better control due to a higher fraction of deactivator.¹²¹



Figure 1.2.2 Simulation of low ppm ATRP of acrylates using three different ligands with copper catalysts.

The following discussion will review the history of catalysts in ATRP ranging from seminal catalysts used in "normal" ATRP which required >10,000 ppm of catalyst to the most recent catalysts with extremely high reactivity. These have allowed for catalyst loadings < 10 ppm while retaining excellent control over the polymerization in systems with activator regeneration.

1.3 Development of Ligands for ATRP Catalysts

Over the course of almost 25 years, a large number of ligands have been employed in copper-catalyzed ATRP with the most successful being nitrogen based. This section will review the ATRP activity of copper catalysts. Specifically, kinetic and thermodynamic parameters will be reviewed as well as a brief overview of the coordination chemistry of these ATRP catalysts.

1.3.1 Bipyridine-based Ligands

2,2'-Bipyridine (bpy) is a bidentate pyridine-based ligand which has been used as ligand for a wide array of applications (**Figure 1.3.1**) such as ATRA, photocatalysis and click-chemistry. In ATRP, it is generally accepted that both the Cu¹ and Cu¹¹ ions are coordinated by two bpy ligands to form the complexes, [Cu¹(bpy)₂]⁺ and [Cu¹¹(bpy)₂X]⁺, respectively. Indeed, this was supported by both solid-state¹⁷²⁻¹⁷³ and solution studies. Single crystal X-ray diffraction
revealed that [Cu^I(bpy)₂]⁺ had a distorted tetrahedral geometry. In some cases, a Cu-X bridged complex, [Cu^I(bpy)X₂]₂, has been observed with the metal centers possessing a distorted tetrahedral geometry.¹⁷⁴ In non-polar solutions, it was proposed that the main species is the bridged [Cu^I(bpy)X₂]₂ species based on UV-Vis-NIR experiments.¹⁷⁵ Extended X-ray absorption fine structure (EXAFS) indicated the presence of the [Cu^I(bpy)₂][Cu^IBr₂] species in styrene and methyl acrylate.¹⁷⁶ However, in polar media, the [Cu^I(bpy)₂]⁺ species was found to be most prevalent.¹⁷⁷ This speciation is important to take note of when conducting ATRP in bulk monomer which is generally non-polar.

The cupric complex, [Cu^{II}(bpy)₂X]⁺ was found to adopt a near perfect trigonal bipyramidal geometry by X-ray diffraction,¹⁷⁸ consistent with Cu^{II} ions preferring 5-coordinate geometries. Electron paramagnetic resonance (EPR) and UV-Vis studies have indicated that this geometry is retained in solution.



Figure 1.3.1 Structures of 2,2'-bipyridine (bpy)-based ligands used in ATRP.

Cyclic voltammetry was conducted on the $[Cu^{II}(bpy)_2X]^+$ complex in acetonitrile at room temperature. A (quasi)reversible peak was observed with a redox potential $E_{1/2} = +20$ mV vs. saturated calomel electrode (SCE).¹⁰⁶ Model studies were conducted using ethyl bromoisobutyrate (EBiB) as alkyl halide for which $K_{ATRP} = 3.9 \times 10^{-9}$. Model studies of activation conducted at 35°C showed $k_a = 9.2 \times 10^{-2}$ M⁻¹s⁻¹ for EBiB in MeCN giving $k_d = 2.3 \times 10^7$ M⁻¹s⁻¹.¹⁰⁶ It should be stressed that these values were obtained using CuBr as the Cu¹ salt and thus these values are only apparent values and are likely underestimated. This is due to competitive complexation of Br⁻ to the Cu¹ center which forms an inactive activator complex. In order to better solubilize catalysts in bulk, aliphatic groups were added to the pyridine ring (Figure 1.3.1). 5-Nonyl (dNbpy) has perhaps been the most studied of these substituted bpy-based ligands. Under otherwise identical conditions as unsubstituted bpy, CV was conducted and gave $E_{1/2} = -50$ mV vs. SCE which is 70 mV more negative than unsubstituted bpy. Since approximately every 59 mV changes K_{ATRP} by one order of magnitude, this would indicate that dNbpy is \approx 20 times more active than bpy. Indeed, $K_{ATRP} = 3.0 \times 10^{-8}$ and $k_a = 6.0 \times 10^{-1} \text{ M}^{-1} \text{s}^{-1}$ which are 9 times and 7 times larger than bpy, respectively. Interestingly, $k_d = 2 \times 10^7 \text{ M}^{-1} \text{s}^{-1}$ which would indicate $E_{1/2}$ has little effect on k_d but rather affects k_a to a much greater extent. The addition of solubilizing aliphatic chains allowed for the first homogeneous ATRP in bulk and exhibited control that was only achieved, at the time, via ionic polymerization.

1.3.2 Substituted Bipyridine-based Ligands

Structural modification of pyridine ring substituents allowed the investigation of electronic effects on ATRP, as has been done for other applications such as asymmetric catalysis,¹⁷⁹ pH sensitivity¹⁸⁰ and photocatalytic activity.¹⁸¹ . As shown in **Figure 1.3.2**, five different ligands were used with various electron donating groups in the 4 and 4' position (EDG; -NMe₂, -OMe, -dN, -Me), unsubstituted bpy and an electron withdrawing group (EWG; -Cl).¹⁸²



Figure 1.3.2 (Top) Bipyridine (bpy) ligands substituted with various electron donating or withdrawing groups and (bottom) normal ATRP of MA using these catalysts.

More electron donating groups (Cl < H < Me < OMe < NMe₂)¹⁸³ gave progressively more negative redox potentials. These five ligands span 583 mV which corresponds an almost 10,000,000 difference in ATRP reactivity. Based on redox potential, the NMe₂-bpy catalyst should have similar reactivity to some of the most active ATRP catalysts.

The substituted bpy catalysts were explored in the normal ATRP of MA and MMA. Specifically, the most active catalyst, $[Cu^{I}(NMe_{2}-bpy)_{2}]^{+}$ resulted in the fastest polymerization while $[Cu^{I}(bpy)_{2}]^{+}$ and $[Cu^{I}(CI-bpy)_{2}]^{+}$ showed virtually no conversion after 25 hours. However, $[Cu^{I}(OMe-bpy)_{2}]^{+}$ was the most successful catalyst. This is because K_{ATRP} is large enough to efficiently catalyze atom transfer but was not too active to terminate a significant number of chains. With NMe₂-bpy much higher than theoretical molecular weights were obtained which indicated poor initiation efficiency from significant amounts of termination at the onset of the reaction. This could be avoided by initial addition of L/Cu^{II}-X deactivator complex at the beginning of the reaction to suppress termination. Catalyst loadings could be decreased to 50 ppm in normal ATRP using the NMe₂-bpy catalyst. This further shows the importance of matching catalyst activity to initiation system. Encouragingly, this work also showed the potential to impose EDG to other ligand scaffolds used in copper catalyzed ATRP in order to increase catalyst activity (*vida supra*).

1.3.3 Linear Polydentate Amine Ligands

The use of simple amines as ligands for copper catalysts in ATRP was first shown in 1997.¹⁸⁴ These ligands are relatively inexpensive and easily accessible compared to bpy and bpy derivatives, the latter of which are not commercially available. Furthermore, copper(I) complexes with many amine-based ligands have shown to be relatively reducing and therefore should be more active in ATRP.¹⁸⁵⁻¹⁸⁶ Initially, three polydentate amines were used in ATRP: tetramethylethylenediamine (TMEDA), N,N,N',N',N' – pentamethyldiethylenetriamine (PMDETA) and 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA) (**Figure 1.3.3**). These three ligands also allowed for the effect of ligand denticity on ATRP.



Figure 1.3.3. Linear polydentate amines initially used in ATRP

Cu¹ complexes with TMEDA exhibit a near perfect tetrahedral geometry and each Cu¹ ion is coordinated by two TMEDA ligands.¹⁸⁷ Using equimolar amounts of TMEDA and CuBr, bridged complexes were isolated. Interestingly, this shows very similar behavior to bpy-based cuprous salts although with very different types of N-donors, as discussed above. Model studies for ATRP activity indicated $K_{ATRP} = 2.0 \times 10^{-6}$ and $k_a = 1.1 \times 10^{1}$ M⁻¹s⁻¹ which would indicate a system which is almost 100 times more active than the unsubstituted bpy-based systems.

TMEDA was first used for the bulk polymerization of MA and St and solution polymerization of MMA. The MA and MMA polymerizations exhibited linear kinetics and increasing molecular weights with conversion and showed D < 1.4. On the other hand, St gave a steadily increasing rate of polymerization indicating a higher concentration of radicals at longer reaction times. An initially high D = 2.5 at 20% conversion was observed which then decreased to 1.3 at 50% but then jumped again to 2.15 at 95% conversion. Compared to bpy and substituted bpy derivatives, the reaction using TMEDA was not only slower but was less effective at controlling the molecular weight.

Cu^I complex with PMDETA was shown to have complex speciation. Due to the tridentate nature of the ligand, the fourth coordination site at the Cu^I center is generally occupied by halide, solvent or monomer. Indeed, upon crystallization in polymerization media, olefin complexes of methyl acrylate, methyl methacrylate and styrene were able to be isolated and characterized as $[Cu^I(PMDETA)(M)]^+$ (M = monomer).¹⁸⁸ Complexes of PMDETA with CuBr₂ form neutral complexes as indicated by solid state studies. Upon completion of a polymerization the Cu^{II} species was precipitated and crystalized and found to be $[Cu^{II}(PMDETA)Br_2]$ by X-ray diffraction.¹⁸⁹ CV on the $[Cu(PMDETA)Br_2]$ complex gave $E_{1/2} = -80$

mV vs. SCE. Model studies for ATRP activity for EBiB indicated $K_{ATRP} = 7.5 \times 10^{-8}$ and $k_a = 2.7 \text{ M}^{-1}$ ¹s⁻¹. Surprisingly, these values are lower than bidentate TMEDA.

The PMDETA ligand was then used under similar polymerization conditions as TMEDA. The rate of polymerization for both MA and St were markedly increased compared to both bpy/derivatives as well as TMEDA. Furthermore, due to the tridentate nature of the ligand, a 1:1 ratio between PMDETA and Cu were required compared to bidentate bpy and TMEDA which required a 2:1 ratio. The kinetics, molecular weights and D can be seen in **Figure 1.3.4**. Low D's were exhibited for conversions < 70%. At higher conversions, the D increased for MA and St most likely due to termination via combination. The lower D compared to bpy under similar conditions was attributed to the decreased steric congestion around the Cu^{II} cationic center and thus facilitated a more efficient deactivation process.



Figure 1.3.4 A) Kinetics B) molecular weights and C) D for the normal ATRP of MA, MMA and St using PMDETA. Reprinted with permission from Ref ¹⁸⁴.

HMTETA is a tetradentate ligand which coordinates to Cu¹ through all four nitrogen atoms in a distorted tetrahedral geometry. This complex can be either cationic or neutral depending on the halide used.¹⁹⁰⁻¹⁹¹ Similar to other Cu^{II} complexes discussed above, $[Cu^{II}(HMTETA)Br]^+$ is a cationic complex with distorted trigonal bipyramidal geometry. Interestingly, redox properties of the HMTETA complex gave $E_{1/2} = -20$ mV which would indicate reactivity that is similar to dNbpy. Indeed, K_{ATRP} was found to be 1.1×10^{-8} with rate coefficients of activation $k_a = 1.4 \times 10^{-1}$ M⁻¹s⁻¹ which corroborate the similar ATRP reactivity between the two complexes. Reactions involving HMTETA as the ligand were conducted and displayed similar kinetics and molecular weights as PMDETA. Contrary to PMDETA, the D values for MA, MMA and St were all less than 1.15 at 75% conversion. Compared to bpy and derivatives of bpy, PMDETA and HMTETA show a significantly increased rate of polymerization as well as better control over molecular weights and D. The increase in the rate was attributed to lower redox potentials which shifted the ATRP equilibrium to the right to give a higher concentration of propagating radicals.

1.3.4 Tetradentate Tripodal Amine Ligands

The use of tri- and tetradentate linear amines as ligands for copper catalyzed ATRP exhibited well-controlled polymerizations of MA, MMA and St (Section 1.3.3). However, these reactions were generally conducted at higher temperature (>90°C) in order to increase both the catalyst solubility and activity of the system. Since activity seemed to increase upon moving towards higher denticity ligands, a ligand based upon methylated tris(2-aminoethyl)amine (TREN) was used. Methylation of the primary amino groups of TREN resulted in tris[2-(dimethylamino)ethyl]amine (Me₆TREN).¹⁹²⁻¹⁹³ Contrary to PMDETA and HMTETA which are linear amines, Me₆TREN has a tetradentate, tripodal structure in that the three dimethylaminoethyl are attached to a central anchoring nitrogen as shown in **Figure 1.3.5**.





Structural studies of Cu¹ complexes chelated by Me₆TREN have indicated that the Cu¹ cation is coordinated by four nitrogen atoms with the axial nitrogen possessing a slightly longer

bond (Cu^I-N_{ax} = 2.200 Å) than the equatorial bonds (Cu^I-N_{eq} = 2.122 Å) as shown in **Figure 1.3.5**. It is best described as distorted trigonal bipyramidal because of the weak interaction with the perchlorate anion (omitted for clarity), although it is most likely this is completely dissociated in solution.¹⁹⁴ In solution it has been proposed that this species exists in equilibrium with the neutral species [Cu^I(Me₆TREN)Br] as well as with a species in which one arm is dissociated from the Cu^I center.¹⁹⁶ The [Cu^{II}(Me₆TREN)Br]⁺ deactivator complex possesses a distorted trigonal bipyramidal geometry^{178, 197} in the solid state.

Assessment of activity of the Me₆TREN-based catalyst in ATRP shows a wide range of parameters across the literature depending on the technique used and the speciation of the catalyst. For example, using CuBr as the cuprous salt gives $K_{ATRP} = 1.5 \times 10^{-4}$ and $k_a = 2.3 \times 10^2$ M⁻¹s⁻¹ for EBiB in MeCN at room temperature.¹⁰⁶ However, these values are apparent values and not the true values since the presence of halides forms the neutral [Cu¹(Me₆TREN)Br] complex which is less efficient for ATRP activation than [Cu¹(Me₆TREN)]+. More recently, it was found that using [Cu¹(MeCN)₄][PF₆] as the cuprous salt gave a significantly larger value $k_a = 1.2 \times 10^4$ M⁻¹s⁻¹ under otherwise similar conditions.¹⁴⁶

ATRP using Me₆TREN as a ligand was initially conducted in bulk MA using ethyl 2bromopropionate (EBrP) as the ATRP initiator.¹⁹³ In just 15 minutes at room temperature, the reaction reached 85% conversion to give well controlled pMA-Br ($M_n = 17,000$; D = 1.18). Catalyst loadings were decreased from 100 mol% to 10 mol % vs [RX]₀ and showed relatively fast polymerization times (>60% conversion in < 1 hour) with a high degree of control over the polymerization (D < 1.10) as shown in **Figure 1.3.6**. Contrary to Me₆TREN, TREN was a poor ligand for bulk ATRP of MA exhibiting initiation efficiencies of 0.2% with limited conversions due to poor solubility of the [Cu(TREN)]⁺ complex. Comparing Me₆TREN to PMDETA and dNbpy, Me₆TREN exhibits a much faster rate of polymerization for acrylates. In just 1 hour, the system using Me₆TREN reached 70% conversion compared to 25% and 12% for PMDETA and bpy, respetively (**Figure 1.3.6C**). For the first time, a catalytic system was developed that was active enough to polymerize acrylates at room temperature even using as little as 10 mol% catalyst relative to initiator.



Figure 1.3.6 A) Kinetics and B) molecular weights and \mathcal{D} vs. conversion for the normal ATRP of MA in bulk using Me₆TREN-base catalysts at room temperature. C) Comparison of the Me₆TREN, PMDETA and dNbpy-based systems under identical conditions.

1.3.5 Picolyl Amine-based Ligands

The use of pyridine-based ligands for ATRP catalysts is well-documented with the seminal reports using bipyridine (bpy) and various para-substituted derivatives (**Section 1.3.1**). After the success of the tetradentate, tripodal amine ligand, Me₆TREN, the use of linear and branched pyridine-based structures was then explored.¹⁹⁸

The tridentate, N, N-bis(2-pyridylmethyl)octylamine (BPMOA)-based catalyst was first used as an ATRP catalyst for the polymerization of MA, MMA and styrene. ¹⁹⁹ Initially, normal ATRP was conducted and gave a homogeneous mixture with a yellow color, indicative of [Cu^I(BPMOA)Br][Br] complex. It was noted that throughout the course of the polymerization, the solution turned gradually green indicative of the formation of [Cu^{II}(BPMOA)X]⁺. With all three monomers, polymerization exhibited kinetics and an increase in molecular weights with conversion as shown in **Figure 1.3.7**. The molecular weights were significantly higher than predicted for the MMA polymerization and was attributed to the fast termination at the onset of the reaction. The *Đ* values of all three systems were < 1.2.



Figure 1.3.7 A) Kinetics, B) molecular weights and C) D of the normal ATRP of MA (50°C), MMA (50°C) and St (110°C) using BPMOA-based catalyst. Reprinted with permission from Ref ¹⁹⁸.

Tris(2-pyridylmethyl)amine (TPMA) is perhaps one of the most well-utilized and studied ligand in copper catalyzed ATRP.^{193, 200} As shown in **Figure 1.3.8**, the Cu¹ activator complex adopts a distorted trigonal bipyramidal geometry due to the coordination of an acetonitrile molecule. Further studies have indicated that this is formally a 4-coordinate distorted tetrahedral complex due to the Cu¹-N_{ax} bond of 2.411 Å which can be considered non-bonding. The deactivator complex adopts an almost perfect trigonal bipyramidal geometry for which the Cu^{II} cation is coordinated by all four nitrogen atoms of the TPMA ligand with a bromide coordinated in the axial position. One important aspect relevant to ATRP is the reorganization energy required upon oxidative halogen atom transfer.²⁰¹ Minimal reorganization is ideal so that deactivation is fast and efficient without the need for structural changes between Cu¹ and Cu^{II} centers.²⁰¹



Figure 1.3.8 Molecular structures of the [Cu^I(TPMA)(MeCN)]⁺ and [Cu^{II}(TPMA)Br]⁺complexes.

Similar to Me₆TREN-based systems, the TPMA catalytic system have been extensively quantified. Indeed, a similar situation arises with regards to the presence or absence of halides. CV showed a relatively reducing complex with $E_{1/2} = -240$ mV vs. SCE which indicates this complex should be around 50,000 times more active than bpy. Values of K_{ATRP} using CuBr were equal to 9.6 x 10⁻⁶ with $k_a = 3.1 \times 10^1$ M⁻¹s⁻¹ for EBiB in MeCN.¹⁰⁶ However, using [Cu^I(MeCN)₄][PF₆] gave values $k_a = 4.5 \times 10^3$ M⁻¹s⁻¹ which is 150 times larger than previously measured due to a larger fraction of [Cu^I(TPMA)]⁺ due to the lack of halides.^{146, 202}

TPMA was initially used as a ligand for the normal ATRP of MA, MMA and St in bulk. Interestingly, no conversion was observed for MMA while MA and St showed 80% in 1 hour and 4 hours, respectively (**Figure 1.3.9**). TPMA was an efficient catalyst using as little as 20 mol% relative to alkyl halide initiator exhibiting both linear kinetics and evolution of molecular weights with conversion. Furthermore, \mathcal{P} <1.10 was observed for both MA and St. For the polymerization of MMA, it was likely that, under the given conditions, significant radical termination at the onset of the reaction led to decreased initiation efficiency. The polymerization with TPMA exhibited some of the most well-controlled systems at this point in the history of ATRP. TPMA-based ligands were also successfully employed in copper-catalyzed ATRA.²⁰³



Figure 1.3.9 A) Kinetics, B) molecular weights and C) D of the normal ATRP of MA (50°C), MMA (50°C) and St (110°C) using BPMOA-based catalyst.

1.3.6 Substituted TPMA Ligands

After the understanding of how electron donating and withdrawing groups affect the activity of bpy-based ligands in copper catalyzed ATRP processes, other pyridine-based ligands were synthesized with electron donating groups. It was shown that TPMA (**Section 1.3.5**) had significant advantages in both robustness and activity over bpy. Therefore, in order to further increase the activity of the TPMA-based catalyst, each pyridine ring was substituted with three electron donating groups: 3,5-dimethyl and 4-methoxy to give tris[(3,5-dimethyl-4-methoxy)methyl]amine (TPMA*³), as shown in **Scheme 1.2.8**.



Scheme 1.2.8 Synthesis of tris[(3,5-dimethyl-4-methoxy)methyl]amine (TPMA*3).

CV of the $[Cu^{II}(TPMA^{*3})]^{2+}$ complex allowed for calculation of $\beta^{II}/\beta^{I} = 2.4 \times 10^{20}$ compared to the unsubstituted $[Cu^{II}(TPMA)]^{2+}$ complex which was $\beta^{II}/\beta^{I} = 3.2 \times 10^{17}$ where β^{II} and β^{I} are the ligand association constants for Cu^{II} and Cu^I, respectively. These values indicated that the L/Cu^{II} oxidization state is 1000 times more stabilized using TPMA^{*3} than TPMA. Furthermore, the measured $E_{1/2} = -420$ mV is 180 mV more negative than TPMA and 120 mV more negative than Me₆TREN which suggested unprecedented ATRP reactivity. K_{ATRP} for MBrP in MeCN at 25°C was quantitated using stopped-flow techniques. It was determined that K_{ATRP} = 1.2 x 10⁻⁴ with activation rate coefficients $k_a = 8.4 \times 10^3 M^{-1} s^{-1} .^{144}$ This k_a value is 2000 times larger than for TPMA which further suggested unprecedented activity. A full description of the $[Cu^{I}(TPMA^{*3})Br]$ and $[Cu^{II}(TPMA^{*3})Br]^{+}$ complexes in solid-state and in solution will be given in Chapter 5.

The TPMA^{*3}-based catalyst was then utilized in ATRP with various initiation systems for the polymerization of MA.¹⁴⁴ In normal ATRP, low conversion (13.5% in 5 hours) was observed due to the extremely high reactivity of the [Cu^I(TPMA^{*3})]⁺ complex which terminated a significant number of chains at the onset of the reaction. Therefore, ATRP systems with activator regeneration were investigated. Using ARGET ATRP with Sn^{II}(EH)₂ as a reducing agent and *e*ATRP, a well-controlled polymerization was observed with catalyst loadings as low as 25 ppm resulted in molecular weights in-line with theoretical and D < 1.10. ICAR ATRP was then studied at various catalyst concentrations (**Figure 1.3.10 A-B**). With 100, 50, 25 and 10 ppm of catalyst relative to monomer, linear kinetics were observed with comparable slopes at steady state, consistent with the kinetics of ICAR being independent on [L/Cu^{II}-X]₀. Although the kinetics were not affected by catalyst loading, the control over MWD was found to be higher upon decreasing the catalyst loadings, indicative of slower deactivation.

Comparing TPMA^{*3} to TPMA under otherwise identical conditions, the control using TPMA^{*3}-based catalyst was significantly improved (**Figure 1.3.10C**). This is because *K*_{ATRP} for the TPMA^{*3}-based system is approximately 1000 times larger. Due to the dynamic equilibrium achieved in activator regeneration systems (ICAR, ARGET, *e*ATRP, etc.), the [L/Cu^{II}-X]/[L/Cu^I] ratio at steady-state much larger for TPMA^{*3} than for TPMA. This gives a larger fraction of deactivator in solution at the same rate of polymerization and thus deactivation, and control, is more efficient.



Figure 1.3.10 (A) Kinetics and (B) molecular weights and D for the ICAR ATRP of MA using the highly active TPMA^{*3}-based catalyst and C) comparing it to the TPMA-based catalyst (red).

This study resulted in a catalyst that was one million times more active than seminally used bpy catalysts and was shown to be efficient for various ATRP systems with activator regeneration. Normal ATRP failed due to the extremely high reactivity of the [Cu^I(TPMA^{*3})]⁺ activator, once again, alluding to the importance of correlating initiation system with catalyst.

1.3.7 Hexadentate Ligands

The success of highly active catalytic systems based on TPMA and Me₆TREN in normal, reverse, SI&NI, AGET, ARGET and ICAR ATRP lead to a decreased output of new ATRP catalysts

since, at the time, their need was not yet apparent. However, in 2006, a new ligand, N,N,N',N'tetrakis(2-pyridylmethyl)ethylenediamine (TPEN) (**Figure 1.3.11**) was studied.²⁰⁴ The hexadentate TPEN ligand contains two aliphatic amines and four pyridyl species and is therefore a hybrid between BPMOA and TPMA.²⁰⁵⁻²⁰⁶ X-ray diffraction studies indicated that in the solid state the Cu¹ complex was a binuclear species in which each TPEN ligand coordinated 2 eq. of CuBr (**Figure 1.3.11 middle**) in a distorted tetrahedral geometry.

On the other hand, isolation of the Cu^{II} species from a polymerization mixture indicated a monomeric species for which each Cu^{II} ion was coordinated by one Br⁻ anion in the axial plane and three pyridinic and one aliphatic nitrogen in the equatorial plane. The second aliphatic nitrogen was weakly coordinated in the second axial coordination site resulting in a distorted octahedral geometry, consistent with the absorption spectrum showing only one peak in the $d \rightarrow d$ transition region.²⁰⁷ ¹H NMR analysis of the Cu^{II} species indicated an equilibrium between monomeric and dimeric species.



Figure 1.3.11 Structure of TPEN ligand and solid-state structures of the $[Cu^{I}_{2}(TPEN)Br_{2}]$ and $[Cu^{II}(K^{5}-TPEN)Br]^{+}$ complex. Reprinted with permission from Ref ²⁰⁴.

The relationship between redox potential and activity in $E_{1/2}$ was clear, in which a linear relationship between $E_{1/2}$ and K_{ATRP} was observed; i.e. a more negative $E_{1/2}$ resulted in higher ATRP activity.²⁰⁸⁻²¹⁰ Values of k_a and K_{ATRP} were found to be $1.1 \times 10^1 \text{ M}^{-1}\text{s}^{-1}$ and 2.0×10^{-6} , respectively. This value of K_{ATRP} is approximately 500 and 30 times larger than those of bpy and PMDETA, respectively, while being 5 and 100 times smaller than those of the TPMA and Me₆TREN-based catalysts for the reaction using EBiB at 25°C.

The normal ATRP of MA using TPEN was significantly faster than both the TPMA and Me₆TREN-based systems under otherwise identical conditions. The reactions with Me₆TREN reached only 40% conversion in 16 hours while the TPEN-based system reached the same conversion in only 4 hours. Use 0.1 mol % of the TPEN-based catalyst resulted in a slower although controlled reaction which was able to reach much higher conversions (>50%) than its TPMA and Me₆TREN counterparts at the same catalyst loadings. Thus, the TPEN-based system has significant activity to polymerize MA under relatively benign conditions but is not active enough to quickly terminate chains to halt the polymerization via the PRE. MMA and St were also polymerized under normal ATRP conditions using as little as 6 ppm catalyst. This ligand was later extended towards use in ATRA where the solvent was found to play a significant role in the efficiency of deactivation.²⁰⁷

1.3.8 Other Ligands

The previously discussed catalysts are among the most successful and well-studied copper-based ATRP catalysts. However, other catalysts have been explored but have not shown the same success as others. This section will briefly review catalysts that show lower activity in ATRP systems.





1.3.8.1 Pyridineimine Ligands

After Matyjaszewski *et al* developed the bpy- and substituted bpy-based catalysts, Haddleton *et al*²¹¹⁻²¹² adopted the same N=C-C=N bpy backbone and synthesized variously substituted 2-pyridineimine-based catalysts (**Figure 1.3.12**). These ligands, similar to bpy, are able to accept electron density from Cu^I into the π^* orbital²¹³ and were suitable for the normal ATRP of MMA at 90°C with molecular weights increasing with conversion although relatively higher D > 1.20. It has been estimated that the values of K_{ATRP} are on the order of 10⁻¹⁰ which would make them poorly suited for lower activity monomers such as MA.

1.3.8.2 Macrocyclic Ligands

Macrocyclic amines were first used in ATRP in 1999 for the polymerization of (meth)acrylamides.²¹⁴ 1,4,8,11-Tetramethyl-1,4,8,11-tetraaacyclotetradecane (Me₄Cyclam; **Figure 1.3.12**) showed a very fast polymerization of dimethylacrylamide and t-butylacrylamide but uncontrolled. This was attributed to a redox-initiated free radical polymerization as opposed to ATRP, indicating that the [Cu^{II}(Me₄Cyclam)Br]⁺ is a poor deactivator. This is supported by X-ray studies which show a Cu^{II}-Br bond of 2.809 Å which is outside bonding distance and is likely an electrostatic interaction.¹⁷⁸ 4,11-Dimethyl-1,4,8,11- tetraazabicyclo[6.6.2]hexadecane²¹⁵ (Cyclam-B; **Figure 1.3.12**) was then complexed to copper and tested in ATRP. Previous studies on the [Cu^{II}(Cyclam-B]²⁺ complex indicated a very strongly bound Cu^{II} complex with $\beta^{II} = 10^{27,216}$ This large stability constant was confirmed by CV²¹⁷ which showed $E_{1/2} = -340$ mV which indicated a very reducing Cu^I complex.²¹⁸

Model studies indicated $K_{ATRP} = 9.9 \times 10^{-5}$ and $k_a = 4.2 \times 10^{-1} \text{ M}^{-1} \text{s}^{-1}$ for the methyl chloroacetate (MCIAc) initiator in MeCN at room temperature. MCIAc is approximately 50 times less active than EBiB for which most of the above studies were conducted and thus direct comparison is difficult. However, Me₆TREN was used under identical conditions, which gave $K_{ATRP} = 3.3 \times 10^{-6}$ and $k_a = 2.7 \times 10^{-1} \text{ M}^{-1} \text{s}^{-1}$ indicating that Cyclam-B is 40 times more active than Me₆TREN, consistent with electrochemical measurements. The normal ATRP of n-butyl acrylate (BA) was fast and decently controlled ($\mathcal{P} < 1.3$) polymerization at room temperature. The best control was obtained when deactivator species was initially added to the mixture. Surprisingly, despite its unprecedented activity, Me₆TREN and TPMA gave lower \mathcal{P} and molecular weights

that aligned better with theoretical. Due to the very high stability of the [Cu^{II}(Cyclam-B)Br]⁺ complex, deactivation may be slow. Separate solid-state studies²¹⁹ also indicated a large rearrangement barrier upon reduction which may further contribute to slow deactivation.

1.3.8.3 Anionic Ligands

As noted in **Section 1.2.3**, the activity of a catalyst in ATRP can be related to the β^{II}/β^{I} ratio, i.e. the relatively stability of L/Cu^{II} to L/Cu^{II}. Thus, it was of interest to determine how negatively charged ligands would affect the activity.²²⁰⁻²²¹ As shown in **Figure 1.3.12**, a TPMA derivative was synthesized in which one arm was replaced by an anionic phenolate group.²²² Three ligands were synthesized, N-(2-hydroxybenzyI)-N,N-bis(2-pyridylmethyl)amine (^HPxDPMA), N-(2-hydroxy-3,5-dimethylbenzyI)-N,N-bis(2-pyridylmethyl)amine (^{Me}PxDPMA) and N-(3,5-di-tert-butyI-2-hydroxybenzyI)-N,N-bis(2-pyridylmethyl)- amine (^{tBu}PxDPMA) and utilized in ICAR ATRP. Although linear kinetic plots were observed, as expected for ICAR ATRP, molecular weight distributions were much broader than with the neutral TPMA. This was attributed to inefficient deactivation. More in-depth studies would be of interest to determine the reason for decreased control relative to catalysts with neutral ligands.

1.3.9 Summary of Copper Catalysts Used in ATRP

To date, there have been a wide variety of catalysts used in copper-catalyzed ATRP, mostly based on nitrogen. Through various model studies, it was found that the activity of the catalytic system depends on several parameters. Measurements of the ATRP equilibrium constant, K_{ATRP} , as well as the activation (k_a) and deactivation (k_d) rate coefficients allowed for the understanding of how catalyst structure affects reactivity in ATRP.^{136, 140} Generally, k_a affects K_{ATRP} more than the value of k_d .

Denticity increases activity in the order bidentate < tridentate < tetradentate. Hexadentate ligands such as TPEN have shown promise although the speciation of the activating and deactivating species becomes more complicated due to competitive complexation between the fifth and six coordinating nitrogen, halide and solvent. The nature of the coordinating ligand also plays a dramatic role in that activity increases in the order aryl amine < aryl imine < alkyl imine < alkyl amine \approx pyridine. The length of the carbon linker between nitrogen atoms also increases the activity in the order C₄ < C₃ << C₂ while the topology of the ligand increases activity in the order of cyclic \approx linear < branched < cyclic branched. The relationship between the above mentioned structural criteria and K_{ATRP} can be seen in **Figure 1.3.13**.



Figure 1.3.13 Relationship between ligand structure and measured ATRP equilibrium constants, K_{ATRP} using EBiB in MeCN at 22°C. Color key (denticity): bidentate (red); tridentate (black); tetradentate (blue); hexadentate (black). Symbol key (type of nitrogen): amine/imine (solid); pyridine (open); mixed (left-half solid); Ligand topology: linear (square); branched (triangle); cyclic (circle). Reproduced with permission from ¹³⁶.

Another important factor that has recently been exploited is that the addition of electron-donating groups to aromatic pyridine-based catalysts has shown to dramatically improve the activity in ATRP.^{144, 182} As discussed previously, the redox potential, $E_{1/2}$, is an effective indicator of activity since it can be linearly correlated to $ln(K_{ATRP})$, as shown in **Figure 1.3.14**. This plot shows how not only the electronics of the ligand but also the coordinating

ability affects $E_{1/2}$ and therefore activity in K_{ATRP} . It is of great interest to continue searching for more reducing Cu complexes in order to increase K_{ATRP} .



Figure 1.3.14 Correlation between redox potential, $E_{1/2}$ of the [Cu^{I/II}(L)Br] couple and values of K_{ATRP} for EBiB in MeCN at room temperature. Reproduced with permission from ¹³⁶.

1.4 Progressive Development of ATRP Initiation Systems

ATRP has made significant strides with regards to initiating systems. From seminal reports using large quantities of air-sensitive Cu¹ complexes to the most recent system which uses < 50 ppm of catalyst and is controlled by ultrasound, ATRP has been developed into a benchmark technique. The follow section will discuss the progressive development of ATRP systems from 1995 until the present day.

1.4.1 Normal ATRP (1995)

In 1995, the first study on copper catalyzed ATRP was reported for the controlled radical polymerization of styrene and methyl acrylate.²²³ This seminal report utilized stoichiometric amounts of CuCl and 2,2'-bipyridine, which was previously used in ATRA. Using the alkyl chloride 1-phenylethyl chloride (1-PECl) as an ATRP initiator, relatively well-defined polystyrene (PS) was synthesized with molecular weights that closely matched theoretical values and with

relatively narrow molecular weight distributions (MWDs) $M_w/M_n < 1.5$ in bulk styrene. Moreover, successful chain-extension of the living PS-Cl macroinitiator with methyl acrylate (MA) in bulk resulted in the PS-*b*-pMA-Cl block copolymer in good yield ($M_n = 13,000; D = 1.35$) (**Figure 1.8.1**).



Figure 1.4.1 A) Normal ATRP of styrene under quasi-heterogeneous conditions using a bipyridine (bpy)-based copper catalyst with target degree of polymerization DP = 100 and B) correlation of various target DPs with theoretical DP under the initial conditions [St]:[1-PECI]:[CuCI]:[bpy] = x:1:1:3 in bulk at 130°C. *Reprinted with permission from*²²³. *Copyright 1995 American Chemical Society*.

This initial contribution was conducted at 130° C due to a low catalyst activity and small rate coefficient of propagation, k_{p} , values for styrene. The chain-extension with MA was also conducted at the temperature in order to solubilize the $[Cu^{I}(bpy)_{2}CI]$ catalyst in bulk monomer. However, even at such high temperatures, fully homogenous systems were not achievable.

Model studies were conducted and showed that in the absence of initiator, copper or ligand, an uncontrolled polymerization was observed. It was only when all components were added that a well-controlled polymerization was achieved. Thus, it was proposed that ATRP was mechanistically similar to ATRA and operated via halogen atom transfer. Later, the same bpy-based catalyst was used to expand both the range of polymerizable monomers as well as the use of various small molecule alkyl halide initiators. Alkyl chloride initiators such as butyl chloride and dichloromethane were used, however these both gave an uncontrolled polymerization due to a much stronger C-Cl bond (10-13 kcal/mol) and poor initiation efficiencies. Here, it was first proposed that the initiation efficiency can be correlated to BDFE.

Non-styrenic monomers such as methyl acrylate and methyl methacrylate (MMA) were then employed using the same 1-PECl initiator with the bpy/Cu^I catalyst in bulk at 130°C (**Figure 1.4.2**). Using the slope of the semi-logarithmic plots, the steady-state radical concentration was calculated and was found to be dependent on the structure of the monomer and decreased according to MMA > St > MA. This trend correlates to the relative stability of the propagating radicals which indicated that the radical concentration in ATRP was dependent on the efficiency of halogen atom transfer.

The effect of halogen species on the ATRP of MA was then conducted (**Figure 1.4.3**).²²⁴ The same structure of the initiator was used however the halide was changed from chloride to bromide under otherwise similar conditions. The polymerization was faster using alkyl bromide compared to alkyl chloride and was due to the weaker BDE of the C-Br bond compared to C-Cl. This lead to a higher concentration of radicals and thus an increased rate of polymerization. Interestingly, significantly better control was found using alkyl bromides despite a faster polymerization. Not only did molecular weights match better with theoretical molecular weights, but dispersities were lower with alkyl bromide (D = 1.15) compared to alkyl chlorides (D = 1.25). A similar effect was observed with St and MMA.

Finally, the effect of [RX]₀, [CuCl]₀ and [bpy]₀ was investigated on both the kinetics and molecular weight control. The rate of polymerization was dependent on [RX]¹[CuCl]^{0.4}[bpy]^{0.6} for which the fractional dependence was due to the heterogeneity of the system. There was no significant effect of [CuCl]₀ on molecular weight control and the [CuCl]₀:[RX]₀ was able to be decreased from 1 to 0.3 with retained control indicating the catalytic nature of the copper complex.

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Figure 1.4.2 Kinetics of the ATRP of St, MA and MMA in the bulk using the [Cu^I(bpy)Cl] catalyst with 1-PECl as an initiator at 130°C. *Reprinted with permission from* ²²⁴. *Copyright 1995 American Chemical Society*.



Figure 1.4.3 Evolution of molecular weight and *Đ* with conversion for the ATRP of MA at 100°C using A) chlorides and B) bromide systems. *Reprinted with permission from* ²²⁴. *Copyright 1995 American Chemical Society*.

These two seminal contributions concluded that there is a fast and reversible equilibrium between dormant and propagating chains. This equilibrium maintains a low concentration of radicals which limits unwanted, chain-breaking processes such as termination and transfer. Other potential mechanisms involving metal insertion and redox radical telomerization were eliminated based on experimental evidence. With the mechanistic groundwork established, new catalytic systems were developed.

1.4.2 Reverse ATRP (1995)

Normal ATRP requires efficient handling of air-sensitive Cu^I salts. This requires the need for multiple reaction vessels to de-oxygenate all species (monomer, solvent, initiator, ligand, etc.) prior to the introduction of Cu^I to the system. Cu^{II} salts, on the other hand, are very stable under ambient conditions and thus are much easier to handle. Upon the seminal ATRP reports which utilized the [Cu^I(bpy)₂X] complex, it was realized that one could start from Cu^{II} complexes if they could be quickly reduced to L/Cu^I. Conventional radical initiators thermally or photochemically decompose into radicals, I[•], which are rapidly trapped by L/Cu^{II}-X complexes to generate L/Cu^I and I-X ATRP initiator as shown in **Scheme 1.4.1**. This was the precedence for reverse ATRP where both the activating catalyst and initiating alkyl halide were formed *in situ*.²²⁵



Scheme 1.4.1 Mechanism of reverse ATRP in the presence of conventional radical initiators such as AIBN. *Reprinted with permission from* ²²⁶. *Copyright 2018 Wiley-VCH Verlag.*

2,2'-Azobis(2-methylpropionitrile) (AIBN) has a decomposition half-life of $t_{1/2} = 10$ h at 65°C, thus to completely and quickly reduce L/Cu^{II} to L/Cu^I, higher temperatures are required. For the polymerization of styrene in bulk, the reverse ATRP was conducted at 130°C. The [L/CuCl₂]₀:[AIBN]₀ ratio was of critical importance with increasing ratios leading to both an increased initiation efficiency and degree of control. At a [CuCl₂]:[AIBN] = 10:1 a well-controlled polymerization was observed with initiation efficiency 95% and D < 1.3. However, as noted in the previous section, the insolubility of the [Cu^{1/II}(bpy)₂X] complexes lead to only a small amount of catalyst present in solution and thus limited control. When using other monomers such as MA, this initiation failed due to faster propagation. In order to circumvent this issue, a catalytic amount of AIBN was used in the presence of the ATRP initiator MCIP. The catalyst loading was decreased even further to 1-2 mol% relative to MCIP while still exhibiting a well-controlled reaction. As will be discussed later, these seminal reports on generating the L/Cu¹ activator *in situ* from the air-stable and easy to handle L/Cu^{II}-X complex were later adapted by various other ATRP systems such as initiators for continuous activator regeneration (ICAR) and activators regenerated by electron transfer (ARGET) ATRP (*vida supra*).

1.4.3 Homogeneous Normal ATRP (1996)

As discussed in the previous section, one potential drawback of Cu/bpy-based catalysts is the solubility of the [Cu^{II}(bpy)₂X] deactivator complex in bulk monomer. In order to help solubilize both the activator and deactivator complex, aliphatic groups were incorporated to the bpy ring in the 4 and 4' positions. As shown in **Figure 1.3.1**, these aliphatic chains include tbutyl, (dTbpy), n-heptyl (dHbpy) and 5-nonyl (dNbpy).²²⁷

The effect these new ligands had on normal ATRP was profound. Normal ATRP was conducted in bulk styrene with dHbpy using 1-PEBr as an ATRP initiator and polydispersity's decreased to 1.04 at high monomer conversions. At the time, these dispersities rivaled living anionic polymerization (**Figure 1.4.4**). The system was then expanded to bulk MA using MBrP as the ATRP initiator. Similarly, to the styrene system, significant control was garnered over the polymerization with D = 1.05. The effect of initially present Cu^{II} was also investigated. These low D's were obtained using commercially available CuBr salts which inherently have 2% Cu^{II}

present. When highly pure CuBr (99.999%) was used, inferior control was observed with D >1.10.

The effect of a homogeneous ATRP system was fully realized in that increasing the amount of deactivator in solution could lead to a much more well-controlled reaction.¹⁸⁴ As will be discussed in great length, catalytic design centered around substituted pyridine-based catalysts will be revitalized some 15 years later and have led to the most active ATRP catalysts to date.





The fractional rate dependences on [CuCl] and [bpy] were observed and was attributed to the heterogeneity of the catalytic system. Upon synthesis of bpy-based ligands with aliphatic solubilizing groups, it was of interest to determine dependence on the components of the system under homogeneous conditions.²²⁸ Indeed, the rate of polymerization was dependent on [dHbpy]₀ only up to 2 equivalents relative to [CuCl]₀ compared to a dependence of [bpy]^{0.6} for the heterogeneous polymerizations. In line with the heterogenous system, the rate of polymerization was dependent on [RX]¹.

For the polymerization of styrene, using 1-PEBr as the alkyl halide initiator, significant amounts of dimerized product were formed at the initial stages. Concurrently, the irreversible formation of L/Cu^{II}-Br species was observed. Therefore, it was proposed that the rate of radical termination decreases until enough deactivator was built up in solution so that the

polymerization is slow enough for a controlled reaction. This set the basis for the persistent radical effect in ATRP which was relatively well-known phenomena for some radical-based organic reactions.^{131-133, 229} Temperature dependence on the rate of polymerization was also investigated. The enthalpies of the pre-equilibrium were calculated to be $\Delta H^{\circ} = 4.8$ and 6.3 kcal mol⁻¹ for bromide and chloride, respectively. Similarly, entropies at equilibrium were $\Delta S^{\circ} = -22$ cal mol⁻¹ K⁻¹ and $\Delta S^{\circ} = -20$ cal mol⁻¹ K⁻¹ for bromide and chloride, respectively. These values were significantly more negative than expected and were rationalized from a large loss of conformational motion around the metal center upon atom transfer.

1.4.4 Simultaneous Reverse and Normal Initiated (SR&NI) ATRP (2001)

At this point in time, there were two common initiating systems; normal ATRP (Section 1.4.1) or reverse ATRP (Section 1.4.2), both of which follow the persistent radical effect. Normal ATRP takes use of direct activation of R-X by L/Cu^I while reverse ATRP generates both the L/Cu^I activator and I-X initiator *in situ* upon quantitative decomposition of conventional radical initiators and subsequent reduction of L/Cu^{II}-X. Both normal ATRP and reverse ATRP have successfully controlled the polymerization of styrenes, methacrylates and acrylates. However, these systems are limited to less active catalysts. In order to circumvent this issue, simultaneous reverse and normal initiated (SR&NI) ATRP was developed using the Me₆TREN-based catalyst under relatively benign conditions.²³⁰ The main difference being the slower decomposition of the radical initiator and in the presence of a conventional ATRP alkyl halide initiator as shown in Scheme 1.4.2. Thus, contrary to reverse ATRP where chains are initiated by I-X, in SR&NI ATRP, chains are initiated similarly to normal ATRP from alkyl halide. Furthermore, SR&NI ATRP allows one to use L/Cu^{II}-X as the initial copper complex. Depending on reaction conditions, namely the [L/Cu^{II}-X]₀/[AIBN]₀ ratio and temperature, a greater fraction of AIBN initiated chains (I-X and I-M-X) will be present.²³¹



Scheme 1.4.2 Mechanism of simultaneous reverse and normal initiated (SR&NI) ATRP.

SR&NI ATRP were conducted under both hetero- and homogeneous conditions. Under heterogeneous conditions, i.e. bulk butyl acrylate (BA), the most well-controlled reaction was observed at lower temperature because less chains were continually generated from AIBN which resulted in a broadening of the molecular weight distribution. In all cases the molecular weights were dependent on the $[M]_0/[RX]_0$ ratio as shown in **Figure 1.4.5A**.

In order to provide a homogeneous system with more efficient deactivation (due to a more soluble L/Cu^{II}-X deactivator complex), 5% MeOH was added. Due to the larger fraction of soluble deactivator, initially formed radicals were trapped more efficiently leading to decreased number of terminated chains and therefore gave a higher initiation efficiency. However, a significantly prolonged induction period was observed due to a reduction of deactivator to activator complex. Nevertheless, the molecular weights were still determined mainly by the [M]₀/[RX]0 ratio as shown in **Figure 1.4.5B**.

Similar systems were extended for the homogeneous SR&NI ATRP of styrene. One of the largest benefits of SI&NI ATRP is the ability to use highly active catalysts.



Figure 1.4.5 A) Dependence of the $[M]_0/[RX]_0$ ratio on molecular weights and \mathcal{D} for the SI&NI ATRP of butyl acrylate under heterogeneous conditions and B) homogeneous conditions using the highly active Me₆TREN-based copper catalyst. Reproduced with permission from Ref ²³⁰.

1.4.5 Activators Generated by Electron Transfer (AGET) ATRP (2005)

The initiating systems starting from L/Cu^{II}-X required either externally generated radicals with generation of ATRP activator and initiator *in situ* as in reverse ATRP or continually generated chains as in SR&NI ATRP. Both of these processes have chains that are initiated from species other than the alkyl halide which can make it rather difficult to synthesize more complex architectures such as block copolymers. Activators generated by electron transfer (AGET) ATRP²³² takes the benefits of SI&NI ATRP such as using a highly active, air-stable L/Cu^{II}-X catalyst but instead of using organic radicals as a reducing agent, non-radical generating reducing agents are used as shown in **Figure 1.4.6 Left**. ²³³

Initially, tin(II) 2-ethylhexanoate (Sn^{II}(EH)₂) was used as a reducing agent for dNbpy-PMDETA- and Me₆TREN- based catalytic systems for the polymerization of styrene, methacrylate and acrylates for both linear and star polymers.²³² The benefits of AGET ATRP become apparent when analyzing the GPC traces of the resulting three-armed star polymer for normal ATRP (**Figure 1.4.6A**), SR&NI ATRP (**Figure 1.4.6B**) and AGET ATRP (**Figure 1.4.6C**). Normal ATRP exhibited a broad molecular weight distribution consistent with stars that were terminated via combination. SR&NI ATRP showed a clear bimodal distribution indicating homopolymer formed from AIBN initiated chains. Encouragingly, AGET showed a pure star copolymer without any low molecular weight homopolymers indicating that the reduction of L/Cu^{II} to L/Cu^{I} does not involve generation of new chains.



Figure 1.4.6 (Left) Proposed mechanism for activators generated by electron transfer (AGET) ATRP and (right) comparison of A) normal ATRP B) SR&NI ATRP and C) AGET ATRP for the synthesis of a three-armed star from the tri-functional initiator (TBriBPE).

dNbpy was used for the polymerization of octadecyl methacrylate at $[RA]_0/[L/Cu^{II}-X]_0 =$ 2, 0.9 and 0.45 for which the latter was found to provide the best control. Similar systems were then used to successfully control the AGET ATRP of styrene, MMA and MA. Ascorbic acid was later used as a reducing agent for AGET ATRP in miniemulsion.²³⁴⁻²³⁵

1.4.6 Activators ReGenerated by Electron Transfer (ARGET) ATRP (2006)

Similar to AGET ATRP, activators regenerated by electron transfer (ARGET) ATRP also makes use of a chemical reducing agent (RA) to generate the L/Cu^I activator species *in situ*. While AGET ATRP typically uses [L/Cu^{II}-X]: $[RX]_0 = 0.1$, ARGET ATRP can gain control over the polymerization of styrene using as low as [L/Cu^{II}-X]: $[RX]_0 = 0.0002$ which correlates to

approximately 1 ppm catalyst loading relative to monomer. The key in ARGET ATRP is that $[RA]_0 > [L/Cu^{II}-X]_0$ but also $[RX]_0 >> [L/Cu^{II}-X]_0$ in order to slowly and continuously reduced L/Cu^{II}-X that is accumulated throughout the course of the reaction as a result of the PRE (**Scheme 1.4.3**). As opposed to normal ATRP and reverse ATRP, and in some cases SR&NI and AGET ATRP, for ARGET ATRP, a highly active catalyst is *required*.



Scheme 1.4.3 Mechanism of activators regenerated by electron transfer (ARGET) ATRP and common reducing agents used.

ARGET ATRP is one of the first widely used and studied methods of ATRP with activator regeneration (Section 1.2.4.2). Thus, ARGET exhibits kinetics that follow the steady-state approximation and therefore a main component of this systems is a dynamic equilibrium for which the [L/Cu^{II}-X]/[L/Cu^I] ratio is defined by [R[•]], [RX] and K_{ATRP} . Upon establishment of the ATRP equilibrium, the steady-state rate of polymerization (i.e. [R[•]]) can be expressed by **Eq** 1.4.1. Therefore, the rate of polymerization is dependent on the rate coefficient of reduction, k_{red} , [L/Cu^{II}-X]₀ and [RA]₀. Various reducing agents including Sn^{II}R₂ compounds,²³⁶ glucose,²³⁷ ascorbic acid,²³⁸ Ag⁰,²³⁹⁻²⁴⁰ and hydrazine¹⁶² have all be implemented in ARGET ATRP. Furthermore, monomers²⁴¹⁻²⁴² or excess ligands²⁴³ can also act as internal reducing agents without the need for an additive.

$$[R \cdot] = \sqrt{\frac{k_{red}[L/Cu^{II} - X][RA]}{k_t}}$$
(Eq. 1.4.1)

The rate of polymerization can be tuned by the type and/or amount of RA. However, it is of utmost importance to ensure that the oxidized species does not negatively impact the polymerization. Some side reactions that have been reported for either the reducing agent or oxidized species in literature are competitive complexation to the metal center, acid/base reactivity and nucleophilic substitution of halide chain-ends.¹⁶¹

1.4.7 Initiators for Continuous Activator Regeneration (ICAR) ATRP (2006)

Initiators for continuous activator regeneration (ICAR) ATRP is analogous to SR&NI as ARGET is analogous to AGET. The key to ICAR ATRP is the slow and continuous regeneration of L/Cu^I activator from an external radical source such as AIBN (**Scheme 1.4.4**).¹⁶² Under the most successful ICAR ATRP conditions, the decomposition of the radical initiator (I) is slow, although this rate can be tuned by changing the type and concentration as well as reaction temperature. Similar to ARGET ATRP, ICAR takes use of a small [L/Cu^{II}-X]₀/[RX]₀ ratio with [I]₀ > [L/Cu^{II}-X]₀.¹⁶³ Typically, ICAR is conducted with catalyst loadings less than 200 ppm relative to monomer. As with reverse, SR&NI, ICAR ATRP can also involve a small fraction of chains being initiated by the radical initiator.



Scheme 1.4.4 Mechanism of initiators for continuous activator regeneration (ICAR) ATRP.

ICAR is also a form of ATRP with activator regeneration and the same dynamic equilibrium exists as in ARGET ATRP and thus relatively active catalysts are required. Kinetically, ICAR ATRP is different than ARGET in that the rate of polymerization does not depend on the nature or concentration of the catalyst. In fact, the kinetics of ICAR more closely resemble RAFT or conventional radical polymerization in that the rate depends only on the rate of decomposition of radical initiator and the rate coefficient of termination (**Eq 1.4.2**). The rate of decomposition is dependent on the rate coefficient of decomposition, k_{dc} , initiation efficiency, *f*, and initiator concentration.

$$[R \cdot] = \sqrt{\frac{fk_{dc}[I_2]}{k_t}}$$
(Eq. 1.4.2)

The seminal report on ICAR ATRP studied the polymerization of St, MMA and BA under various conditions. St was successfully polymerized using as little as 50 ppm catalyst. dNbpy, PMDETA, TPMA and Me₆TREN were used as ligands and it was found that the effect of catalyst has a negligible effect on the kinetics of ATRP despite over 4 orders of magnitude differences in K_{ATRP} . Under the same reaction conditions, the control of the polymerization was significantly dependent on the activity of the catalyst. Dispersities with Me₆TREN and TPMA were D < 1.12 while PMDETA and dNbpy were D > 1.6. The main reason for the decrease in D is because the amount of L/Cu^{II}-X deactivator present in solution is dependent on K_{ATRP} . Larger values give a larger fraction of deactivator in solution and thus molecular weights are better controlled due to a faster rate of radical deactivation.

Since SR&NI and ICAR use the same components, an interesting question arose as to what kinetically differentiates the two systems.²⁴⁴ Technically, they are different in only the $[L/Cu^{II}-X]_0$ as well as how fast it is reduced to the L/Cu^{I} complex.



Figure 1.4.7 (Left) PREDICI simulations of the effect of rate coefficient of decomposition of radical initiator, k_{dc} , on the rate of polymerization and (right) relation between rate of decomposition to propagation and copper concentration and its effect on the kinetic regime of SR&NI vs. ICAR ATRP. Adapted from Ref ²⁴⁴.

Once the thermal initiator is consumed in SR&NI ATRP, the kinetics should follow that of normal ATRP i.e. subjected to the PRE. ICAR ATRP follows steady-state kinetics for which the decomposition of AIBN becomes rate limiting. In order to assess the criteria which define whether SR&NI or ICAR define the system, a catalyst concentration $[L/Cu^{II}-X]_0 = 2 \text{ mM}$ and $[AIBN]_0 = 1 \text{ mM}$ was set to allow for a maximum of one reduction of each $L/Cu^{II}-X$ species. This catalyst loading is considered high for ICAR but low for SR&NI. As shown in **Figure 1.4.7**, when the decomposition rate coefficient was $k_{dc} < 3 \times 10^{-5} \text{ s}^{-1}$, the overall polymerization kinetics exhibited an induction period with a steady-state of radicals (ICAR). However, at faster decomposition rates ($k_{dc} > 3 \times 10^{-4} \text{ s}^{-1}$), the rate of polymerization followed the kinetic regime of SR&NI in which the rate of polymerization gradually decreased due to the PRE. The borderline is defined by the k_{dc}/k_p ratio for which the switch is around 10^{-7} M. At high ratios, the kinetics follow SR&NI while at lower ratios, ICAR ATRP predominates. A similar borderline case can be imagined between AGET and ARGET. However, instead of the decomposition of AIBN determining the kinetic regime, the rate of reduction of L/Cu^{II}-X by the reducing agent will define AGET or ARGET.

1.4.8.1 Electrochemically Mediated ATRP (eATRP) (2011)

The essence of ATRP is the redox-active nature of the L/Cu^{I/II} couple. Indeed, the activity of many catalytic systems can be examined using electrochemical techniques such as cyclic voltammetry (CV) (**Section 1.2.4**). It was envisaged that one could modulate ATRP by direct electrochemical reduction of the L/Cu^{II}-X complex to the L/Cu^I activator species.^{148, 245-248} This is similar to AGET or ARGET, but instead of employing chemical reducing agents, electrochemical current was used to directly generate the activator complex (**Scheme 1.4.5A**). Another benefit of "external" electrochemical regulation is the ability to obtain temporal control for which the polymerization can effectively be turned on and off at will.

As shown in **Scheme 1.4.5B**, a successful *e*ATRP requires a working, reference and counter electrodes to be immersed in the polymerization mixture. Due to the heterogeneity of the electrochemical process, constant stirring is required to continually replenish the diffusion layer. Another drawback is the requirement for supporting electrolytes in organic media.



Scheme 1.4.5 (A) Proposed mechanism and (B) general setup of *e*ATRP.

The rate of *e*ATRP was dependent on the applied potential in relation to the reduction potential, E_{cat} , of the [Cu^{II}(L)Br]⁺ complex, which can be obtained by a simple CV experiment.²⁴⁶ Generally, the rate of polymerization increases by applying a more negative potential. This is because the rate of polymerization is dependent on the [L/Cu^{II}]/[L/Cu^{II}-X] ratio, which is in turned determined by the applied potential.

Initially using the $[Cu^{II}(Me_6TREN)Br]^+$ catalyst, the controlled polymerization of acrylates was achieved with D < 1.10. Temporal control was also obtained by switching the current on and off for which a cessation in rate was observed with no detrimental effects on the molecular

weights or \mathcal{D} . *e*ATRP has successfully been used for the synthesis of complex macromolecular architectures such as stars, brushes and block copolymers²⁴⁹⁻²⁵⁴ as well as for the polymerization as some historically challenging monomers in ATRP such as acrylamides^{250, 255} and methacrylic acid.²⁵⁶

1.4.8.2 Simplified Electrochemically Mediated ATRP (*se*ATRP) (2015)

Electrochemically mediated ATRP (eATRP) was one of the first examples of an externally regulated process and was able to be conducted using ppm levels of catalyst. However, typical *e*ATRP experiments use a three-electrode system which requires one to use potentiostatic conditions where a constant potential is applied to reduce the L/Cu^{II}-X species. The three-electrode system uses a working electrode, counter electrode and reference electrode for which the reference and counter electrodes are separated from the reaction mixture in order to prevent contamination or side reactions. In order to "simplify" *e*ATRP, a sacrificial counter electrode was used which did not require any separation from reaction media permitting the use of an undivided cell but also operating under galvanostatic conditions.²⁵⁷ Galvanostatic conditions allow the possibility of a two electrode systems with a much more simpler current generator as opposed to a more expensive potentiostat.

Aluminum was chosen as a sacrificial electrode. Under potentiostatic conditions, the *se*ATRP of BA was fast and efficient, reaching >90% conversion in three hours with both molecular weights and *D*'s being well-controlled. Scanning electron microscopy (SEM) was conducted on both pristine and AI wire after polymerization. The latter was found to be porous which was indicative of oxidation to AI^{III} and formation of AI₂O₃ with residual water. Inductively coupled plasma – mass spectroscopy (ICP-MS) of the purified polymers showed residual AI and Cu to be 5.2 and 16 ppm, respectively.

To further simplify the setup, *se*ATRP was conducted under galvanostatic conditions i.e. with a Pt mesh working cathode and an Al wire counter/sacrificial electrode. The applied currents were determined from the polymerizations under potentiostatic conditions and were found to be cathodic currents of 0.713 mA for the first 1.2 hours and 0.297 mA for hours 1.2 to 4. This is consistent with the need to reduce enough L/Cu^{II}-X to establish the [L/Cu^{II}-X]/[L/Cu^I]

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ratio at the beginning. This is then followed by a steady-state in [L/Cu¹]. In order to suppress Cu^0 deposition on the working electrode a multi-step cathodic current procedure was used: 1.03, 0.53, 0.4, and 0.28 for 30 minutes each. A well-controlled polymerization was observed with >80% conversion being reached and *D* < 1.10. It is envisioned that the two-electrode system under galvanostatic conditions will dramatically improve on the ease of use for electrochemically mediated ATRP. Other non-platinum electrodes have also shown promise as working electrodes in eATRP.²⁵⁸⁻²⁵⁹

1.4.9 ATRP in the Presence of Cu⁰ (SARA ATRP) (1997-2014)

In order to "scavenge" excess L/Cu^{II}-X that was accumulated due to the PRE, Cu⁰ was added to a normal ATRP reaction in order to regenerate the L/Cu^I activator.²⁶⁰ The effect on the polymerization of MA was significant. As shown in **Figure 1.4.8**, in the presence of only [Cu^I(dNbpy)₂Br] (i.e. normal ATRP), 95% conversion was achieved in 9 hours with wellcontrolled molecular weights. However, in the presence of Cu⁰ powder, a polymerization was faster by a factor of 10. The same rate of polymerization was observed when only Cu⁰ and [Cu^{II}(dNbpy)₂Br] were initially placed in the reaction mixture. This system was also expanded to St and MMA.



Figure 1.4.8 Dependence on the A) rate of polymerization and B) molecular weights and \mathcal{D} for ATRP in the presence and absence of Cu⁰ powder. *Reprinted with permission from* ²⁶⁰. *Copyright 1997 American Chemical Society.*

Mechanistically, the increased rate of polymerization was due to the gradual reduction of the persistent radical, L/Cu^{II}-X. Similar systems were developed for nitroxide mediated
radical polymerization (NMP) where the nitroxide TEMPO was removed via reaction with various acids²⁶¹ or radical initiators.²⁶² However, unlike those NMP systems, ATRP in the presence of Cu⁰ also regenerated the active catalyst. An added radical generation pathway involving activation of (macro)alkyl halides by Cu⁰ was also observed. The proposed mechanism in the presence of Cu⁰, is shown in **Scheme 1.4.6**.



Scheme 1.4.6 Proposed mechanism (1997) of ATRP in the presence of Cu⁰. Adopted from Ref ²⁶⁰.

It should be noted that this system is intrinsically different than reverse ATRP (**Section 1.4.2**). In reverse ATRP, the initially added L/Cu^{II} complex is quantitatively reduced to the L/Cu^I activator at the beginning of the reaction. The L/Cu^I formed *in situ* then enters into the ATRP equilibrium and follows the normal ATRP regime i.e. persistent radical effect. In the presence of Cu⁰ however, the L/Cu^{II}-X complex is *slowly and continually* reduced by comproportionation to the L/Cu^I activator complex.

As discussed above, the use of zero-valent metals, namely Cu⁰ but also Fe⁰, Zn⁰ or Mg⁰, have been used in ATRP since 1997 and is perhaps the most robust and easy-to-use ATRP system.^{260, 263} Due to the additional reactions Cu⁰ catalyzes, the mechanism of this system has been long debated. It was not until 2014 when the controversy was seemingly put to rest.^{104,}

 $^{165, 264}$ Although it will not be thoroughly discussed, inorganic sulfites such as Na₂S₂O₄ can also be used in SARA ATRP.²⁶⁵⁻²⁶⁷

As shown in **Scheme 1.4.7**, the two mechanisms are supplemental activator and reducing agent (SARA) ATRP and single electron transfer living radical polymerization (SET-LRP).²⁶⁸ It should be stressed that these two mechanisms employ the exact same reagents and rather only differ in the relative kinetic contributions of the specific reactions.^{109, 269-271}

In SARA ATRP, it is proposed that the vast majority of (macro)alkyl halide activation is by L/Cu^{II} with deactivation occurring by L/Cu^{II}-X. Activation by Cu⁰ is only proposed to be a slower, "supplemental" activator of alkyl halides. Deactivation by L/Cu^I-X is not considered relevant. Furthermore, it is proposed that both the disproportionation reaction ($2 \text{ L/Cu}^I \rightarrow \text{Cu}^0 + \text{ L/Cu}^{II}-X + \text{L}$) and comproportionation reaction ($Cu^0 + \text{ L/Cu}^{II}-X + \text{L}$) are overall slow processes, however comproportionation dominates. In SARA ATRP, activation occurs via an inner sphere electron transfer (ISET) mechanism.^{165, 264} Finally, although in SARA ATRP high chain-end functionality is obtained, termination does indeed occur, as for all radical processes.

SET-LRP, on the other hand, assumes that all activation of (macro)alkyl halides occurs via Cu⁰. The generated L/Cu^{II} species "instantaneously" disproportionates to nascent Cu⁰ and L/Cu^{II}-X. Thus, it is assumed that comproportionation is negligible. Furthermore, SET-LRP assumes an outer sphere electron transfer (OSET) for the activation reaction. One common theme between the two mechanisms is that L/Cu^{II}-X is the main deactivator of radicals. Finally, it is assumed that there is no termination in SET-LRP.

The kinetics of RDRP in the presence of Cu⁰ were subjected to an in-depth study via the use of computational,¹²⁰ kinetic model studies^{104, 164, 166-167, 272-275} and electrochemical studies.^{120, 276} It was concluded that the majority of (macro)alkyl halide chain-ends were activated by L/Cu¹ (>99%) and that Cu⁰ only played a small role in the overall activation (<1%). In the organic media investigated, both disproportionation and comproportionation were slow although comproportionation was faster than disproportionation. It was found that it should take multiple days to fully establish equilibrium which is typically longer than most polymerizations take to reach quantitative conversion.



Scheme 1.4.7 Proposed mechanisms of (top) supplemental activator and reducing agent (SARA; 2014) ATRP and single electron transfer living radical polymerization (SET-LRP). Reprinted with permission from Ref ²⁶⁴.

A special situation arises in aqueous media. This is because the disproportionation/ comproportionation equilibrium does indeed favor disproportionation.^{104, 277} However, the rate of alkyl halide activation by L/Cu¹ increases by a factor of at least 10² leading to values of K_{ATRP} that are much larger in aqueous systems than in organic media. Thus, it is not only important to consider thermodynamics, but also kinetics. The kinetics of disproportionation are dependent on [L/Cu¹]². In ATRP with activator regeneration (i.e. SARA ATRP), the [L/Cu^{II}-X]/[L/Cu^I] ratio is dynamic and [L/Cu^I] is related to K_{ATRP} . Because K_{ATRP} is much larger in aqueous media, the amount of L/Cu^I at any given point is small, which leads to [RX] >> [L/Cu^I]. This means that L/Cu^I will preferentially activate alkyl halide before it will disproportionate with a second equivalent of L/Cu^I. In fact, L/Cu^I will activate alkyl halides at least 10⁷ times faster than it will disproportionate. This is a special case of competitive equilibria²⁷⁸⁻²⁷⁹ in which, even though the equilibrium favors disproportionation, this reaction can effectively be suppressed due to the much faster activation of alkyl halides. Thus, even in aqueous media, ATRP in the presence of Cu⁰ still follows the SARA ATRP mechanism. In both aqueous and organic media, the rate of activation with an ISET mechanism was 10⁹ times faster than an OSET process and calculated rate coefficients of activation by Cu⁰ via Marcus theory were much smaller than experimentally observed.¹⁴⁵ These in-depth studies confirm the SARA ATRP mechanism in both organic and aqueous media and that none of the postulations of SET-LRP were correct. These model studies have been used to better model the overall polymerization process.^{167-168, 275}

1.4.9 Photochemically-Mediated ATRP (photoATRP) (2012)

The use of photochemistry to reduce L/Cu^{II}-X was explored in both organic and aqueous media.²⁸⁰⁻²⁸¹ The use of light in ATRP was not a completely novel concept, but previous reports required the use of a photoinitiator.²⁸²⁻²⁸⁵ In 2000, it was reported that 2,2-dichloroacetophenone could be used as a photo initiator to increase the rate of normal ATRP.²⁸⁶ Yagci *et al* later reported that L/Cu^{II}-X could be photochemically reduced to L/Cu^I in the presence of methanol.²⁸⁷ Hawker *et al* used the Ir^{III}(ppy)₃ (ppy = 2-pyridylphenyl) photoredox catalyst to activate alkyl halide chain-ends in an ATRP-like mechanism for methacrylates.²⁸⁸ However, an ATRP system for the polymerization of both acrylates and methacrylates using ppm level of Cu catalyst in the absence of a photoinitiator was yet to be developed .

The wavelength of the irradiation source significantly affected the rate of polymerization for MA using the TPMA*³-based catalyst.²⁸⁰ Red (631 nm) irradiation gave little to no polymerization after 10 hours while violet (392 nm) gave 70% conversion after 24 hours. Sunlight was shown to be the most efficient irradiation source for which 80% conversion was reached in just 12 hours. MMA was able to be polymerized using TPMA/Cu and showed the same effects with respect to irradiation source as for MA. pMMA-pEA-Br (pEA = poly ethyl acrylate) block copolymers were efficiently synthesized using *photo*ATRP. Furthermore, temporal control was exhibited when the polymerization was shut off upon turning off the irradiation source. Finally, oligo(ethylene oxide) methacrylate (OEOMA) was able to be controlled in aqueous systems.

The proposed mechanism of *photo*ATRP involved direct photochemical homolysis of the L/Cu^{II}-X bond to generate the L/Cu^I activator and a halogen radical, X[•]. Further mechanistic work showed that the main source of radical generation occurred via a reductive quenching mechanism between L/Cu^{II}-X in the excited state with uncoordinated ligand Me₆TREN, as shown in **Scheme 1.4.8**.²⁸⁹⁻²⁹² It was shown that triethylamine had the same effect as excess ligand and only varied with the concentration of aliphatic nitrogen. There were also small contributions of radical generation in a photochemical ICAR-type mechanism. Low ppm *photo*ATRP has also been successfully expanded to aqueous systems ²⁹³⁻²⁹⁵ and for the polymerization of semi-fluorinated monomers.²⁹⁶



Scheme 1.4.8 Proposed mechanism of photochemically mediated ATRP (*photo*ATRP). Reprinted with permission from Ref ²⁸⁹.

1.4.11 Metal-Free/Organo Catalyzed ATRP (oATRP) (2015)

Recently, a push towards metal-free catalysis has been realized. Hawker *et al* showed the first use of an organic photoredox catalyst, 10-phenylphenothiazine (Ph-PTZ), to control the polymerization of MMA under UV irradiation at room temperature.²⁹⁷ The polymerization had linear kinetics as well as increasing molecular weights with conversion however relatively high

D's were observed. Electrospray ionization mass spectrometry (ESI-MS) was used to confirm a bromide chain-end.

This seminal paper was later expanded by our group for the metal-free ATRP of acrylonitrile using Ph-PTZ and two new organic photoredox catalysts, 10-(4-methoxyphenyl)-phenothiazine (4-MeOPh-PTZ) and 10-(1-naphthalenyl)-phenothiazine (Nap-PTZ) (**Figure 1.4.9**).²⁹⁸ All three photoredox catalysts exhibited controlled polymerizations with molecular weights by NMR matching theoretical however with D > 1.40 in most cases. Nevertheless, the presence of bromide-capped chains was confirmed by ¹H NMR spectroscopy.



Figure 1.4.9 Structure of three photoredox catalysts used in metal-free ATRP.

The intimate mechanism was then studied using nine different photoredox catalysts for the polymerization of MMA.²⁹⁹ Kinetic, electrochemical, photophysical and theoretical calculation studies were conducted in order to relate structure of the photocatalyst to their reactivity for both activation of (macro)alkyl halide and deactivation of propagating radicals. As shown in **Scheme 1.4.9**, the photocatalyst enters its excited state via absorption of a photon of sufficient energy which then activates alkyl halides via an oxidative quenching mechanism to generate the free radical. Deactivation involves associative electron transfer of an ion pair between the oxidized radical cation photocatalyst and bromide ion and the propagating radical to complete the catalytic cycle. Indeed, ion pair strength was shown to be an important factor for the level of control over polymerization.



Scheme 1.4.9 Proposed catalytic cycle of MMA using Ph-PTZ photoredox catalyst.

Recently, significant mechanistic and catalytic understanding have been made.³⁰⁰⁻³⁰⁶ It is now accepted that both the singlet excited state photocatalyst (¹PC*) and the triplet excited state photocatalyst (³PC*) can participate in the activation reaction. Although the ¹PC* is more reducing than ³PC*, the former has a much shorter excited-state lifetime and thus the largest contribution of activation may come from ³PC*.³⁰⁶⁻³⁰⁷ Most recently, it has been proposed that the ability to access a charge-transfer (CT) triplet excited state is paramount to stabilize the ³PC* species. This was supported from a significant effect of solvent polarity on the *o*ATRP of MMA. This arises from faster inter-system crossing (ISC) from ¹PC* to ³PC*. Furthermore, more polar solvents stabilize the 2PC**Br⁻ ion pair which is required for efficient deactivation. This catalytic understanding and design has resulted in a significant increase in level of control with D < 1.10 being achieved for MMA. Many other *o*ATRP catalysts have been synthesize and studied in such there are five main classes including polycyclic aromatic hydrocarbons,³⁰⁸ phenothiazines,^{297, 299} dihydrophenazines,³⁰² phenoxazines³⁰³ and carbazoles.³⁰⁹ *o*ATRP has

been used to synthesize star copolymers using a core-first approach³¹⁰ as well as employed in a continuous flow reactor.³¹¹

1.4.12 Mechanically/Ultrasound Induced ATRP (*mechano*ATRP) (2017)

Expanding on previous systems using external stimuli such as *e*ATRP, *photo*ATRP and *o*ATRP, ultrasound was most recently investigated as a mechanical stimulus for ATRP. Barium titanate (BiTiO₃) nanoparticles were used as a piezoelectric material in the presence of ultrasound to generate the [Cu¹(Me₆TREN)]⁺ activator from the corresponding deactivator complex.³¹² Polymerization kinetics and molecular weights indicated a living polymerization although it was not clear whether an ICAR or ARGET-type mechanism is at play. This study, although an activator regeneration-like system was used, employed the use of 10,000 ppm catalyst loading taken only to low molecular weights (< 2500 Da).

Our group later expanded on this system by using the [Cu^{II}(TPMA)Br]⁺ catalyst under low ppm conditions (<100 ppm) for which molecular weights >20,000 were obtained.³¹³ Due to the low catalyst loadings, temporal control was exhibited for the first time. Barium titanate (BaTiO₃) modified with pMMA was later used to suppress particle aggregation and also exhibited efficient living characteristics although a much slower reaction was observed. Model experiments showed that the polymerization follows an ARGET-like mechanism where the piezoelectric species reduces the L/Cu^{II}-X complex as opposed to externally generating electrons/radicals in an ICAR-like process.

In order to decrease the required amount of piezoelectric compounds, other materials were investigated, namely zinc oxide (ZnO) nanoparticles.³¹⁴ Using ZnO, the loadings of were reduced to 0.1% compared to 4.5% using BaTiO₃. The mechanism was also investigated to discriminate between the possible pathway of activator regeneration. Vast majority of regeneration occurred via a mechano-induced electron transfer (MET) from the piezoelectric material to the L/Cu^{II}-X deactivator (**Scheme 1.4.10**). In order to conserve spin, the hole that is generated on the piezoelectric surface must be replaced which was presumed from the excess TPMA ligand. This was supported from the rate of polymerization scaling with [TPMA]₀.



Scheme 1.4.10 Proposed mechanism and radical generation pathways in mechanoATRP.

*Mechano*ATRP was most recently used in aqueous systems for the polymerization of OEOMA and 2-hydroxyethyl acrylate (HEA) conducted in the absence of piezoelectric materials.³¹⁵ In aqueous systems ultrasonic waves generate hydroxyl radicals which can either directly react with monomer in an ICAR-like mechanism or can undergo hydrogen atom abstraction (HAA) with alcohols such as ethanol to form H₂O and CH₃CH[•]OH radicals which can then add to monomer. Indeed, the generation of ethanol-based radicals was supported with TEMPO trapping experiments. This novel method removes the need for externally added piezoelectric materials and significantly increases the environmentally friendliness of this low ppm ATRP technique.

1.5 ATRP Using Pseudo-Halogens

Pseudo-halogens such as thiocyanate or dithiocarbamates (DT) can also be activated by L/Cu^I complexes resulting in propagating radicals. Dithiocarbamates are commonly used as RAFT agents for the polymerization of less active monomers. One of the drawbacks of RAFT is the need for externally generated radicals using conventional radical initiators. This makes synthesis of high molecular weight polymers difficult, as well as the synthesis of complex molecular architectures - due to continual formation of new chains. The interest arose to directly activate the CTA by L/Cu^I complexes in order to abolish the need for externally generated radicals.

Various dithiocarbamates were synthesized with primary, secondary and tertiary alkylcyano leaving groups as well as isobutyryl and phenylacetate leaving groups.³¹⁶ Using ethyl methacrylate dithiocarbamate (EMADC), an inefficient RAFT agent for the polymerization of styrene, little to no control was achieved in a typical RAFT polymerization. Contrary, the [Cu¹(PMDETA)Br] complex was used as an activating agent, linear kinetics and a linear growth of molecular weight with conversion was observed using acrylonitrile dithiocarbamate (ANDC), methacrylonitrile dithiocarbamate (MANDC), EMADC and methyl phenylacetate dithiocarbamate (MPADC) (**Figure 1.5.1**). Low conversion with little control was achieved using CMDC, indicating the need for a secondary or tertiary leaving group. For the ATRP of MMA, MANDC was required as EMADC did not provide control indicating a cyano-stabilizing group was required.



Figure 1.5.1 (Top) Structures of dithiocarbamates used as pseudo-halogens in ATRP and (bottom) kinetics (A) and molecular weights and \mathcal{D} (B) for the ATRP of St using dithiocarbamates and the [Cu^I(PMDETA)Br] complex. Adopted from Ref ³¹⁶.

The effect of ligand on the ATRP of pseudohalogen was also investigated using EMADC and MANDC with the ligands TMEDA, bpy, PMDETA, BPMODA, HMTETA, Me₆TREN and TPMA. The best results were achieved with the tridentate ligands PMDETA and BPMODA. The most

active ATRP catalysts with halides, TPMA and Me₆TREN, resulted in free-radical polymerization when used with trithiocarbamates. The opposite activities, with respect to ligand activity, for halides and pseudohalide dithiocarbamate encouraged the use of model studies to investigate the observed differences.

Model studies were investigated for alkyl bromide and dithiocarbamate analogs to determine the activation rate coefficients, k_a , and K_{ATRP} equilibrium constants. Values of k_a were smaller for dithiocarbamates EMADC and MANDC than for the alkyl bromide ethyl α -bromoisobutyrate (EBiB) using PMDETA ligand. However, deactivation rate coefficients, k_d , (calculated from $k_d = k_a/K_{ATRP}$) were comparable if not larger than for bromide. Interestingly, values of k_a for the activation of EMADC were similar for HMTETA, PMDETA and Me₆TREN, despite the latter being over 1000x more active for alkyl bromides. The activity of the dithiocarbamates increased in the order ester < cyano while the activity of the ligand increased in the order Me₆TREN = HMETEA << PMDETA. This ligand activity is dramatically different than the order for alkyl halides which follows HMTETA < PMDETA << Me₆TREN.¹⁰⁶

CV was then used to compare the association constants of halides and dithiocarbamates for the Me_6TREN complex. It was found that association constants to Cu/L for DT are approximately 25 times larger than Cl⁻ and 2000 times larger than Br-. It was proposed that the large association constants for the [Cu^{II}(Me₆TREN)(DC)]⁺ complex cause it to be an inefficient deactivator of radicals which would explain the uncontrolled polymerization using this system.

Concurrent ATRP/RAFT systems were explored using trithiocarbonates (TTC) and dithiobenzoates (DTB) using various [Cu^I(L)Br] (L = bpy, PMDETA or Me₆TREN) catalysts.³¹⁷⁻³¹⁸ For the polymerizations of St with cumyl dithiobenzoate (CDTB) (**Figure 1.5.2**) the polymerization rates for PMDETA and Me₆TREN were similar and both showed very good control with D < 1.10 and theoretical molecular weights aligning with experimental, indicating high initiation efficiency. In the presence of Cu⁰, the reaction was faster due to regeneration of the L/CuI activator and possible direct activation of CDTB.

The polymerization of MMA resulted in a controlled reaction both from typical RAFT (externally generated radicals) and L/Cu¹ initiated systems. A similar effect of Cu⁰ was observed for MMA as for styrene. pMMA-b-PS block copolymers could be synthesized using either

conventional RAFT or concurrent ATRP/RAFT. The concurrent system exhibited a much cleaner shift compared to conventional RAFT due to the lack of continuously generated chains (**Figure 1.4.12 Right**).



Figure 1.5.2 (Left) structures of cumyl dithiobenzoate (CDTB) and the ATRP/RAFT trithiocarbonate initiator DiBrTTC and (right) chain-extension of the macroRAFT initiator pMMA-SCDPh using conventional RAFT (red) or ATRP/RAFT (blue). Adopted from Ref ³¹⁷.

Using an initiator containing a TTC and bromoisobutyrate group, RAFT polymerization was successfully conducted for styrene and acrylates without intervention of halogen transfer processes. However, in the presence of the [Cu^I(PMDETA)Br] catalyst, the TCC moiety and alkyl halide was activated and was able to control the polymerization of MMA. In the presence of the less active [Cu^I(bpy)₂Br] catalyst, only the alkyl halide moiety was activated. This was the first example of ATRP using TCC as a pseudohalogen.

1.6 Other Commong Metals

Although copper has been the most extensively studied metal in ATRP, both Ru- and Febased complexes have been extensively studied in ATRP. Each of these metals have specific drawbacks, but also present with unique opportunities.⁶⁹

1.6.1 Ruthenium

Ruthenium catalyzed ATRP was discovered almost concurrently with copper catalyzed ATRP. While more expensive than copper-based systems, Ru complexes also lack the same reactivity and tunability of copper-based systems. On the other hand, halidophilicty, *K*_x, of the

Ru-center is significantly higher than for many copper systems. One added benefit of ruthenium catalysts is the wide array of ligands that could potentially be utilized.

Initially, the triphenylphosphine dichloride complex, [Ru(PPh₃)₃(Cl)₂], was used in Rucatalyzed ATRP.⁶⁰ Later, an anionic phosphine ligand containing sulfonate functionality was able to be easily removed from the polymerization mixture.³¹⁹ Interestingly, dihydride complexes, [Ru(PPh₃)₃(H)₂], were more reactive³²⁰ than the analogous dichloride complexes. Chiral phosphines, including binuclear complexes, were also used to varying degrees of success.³²¹

N-Heterocyclic carbenes (NHC) offer an interesting opportunity for Ru-catalyzed ATRP since they are strong σ -donors and can be functionalized. The substituents of the NHC in [Ru(Ar)(NHC)(Cl)₂] (Ar = *p*-isopropyltoluene) complexes determined whether a well-controlled polymerization was observed or redox initiated free radical polymerization occurred.^{95, 322} Not only did the substituents affect redox properties but also the association constants between Ru^{II} and the aryl ring, the latter of which was required to dissociate to form the active ATRP complex.

Catalysts with both phosphorous and carbon-based ligands were also shown to be quite active in ATRP. The [Ru(PPh₃)₃(Ind)Cl] complex was much more active than the seminally used [Ru(PPh₃)₃Cl₃] complexes and was attributed to both a decreased reduction potential but also ring slippage to accommodate a halide upon activation.^{92, 323} Addition of electron donating groups to the indenyl ligand further increased both activity and control.³²⁴⁻³²⁵ Other systems using nitrogen and carbon or oxygen-based ligands have also been explored. ³²⁶⁻³²⁷

1.6.2 Iron

Iron has the benefit of being earth abundant and even cheaper, and possibly more biofriendly, than copper. Iron has long been used in ATRP with a wide range of success. The first report of Fe-mediated ATRP was in 1997 for MMA and St using the relatively simple [Fe(NR₃)₃(Br)₂] complex (R = butyl or octyl).^{61, 328} The same report took use of substituted bpy ligands, as well as triphenylphosphines, trialkyl phosphines and trialkylphosphites. It was later shown that diamine ligands polymerized styrene through either an ATRP mechanism or

catalytic chain-transfer (CCT) mechanism.³²⁹⁻³³¹ This was a first instance of competitive processes between organometallic intermediates and halogen atom transfer using iron complexes. The spin-state of the resulting Fe^{III} species determined the pathway, with a high spin system (S = 5/2) promoting ATRP while intermediate spin (S = 3/2) promoted CCT.³³² The accessibility of various spin states for iron are postulated to be one reason Fe-mediated ATRP is more complex than Cu mediated ATRP.

More complex ligands such as iminopyridine- and aminopyridine- based ligands were explored in ATRP.³³³⁻³³⁴ Amine-bis(phenolate) ligands have shown promise in the controlled polymerization of MMA and St for which concurrent ATRP and OMRP mechanism were proposed.³³⁵⁻³³⁷

Perhaps the most versatile catalyst has also been the simplest. Ferrous halides such as $FeBr_2$, in the presence of additional halides, can generate anionic complexes such as $[Fe^{II}Br_4]^2$, $[Fe^{III}Br_4]^-$ or $[Fe^{III}Br_5]^{2-}$ in solution.³³⁸ It was later found that the $[Fe^{II}(S)Br_3]^-$ (S = solvent) is the main activator while $[Fe^{III}Br_4]^-$ is the main deactivator³³⁹ while added triarylphosphines³⁴⁰ generally act as a reducing agent for Fe^{III} in addition to ligand. Less polar solvents gave faster rates of activation. Iron halide complexes have been extensively explored in *photo*ATRP of MMA and have exhibited some of the most well-controlled Fe-mediated ATRP systems.³⁴¹⁻³⁴³

As noted above, iron mediated ATRP presents with a complex mechanistic scenario for which either OMRP or ATRP can control the reaction. This interplay has been correlated with the spin state of the complex and will depend on the nature of the radical and ligand scaffold. These two mechanisms are themselves not detrimental since they both result in a living dormant state. However, OMRP intermediates have been shown to undergo catalytic chain transfer (CCT) and catalytic radical termination (CRT) resulting in a significant number of deadchains. This complex scenario between ATRP/OMRP/CRT is proposed to be a main reason why acrylates are difficult to polymerize by iron-mediated ATRP.

1.7 Aqueous ATRP Systems

Aqueous ATRP presents unique opportunities such as preparation of water-soluble polymers³⁴⁴ synthesis of protein-polymer conjugates³⁴⁵ or other bio hybrids.³⁴⁶ However, it was

initially difficult to achieve control over the polymerization in aqueous media. Several hypotheses have been put forth to explain the difficulties of aqueous ATRP. One such reason are the large values of K_{ATRP} which inherently lead to a greater concentration of radicals and thus more radical termination.¹⁰⁷ Recent efforts have shown that K_{ATRP} can increase up to 5-orders of magnitude in water compared to common organic solvents.^{104, 107, 347} Furthermore, in aqueous media, the deactivator species, $[LCu^{II}-X]^+$, undergoes significant amounts of halide dissociation to form the $[LCu^{II}(H_2O)]^{2+}$ complex which does not deactivate radicals, leading to loss of control.^{102, 348-350} Thus, salts with Br and Cl anions should be added.^{238, 345, 351} Finally, pH is of fundamental importance in any aqueous system. Under acidic conditions, the catalyst complex may be destroyed while under too basic conditions, hydrolysis of the chain-end occurred.

1.7.1. Effect of pH

Under basic conditions, formation of the [LCu^{II}-OH]⁺ is observed due to the much stronger coordination of OH⁻ as compared to H₂O or even X⁻. Moving from pH \approx 5.5 to pH > 10, a significant negative shift is observed in the voltammogram of both the TPMA and Me₆TRENbased complexes. This indicates that the [LCu^{II}(OH)]⁺ complex is significantly more stable than the [LCu^{II}(H₂O)]²⁺ complex.^{108, 352} It is important to note that even though the L/Cu^I-OH complex possesses a more negative redox potential, it should not be more active in ATRP than L/Cu^I due to the lack of a coordination site for halogen atom transfer. Under acidic conditions, a shoulder in the voltammograms is observed indicating the presence of a second redox active species, which potentially be partially dissociated ligand due to protonation. In fact, this was the original reason that acidic monomer such as (meth)acrylic acid (MAA or AA) could not be polymerized by ATRP.

Recently, an in-depth investigation into the polymerization of MAA by *e*ATRP revealed intramolecular chain-end lactonization as the main reason for the lack of efficient ATRP as opposed to formation of L/Cu^{II}-OR (R = H or OCR) or protonation of the ligand (**Scheme 1.7.1**).²⁵⁶ In fact, polymerization at pH = 0.9 was better controlled than at pH = 2.2 indicating that protonation of the catalyst is not significant. High molecular weight pMAA was obtained

which gave $M_n = 87000$ and D = 1.34 showing the versatility of the system. pMAA was also polymerized by SARA ATRP which also showed a well-controlled polymerization and was approximately 4 times faster although with relatively broader molecular weight distributions (D= 1.42). The mechanism of the intramolecular lactonization under these conditions is of particular interest both for expansion towards small molecule synthesis as well as the polymerization of AA which is proving to be problematic.



Scheme 1.7.1 Lactonization of pMAA chain-end between penultimate chain-end carboxylate and chain-end alkyl bromide. Reprinted with permission from Ref ²⁵⁶.

1.7.2. Association Constants of Copper Complexes in Aqueous Media

The association of ligand to Cu^I and Cu^{II} were studied in aqueous media using electrochemical methods. For TPMA, Me₆TREN and PMDETA, $\beta^{I} \approx 10^{14}$, 10^{11} and 10^{8} while $\beta^{II} \approx$ 10^{18} , 10^{16} and 10^{12} , respectively.¹⁰⁸ The trend of these values are consistent with values in organic media.¹⁰¹ To quantify halide association constants to Cu^{II}, also known as halidophilicity, competitive complexation experiments were conducted using azides and halides. It was found that $\beta_{Br}^{II} = 8$, 4 and 0.8 for TPMA, Me₆TREN and PMDET` A, respectively. Comparing these values to the values in organic media which are typically > 10⁴, one can see why deactivation is less efficient in water and excess of slats with halide anions should be added.

1.7.3. Quantification of ATRP Activity in Aqueous Media

As noted above, the high activity of copper catalysts in aqueous media can be detrimental to the polymerization due to excessive termination. Values of K_{ATRP} for 2-hydroxyethyl α -bromoisobutyrate (HEBiB) in water were measured by the electrochemistry as discussed in **Section 1.2.4** for three different ligand systems, TPMA, Me₆TREN and PMDETA and were 1.8 x 10⁻¹, 8.0 x 10⁻¹ and 4.6 x 10⁻², respectively. The same reaction conducted in MeCN

yields values of 9.7 x 10^{-6} , 1.5 x 10^{-4} and 7.5 x 10^{-8} which are, on average, 10,000 times smaller than in water.¹⁰⁸

An in-depth study was also conducted to quantify rate coefficients of activation, k_a , in aqueous/polymerization media.¹⁵⁰ Using the same HEBiB initiator, $k_a = 2.6 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ and 5.4 x $10^6 \text{ M}^{-1}\text{s}^{-1}$ were determined in pure water for Me₆TREN and TPMA, respectively. These values are around 1000 times larger than in MeCN and indicate that the increase in ATRP activity originated mainly in much faster rate of activation as opposed to slower rates of deactivation. In polymerization media (H₂O:M = 4:1), values of k_a were approximately one order of magnitude smaller than in pure water, presumably due to the decreased polarity. The comparison between K_{ATRP} vs. k_a and k_d in MeCN and water is shown in **Figure 1.7.1**.



Figure 1.7.1. Relationship between K_{ATRP} and k_a or k_d in MeCN (red) or water (blue) and structures of alkyl halides. Values are taken from Ref's ^{146, 150, 202}.

1.7.4. Polymerization Systems in Aqueous Media

In order to achieve a well-controlled ATRP reaction in aqueous media two main criteria should be met. First, additional halide should be added in order to shift the equilibrium towards deactivator complex in order to maintain sufficient control. Second, low ppm systems are typically better suited for aqueous systems as opposed to systems with large amounts of copper i.e. normal, reverse, SR&NI or AGET ATRP. In the latter systems, the extremely high reactivity of the L/Cu¹ species coupled with the large concentration of activator can lead to significant amounts of termination, although normal ATRP with 90% CuBr₂ was effective in water.³⁴⁵ Generally this should be limited to relatively less reactive catalysts. Contrary to normal ATRP, low ppm systems have a dynamic [L/Cu¹¹-X]/[L/Cu¹] ratio which will automatically adjust with *K*_{ATRP}. Thus, in aqueous polymerization, the concentration of L/Cu¹ is low to the point that excess termination does not occur. Indeed, aqueous low ppm systems have been developed such as SARA ATRP,^{104, 353} *photo*ATRP,²⁹³ *mechano*ATRP,³¹⁵ *e*ATRP,^{148, 250, 255} ARGET²³⁸ and ICAR³⁵¹ that give well-controlled polymerizations. This fundamental understanding of aqueous ATRP has allowed for the further development of ATRP in dispersed media.

1.8 ATRP in Dispersed Media

The development of controlled radical polymerization procedures in dispersed media minimizes the environmental impact and the cost of the process.³⁵⁴⁻³⁵⁵ However, ATRP in dispersed systems such microemulsion,³⁵⁶⁻³⁵⁷ miniemulsion^{234, 358-364} and emulsion³⁶⁵⁻³⁶⁸ is less explored. The challenge of simultaneously achieving controlled polymerization and good colloidal stability is hampered by the partition of ATRP catalysts between the aqueous phase and the hydrophobic phase. It follows that the localization of Cu complexes in this context is crucial.¹⁰⁰

Among all dispersed media, miniemulsion "localizes" the polymerization into hydrophobic monomer droplets, formed by applying high shearing forces to a mixture of monomer, water, catalyst, surfactant and co-surfactant. Since the catalyst must be confined into monomer droplets, hydrophobic Cu complexes were specifically synthesized for

miniemulsion ATRP.³⁶⁹ Until the 2012, most hydrophobic ATRP catalysts were based on dNbpy or bis(2-pridylmethyl)octadecylamine (BPMODA; **Figure 1.8.1**). These worked well for normal ATRP in miniemulsion but were unable to efficiently mediate the low ppm ATRP in miniemulsion due to the low K_{ATRP} values. A more active, albeit still hydrophobic catalyst, (bis]2-(4-methoxy-3,5-dimethyl)pyridylmethyl]octadecylamine (BPMODA*; **Figure 1.8.1**) was synthesized. The activity of the [Cu(BPMODA*)Br]⁺ catalyst was assessed by CV and it was found to be 106 mV more negative than BPMODA indicating an increase in K_{ATRP} by almost a factor of 100. Partition experiments showed that the incorporation of electron donating groups had no effect on the hydrophobicity of the complex. Both homo- and heterogeneous ATRP exhibited significantly better control using BPMODA* compared to BPMODA.



Figure 1.8.1 Structures of BPMODA, BPMODA* and BPMEA ligands for used in dispersed media ATRP.

However, extensive purification was needed to remove these complexes from produced polymers, and the relative amount of confined Cu^I and Cu^{II} species could not be tuned by electrical stimuli, because electrons were released in the aqueous phase. The communication between electrode and hydrophobic phase was made possible by using a dual catalytic system, in which a hydrophilic catalyst "shuttled" electrons from the electrode to a hydrophobic catalyst inside droplets.³⁷⁰ Due to both the high hydrophobicity and relatively high activity, BPMODA* was chosen as the organic phase catalyst while the ligand used for the aqueous-phase catalyst was varied between bpy, N,N'-bis(2-pyridylmethyl)-2-hydroxyethylamine (BPMEA) and TPMA. BPMDEA showed not only the fastest rate of polymerization but also the best control. The proposed mechanism was proposed to occur via electrochemical generation of [Cu^I(BPMEA)]⁺ at the working electrode which migrated into the monomer droplet and

reduced [Cu^{II}(BPMODA*)Br]⁺ to generate the organic-phase ATRP activator [Cu^I(BPMODA*)]⁺ which catalyzed ATRP. An important aspect to this system is that the aqueous phase catalyst must be sufficiently more reducing than the organic phase catalyst. However, despite enabling efficient *e*ATRP in miniemulsion, Cu contamination in the polymer very high.

Inspired by the concept of a shuttle-catalyst, a new system was later developed, based on a the [Cu^{II}(TPMA)Br]⁺ complex and an inexpensive anionic surfactant, sodium dodecyl sulfate (SDS). SDS was considered harmful for ATRP catalysts, because it can interact with Cu and poison the catalyst. In contrast, this interaction was exploited to obtain a surfactant-catalyst, which tuned miniemulsion polymerizations by a combination of interfacial catalysis (Cu/TPMA bound to SDS, at the surface of monomer droplets) and ion-pair catalysis ([Cu^{II}(TPMA)][DS] and [Cu^{II}(TPMA)Br][DS] ion pairs inside droplets).³⁶² Indeed, cyclic voltammetry showed that, under typical conditions for miniemulsion *e*ATRP, 95% of the copper complex was bound to SDS, while only 1% was inside of the hydrophobic monomer. As shown in **Scheme 1.8.1**, the L/Cu^{II}-X complex can be reduced while either bound to the monomer droplet or upon diffusion into the continuous phase, although the former contributes most to the overall reduction mechanism. Since both initiator and monomer are confined to the organic phase, ATRP activation and deactivator can occur via bound catalyst or catalyst that has diffused into the monomer droplet. Again, though, the predominant ATRP occurs at the surface bound catalyst.



Scheme 1.8.1 Proposed mechanism of ion-pair and interfacial catalysis in eATRP (e⁻ from current) or ARGET (e⁻ from reducing agent) in miniemulsion. Reprinted with permission from Ref ³⁶².

Well-controlled miniemulsion *e*ATRPs of n-butyl acrylate (BA) was performed with [Cu(TPMA)][DS], even using as little as 100 ppm of catalyst. The resulting polymers were chain-

extended with different monomers, proving the excellent retention of chain-end functionality. Moreover, by crashing the final latex, the hydrophilic [Cu^{II}(TPMA)Br]⁺ moved to the aqueous phase, minimizing metal contamination in precipitated polymers (*e.g.* 14 ppm of Cu were measured in the precipitated polymer, when using 700 ppm of Cu for the polymerization).

This catalytic system was also successfully applied to activators re-generated by electron transfer (ARGET) ATRP in miniemulsion, replacing electrons with ascorbic acid as water-soluble reducing agent, which established the ratio between Cu¹ and Cu¹¹ species.³⁶¹ Miniemulsion ARGET ATRP of n-butyl methacrylate was well-controlled even when decreasing Cu loading to 50 ppm, thus measuring only 0.3 ppm of Cu into the precipitated polymer. Furthermore, well-defined macromolecular stars and brushes were prepared by using suitable multi-armed macroinitiators.

The ultimate goal for ATRP in dispersed media is to develop a procedure for *ab initio* emulsion polymerization, which does not require high shearing forces and a co-surfactant. In *ab initio* emulsion polymerizations, radical initiation and particle nucleation occur into the aqueous phase, then monomer molecules diffuse from large droplets to generated particles, where the polymerization proceeds. These different localizations make emulsion ATRP very challenging. However, [Cu^I(TPMA)]⁺ can initiate chains in water, and then control the polymerization in growing particles by interfacial and ion-pair catalysis, by interacting with SDS. Indeed, successful *ab initio* emulsion ARGET ATRP of several (meth)acrylates was performed, forming stable latexes and polymers with low dispersity. SDS loading was reduced below 3 wt% (relative to monomer), and block copolymers and gradient copolymers were prepared. The proposed setup is inexpensive and easy to integrate into existing plants for emulsion free radical polymerizations. High solid contents and polymerization of other very hydrophobic monomers, from styrene to lauryl- and stearyl (meth)acrylates could be tackled to broaden the applicability of this system.

1.9 Oxygen Tolerant ATRP

One aspect of all radical polymerizations is the inherent sensitivity of radicals to be quenched by oxygen forming peroxy radicals which consequentially kill chains.³⁷¹ Furthermore,

in ATRP, is the sensitivity of many L/Cu^I complexes to oxygen forming L/Cu^{III}-(O₂) species which decompose into L/Cu^{III}-OOH species which can then further decompose. Thus, it is very important in ATRP to carefully deoxygenate the reaction mixture. One method to remove oxygen is by the addition of a large excess of reducing agent such as ascorbic acid,²³⁸ or Sn^{II} compounds^{235, 372} in a closed container. These systems work by reducing the formed L/Cu^{II}-OOH complex back to L/Cu^I until all of the oxygen is consumed. Clearly, this method is not the most practical. Previous work has shown that the use of glucose oxidase (GOx) was effective in the removal of oxygen for free radical polymerization³⁷³ as well as in RAFT polymerization.³⁷⁴⁻³⁷⁶ GOx works by transforming O₂ into H₂O₂ using glucose.³⁷⁷⁻³⁷⁹ However, in ATRP, the formed H₂O₂ can also oxidize L/Cu^I complexes while concurrently initiating new chains leading to polymers with molecular weights significantly lower than theoretical.



Scheme 1.9.1 (A) Aerobic respiration and B) "breathing" ICAR ATRP. Reproduced with permission from ³⁸⁰.

To circumvent this issue, pyruvate was added to an ICAR ATRP reaction mixture as a hydrogen peroxide scavenger as shown in **Scheme 1.9.1**.³⁸⁰ The reaction between H₂O₂ and Py yields CO₂, acetate and water all of which do not interfere with typical components of the ATRP system. This system is inspired by aerobic respiration occurring in cells which glucose and oxygen are converted to CO₂ and ATP. The polymers obtained using "breathing" ATRP exhibited low *D*s and reached >90% conversion in just 2 hours. The reactions could be conducted in vessels open to air by continuous elimination of oxygen. This system was then

extended to synthesizing bio-conjugates by grafting OEOMA₅₀₀ from the protein bovine serum albumin. This study opens up the possibility of other "breathing" ATRP systems such as photoATRP or ARGET ATRP.

1.10 Removal/Recycling of ATRP Catalysts

One recognizable drawback, as with any catalytic system, is the removal of the metal complex from the final material. To an extent, the need for purification was circumvented by the development of low ppm systems which can be conducted using < 10 ppm of catalyst which gives essentially colorless polymers. However, for more advanced materials such as electronics or biomedical applications, further removal may be required.³⁸¹⁻³⁸² Historically, the copper complex has been removed by passing the polymer solution through silica or neutral alumina columns,³⁸³ stirring with an ion-exchange resin,³⁸⁴ or precipitation into a nonsolvent.³⁸⁵

If silica or alumina are not able to be used such as with polar side chains such as poly(ethylene oxide) (PEO), new techniques must be developed. One such technique is electrodeposition.^{247, 386-387} The L/Cu complex (L = N-morpholine-2-pyridylmethanimine) could undergo a three-electron reduction process which results in the quantitative removal of copper without degradation of the polymer. More common ATRP catalysts based on Me₆TREN could undergo electrodeposition on a Pt working electrode.

1.10.1 Biphasic Catalysis

Bi-phasic catalysis offers a unique opportunity for catalyst removal and recyclability. A highly fluorinated ligand based on PMDETA was used in normal ATRP in a perfluoromethyl cyclohexane and toluene mixture at 90°C (**10.1**; **Figure 1.10.1**).³⁸⁸ Upon cooling to room temperature, the reaction mixture separated into a layer containing the catalyst and a layer containing the polymer. Other fluorinated ligands based on bpy (**10.2**; **Figure 1.10.1**) were synthesized and were able to exhibit selective solubility in toluene with temperature.³⁸⁹ This allowed for homogeneous ATRP at elevated temperatures with precipitation at room temperature allowing for the separation and reuse of the catalyst up to three times.



Figure 1.10.1 Fluorinated ligands used as ligands for biphasic ATRP.

Ionic liquids have also shown promise in ATRP as a component for biphasic catalysis. 1butyl-3-methylimidazolium hexflourophosphate was used as a solvent for normal ATRP of MMA using pyridylmethylimine-based catalyst.³⁹⁰ While the catalyst was efficiently separated from the polymer (0.17% by ICP) by washing with toluene, the control over the polymerization was lacking with higher than expected molecular weights and broad molecular weight distributions (D > 1.40). It was later found that acrylates with short carbon side chains (C₁₋₄) gave better controllability due to the miscibility of the monomer with the ionic liquid.³⁹¹ Fe-based ATRP was also conducted in ionic liquids in the absence of additional liquids.³⁹²

Thermoregulated phase-transfer catalysis (TRPTC) has also been used in aqueous/organic biphasic systems for AGET ATRP. The key was a thermoresponsive PEGsupported pyridyl ligand (10.3; **Figure 1.10.3**).³⁹³⁻³⁹⁵ At 90°C the reaction is homogeneous but phase separates at room temperature allowing for easy decanting. A similar system³⁹⁶ has been developed for ICAR ATRP in which a the [Cu^{II}(TPMA)Br]⁺ complex resides in the aqueous phase while the monomer, initiator and AIBN reside in the organic (toluene) layer, as shown in **Figure 1.10.2**. Heating to 75°C allowed for enough of the deactivator to diffuse to the organic layer to trigger the polymerization. Upon cooling, the catalyst efficiently diffused to the aqueous layer resulting in polymer separated materials.



Figure 1.10.2. Photographs for diffusion regulated phase-transfer catalysis (DRPTC)-based ICAR ATRP for catalyst separation and recycling. Reprinted with permission from Ref 396 © 2015 Wiley-VCH.

1.10.2 Supported Catalysts for ATRP

The ultimate goal of solid-supported catalysis is to have the reactivity of a homogeneous system while retaining the recycling and reusability of a heterogeneous systems.³⁹⁷ Polyethylene (PE) was first used as a "soluble support" because it is soluble in toluene at high temperature (>100°C) but precipitates a lower temperatures. Indeed, a pyridylimine ligand grafted from a polyethylene oligomer, although its low reactivity hampered the controllability of the polymerization.³⁹⁸ Later, amine-based ligands grafted from PE-polyethylene glycol (PEG) block copolymers were investigated, again due to the solubility at 75°C and precipitation at room temperature.³⁹⁹⁻⁴⁰⁰ The ATRP of St using this system provided much better control with D < 1.20 with the ability to recycle the catalyst up to three times. The solubility/insolubility using an external stimulus was later expanded to stilbene-based catalysts which can isomerize from the soluble *trans*- isomer to the insoluble *cis*- isomer upon UV irradiation.³⁸⁵ Although, this was hampered by the lack of reversibility of the isomerization.

Physical or chemical immobilization of an ATRP catalyst on a solid support is attractive in that catalyst removal would be fast and near-quantitative. In an early report, the [Cu(HMTETA)]⁺ complex was physically adsorbed onto silica gel and provided a well-controlled polymerization.⁴⁰¹ The catalyst was found to retain 80% and 50% of its reactivity upon its second and third uses, respectively. This same system was used in a continuous-flow system which allowed for in situ separation and recycling of the catalyst.⁴⁰² Later, the

[Cu^{II}(PMDETA)Br]⁺ complex was adsorbed to hydrated clay and was able to be reused 21 times without noticeable loss in activity in AGET ATRP using ascorbic acid as a reducing agent.⁴⁰³⁻⁴⁰⁴ Residual catalyst loadings were found to be 0.2 ppm using atomic absorption spectroscopy.

The use of chemi-adsorbed ATRP was first conducted by our group using various amines grafted from various silica and cross-linked polystyrene supports.⁴⁰⁵⁻⁴⁰⁶ The control over the polymerization was poor with *Đ* ranging from 1.5 to 10. The control could be increased by addition of more catalyst and/or deactivator although the limitations of heterogeneous ATRP could be realized. This is because control in ATRP is governed by the rate of deactivation which approaches diffusion-controlled limits. Grafting the copper complex to silica nanoparticles can severely hamper the diffusion of the deactivator. The effect of spacer between silica gel and catalyst was later investigated although similar results were obtained.⁴⁰⁷ Complex architectures such as stars, graft and bottle-brush copolymers were synthesized using a hybrid catalyst system with no observable difference between the hetero- and homogeneous normal ATRP systems.⁴⁰⁸⁻⁴⁰⁹



Figure 1.10.3. Illustrations of (a) a Covalently Solid-Supported Catalyst and (b) a Reversibly Supported Catalyst in the Synthesis of Polymer Architectures. Reproduced with permission from Ref ⁴¹⁰. © 2004 American Chemical Society.

Magnetic nanoparticles, namely iron oxide (Fe₃O₄), have also been used as a solid support for ATRP catalysts with the goal of easy catalyst separation.⁴¹¹ When initially added deactivator was added to the reaction mixture, a well-controlled normal ATRP reaction with 85% initiator efficiency and D < 1.20 was obtained. Furthermore, the catalysts were easily removed by an external magnet while retaining most of its control upon reuse. The activator complex could also be regenerated using an amine of Sn^{II} reducing agent. Similar solidsupported catalysts were later used in ATRA.⁴¹² A study by Zhu et al showed that while activation likely does occur at the surface, deactivation is most likely to occur in solution from leached, or purposely added deactivator. The lack of deactivation at the surface is proposed to be due to geographic isolation of deactivation sites as opposed to lack of polymeric diffusion to the surface bound deactivator.⁴¹³ In order to attempt to circumvent this, immobilization of an ATRP catalyst via reversible hydrogen bonding⁴¹⁰ has been investigated, as shown in **Figure 1.10.3**. Indeed, this method was shown to provide a well-controlled polymerization using D <1.20. The removal and/or possibility of catalyst reuse seems to be severely limited in both synthesis of a sufficiently active catalyst while also provided fast enough deactivation.

1.11 Future Outlook

Catalyst design has been at the forefront of ATRP research since 1995, continuously looking for more active, robust and inexpensive catalysts. An in-depth understanding of structure-reactivity relationships was achieved through systematic evaluation of many different catalysts. Since seminal bpy-based catalysts were used, the activity of new catalysts has been increased over 10,000,000 times. This has allowed for new initiation methods to be developed in which the L/Cu^{II} activator is slowly and continuously regenerated from L/Cu^{II}-X which built-up is due to unavoidable termination. External stimuli such as electrical current, irradiation and mechanical have all been used to moderate ATRP. Although not based on copper, metal-free ATRP has proven to be a potentially powerful catalytic system although, to date, the monomer scope is quite narrow with MMA being most successful.

The copper-based low ppm systems all require the need of highly active catalysts in order to obtain control over the polymerization. This is because the $[L/Cu^{II}-X]/[L/Cu^{I}]$ ratio dynamically changes and depends on [R[•]], [RX] and most importantly, K_{ATRP} . Thus, for higher active catalysts, a larger fraction of total copper will be in for the form of the deactivator than activator. This benefit is two-fold. On one hand, deactivation will be more efficient due to a higher concentration of deactivator and thus will provide for better control. On the other, a decreased fraction of [L/Cu^I] suppresses unwanted side-reactions catalyzed by L/Cu^I such as catalytic radical termination (CRT).^{169, 171} CRT has been shown to be the dominate mode of

termination for acrylates in ATRP and has been the subject of intense research, much of which will be discussed in coming chapters.

Another area of great interest is the development of new methods to more quickly and accurately quantify reactions occurring in ATRP. Accurate, in-depth understanding of the kinetics of ATRP are paramount when looking to scale up polymerizations as well as for further mechanistic understanding. In the past decade, new methods involving electrochemistry have been used to measure a variety of kinetic and thermodynamic parameters such as k_a , k_d , k_{CRT} , k_t , K_{ATRP} , K_X and K_{OMRP} . Electrochemistry is a powerful tool since experiments can be simulated in order to obtain a more accurate mechanistic picture. Unfortunately, these simulations require the accurate knowledge of many parameters which change with ligand, temperature, solvent, alkyl halide, etc. However, as these techniques become better utilized, it seems that an "encyclopedia" of ATRP parameters will likely be "published".

Finally, the largest potential impact of more active catalysts would be to further expand the monomer scope for ATRP. For instance, monomers with highly reactive, nucleophilic radicals such as vinyl acetate (VOAc) and N-vinylpyrrolidone (NVP) can be relatively wellcontrolled using xanthates as a chain-transfer agent in MADIX RAFT. However, due to the large BDFE of the VOAc-Br and NVP-Br dormant species, current catalysts are not reactive enough to activate these strong (macro)alkyl halide bonds. Thus, an ongoing quest for more active catalysts is imperative. Although new ligand topologies are possible, it seems as though the most promising method is to increase electron donation to the copper center via rational ligand design. It is hopeful with increasingly active ligands and further understanding of side reactions, less active monomers such as VOAc and NVP will soon be polymerizable via ATRP.

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Chapter 2.

Development & Understanding of Photochemistry in ATRP

2.1 Preface

As Chapter 1 reviewed in detail, the development of ATRP with activator regeneration, also known as "low ppm" ATRP, has allowed for catalyst loadings to be significantly decreased to < 10 ppm relative to monomer. These systems use highly active copper catalysts with the addition of a reduction mechanism for L/Cu^{II}-X which is built-up due to the persistent radical effect (PRE). A number of methods have been developed for the slow and continuous regeneration of the L/Cu^I complex and include chemical reducing agents as in activators regenerated by electron transfer (ARGET), conventional radical initiators as in initiators for continuous activator regeneration (ICAR) or by use of electrochemical current as in *e*ATRP.

A recently developed low ppm system takes use of irradiation to photochemically reduce the L/Cu^{II}-X species in *photo*ATRP. This chapter discusses in-depth mechanistic studies that helped to elucidate the mechanism of activator regeneration in *photo*ATRP. It was found that the vast majority of radicals are generated via a reductive quenching mechanism between excited state deactivator complex [L/Cu^{II}-X]* with an aliphatic amines electron donor. Other methods of radical generation were quantified such as i) photolysis of alkyl halide; ii) photochemical electron transfer between ligand and monomer; and iii) photochemical electron transfer between alkyl halide and ligand. Kinetic simulations indicated that catalytic radical termination (CRT) is the dominant pathway of radical termination leading to rate law dependent on ([Ligand][RX] K_{ATRP})^{1/2}.

^{*}Work in this section was published:

^{1. &}lt;u>**TG Ribelli**</u>, D Konkolewicz, S Bernhard, K Matyjaszewski. "How are Radicals (Re)Generated in photoATRP." J. Am. Chem. Soc. **2014**, 136, pp 13303-13312. © 2014 American Chemical Society

^{2. &}lt;u>TG Ribelli</u>, D Konkolewicz, X Pan, K Matyjaszewski. "Contribution of Photochemistry to Activator Regeneration in ATRP." *Macromolecules*, **2014**, 47, pp 6316-6321. © 2014 American Chemical Society

The effect of photochemical processes on ICAR ATRP was also studied. It was determined that, unless the rate of activation regeneration was slow (i.e. reduction of L/Cu^{II}-X), then photochemistry did not significantly contribute to the overall rate of regeneration. Only at low [AIBN]₀ or low temperatures did photochemistry contribute.

The work presented in this chapter was a collaborative effort between myself and Prof. Dominik Konkolewicz. Dominik taught me how to carefully design, execute and analyze the necessary experiments. He also taught me the basics of kinetic simulations using the PREDICI software. Prof. Xiangcheng Pan helped with the characterization of the hood lighting. I would like to also thank Prof. Stefan Bernhard for discussions involving photochemical phenomena important to the study.

2.2 How Are Radicals (Re)Generated in Photochemical ATRP?

2.2.1 Preface

The polymerization mechanism of photochemically mediated Cu-based atom transfer radical polymerization (ATRP) was investigated using both experimental and kinetic modeling techniques. There are several distinct pathways that can lead to photochemical (re)generation of Cu¹ activator species or formation of radicals. These (re)generation pathways include direct photochemical reduction of the Cu^{II} complexes by excess free amine moieties and unimolecular reduction of the Cu^{II} complex, similar to activators regenerated by electron transfer (ARGET) ATRP processes. Another pathway is photochemical radical generation either directly from the alkyl halide, ligand, or via interaction of ligand with either monomer or with alkyl halides. These photochemical radical generation processes are similar to initiators for continuous activator regeneration (ICAR) ATRP processes. A series of model experiments, ATRP reactions, and kinetic simulations were performed to evaluate the contribution of these reactions to the photochemical ATRP process. The results of these studies indicate that the dominant radical (re)generation reaction is the photochemical reduction of Cu^{II} complexes by free amines moieties (from amine containing ligands). The unimolecular reduction of the Cu^{II} deactivator complex is not significant, however, there is some contribution from ICAR ATRP reactions involving the interaction of alkyl halides and ligand, ligand with monomer, and the photochemical cleavage of the alkyl halide. Therefore, the mechanism of photochemically mediated ATRP is consistent with a photochemical ARGET ATRP reaction dominating the radical (re)generation with contributions from photochemical ICAR ATRP processes.

^{*}Work in this section was published: <u>TG Ribelli</u>, D Konkolewicz, S Bernhard, K Matyjaszewski. "How are Radicals (Re)Generated in photoATRP." *J. Am. Chem. Soc.* **2014**, 136, pp 13303-13312. © 2014 American Chemical Society

2.2.2 Introduction

Reversible deactivation radical polymerization (RDRP) techniques have revolutionized the fields of polymer chemistry and materials science over the past two decades. These RDRP methods allow well-controlled polymers with complex architectures to be synthesized as was traditionally possible only with ionic polymerizations.¹ However, RDRP methods have tolerance to functional groups and impurities similar to conventional radical polymerization.² The most popular RDRP methods are nitroxide mediated polymerization (NMP),³ atom transfer radical polymerization (ATRP),⁴ and reversible addition-fragmentation chain transfer (RAFT) polymerization.⁵ ATRP is one of the most widely used techniques since it can be performed under mild conditions, it is compatible with a wide range of monomers, and it gives excellent control over the polymer structure.^{4, 6-7}

In ATRP, control over the polymer structure is gained through a catalytic cycle in which a low oxidation state transition metal catalyst activates an alkyl halide to generate an alkyl radical and an oxidized form of the transition metal complex.^{4, 6} This alkyl radical can add several monomer units before being deactivated by the high oxidation state deactivator complex to reform the alkyl halide and the activator complex. This process can be repeated for each alkyl halide over several cycles, allowing the uniform growth of the polymer chains. In the majority of cases, the activator and deactivator complexes are L/Cu¹ and L/ Cu¹¹-X, respectively. However, one limitation of normal ATRP, where alkyl halides and activator complexes are used, is that each radical termination event leads to the irreversible formation of the deactivator complex by the persistent radical effect.^{6, 8} Therefore, high concentrations of the activator complex were required to maintain an acceptable rate of polymerization throughout the reaction.^{4, 9} Throughout the remainder of this article, the activator complex will refer to L/Cu¹ complexes, and the deactivator complex will refer to L/Cu¹¹-X.^{4, 10}

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Scheme 2.1. ATRP processes with (re)generation processes.

In recent years, various methods have been developed that allow ATRP to proceed with catalyst concentrations at or below 100 ppm.⁹ These low catalyst loadings are possible when the excess deactivator complex is reduced to the activator complex, as indicated in **Scheme 2.1**. This reduction can occur by various methods, including: addition of a chemical reducing agent as is done in activators for continuous activator (re)generation by electron transfer (ARGET) ATRP,⁹ adding an external radical initiator, as is done in initiators for continuous activator (re)generation (ICAR) ATRP,⁹ applying a reducing current, as occurs in electrochemically mediated ATRP,¹¹ using zerovalent metals or sulfite species as supplemental activators and reducing agents (SARA) in ATRP,¹²⁻¹⁵ or to photochemically regenerate activator species.¹⁶⁻²⁰ Photochemically mediated ATRP, or photoATRP, processes have received considerable attention recently¹⁶⁻³⁰ due to the simple preparation, minimal use of additives, and opening the option of using sunlight.¹⁹⁻²⁰ The option of photochemical and sunlight driven processes has also been used for other RDRP processes such as RAFT,³¹⁻³² and the combination of RAFT with iridium or ruthenium catalysts.^{23, 28, 30} Additionally, photochemically controlled organic transformations have received considerable interest in the recent literature.³³⁻³⁵

Despite the facile nature of photoATRP, there are several unanswered questions regarding the mechanism of radical formation and activator (re)generation in this photochemical process. These include: do Cu¹ species participate in photochemical processes?; does the X-Cu^{II}/L deactivator complex undergo unimolecular photochemical reduction?; can Cu^{II} species participate in photochemical redox through other pathways?; and to what extent do the alkyl halide and excess ligand contribute to the photochemical radical generation? In earlier work, careful measurement of the activation rate of alkyl halides by Cu¹ species showed negligible dependence on the presence of a UV photon source.^{19, 22} This indicates that photochemically enhanced alkyl halide activation through excited Cu¹ complexes is not kinetically significant, in contrast to the iridium mediated RDRP processes.^{21, 23, 25} Therefore, the Cu mediated ATRP with typical ligands in the presence of light must proceed by radical formation and activator (re)generation, rather than through enhanced activity of the Cu¹ complex.

There are several possible ways that the activator and radical species can be regenerated photochemically. One pathway is the unimolecular photochemical cleavage of the L/Cu^{II} - halogen bond in the excited state to give the L/Cu^I activator complex and a halogen radical, as proposed in various reports and shown in the top line of **Scheme 2.2**.¹⁶⁻¹⁹ This process would be a hybrid of ICAR and ARGET ATRP, since Cu^{II} is reduced in the presence of light by electron transfer as in ARGET while giving a halogen radical that can initiate new chain, as in ICAR ATRP. An alternative radical (re)generation mechanism has the photoexcited alkyl halide, ligand, or their combined interaction, generating radical species which can react with monomer in a photochemical mechanism akin to ICAR ATRP, as shown in lines 2-4 of **Scheme 2.2**.²⁰

In the case of the alkyl halide, homolytic cleavage of the carbon-halogen bond is anticipated as shown in line 2 of **Scheme 2.2**.³⁶⁻³⁷ In the case of the photochemical interaction involving the ligand, the nitrogen centered radical cation is expected to be generated.³⁷ To conserve both charge and spin, a second molecule must accept this electron. This alternative molecule can be an electron poor alkene, such as a (meth)acrylate moiety as shown in the third line of **Scheme 2.2**.³⁷ Alternatively, the ligand and alkyl halide can photochemically generate the nitrogen centered radical cation, an alkyl radical and a halide anion, as shown in line 4 of **Scheme 2.2**.²⁰ A final possibility is that the Cu^{II} complexes in the excited state can react with electron donating species (e.g. amine), reducing the Cu^{II} species and generating a radical cation species from the ligand, as shown in line 5 of **Scheme 2.2**.

It should be noted that all of these photochemical radical (re)generation pathways are parallel pathways and are not concerted two or three photon processes. All photochemical

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(re)generation of radicals are one photon processes. These pathways are shown in **Scheme 2.2**. In all cases where the nitrogen centered radical cation is generated, it rapidly undergoes proton transfer, giving a protonated amine and a carbon centered radical.³⁷ This carbon centered radical can then add to monomer which would result in the formation of a new chain with a positively charged end group. This chain end can either stay as the ionic species or it can become deprotonated to give the neutral amine.



Scheme 2.2. Proposed activator (re)generation pathways in photoATRP. Top is direct reduction of $L/Cu^{II}-X$, middle is the generation of radicals by the reactions of an alkyl halide and/or a ligand, and bottom is the photochemical reduction of Cu^{II} by an electron donor.

In this work, the kinetic contribution of all pathways shown in **Scheme 2.2** are evaluated for the polymerization of MA in DMSO catalyzed by Cu/Me₆TREN (Me₆TREN = tris(2-(dimethylamino)ethyl)amine) complexes. The contributions are determined using a combination of experimental and simulation techniques.

2.2.3 Experimental

Materials. Tris(2-(dimethylamino)ethyl)amine (Me₆TREN) was synthesized as reported in the literature.³⁸ Methyl acrylate (MA, Sigma-Aldrich, 99%) was passed over a column of basic alumina to remove inhibitor prior to use. Dimethylsulfoxide (DMSO, Fisher Scientific, 99.9%)

was bubbled with nitrogen gas for 30 minutes prior to use. Copper(II) bromide (CuBr₂, Acros Organics, >99%), copper(II) trifluoromethanesulfonate (Cu(OTf)₂, Sigma-Aldrich, 98%), triethylamine (TEA, Sigma-Aldrich, >99%), ethyl 2-bromoisobutyrate (EBiB, Sigma-Aldrich, 98%), and methyl 2-bromopropionate (MBP, Sigma-Aldrich, 98%) were used as received.

Instrumentation. Gel permeation chromatography (GPC): GPC was used to determine number average molecular weight (M_n) and M_w/M_n values. The GPC was conducted with a Waters 515 HPLC Pump and Waters 2414 Refractive Index Detector using PSS columns (Styrogel 10², 10³, 10⁵ Å) in tetrahydrofuran (THF) as an eluent at a flow rate of 1 mL/min at 35 °C. The column system was calibrated with 12 linear poly(methyl methacrylate) (PMMA, $M_n = 800 \sim 2,570,000$) standards. Conversion of monomer was determined by ¹H NMR spectroscopy. Absolute values of molecular weight of PMA were calculated utilizing universal calibration as reported in literature.³⁹

Nuclear Magnetic Resonance (NMR): Monomer conversion was measured using ¹H NMR spectroscopy, using a Bruker Avance 300 MHz spectrometer at room temperature.

UV-Visible Spectroscopy: All characterizations were performed using a Varian Cary 5000 UV/Vis/NIR spectrometer.

Photoreactor: The samples were illuminated in a custom designed, multi-well photoreactor: A 5 m long 24 W LED strip with 300 diodes (392 nm: <u>superbrightleds.com</u> WFLS-UV300) was mounted inside an 8 inch (203 mm) galvanized steel tube in a spiral pattern.¹⁹ The intensity of the photoreactor was 0.90 ± 0.05 mW/cm².¹⁹ The 60 mm high illumination zone was centered on the samples, which were magnetically stirred in a Schlenk flask under nitrogen.

Procedures. Typical photopolymerization procedure: To a vial, Me₆TREN (6.1 mg, 0.027 mmol), EBiB (29 mg, 0.15 mmol), and MA (3.80 g, 44.1 mmol) were added. The contents of the vial were homogenized by vigorous shaking and transferred to a Schlenk flask equipped with a magnetic stirrer. To this mixture, 25 μ L of a 0.18 M solution of CuBr₂ (0.0045 mmol Cu) in DMSO was added. The flask was sealed with a glass stopper and subjected to two freeze-pump-

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thaw cycles. The flask was placed under nitrogen, and 2 mL of DMSO that had been bubbled with nitrogen for at least 30 min, was added using a syringe. The reaction mixture was subjected to 3 additional freeze-pump-thaw cycles, then placed under nitrogen. The reaction mixture was put into the photoreactor and irradiated at 392 nm.

2.2.4 Results and Discussion

2.2.4.1 Photochemical Characterization and Polymerization Kinetics

To confirm the significance of the photochemical processes, the kinetics of the same reaction were monitored both with and without light. As illustrated in **Figure 2.1(a)**, the polymerization proceeds efficiently in the presence of light, while in the absence of light the reaction is significantly retarded, and is almost non-existent. However, if this same reaction is re-exposed to light, it progresses again and leads to relatively rapid polymerization. This cycle can be repeated multiple times. **Figure 2.1(b)** indicates that the control over the polymer architecture is very good, even with the intermittent cycles of light irradiation and darkness. The molecular weight is close to the theoretical value at all times, and the dispersities are low, ultimately reaching values below $M_w/M_n < 1.05$.



Figure 2.1. Polymerization with intermittent "on" and "off" periods. (a) Semilogarithmic plot and (b) Evolution of M_n (solid points) and M_w/M_n (hollow points) with conversion. Conditions: [MA]₀:[EBiB]₀:[Cu^{II}Br₂]₀:[Me₆TREN]₀=300:1:0.03:0.18, in DMSO, [MA]₀=7.4 M, 25 °C, irradiated by 392 nm light (0.9 mW/cm²).

As in any other light induced process, it is necessary to characterize the polymerization components photochemically. In the literature, the solvent and monomer alone have shown very little photochemical activity,¹⁹⁻²⁰ therefore only the alkyl halide initiators, ligand, and CuBr₂/ligand complex are expected to participate in photochemical reactions. These species, at the concentrations present in polymerization, were characterized by UV/Vis/NIR spectroscopy, as shown in Figure 2.2. The data in Figure 2.2 indicates that in the region near 400 nm, the strongest absorbance is due to the $CuBr_2/Me_6TREN$ complex, with only very weak absorbance due to the alkyl halides MBP and EBiB, and the ligand Me₆TREN, although the oxidized ligand has a light-yellow color, after it has been exposed to air for a long time. In all photochemical processes the first step is the absorbance of the incident photon. In fact, the efficiency of photochemical reactions is not only limited by the intensity of the light source. The absorptivity of the chromophore, the opacity of the secondary reagents, and the quantum yield of the desired pathway are other contributing factors. Quantum yields cannot exceed unity and will not be able to offset the effects of a very low absorbance (such as A<0.02 at 390 nm for Me₆TREN). The involvement of a Cu^{II} chromophore, an open-shell, d⁹ transition metal ion with a rich spectral signature, is much more likely.



Figure 2.2 UV-Vis-NIR data taken under conditions $[CuBr_2/L]=0.74 \text{ mM}$, [L]=4.5 mM, [EBiB]=[MBP]=25 mM, where L=Me₆TREN in MA/DMSO = 2/1 (v/v).

In the earliest developments of Cu mediated photochemical ATRP, the mechanism was proposed to occur by the homolytic cleavage of the Cu^{II}-halogen bond through a ligand to metal

charge transfer in the excited state of the X-Cu^{II}/L deactivator complex. This would lead to the formation of a halogen radical and a Cu^I/L complex. This pathway is unimolecular and therefore should proceed with no free ligand. **Figure 2.3(a)** gives the polymerization kinetics with a ratio of either [CuBr₂]:[Me₆TREN] = 1:1 or 1:6. In the case where [CuBr₂]:[Me₆TREN] = 1:1 the concentration of uncoordinated Me₆TREN is very low due to the strong binding between Cu^{II} and Me₆TREN,⁴⁰ whereas [CuBr₂]:[Me₆TREN] = 1:6 gives 5 equivalents of uncoordinated Me₆TREN relative to the CuBr₂/Me₆TREN complex. The kinetics in **Figure 2.3(a)** show virtually no polymerization when all of the ligand was bound to the metal, i.e. [CuBr₂]:[Me₆TREN] = 1:1, while a relatively rapid polymerization, reaching over 65% conversion in 6 h is attained with an excess of ligand, i.e. when [CuBr₂]:[Me₆TREN] = 1:6. This indicates that unbound ligand must be involved in the photopolymerization. **Figure 2.3(b)**indicates that the polymers synthesized using an excess of ligand are well controlled with narrow molecular weight distributions. Although it has been reported that excess ligand can reduce end-group fidelity, at such low concentration of ligand, it can be reasonably assumed that excess ligand does not decrease end group functionality.

The lack of polymerization with no free ligand also suggests that the unimolecular photochemical reduction of Cu^{II} is kinetically insignificant at 392 nm. These results agree very well with the UV initiated polymerizations performed by Haddleton et al.²⁰ who also showed that an excess of the ligand is necessary for the photopolymerization to occur under similar conditions.



Figure 2.3. (a) Kinetics of polymerization under the conditions:

 $[MA]_0:[EBiB]_0:[Cu^{II}Br_2]_0:[L]_0=300:1:0.03:0.03 \text{ or } 0.18, \text{ in DMSO}, [MA]_0=7.4 \text{ M}, 25 ^{\circ}C, \text{ irradiated by 392 nm light (0.9 mW/cm²), where L= Me_6TREN. (b) Evolution of the molecular weight distributions for the system with <math>[MA]_0:[EBiB]_0:[Cu^{II}Br_2]_0:[L]_0=300:1:0.03:0.18.$

To confirm that the homolytic cleavage of the Cu^{II} halogen bond is not the key driving force in the photochemical reduction of Cu^{II} to Cu^I, a similar polymerization to the one in Figure **2.3(a)** was performed with copper(II) triflate (Cu^{II}(OTf)₂) instead of CuBr₂. In both systems the ratio [Cu^{II}]₀:[Me₆TREN]₀=1:6 was used. In the case of the Cu^{II}(OTf)₂, there was no added halide salt, so there was no halide binding to Cu^{II} at the start of the reaction. Therefore, if the homolytic cleavage of the Cu halogen bond was kinetically significant, the polymerization with the Cu^{II}(OTf)₂ should be much slower than the reaction with Cu^{II}Br₂. However, the polymerization with $Cu^{\parallel}(OTf)_2$ was initially faster than the reaction with $Cu^{\parallel}Br_2$ clearly indicating that the homolytic cleavage of the Cu^{II}-halogen bond is not kinetically significant. Both the Cu^{II}(OTf)₂ and Cu^{II}Br₂ reactions show good agreement between the experimental and theoretical molecular weights, although the M_w/M_n values are higher for the Cu^{II}(OTf)₂ system compared to the Cu^{II}Br₂ one. The reason for the broader molecular weight distributions in the Cu^{ll}(OTf)₂ system is that there is initially no deactivator complex in the triflate system. When starting from Cu^{II}(OTf)₂, the Br-Cu^{II}/Me₆TREN deactivator complex can only be formed by the loss of bromine from a chain end. This can occur via two pathways. The first is by interaction of an alkyl halide with excess ligand in the presence of light to give an alkyl radical, radical cation and halogen anion, as shown in Scheme 2.2. This bromide anion can than coordinate with the $Cu^{II}/Me_{6}TREN$ complex to form the deactivator species. Alternatively, after the photoreduction of Cu^{II}/Me₆TREN in the presence of amines, the generated Cu^I/Me₆TREN complex can activate an alkyl halide to give a radical and Br-Cu^{II}/Me₆TREN. This process of deactivator formation is not instantaneous and therefore, in the initial stages of polymerization, the concentration of deactivator is low which leads to broader molecular weight distributions.

2.2.4.2 Model Experiments

A series of model experiments were performed to elucidate the polymerization

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mechanism. These model experiments are similar to the well-controlled polymerization under the conditions: [MA]₀:[EBiB]₀:[CuBr₂]₀:[Me₆TREN]₀ = 300:1:0.03:0.18, with [MA]₀=7.4 M at 25 °C using 392 nm irradiation. The differences are that one or more components are removed from the system to determine the importance/contribution of that component to the overall polymerization. In some cases, the alkyl halide initiator is changed from the more active tertiary EBiB to the less active secondary MBrP.⁴¹ **Figure 2.4 (a)** and **Table 2.1** give the kinetics of the polymerization for each model experiment. It is important to note that all of these polymerizations required light, since control experiments performed in the dark yielded no polymer.

Table 2.1. Summary of all model experiments performed under photochemical conditions, using irradiation at 392 nm. In all cases L refers to Me₆TREN, and all reactions were performed in DMSO with [MA]=7.4 M.

Entry	Conditions	Time	Conversion	Mn	$M_{\rm w}/M$
		(h)			n
1	[MA] ₀ :[EBiB] ₀ :[CuBr ₂] ₀ :[L] ₀ =300:1:0.03:0.18	6	0.65	1.6×10 ⁴	1.04
2	[MA] ₀ :[EBiB] ₀ :[Cu(OTf) ₂] ₀ :[L] ₀ =300:1:0.03:0.18	6	0.96	2×10 ⁴	1.03
3	[MA] ₀ :[EBiB] ₀ :[CuBr ₂] ₀ :[L] ₀ =300:0:0:0	6	0.03	-	-
4	[MA] ₀ :[EBiB] ₀ :[CuBr ₂] ₀ :[L] ₀ =300:0:0:0.18	5	0.25	9×10 ⁵	2.1
5	[MA] ₀ :[EBiB] ₀ :[CuBr ₂] ₀ :[L] ₀ =300:1:0:0	3	0.18	2×10 ⁶	2.2
6	[MA] ₀ :[EBiB] ₀ :[CuBr ₂] ₀ :[L] ₀ =300:1:0:0.18	3	0.49	5×10 ⁵	1.9
7	[MA] ₀ :[MBrP] ₀ :[CuBr ₂] ₀ :[L] ₀ =300:1:0:0	6	0.02	-	-
8	[MA] ₀ :[MBrP] ₀ :[CuBr ₂] ₀ :[L] ₀ =300:1:0:0.18	1.5	0.16	5×10 ⁵	2.1
9	[MA] ₀ :[EBiB] ₀ :[CuBr ₂] ₀ :[L] ₀ =300:0:0.03:0.18	6	0.06	4×10 ⁴	1.2
10	[MA] ₀ :[EBiB] ₀ :[CuBr ₂] ₀ :[L] ₀ =300:0:0.03:0.18	24.25	0.13	2×10 ⁵	2.4
11	[MA] ₀ :[EBiB] ₀ :[CuBr ₂] ₀ :[L] ₀ : [TEA] ₀ =300:1:0.03:0.03:0.6	6	0.66	2×10 ⁴	1.04

MA alone, and MA with MBP gave virtually no polymerization, even after 6 hours. After the same time, the polymerization mixture containing MA, EBiB and CuBr₂/Me₆TREN and a 5fold excess of free Me₆TREN to Cu exceeded 60% conversion. The systems containing only MA plus EBiB or MA plus Me₆TREN are fairly slow, reaching just 18% conversion in 3 hours and 25% conversion in 5 hours, respectively. The Me₆TREN only polymerization is shown in **Figure 2.4(a)**, This indicates that photochemical radical generation from MA alone, Me₆TREN, EBiB, or MBrP is not responsible for the relatively rapid polymerization.



Figure 2.4. (a) Kinetics and (b) kinetics of RX + L (RX = EBiB or MBP) (c) evolution of M_n and (d) M_w/M_n with conversion for the various model polymerization of MA in DMSO, with conditions: $[MA]_0:[EBiB]_0:[CuBr_2]_0:[L]_0=300:0-1:0-0.03:0-0.18$ with $[MA]_0=7.4$ M, 392 nm irradiation (0.9 mW/cm²) at 25 °C. In all cases the ratios in the caption are relative to $[MA]_0=300$. Inset of (c) gives the low molecular weight range of the series.

An interesting question arises in the presence of both alkyl halide and amine-based ligands. In the literature, the photochemical radical generation due to alkyl iodide chain ends and amine-based ligands gave rapid and well-controlled polymerization.^{24, 42} Therefore, either EBiB or MBP was combined with Me₆TREN and monomer to investigate if similar synergies exist between alkyl bromides and amine ligands. As shown in **Figure 2.4(b)** and **Table 2.1**, the polymerization with EBiB, Me₆TREN and monomer was relatively rapid, reaching 49%

conversion in 3 hours. This rate of polymerization is similar to that of photoATRP. With no Cu assisted activation of alkyl halide, the rate of EBiB groups becoming radical species is very low, and EBiB can remain in the reaction mixture for the whole reaction. However, in the Cu mediated polymerization, after the initial phase of the reaction the EBiB initiator is converted to the secondary poly(acrylate)-Br chain end, which closely resembles MBP. Therefore, the kinetics of the reaction mixture containing MBP, Me₆TREN and MA were investigated, as shown in **Figure 2.4(a)** and **Table 2.1**. The polymerization containing MBP, Me₆TREN and MA reached 16% conversion after 1.5 hours. In contrast the photoATRP systems that contain Cu species and a similar concentrations of alkyl halide and free ligand had a 2-2.5-fold faster polymerization rate.

These results indicate that there is a synergistic radical generation between the secondary poly(acrylate) like alkyl halide and the ligand. However, this synergy alone is insufficient to explain the relatively rapid polymerization from the standard photoATRP experiment ([MA]₀:[EBiB]₀:[Cu^{II}Br₂]₀:[L]₀=300:1:0.03:0.18). As highlighted in the supporting information, the steady state rate of photopolymerization was used to determine the apparent rate coefficients of photochemical radical generation from reactions containing individual components, (EBiB, MBP and Me₆TREN), as well as the bimolecular radical generation rate coefficients between both EBiB and Me₆TREN as well as MBP and Me₆TREN. The apparent rate coefficients of radical generation for each component and interaction are given in **Table 2.2**. These reactions are essentially photochemically driven ICAR reactions.

Figure 2(c) shows the evolution of M_n with conversion, and Figure 2.4(d) gives M_w/M_n with conversion for all experiments in Table 2.1. In all cases where Cu was absent, broad molecular weight distributions were obtained, with M_w/M_n >1.5. Furthermore, in all systems with no Cu, the M_n values were relatively constant and ranging from 5×10^5 to 2×10^6 . This indicates that these polymerizations with no Cu in the system have a relatively small number of end groups, and that the alkyl halide was not initiating efficiently in the absence of Cu. Based on the molecular weight and conversion data, the radical transfer coefficient for poly(methyl acrylate) to Me₆TREN as well as EBiB were determined, as highlighted in the supporting information. The transfer to MBP was assumed to be close to zero, since the molecular weights

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obtained for the polymerization containing MBP, Me₆TREN and MA were very similar to the molecular weights obtained for the polymerization containing Me₆TREN and MA only. The final system investigated as a model reaction contains MA, CuBr₂/Me₆TREN and a 5-fold excess of free Me₆TREN to Cu, but no added alkyl halide. As indicated in **Figure 2.4(a)** and **Table 2.1**, this polymerization is relatively slow, reaching only 6% conversion after 6h and, 13% conversion after 24.25 h. **Figure 2.4(c)** and **Figure 2.4(d)** show the evolution of M_n and M_w/M_n with conversion for the reaction with no added alkyl halide. M_n grows with conversion, although in a non-linear fashion, and the M_w/M_n values were initially low, but eventually exceeded 2. This is consistent with previously published data,¹⁹ and indicates the formation of new chains after the reduction of Cu^{II}, as well as the growth of chains formed earlier in the reaction.

To confirm that the Cu^{II}Br₂/Me₆TREN complex is indeed reduced in the presence of an excess of Me₆TREN, the concentration of Cu^{II} was monitored by UV-Vis-NIR spectroscopy without added alkyl halides. As shown in **Figures 2.5(a-b)**, the Cu^{II} complex was efficiently reduced in the presence of a threefold excess of Me₆TREN to Cu^{II}Br₂/Me₆TREN in both pure DMSO and the polymerization medium containing MA and DMSO, with MA/DMSO-2/1 (v/v) [MA]=7.4 M. However, as shown in **Figure 2.5(c-d)** when all the Me₆TREN was coordinated to Cu, i.e. no free Me₆TREN, virtually no reduction of Cu^{II}Br₂/Me₆TREN occurred. These UV-Vis-NIR data in **Figure 2.5** agree well with the polymerization data, and the literature,²⁰ clearly indicating that the photochemical polymerization and reduction of Cu^{II}Br₂/Me₆TREN requires an excess of ligand to proceed.



Figure 2.5. Evolution of UV-Vis spectra as a function of time. Conditions are (a) $[CuBr_2] = 2.2$ mM, [L] = 8.8 mM in DMSO (b) $[CuBr_2] = 2.2$ mM, [L] = 8.8 mM in MA/DMSO = 2/1 (v/v) (c) $[CuBr_2] = 2.2$ mM, [L] = 2.3 mM in DMSO (d) $[CuBr_2] = 2.2$ mM, [L] = 2.3 mM in MA/DMSO = 2/1 (v/v). In all cases the samples were irradiated with 392 nm radiation (0.9 mW/cm²), at 25 °C.

The model experiments suggest that there are two processes of radical generation. The first is analogous to ICAR ATRP and proceeds by the photochemical generation of radicals directly from alkyl halides, amines or their combined interaction. The second, comparable to ARGET ATRP, includes photochemical reduction of the Cu^{II}/L complexes in the presence of amines which can act as electron donors. The contributions of the ICAR and ARGET processes will be evaluated through simulations later in the manuscript.

An important question that remains after these model experiments is whether the Me_6TREN ligand is unique in its ability to promote photochemical ATRP. To answer this question, a polymerization of MA with EBiB Cu^{II}Br₂/Me₆TREN with a 20-fold excess of triethylamine (TEA) to Cu was used instead of 5 eq of free Me₆TREN. This larger excess of TEA
was used to ensure the concentration of tertiary amine groups remained constant. As seen in **Figure 2.6(a)**, the rate of the polymerization was virtually the same for Me₆TREN and TEA. This indicates that the rate of the reaction depends only on the concentration of free amine groups in the medium, and that an excess of TEA can be used instead of Me₆TREN. **Figure 2.6(b)** compared the evolution of M_n and M_w/M_n with conversion for these two systems. The system with an excess of TEA shows similar control over the polymer architecture and molecular weight distribution as the reaction with an excess of Me₆TREN. This further indicates that the nature of the amine is not important in photochemical ATRP, but instead only the concentration of the aliphatic amine.



Figure 2.6. (a) Polymerization kinetics and (b) evolution of M_n and M_w/M_n with conversion for the polymerization of MA in DMSO under the conditions: $[MA]_0:[EBiB]_0:[CuBr_2]_0:[L]_0 = 300:1:0.03:0.18$ as well as $[MA]_0:[EBiB]_0:[CuBr_2]_0:[L]_0:[TEA]_0=300:1:0.03:0.03:0.6$, at 25 °C irradiated with 392 nm light (0.9 mW/cm²).

2.2.4.3 Effect of Reaction Conditions on the Photopolymerization

In this section, the effects of reaction conditions, including added ligand, copper and alkyl halide concentrations were investigated. The reaction conditions are designed such as the other species remain at a constant concentration in order to precisely determine the effect of the reaction parameter on the polymerization. These variations in the reaction conditions help elucidate the mechanism and provide optimal conditions for the polymerization. A summary of the experiments performed is given in **Table 2.2**.

Table 2.2. Summary of all variations of photochemical polymerization conditions, using irradiation at 392 nm (0.9 mW/cm²). In all cases L refers to Me₆TREN, and all reactions were performed in DMSO with [MA]=7.4 M. The parameter being varied from the standard polymerization of Entry 1 is highlighted in bold. Polymerizations were stopped between 55-65% to ensure good signal to noise ratio in the NMR signal for estimating monomer conversion. For all molecular weight data, a Mark-Houwink correction was applied, using parameters in the literature.³⁹ All systems with Cu exhibited molecular weights close to theoretical values within SEC error.

Entry	Conditions	Time (h)	Conversion	Mn	$M_{\rm w}/M$
					n
1	[MA] ₀ :[EBiB] ₀ :[CuBr ₂] ₀ :[L] ₀ =300:1:0.03:0.18	6	0.65	1.6×10 ⁴	1.04
2	[MA] ₀ :[EBiB] ₀ :[CuBr ₂] ₀ :[L] ₀ =300:1:0.03: 0.03	6	0.02	-	-
3	[MA] ₀ :[EBiB] ₀ :[CuBr ₂] ₀ :[L] ₀ =300:1:0.03: 0.06	6	0.42	9.5×10 ³	1.05
4	[MA] ₀ :[EBiB] ₀ :[CuBr ₂] ₀ :[L] ₀ =300:1:0.03: 0.12	6	0.66	1.3×10^{4}	1.03
5	[MA] ₀ :[EBiB] ₀ :[CuBr ₂] ₀ :[L] ₀ =300:1: 0.015 :0.165	6	0.63	1.4×10 ⁴	1.05
6	[MA] ₀ :[EBiB] ₀ :[CuBr ₂] ₀ :[L] ₀ =300:1: 0.006 :0.174	6	0.64	1.3×10 ⁴	1.09
7	[MA] ₀ :[EBiB] ₀ :[CuBr ₂] ₀ :[L] ₀ =300: 2 :0.03:0.18	6.25	0.74	9.3×10 ³	1.04
8	[MA] ₀ :[EBiB] ₀ :[CuBr ₂] ₀ :[L] ₀ =300: 0.5 :0.03:0.18	6.25	0.57	2.6×10 ⁴	1.02

The first parameter investigated was the concentration of the ligand in the system. **Figure 2.7(a)** shows effect of the ligand concentration on the polymerization kinetics. In **Figure 2.7(a)** the concentration of free Me₆TREN was varied from 0 to 5 equivalents relative to Cu/Me₆TREN. The system in which no free ligand was present resulted in no polymerization while increasing the concentration of ligand lead to an increased rate as illustrated in **Figure 2.7 (a)**. These data are consistent with the model experiments in the previous section, which indicated that the uncoordinated ligand is necessary for radical (re)generation. This indicates that the steady state rate of the reaction is proportionational to the square root of the ligand concentration. These square root rate laws are common in ATRP reactions with activator (re)generation being the rate limiting step.⁴³⁻⁴⁴ **Figure 2.7(b)** displays the evolution of M_n and M_w/M_n with conversion for the polymerizations with different ligand concentrations. Unlike the polymerization rate, the control over the polymer architecture does not depend on the ligand concentration. This is consistent with the idea that the ligand contributes to radical (re)generation, however, once the radical is generated, the Cu¹/Cu¹¹ based ATRP reactions are responsible for deactivating the radical and exchanging it among all the polymer chains.



Figure 2.7. (a) Kinetics and (b) Evolution of M_n and M_w/M_n with conversion for polymerization of MA in DMSO under the conditions: [MA]₀:[EBiB]₀:[CuBr₂]₀:[L]₀=300:1:0.03:0-0.18, [MA]=7.4 M, irradiated by 392 nm light (0.9 mW/cm²) at 25 °C.

The second reaction parameter investigated was the concentration of Cu. In these systems, the Cu^{II}Br₂/Me₆TREN concentration was varied, keeping the concentration of free ligand equal to 0.15 equivalents to the EBiB initiator. In this way, the concentration of the Cu complexes was varied between 20 and 100 ppm with respect to monomer, keeping the absolute concentration of free ligand and alkyl halide constant. As indicated in **Figure 2.8(a)**, the initial concentration of Cu^{II}Br₂/Me₆TREN has minimal impact on the rate of the polymerization. This is a surprising result since the reduction of Cu^{II} species is a significant mode of activator (re)generation. Therefore, lower Cu^{II} concentrations should lead to lower rates of polymerization, as has been observed in ARGET ATRP reactions and *e*ATRP processes. The reason for the independence of the polymerization rate on the Cu concentration will be discussed in the subsequent section.

Figure 2.8(b) shows the evolution of M_n and M_w/M_n with conversion for the experiments with different concentrations of Cu^{II}Br₂/Me₆TREN. The Cu^{II}Br₂/Me₆TREN concentration had minimal impact on the evolution of M_n with conversion, since all experimental M_n values agreed well with the theoretical predictions. However, the initial concentration of Cu^{II}Br₂/Me₆TREN had a significant impact on the M_w/M_n values. The narrower

molecular weight distributions with higher Cu^{II}Br₂/Me₆TREN concentrations are expected, since higher catalyst concentrations lead to shorter transient radical lifetimes, higher rates of radical exchange and consequently more uniform polymers.



Figure 2.8. (a) Kinetics and (b) Evolution of Mn and Mw/Mn with conversion for polymerization of MA in DMSO under the conditions: $[MA]_0:[EBiB]_0:[CuBr_2]_0:[L]_0=300:1:0.006-0.03:0.156-0.18, [MA]=7.4 M, irradiated by 392 nm light (0.9 mW/cm²) at 25 °C.$

The final reaction parameter investigated was the concentration of the EBiB initiator added to the reaction system. **Figure 2.9(a)** shows the kinetics of polymerization with EBiB concentrations that target a degree of polymerization (DP) of 150, 300 and 600. Interestingly, the steady-state rate of polymerization increases with increasing alkyl halide concentration. This is an unexpected result because in ATRP processes with activator regeneration such as ICAR or ARGET ATRP, the rate of polymerization is independent of alkyl halide concentration. This is because, at steady state, the concentration of radicals is only dependent on the rate of Cu¹ regeneration and the rate of radical termination. In most low copper ATRP processes both of these processes are independent of alkyl halide concentration. Moreover, the photochemical generation of radicals by RX and L is too slow to explain the overall polymerization rate. The dependence of the steady-state polymerization rate is approximately square root in the alkyl halide concentration. The kinetic analysis and derivation of the mechanism will be developed in the subsequent section. **Figure 2.9(b)** shows the evolution of M_n and M_w/M_n with conversion. As expected, varying the initial EBiB concentration affects the evolution of M_n with conversion, and in all cases the rate of M_n growth is close to the theoretical M_n , determined as the conversion × $[MA]_0/[EBiB]_0 × M_{MA}$, where M_{MA} is the molecular weight of methyl acrylate. Furthermore, the M_w/M_n values depend on the initial concentration of EBiB, with the higher target DPs leading to more uniform chains. This observation in **Figure 2.9(b)** is consistent with the typical observations for ATRP with constant deactivator concentrations.⁴



Figure 2.9. (a) Kinetics and (b) Evolution of Mn and Mw/Mn with conversion for polymerization of MA in DMSO under the conditions: [MA]₀:[EBiB]₀:[CuBr₂]₀:[L]₀=300:0.5-2:0.03:0.18, [MA]=7.4 M, irradiated by 392 nm light (0.9 mW/cm²) at 25 °C.

These experiments indicate a complex reaction pathway involving several competing pathways to radical (re)generation and radical loss. Therefore, the subsequent sections use the rate coefficients derived from either the literature or model experiments to simulate the photopolymerization. These simulations allow a complete description of the polymerization and allow the contribution of various radical (re)generation pathways to be evaluated.

2.2.4.4 Simulations of Photochemically Controlled ATRP

Kinetic simulations are a convenient way of assessing the contributions of various reactions to a complex polymerization process. However, these simulations are only indicative of a reaction mechanism if the relevant rate coefficients are well understood. An attractive feature of the polymerization of MA in DMSO, 2/1 (v/v), with Cu/Me₆TREN as the catalyst is that many of the rate coefficients are known in the literature.¹³ Although certain Cu¹ complexes can disproportionate under some reaction conditions,^{13, 45-46} the recent analysis in the literature

indicates that the Cu^IBr/Me₆TREN complex disproportionates very slowly in the polymerization medium of MA/DMSO=2/1 (v/v) with an excess of ligand, and therefore can be neglected.¹³ Additionally, the rate of radical (re)generation through photochemical reactions involving alkyl halides, ligands and Cu^{II} complexes or their combined interaction have been determined, as outlined in the supporting information, as well as the rates of radical transfer to the alkyl halides and amine based ligand. The reactions considered and the associated rate coefficients are given in **Table 2.3**.

Table 2.3. List of reactions relevant to Photochemically mediated ATRP processes.

Entry	Reaction	Rate coefficient	Reference
		at 298K ^e	

ATRP

2.1	$RBr + Cu'Br/L \rightarrow R\bullet + Cu''Br_2/L$	$k_{a1} = 2 \times 10^3$	13, 41
2.2	$R\bullet + Cu^{II}Br_2/L \rightarrow RBr + Cu^{I}Br/L$	$k_{d1} = 5 \times 10^7$	13, 41
2.3	$P_jBr + Cu^lBr/L \rightarrow P_j \bullet + Cu^{ll}Br_2/L$	$k_{\rm a} = 2 \times 10^2$	13
2.4	Pj● + Cu ^{II} Br2/L → PBr + Cu ^I Br/L	$k_{\rm d}$ = 2.8 x 10 ⁸	13

Radical Propagation

2.5	$R \bullet + MA \rightarrow P_1 \bullet$	$k_{\rm add,EBiB} = 7.3 \times 10^2$	47-48
		$k_{\rm add,other} = 1.6 \times 10^4$	
2.6	$P_{j}\bullet + MA \rightarrow P_{j+1}\bullet$	$k_{\rm p}$ = 1.56 x 10 ⁴	47

Conventional Radical Termination

2.7	$R \bullet + R \bullet \rightarrow D_0$	$k_{\rm t0} = 2 \times 10^9$	49
2.8	$R\bullet + P_j \bullet \rightarrow D_j$	$k_{\rm t0} = 2 \times 10^9$	49
2.9	$P_{j} \bullet + P_{j} \bullet \rightarrow D_{j+k}$	$k_{\rm t} = 1 \times 10^8$	49

Catalytic Radical Termination

2.10	$R \bullet + Cu'Br/L \rightarrow D_0 + Cu'Br/L$	$k_{\rm tx0} = <100$	This Work ^c
2.11	$P_j \bullet + Cu^I Br/L \rightarrow D_j + Cu^I Br/L$	$k_{\rm tx} = 4 \times 10^3$	This Work
	Radical Transfer		
2.12	$P_j \bullet + L \rightarrow D_j + R \bullet$	$k_{\rm tr,L} = 2.8 \times 10^3$	This Work
		$k_{\rm tr, EBiB} = 2.3 \times 10^2$	
2.13	$P_j \bullet + RBr \rightarrow D_j + R \bullet$		This Work ^d
	Photochemical Radical		
	(Re)Generation		
2.14	$L + MA \rightarrow 2 R \bullet$	<i>k</i> _{r2L,M} = 1.5 x 10 ⁻⁹	This Work
2.15	RBr \rightarrow 2 R•	$k_{r1EBiB} = 2.9 \times 10^{-9} \mathrm{s}^{-1}$	This Work ^d
2.16	RBr + L → 2 R•	$k_{\rm r2EBiB,L} = 6.2 \times 10^{-6}$	This Work
2.17	$RBr + L \rightarrow 2 R \bullet$	$k_{r2MBP,L} = 1.4 \times 10^{-6}$	This Work
2.18	CuIIBr2/L + L → CuIBr/L + R•	$k_{r2CuBr,L} = 1 \times 10^{-3}$	This Work
2.19	Cu ^{II} (OTf) ₂ /L + L → Cu ^I OTf/L + R•	$k_{\rm r2CuOTf,L} = 1 \times 10^{-2}$	This Work

^aThe value k_{a1} for the α -bromoisobutyrate was taken to be 10 times larger than the value k_a measured for the 2-bromopropionate, which is consistent with the work of Tang et al.⁴¹. ^bThe deactivation rate coefficient k_{d1} for the isobutyrate radical was taken to be 6 times smaller than the value k_d measured for the propionate radical, which is consistent with the work of Tang et al.^{41 c} For the reaction of Cu¹ mediated radical loss for tertiary isobutyrate radicals was previously observed to be negligible and therefore taken to be 0.^{50 d} For the reactions of transfer to MBP and PMA-Br the rate coefficient is so low that it could not be determined, therefore was taken to be 0. ^e The units for all rate coefficients are M⁻¹s⁻¹ unless otherwise noted ^f In all reactions, L = Me₆TREN

As mentioned in the text, specific association between the various Cu complexes, halides and ligands is not explicitly considered, but instead the activity of Cu¹ is based on the total Cu¹ concentration, and similarly the activity of Cu¹¹ is based on the total Cu¹¹ concentration. The only exception is when Cu¹¹(OTf)₂ is used, since these salts form Cu¹¹ complexes without a bound halogen. This Cu¹¹/Me₆TREN complex without a bound halide anion cannot deactivate radicals and is considered as a complex that is distinct from the Cu^{II} deactivator complex. The photochemical radical (re)generation processes (reactions 2.14-2.19) require additional explanation. As listed, small molecule radicals, R^{II}, are generated in each process. For simplicity these species are assumed to have the same reactivity as all other small molecule radicals. However, as will be discussed subsequently, this is an approximation, designed to simplify the simulations, and likely structures of these products will be proposed. Whenever Me₆TREN becomes a radical R^{II}, this radical has a positive charge that is omitted for clarity. Additionally, reactions 16-18 will produce 1 equivalent of free bromide anion, however, bromide anion is a spectator in all ATRP reactions and the only situation where this generated bromide can be significant is when Cu^{II}(OTf)₂/Me₆TREN is used. In that case, the association to Cu^{II} of the generated bromide in reactions 12.6-2.17 was factored into the simulations, and the association is assumed to be very fast. Other things not considered are chain length dependent termination.^{49, 51-53}

In all simulations, the small molecule alkyl halide was chosen to be EBiB or MBP, designed to closely match the experimental conditions. All rate coefficients for reduction were based on an experimentally measured relevant reduction reaction. The rate coefficients: k_{r1EBiB} ; k_{r1MBP} ; k_{r1L} ; $k_{r2EBiB,L}$; and $k_{r2MBP,L}$ were estimated from the polymerization rate of the relevant reaction. The rate coefficient for bimolecular reduction of Cu^{II} species by Me₆TREN, $k_{r2CuBr,L}$, was estimated from the reduction of CuBr₂ by an excess of Me₆TREN as shown in **Figure 2.3 and Figure 2.5**. It is important to note that the Cu^{II}/Me₆TREN complex without a bound halogen was measured to have a reduction rate 10 times faster than the Cu^{II}/Me₆TREN with a bound halogen, as seen in **Figure 2.5**. This is consistent with the fact that the Cu^{II}/Me₆TREN complex without a bound halogen is approximately 250 mV more reducing than the Cu^{II}/Me₆TREN without a bound halogen.⁵⁴ The rate of Cu^{II} mediated radical loss, k_{tx} ,^{50,55} was estimated from the supporting information. This value of $k_{tx} = 4000 \text{ M}^{-1}\text{s}^{-1}$ is lower than that measured in previous work,⁵⁰ but this could be due photochemically promoted dissociation of the organometallic P-Cu^{II} intermediate to regenerate Cu^{II} and the radical.

As expected, the rate of polymerization with MBP was zero, while the system with

Me₆TREN only was relatively slow. Similarly, the polymerization rate with CuBr₂/Me₆TREN and an excess of Me₆TREN was very slow, which agrees well with the experimental data. The polymerization rate in the system using MBP and Me₆TREN was faster than the systems with MBP only and Me₆TREN only. These results are broadly consistent with the experiments. Finally, the polymerizations with the alkyl halide, Cu^{II} and an excess of ligand were relatively fast. In particular, for the system that started with CuBr₂ there was a non-trivial induction period of approximately 2-2.5 h, followed by relatively rapid polymerization. The long induction period is predominantly due to the slow addition of the small molecule isobutyryl radical to the monomer, and it is possible that the true addition rate coefficient is somewhat higher than the one estimated in the literature. Furthermore, the system where Cu^{II}(OTf)₂ was used instead of Cu^{II}Br₂, the polymerization showed a much shorter induction period (almost none) with very rapid polymerization at the start of the reaction. However, as the reaction proceeded, the polymerization rate decreased toward the rate of polymerization in the system which started with Cu^{II}Br₂. In all cases the simulations agree well with the experimental data.

All polymerizations in the absence of Cu species showed high molecular weights, consistent with the experimental data. The simulated evolution of M_n with conversion for the system with CuBr₂/Me₆TREN and an excess of Me₆TREN showed a non-linear, diminishing evolution of M_n with conversion, which is consistent with the experimental data. Finally, the systems with Cu^{II}, alkyl halide and an excess of Me₆TREN showed linear evolution of the simulated molecular weight with good agreement between the simulated and theoretical molecular weight. It is important to note that the triflate system has an initial period with high molecular weights and poor agreement between the theoretical and simulated molecular weight. This is due to inefficient deactivation during the early phase of the reaction, due to a very low concentration of the Cu^{II} deactivator complex.

As expected, all polymerizations without Cu give broad molecular weight distributions. The polymerization with only monomer, $CuBr_2/Me_6TREN$, and an excess of Me_6TREN initially gave narrow molecular weight distributions. The higher M_w/M_n values obtained at the end of the reaction can be attributed to the formation of new chains generated by the radical (re)generation processes. The polymerization with alkyl halide, an excess of Me_6TREN and

Cu^{II}(OTf)₂/Me₆TREN, initially showed broad molecular weight distributions, due to slow initiation, although these decreased at higher conversion. Finally, the polymerization with alkyl halide, an excess of Me₆TREN and Cu^{II}Br₂/Me₆TREN showed narrow molecular weight distributions throughout the reaction. These results all agree well with the experimental observations. Only the systems which had alkyl halide, ligand and Cu^{II} added to the system had a high fraction of living chains.

To determine the kinetic contributions of the various reactions to the overall polymerization process, the concentrations of all species in the polymerization, under the conditions: [MA]:[EBiB]:[Cu^{II}Br₂/Me₆TREN]:[Me₆TREN]=300:1:0.03:0.15 was determined. The dominant reactions are propagation (*R*_p), and the ATRP reactions of alkyl halide activation by Cu^I (*R*_a), and radical deactivation by Cu^{II} (*R*_d). The rates of alkyl halide activation by Cu^I and radical deactivation by Cu^{II} are equal from the start of the reaction, implying that the ATRP equilibrium is maintained throughout the reaction. The next most significant reactions are radical loss, and radical (re)generation by the reduction of Cu^{II} by ligand. These reactions are conventional radical termination, and radical (re)generation by the photochemical reaction between the alkyl halide and the ligand. These reactions occur 1 order of magnitude slower than the radical (re)generation of Cu^{III} by ligand. Finally, the radical (re)generation from the ligand plus monomer, is the slowest reaction occurring 2 orders of magnitude slower than the radical (re)generation by the reduction of Cu^{III} by ligand at the start of the reaction, and it decreases with conversion.

The total rate of radical loss due to both CRT and conventional radical termination are plotted, as well as the total rate of radical generation. The radical (re)generation rate is given by $R_{regen} = 2 R_{r1L} + 2 R_{r1RX} + 2 R_{r2RX,L} + 2 R_{r2Cu,L}$. This accounts for the fact that in all (re)generation processes two radicals are formed, or one radical and one Cu¹, which can activate an alkyl halide soon after the Cu¹ is formed, generating a second radical. The rate of radical generation equals the rate of radical termination from about 60% conversion onwards.



Figure 2.10. Fraction contributions of activator regeneration from each reaction considered for the simulated polymerization under the conditions, $[MA]_0:[RX]_0:[Cu^{II}Br_2/L]_0:[L]_0 = 300:1:0.03:0.15$ in DMSO, [MA] = 7.4 M at 25°C under 392 nm irradiation (0.9 mW/cm²).

The data indicates that under polymerization conditions the dominant mode of radical (re)generation is the photochemical reaction between the Cu^{II} complex and the ligand in a reaction similar to ARGET ATRP. Once the Cu^I and radical are generated, they enter the ATRP equilibrium. Although these reactions contribute much less, there is also direct radical generation through photochemical reactions involving the alkyl halide and ligand. These reactions are essentially photochemical ICAR ATRP reactions.

However, under these polymerization conditions the dominant radical generation mode is the ARGET like process, and the dominant radical loss mode is Cu^I mediated catalytic radical termination. Therefore, an approximation to the steady state condition, $2R_{regen} = R_{t}$, is given below:

$$2k_{r_{2Cu,L}}[Cu^{II}][L] = k_{tx}[Cu^{I}][R]$$
(2.20)

which can be rewritten to give:

$$[R^{T}] = \frac{2k_{r2Cu,L}[Cu^{T}][L]}{k_{tx}[Cu^{T}]}$$
(2.21)

Since the ATRP equilibrium, $K_{ATRP} = \frac{[R^{\bullet}][Cu^{II}]}{[RX][Cu^{I}]}$, is maintained through this reaction, the radical

concentration can be expressed as follows:

$$[\mathbf{R}^{T}] = \sqrt{K_{\text{ATRP}}} \frac{2k_{\text{r2Cu,L}}[\mathbf{L}][\mathbf{RX}]}{k_{\text{tx}}}$$
(2.22)

This scaling law is consistent with the experiment data. Simulations indicate that the mechanism of this Cu mediated ATRP process is a combination of photochemical ARGET ATRP and photochemical ICAR ATRP. The dominant radical (re)generation reaction is the ARGET like photochemical reduction of Cu^{II} by the excess of amines. Since amines are good electron donor species, the product is a Cu^I complex and the amine centered radical cation. After proton abstraction it forms a carbon centered radical,³⁷ which reacts with monomer. The overall mechanism consistent with the experimental data is shown in **Scheme 2.3**.



Scheme 2.3. Proposed mechanism of photochemical ATRP. Reactions with the highest rate are in bold, with reactions that dictate the polymerization rate as thin solid lines, and reactions with a small contribution as dashed lines.

2.2.5 Conclusions

A detailed study of the kinetics of photochemically mediated ATRP in polar media was performed, using 392 nm irradiation. Both experimental and kinetic simulation techniques were used to probe the mechanism of activator and radical (re)generation in the photoATRP process. The results of these experiments and simulations show that the dominant mode of activator (re)generation is the photochemically mediated reduction of Cu^{II} complexes by an excess of amine groups. This is a photochemical ARGET ATRP process, with the amine becoming oxidized to the corresponding radical cation, which can initiate a new chain after proton transfer. The second most significant step is the synergistic radical generation between alkyl halide species and the ligand, which is similar to a photochemical ICAR ATRP. The ICAR like process occurs approximately 1 order of magnitude slower than the ARGET like process. Other processes such as direct photochemical cleavage of the alkyl halide, photochemical radical generation from the ligand, or ligand with monomer are minor reactions with very low contribution. The unimolecular reduction of the Cu^{II} deactivator complex does not occur to any appreciable extent. Kinetic simulations revealed that main role of these photochemical reactions is to supplement radicals lost to termination, and that control over the polymerization is governed by the classical ATRP activation and deactivation reactions. Thus, photochemically mediated ATRP is a predominantly photochemically mediated ARGET ATRP with contributions from photochemically mediated ICAR ATRP. With the mechanistic insight gained through this study, photochemically mediated ATRP can be used to precisely tune polymer properties for a wide variety of materials applications.

2.3 Contribution of Photochemistry to Activator Regeneration in ATRP

2.3.1 Preface

With the recent interest in photochemically mediated atom transfer radical polymerization (ATRP), an interesting question arises: how significant are the photochemical processes in ATRP reactions that are supposed to be chemically controlled, such as initiators for continuous activator regeneration (ICAR) ATRP? A comparison of the rates of polymerization under ICAR ATRP conditions under ambient lighting and in the dark indicates negligible difference in the polymerization rate, under the conditions [MA]:[EBiB]:[TPMA*²]:[CuBr₂]:[AIBN] = 300:1:0.12:0.03:0.2 in anisole 50% (v/v) at 60 °C, where TPMA*² is 1-(4-methoxy-3,5-dimethylpyridin-2-yl)-N-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-N-(pyridin-2-yl)methyl)methanamine. This indicates that under typical ICAR conditions, activator regeneration is almost exclusively due to the chemical decomposition of AIBN, not ambient lighting. To further investigate the effect of light on the activator regeneration, experiments were performed

combining ICAR and photochemical processes in a 392 nm photoreactor of intensity 0.9 mW/cm². In this process, termed PhICAR (photochemical plus ICAR) ATRP, the overall rate of activator regeneration is the sum of the rates of activator regeneration by chemical (ICAR) decomposition of AIBN, and the photochemical activator regeneration. At low AIBN concentrations (0.035 equiv. with respect to ATRP initiator), the contribution of the photochemical processes in the 392 nm photoreactor is approximately 50%. At higher AIBN concentrations (0.2 equiv. with respect to ATRP initiator), the contribution of photochemical processes to the overall polymerization drops to 15%, due to the higher rate of chemically controlled processes.

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2.3.2 Introduction

Reversible deactivation radical polymerization (RDRP) methods provide access to well controlled polymers with complex architectures to be synthesized using radical intermediates.⁵⁶⁻ ⁵⁷ This allows the complex polymers traditionally prepared via ionic polymerizations to be synthesized with tolerance to functional groups similar to conventional radical processes.^{2, 58} The three most commonly used RDRP methods are nitroxide mediated polymerization (NMP),^{3, 59} atom transfer radical polymerization (ATRP),^{4, 6, 60-61} and reversible addition-fragmentation chain transfer polymerization (RAFT).^{5, 62-63} In ATRP, control over the macromolecular architecture is gained by a transition metal mediated activation and deactivation cycle of alkyl halides and alkyl radicals respectively.⁴ Recently, photochemically controlled RDRP methods have received significant attention, since the polymerization can be controlled by the light source, with no compromise over the control over the polymer microstructure.^{16-22, 24-25, 28-29, 64-65} Among the most studied systems are photochemically controlled transition metal mediated reactions.^{16-17,} ^{19-21, 65} These reactions include polymerizations where the metal complex effectively exchanges the radical with dormant chains like in ATRP,¹⁶⁻²¹ and reactions where the metal complex photochemically generates the radical, with control gained through degenerative exchange, for instance as in RAFT.²²⁻²³

In the past few years, it has been possible to perform ATRP reactions with parts per million catalyst loadings.^{9, 44, 66-67} Traditionally, low catalyst loadings were not possible, since with low catalyst concentrations a small fraction of terminated chains would lead to the irreversible formation of the deactivator complex,^{4, 44} which would significantly retard the polymerization according to the persistent radical effect.^{4, 8} However, this issue can be overcome by continuously regenerating the activator by reducing the deactivator complex.^{9, 44} There are several methods that can be used to reduce excess deactivator species, including photochemically regenerating the activator complex from the deactivator complex,¹⁶⁻²² adding a chemical reducing agent, as in activators regenerated by electron transfer (ARGET) ATRP,⁶⁶⁻⁶⁷ adding a conventional radical initiator, as in initiators for continuous activator regeneration (ICAR) ATRP,⁹ using supplemental activators and reducing agents such as zerovalent metals or sulfites,^{12-13, 68-71} or electrochemically

reducing the deactivator complex,^{11, 72-73} A general scheme of Cu mediated ATRP with activator regeneration is shown in **Scheme 2.4**.



Scheme 2.4 Mechanism of ATRP with activator regeneration. Note that the reduction can be chemical or photochemical.

In photochemically mediated ATRP, the classical ATRP reactions of activation by the low oxidation state complex and deactivation by the high oxidation state complex ensure uniform growth of the polymer chains.^{16, 18-19} The role of the photochemical reactions is to (re)generate the activator complex.¹⁶⁻²¹ This can be seen by the significant decrease or cessation of the polymerization when the light source is removed, with the rapid recommencement once the reaction is irradiated again.¹⁶⁻²²

A recently published paper²⁶ described polymerizations of methacrylates in the presence of a fluorescent light bulb (λ = 400-750 nm). Two fluorescent lamps at a distance 10 cm from the reactor generated the activating Cu^I species from the air-stable Cu^{II} deactivating species. By monitoring the reaction by UV-Vis-NIR spectroscopy, a slow but noticeable, reduction of the Cu^{II} species was observed. This photochemical generation of activator species resulted in the controlled polymerization of methyl methacrylate (MMA) with good correlation between theoretical and experimental molecular weights.

The studies showing that fluorescent light generated the Cu¹ species raised the question: Do photochemical process affect low ppm ATRP processes such as ARGET or ICAR ATRP? Both of these methods employ chemical reducing agents such as ascorbic acid (ARGET) or radical initiator (ICAR) to regenerate the Cu¹ activating species. However, most ICAR or ARGET ATRP reactions are conducted under ambient hood lighting and, until recently, concurrent photochemical regeneration of Cu^I was not considered. It was a point of curiosity as to how much, if any, these photochemical processes contributed to the overall regeneration of Cu^I, previously thought to occur completely by chemical reducing agents. In this article, we assess the contributions of both photochemical and chemical regeneration of the activating species by performing ICAR ATRP reaction in the dark, under ambient light and under 392 nm irradiation.

2.3.3 Experimental

Materials. Unless otherwise specified all chemicals were used as received from commercial suppliers, *e.g.*, Aldrich, TCI. Tris(2-(dimethylamino)ethyl)amine (Me₆TREN) was synthesized as reported in the literature.¹ Methyl acrylate (MA, Aldrich, 99%) was passed over a column of basic alumina to remove inhibitor prior to use. 2,2'-Azobis(2-methylpropionitrile) (AIBN, Aldrich, 98%) was recrystallized from MeOH prior to use.

Instrumentation. Gel permeation chromatography (GPC): GPC was used to determine number average molecular weight (M_n) and M_w/M_n values. The GPC was conducted with a Waters 515 HPLC Pump and Waters 2414 Refractive Index Detector using PSS columns (Styrogel 10², 10³, 10⁵ Å) in tetrahydrofuran (THF) as an eluent at a flow rate of 1 mL/min at 35 °C. The column system was calibrated with 12 linear poly(methyl methacrylate) (PMMA, $M_n = 800 \approx 2,570,000$) standards. Conversion of monomer was determined by ¹H NMR spectroscopy. Absolute values of molecular weight of PMA were calculated utilizing universal calibration as reported in literature.²

Nuclear Magnetic Resonance (NMR): For ligand synthesis, NMR spectra were measured using spectrometers at 300 MHz (¹H) and 75 MHz (¹³C). Monomer conversion was measured using ¹H NMR spectroscopy, using a Bruker Avance 300 MHz spectrometer at room temperature.

UV-Visible Spectroscopy: All characterizations were performed using a Varian Cary 5000 UV/Vis/NIR spectrometer.

Mass spectra: Recorded on a mass spectrometer with a *Varian* Saturn 2100T *MS* with 3900 GC using an EI source. In each case, characteristic fragments with their relative intensities in percentages are shown. Electrospray mass spectra were measured on a Thermo-Fisher LCQ ESI/APCI Ion Trap containing a quadrupole field ion trap mass spectrometer with electrospray ionization (ESI).

Photoreactor: The samples were illuminated in a custom designed, multi-well photoreactor: A 5 m long 24 W LED strip with 300 diodes (392 nm: <u>superbrightleds.com</u> WFLS-UV300) was mounted inside an 8 inch (203 mm) galvanized steel tube in a spiral pattern.³ The intensity of the photoreactor was 0.90 ± 0.05 mW/cm².³ The 60 mm high illumination zone was centered on the samples, which were magnetically stirred in a Schlenk flask under nitrogen. A Thor Labs PM100D light meter, with a S120VC detector was used to measure the intensity of the ambient light in the fume hood which was found to be 0.3 ± 0.1 mW/cm².

Procedures

Synthesis of bis-(4-methoxy-3,5-dimethyl-pyridin-2-ylmethyl)-pyridin-2-ylmethyl-amine (*TPMA**²). 1.46 g 2-picolylamine (13.5 mmol), 6.0 g 2-Chloromethyl-4-methoxy-3,5-dimethylpyridine hydrochloride (27 mmol) and 7.25 g of Na₂CO₃ were weight in a two necked flask and solved in 200 mL HPLC grade CH₃CN. Then, 3 mg of TBABr were added to the stirred solution under nitrogen. The mixture was heated to reflux and followed by mass spectroscopy and TLC for 48h. The mixture was allowed to cool to room temperature and poured into 150 mL 1 M NaOH. After extraction with CH₂Cl₂ (3 times), the combined organic fraction was dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure to give an orange/brown crude product (m=6.177 g). Purification over alumina (MeOH:EtOAc=5:95) gave 4.9 g (= 89%) of a yellowish, crystalline solid. R_f: 0.55; ¹H NMR (300 MHz, CDCl₃) δ ppm: 8.475 (m, 1H), 8.151 (s, 2H), 7.540 (m, 1H), 7.200 (m, 1H), 7.091 (m, 1H), 3.776 (s, 6H), 3.679 (s, 6H), 2.202 (s, 6H), 1.906 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ ppm: 164.1, 159.7, 157.2, 148.7, 148.5, 136.0, 126.5, 125.2, 124.4, 121.9, 60.5, 59.8, 59.3, 13.3, 10.5; MS (ESI) m/z: 407.2 [M+H]⁺.

Lighting Environments. Reactions were conducted using three different lighting environments: dark, ambient hood lighting and a violet photoreactor. All reactions were conducted in an oil bath at 60 °C unless otherwise noted. Dark reactions were conducted by placing the flask in an oil bath that was then covered by a box. To ensure that light was not reaching the reaction mixture, the box was further covered with aluminum foil. For all reactions using ambient light, the flask was placed in an oil bath open to hood lighting. For all reactions using violet lighting, a cylindrical photoreactor with violet LED lights ($\lambda = 392 \text{ nm} \pm 7 \text{ nm}$) was placed around the oil bath and the top was then covered with aluminum foil.

Typical Polymerization using TPMA*². A stir bar was placed into a Schlenk flask of which was then sealed off to the atmosphere, placed under vacuum and backfilled with N₂. In a separate vile, CuBr₂ (0.0044 mmol), TPMA*2 (0.018 mmol, 7.2 mg), EBiB (0.15 mmol, 29.3 mg), AIBN (0.005-0.03 mmol, 0.85-4.85 mg), methyl acrylate (44.4 mmol, 3.82 g) and anisole (4 mL) were mixed and stirred vigorously for 5 minutes. This mixture was charged into the flask using an airtight syringe. The solution was degassed by 4 freeze-pump-thaw cycles and then backfilled with N₂. The flask was placed in an oil bath at 60°C. The different lighting environments were obtained by methods mentioned above.

Typical Polymerization using Me₆TREN. A stir bar was placed into a Schlenk flask of which was then sealed off to the atmosphere and placed under vacuum and backfilled with N₂. In a separate vile, CuBr₂ (0.004 mmol), Me₆TREN (0.018 mmol, 4.1 mg), EBiB (0.15 mmol, 29.3 mg), AIBN (0.005-0.03 mmol, 0.85-4.85 mg), methyl acrylate (44.4 mmol, 3.82 g) and anisole (4 mL) were mixed and stirred vigorously for 5 minutes. This mixture was charged into the flask using an airtight syringe. The solution was degassed by 4 freeze-pump-thaw cycles and then backfilled with N₂. The flask was placed in an oil bath a 60°C. The different lighting environments were obtained by methods mentioned above.

2.3.4 Results and Discussion

The initial question that must be answered is how significant are ambient light driven photochemical processes in ATRP reactions? To answer this question ICAR ATRP was performed under typical conditions, 100 ppm of Cu catalyst, and a ratio of alkyl halide to AIBN of

[RX]:[AIBN]=1:0.2. In this study, a new ligand 1-(4-methoxy-3,5-dimethylpyridin-2-yl)-*N*-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-*N*-(pyridin-2-ylmethyl)methanamine (TPMA*2) was used, since it is similar to the reported tris((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amine (TPMA*3),⁴² but can be synthesized in one step (cf. SI).

To assess the influence of ambient light on this typical ICAR ATRP at 60°C, two polymerizations of methyl acrylate (MA) were performed. One under ambient light from a fluorescent lamp in a fume hood which gives a broad range emission of intensity 0.3 ± 0.1 mW/cm² at the reaction site which is approximately 1 m from the light source. The other placed in a box to keep it in the dark. **Figure 2.11(a)** shows the kinetics and **Figure 2.11(b)** gives the evolution of M_n (solid points) and M_w/M_n (hollow points) with conversion for both experiments. **Figure 2.11(a)** shows a relatively rapid polymerization for both experiments, exceeding 65% monomer conversion in 6 h. Virtually no effect of ambient light from the fluorescent light was observed, since both the reaction under ambient light and in dark had the same rate of reaction, within the typical experimental uncertainty. **Figure 2.21(b)** indicates that both ICAR ATRP reactions were well controlled, with good agreement between the theoretical and experimental M_n , and low M_w/M_n values. Overall, the results of **Figure 2.11** indicate that well-controlled polymers can be synthesized by ICAR ATRP, and that under these typical conditions ambient light has minimal influence over the polymerization rate or activator regeneration.



Figure 2.11 (a) Semilogarithmic kinetic plot, (b) Evolution of M_n and M_w/M_n with conversion for polymerization under the conditions: [MA]:[EBiB]:[TPMA*²]:[CuBr₂]:[AIBN] = 300:1:0.12:0.03:0.2 in anisole 50% (v/v) at 60°C.

These results differ from those reported recently using the light source only 10 cm away from the reaction mixture.²⁹ The experiments conducted in this study were carried out at a distance of 1 m due to the design of the fume hood. **Figure 2.12** shows the intensity of the hood lighting with respect to the distance from the light source.



Figure 2.12 Intensity of irradiation as a function of distance from the light source of two different fume hoods. In hood 1, the light intensity was measured with both the ambient lab lighting turned on (blue) and turned off (red). The intensities were measured using a Thor Labs PM100D light meter with a S120VC detector.

The intensity varied inversely with distance, i.e. the further away from the source, the less intense the irradiation becomes. It is consistent with the assumption that our "photoreactor" is a long cylinder and that the intensity should vary with 1/distance. The higher intensity light provides more photons to the system. In a recent paper,²⁶ a reduction of Cu^{II} to Cu^I occurred using the light source at a distance of 10 cm. However, our system had the ambient light source 10 times further away (1 m), and the contributions of ambient hood lighting should be 10 times lower.

Given the insignificant contribution of ambient light on the ICAR ATRP of MA, it was necessary to determine if the CuBr₂/TPMA^{*2} system was photoactive. To achieve this, an AIBN free polymerization mixture was prepared, and analyzed by UV-Vis spectroscopy. The reaction mixture showed a strong absorption below 450 nm, as well as a weaker absorption between 700 and 1100 nm, both of which are attributed to the CuBr₂/TPMA^{*2} complex.¹⁸ The strong absorption below 450 nm indicates that a reactor with a narrow emission around 392 nm with intensity 0.9 mW/cm²,¹⁸ would be an appropriate photoreactor.

As indicated by the red circles in **Figure 2.13(a)**, when the AIBN-free reaction mixture was placed in the 392 nm photoreactor, there was a relatively slow polymerization, reaching 55% conversion in 27.5 h. This indicates that in a relatively high energy reactor, the photochemical processes are still significantly slower than the ICAR processes with a ratio of [RX]:[AIBN]=1:0.2. However, **Figure 2.13(a)** indicates that using a lower concentration of AIBN of [RX]:[AIBN]=1:0.035, in the absence of irradiation, gives an ICAR ATRP at 60 °C, with a similar rate of polymerization to photoATRP.





Figure 2.13 (a) Semilogarithmic kinetic plot, (b) Evolution of M_n and M_w/M_n with conversion for polymerization under the conditions : [MA]:[EBiB]:[TPMA*2]:[CuBr₂]:[AIBN] = 300:1:0.12:0.03:0-0.035 in anisole 50% (v/v) at 60 °C. The photoreactor emission was centered at 392 nm with intensity 0.9 mW/cm².

Since the purely photochemically mediated ATRP, and the ICAR ATRP carried out in dark with a ratio of [RX]:[AIBN]=1:0.035 had the same rate of polymerization, it would be interesting to see the effect of combining the two regeneration mechanisms. This process with combined photochemical and ICAR ATRP processes was termed PhICAR ATRP. It can be achieved by e.g., placing the ICAR ATRP reaction mixture in the 392 nm photoreactor at 60 °C. This leads to both the ICAR ATRP and the photoATRP processes contributing in tandem. **Figure 2.13(a)** indicates that the polymerization rate of the PhICAR ATRP is approximately twice that of the individual components. Therefore, the ICAR ATRP with [RX]:[AIBN]=1:0.035 and the photoATRP with 100 ppm Cu contribute equally, and when combined, the rate of polymerization is the sum of the individual contributions.

As indicated in **Figure 2.13(b)**, the photoATRP, ICAR ATRP and PhICAR ATRP all resulted in well-defined polymers. This was confirmed by the good agreement between experimental and theoretical M_n values for all three reactions, as well as the narrow molecular weight distributions with M_w/M_n < 1.1 at high conversions. The experimental M_n values lower than theoretical could be due to new chains being generated by AIBN or intrinsic errors in the SEC system.

In **Figure 2.13**, the contributions of the photoATRP and ICAR ATRP were very similar, and both rates of polymerization were relatively low. In **Figure 2.14**, a similar investigation is presented, although with higher AIBN concentrations and the same 392 nm photoreactor. Since the PhotoATRP process is not related to the AIBN concentration, it allows the influence of activator regeneration due to AIBN dissociation to be varied independently of the photochemical activator regeneration.

As indicated in **Figure 2.14(a)**, the increase of AIBN concentrations from [RX]:[AIBN]=1:0.035 to [RX]:[AIBN]=1:0.2 lead to faster ICAR ATRP reactions. Furthermore, at higher [AIBN], the contribution of the photochemical reaction is much smaller, in relative terms, than for the case [RX]:[AIBN]=1:0.035. In fact, at the ratio [RX]:[AIBN]=1:0.2, the contribution of the photochemical process is almost negligible, in comparison with the ICAR process. This shows that with higher AIBN concentrations, the ICAR, or traditional chemical regeneration pathway, dominates over the photochemical pathway, with 392 nm irradiation at 0.9 mW/cm² under conditions similar to those used here. Under the studied conditions, the photoATRP pathway is only significant at low AIBN concentrations. Interestingly, a first order rate dependence in [AIBN] was exhibited, contrary to the ICAR ATRP rate law which shows that the rate of polymerizations should be dependent on [AIBN]^{1/2}. This linearity in [AIBN] could be due to Cu¹ catalytic radical termination, which will be discussed later in this manuscript.

Figure 2.14 (a) Semilogarithmic kinetic plot, (b) Evolution of M_n with conversions and (c) M_w/M_n with conversion for polymerization under the conditions: [MA]:[EBiB]:[TPMA*2]:[CuBr₂]:[AIBN] = 300:1:0.12:0.03:0-0.2 in anisole 50% (v/v) at 60°C. The photoreactor emission was centered at 392 nm with intensity 0.9 mW/cm².

Figure 2.14(b) indicates that in all reactions the M_n grew linearly with conversion, with good agreement between the theoretical and experimental M_n values. Finally, **Figure 2.14(c)** shows that all polymers synthesized had narrow molecular weight distributions, with M_w/M_n <1.1 at high conversion, highlighting the excellent control over the polymeric structure in these processes. A summary of all experiments shown in Figure 4 is given in Table 1, including the slope of the semi-logarithmic plot, or the apparent rate of polymerization, k_p^{app} .

An important question related to the tandem photo/ICAR ATRP processes is whether the 392 nm light used here contributes to the photochemical dissociation of AIBN.^{43,44} AIBN absorbs very weakly around 390 nm, with an extinction coefficient of 2×10^{0} M⁻¹ cm⁻¹ at 392 nm, which is much lower than the extinction coefficient of 2.2×10^{3} M⁻¹ cm⁻¹ at 392 nm for the CuBr₂/TPMA^{*2} complex. Furthermore, the photo/ICAR ATRP reactions with higher AIBN concentrations show very weak rate enhancements over the ICAR ATRP experiments in the dark. This indicates that photochemically induced dissociation of AIBN is insignificant at 392 nm light. Thus, if there was significant photochemical dissociation of AIBN at 392 nm, there would be a larger increase in the rate of PhICAR vs ICAR for the higher AIBN loadings.

If higher intensity or shorter wavelength radiation sources were used, the influence of photochemical ATRP could be greater, even at higher AIBN concentrations. Additionally, if shorter wavelengths were used the photochemical decomposition of AIBN cannot be neglected and would also contribute to the rate of polymerization. Additionally, the temperature of the system would also influence the system, with lower temperatures increasing the relative contribution of the photochemical pathway, by decreasing the rate of thermal dissociation of AIBN.

The data in **Figure 2.14**, and **Table 2.3** were used to assess the influence of both the photochemical and ICAR ATRP activator regeneration processes on the polymerization rate, k_p^{app} . To determine the influence of the photochemical and ICAR processes, a normalized "contributions" were assigned. The contributions were chosen on the basis that both the ICAR ATRP with [RX]:[AIBN]=1:0.035 and pure PhotoATRP had essentially the same rate of polymerization. Therefore, both of these processes were assigned a total of 1 contribution. The normalized ICAR contribution was taken as a ratio of the AIBN used, to the AIBN concentration

used in the polymerization with [RX]:[AIBN]=1:0.035. Therefore, [RX]:[AIBN]=1:0.085 gives a total of 2.4 contributions, and [RX]:[AIBN]=1:0.2 gives 5.7 contributions. Finally, if PhICAR was performed an additional 1 contribution was added, since photoATRP gives 1 contribution. The total contributions are also included in Table 1.

Additionally, the fractional contribution of the photochemical process was determined and shown in Table 1. Whenever the reaction was performed in the dark the fractional photochemical contribution was taken to be 0. Otherwise, the fractional photochemical contribution is given by 1/Normalized contribution. This was chosen since the photochemical process always adds 1 normalized contribution, therefore the fraction of activator regeneration due to photochemical processes is 1 divided by the total contributions. As seen in **Table 2.4**, with low AIBN concentrations the contribution of photochemical processes to the PhICAR ATRP is relatively high at 0.5. Whereas at high AIBN concentrations the contribution of the photochemical processes to the PhICAR ATRP is only 0.15, which is relatively small.

Entry	[RX]:[AIBN]	hν	Normalized	Fractional	time	conversion	, Mn	M _w /M _n	k_{p}^{app}
			Contribution	Photochemical Contribution	(h)				(h⁻¹)
1	1:0	Yes	1	1	27	0.56	1.3x10 ⁴	1.06	0.030
2	1:0.035	No	1	0	27	0.58	1.2x10 ⁴	1.04	0.032
3	1:0.035	Yes	2	0.5	14	0.62	1.3x10 ⁴	1.05	0.071
4	1:0.085	No	2.4	0	12	0.62	1.6x10 ⁴	1.06	0.081
5	1:0.085	Yes	3.4	0.29	10	0.68	1.8x10 ⁴	1.06	0.12
6	1:0.2	No	5.7	0	6	0.67	1.4x10 ⁴	1.05	0.19
7	1:0.2	Yes	6.7	0.15	6	0.73	1.5x10 ⁴	1.05	0.21

Table2.4.SummaryofPhICARATRPexperiments.Inallcases[MA]:[EBiB]:[TPMA*2]:[CuBr2]:[AIBN]= 300:1:0.12:0.03:0-0.2 in anisole 50% (v/v) at 60 °C. Thephotoreactor emission was centered at 392 nm with intensity 0.9 mW/cm2.

As shown in **Figure 2.15**, an almost perfect linear correlation, passing through the origin, is observed between k_p^{app} and the normalized contributions to activator regeneration. This is an unexpected result since ATRP reactions with activator regeneration often show square root dependences between the concentration of reducing agent and polymerization rate.^{28,31,35,36,45,46}

Figure 2.15 Correlation of k_p^{app} with the total regeneration contributions for PhICAR and ICAR ATRP. Data taken from **Table 2.3**.

This square root dependence stems from the balance of radical gain (from activator regeneration, R_g) equaling the rate of radical loss (from conventional radical termination, R_t) at steady-state, as shown in **Eq. 2.23**

$$R_g = R_t \tag{2.23}$$

where,

$$R_g = 2fk_{azo}[AIBN] \quad \text{and} \quad R_t = 2k_t [R^\bullet]^2$$
(2.24)

and therefore

$$[R^{\bullet}] = \sqrt{\frac{fk_{azo}[AIBN]}{k_t}}$$
(2.25)

which would lead to the square root dependence in [AIBN]. However, the square root dependence is not exhibited in these systems as shown in **Figure 2.15**.

It was previously reported that very active Cu^I complexes based on tris(2-(dimethyl)aminoethyl)amine (Me₆TREN), and tris(pyridylmethyl)amine (TPMA) ligands lead to radical loss by catalytic radical termination,^{45,46} which has a different scaling law, proportional to Cu^I and radical concentration rather than radical concentration squared as shown in **Eq. 2.26**.

$$R_{t,Cu(I)} = k_{t,Cu(I)} [Cu^{I}] [R^{\bullet}]$$
(2.26)

This mode of termination explains the external first order kinetics in [AIBN], as shown in Eq. 2.27.

$$[R^{\bullet}] = \frac{2fk_{azo}[AIBN]}{k_{t,Cu(I)}[Cu^{I}]}$$
(2.27)

Finally, a different catalytic system, based of Me₆TREN, was chosen to show that the ambient light has minimal effect on typical ICAR ATRP reactions. As seen in Figure **2.16(a)**, the presence of ambient light has only a very small effect on the rate of ICAR ATRP, with [RX]:[AIBN]=1:0.1, and Me₆TREN based catalysts. Although there is a slight difference with the Me₆TREN system, the majority of the activator regeneration (> 90%) is due to the thermal dissociation of AIBN. As with the other systems, **Figure 2.16(b)** shows that the ICAR ATRP processes are well controlled, with good agreement between the theoretical and experimental M_n , and with M_w/M_n <1.1 at high conversion.

The overall implications of the results are that most ATRP reactions with chemical activator regeneration are dominated by the chemical processes, with minimal contribution from photochemical processes due to ambient light. This indicates that most ICAR ATRP, or ARGET ATRP reactions are well described as such, and that photochemical activator regeneration due to ambient light has minimal influence on the polymerization. When higher intensity light sources or an excess of the electron donor (e.g. alkyl amine) are used, the photochemical processes can contribute to a greater extent.



Figure 2.16 (a) Semilogarithmic kinetic plot, (b) Evolution of M_n and M_w/M_n with conversion for polymerization under the conditions: [MA]:[EBiB]:[Me₆TREN]:[CuBr₂]:[AIBN] = 300:1:0.12:0.03:0.1 in anisole 50% (v/v) at 60 °C. The irradiation was centered at 392 nm with intensity 0.9 mW/cm².

2.3.5 Conclusions

A series of experiments were performed to determine the significance of photochemical activator regeneration in ICAR ATRP. Ambient laboratory lighting of intensity 0.3 mW/cm² (fluorescent light at a distance 1 m from the reaction flask) has negligible influence on the rate of polymerization in ICAR ATRP under the studied conditions of [MA]:[EBiB]:[TPMA*2]:[CuBr₂]:[AIBN] = 300:1:0.12:0.03:0.2 or [MA]:[EBiB]:[Me₆TREN]:[CuBr₂]:[AIBN] = 300:1:0.12:0.03:0.1 in anisole 50% (v/v) at 60 °C. This indicates that under typical conditions, the chemical activator regeneration dominates the photochemical one. With a 392 nm photoreactor of intensity 0.9 mW/cm², the rate of polymerization was a linear composite of the rate dictated by the photochemical process and the rate dictated by the thermal dissociation of AIBN. At low AIBN concentrations (0.035 equiv. with respect to ATRP initiator) the contribution of the photochemical processes is approximately 50%, while at higher AIBN concentrations (0.2 equiv. with respect to ATRP initiator) the contribution of photochemical processes drops to 15%. These results indicate that unless photochemical activator regeneration is intentionally targeted, the ICAR or ARGET ATRP processes are the dominant modes of activator regeneration.

2.4 References

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Chapter 3.

ATRP in the Presence of Zero-Valent Metals

3.1 Preface

As discussed in Chapter 1 zero-valent metals such as Fe⁰, Mg⁰ and Cu⁰ have been extensively used in ATRP. These systems provide benefit since the reactions are easy to prepare and are heterogeneously mediated, meaning separation and recyclability are possible. Cu⁰ is by far the most widely used zero-valent metal and provides with two added benefits. Cu⁰ can both directly activate alkyl halides but also reduce L/Cu^{II}-X to two equivalents of L/Cu^I through a process known as comproportionation.

A significant debate was ongoing in the literature about the mechanism of this process, namely supplemental activator and reducing agent (SARA) ATRP or single electron transfer living radical polymerization (SET-LRP). Mechanistic studies were conducted to show that the SARA mechanism holds true in both aqueous and organic media. In this chapter, model studies of alkyl halide activation by Cu⁰ and comproportionation between L/Cu^{II}-X and Cu⁰ were studied using a variety of ligands, alkyl halides and solvents. It was found that systems that stabilized Cu^I (i.e. acetonitrile, TPMA) showed the fastest rates although the rate of these processes was limited by physical processes such as adsorption/desorption. The rate of activation by Cu⁰ was then studied at varying concentrations to identify key steps in the activation process occurring at the Cu⁰ surface. Two heterogeneous mechanistic models were proposed based on either the Eley-Rideal or Langmuir-Hinshelwood mechanisms.

^{*}Work in this section was published:

 <u>TG Ribelli</u>, P Krys, Y Cong, K Matyjaszewski. "Model Studies of Alkyl Halide Activation and Comproportionation Relevant to RDRP in the Presence of Cu⁰." *Macromolecules*. 2015. 48, pp 8428-8436 © 2015 American Chemical Society

 <u>2.</u> KF Augustine, <u>TG Ribelli</u>, M Fantin, P Krys, K Matyjaszewski. "Activation of Alkyl Halides at the Cu⁰ Surface in SARA ATRP: An Assessment of Reaction order and Surface Mechanism." J. Polym. Sci., Part: A. 2017 55, pp 3048-3057. © 2017 Wiley

 <u>3.</u> VA Williams, <u>TG Ribelli</u>, P Chmielarz, S Park, K Matyjaszewski. "A Silver Bullet: Elemental Silver as an Efficient Reducing Agent for Atom Transfer Radical Polymerization of Acrylates." J. Am. Chem. Soc. 2015, 137 (4), pp 1428-1431 © 2015 American Chemical Society

Finally, a new low ppm Cu system was developed using Ag⁰ as a zero-valet metal for the polymerization of acrylates. There was no significant contribution of a SARA-type mechanism but rather an ARGET mechanism was found for which Ag⁰ acts solely as a one electron reducing agent. Catalyst loadings were able to be decreased down to 10 ppm while retaining excellent control over the molecular weight. Furthermore, it was shown that the Ag⁰ wire could be reused up to 6 times without negative effects on the polymerization.

The work with Cu⁰ was conducted by myself, Kyle Augustine, Dr. Pawel Krys and Yidan Cong. Pawel and myself conducted most of the analysis. Very useful mechanistic discussions with Dr. Marco Fantin were of great use. Ag⁰ ATRP was initially conceived by Dr. Sangwoo Park with the majority of the work and manuscript preparation/revision being conducted by Dr. Valerie Williams and myself.

3.2 Model Studies of Alkyl Halide Activation and Comproportionation Relevant to RDRP in the Presence of Zero-Valent Metals

3.2.1 Preface

Model studies of alkyl halide activation by Cu⁰ and comproportionation between Cu^{II}/L and Cu⁰ in the presence of tris(2-dimethylamino)methylamine (Me₆TREN), tris(2pyridylmethyl)amine (TPMA) and N,N,N',N'',Pentamethyldiethylenetriamine (PMDETA) as ligands were conducted and quantified in dimethylformamide (DMF), dimethylsulfoxide (DMSO) and acetonitrile (MeCN). When more active alkyl halides such as ethyl α bromophenylacetate (EBPA) were used, the rate coefficient of activation by Cu^0 , k_{a0} , were the same as the rate coefficient of comproportionation, $k_{\rm comp}$ indicating that desorption of the newly formed Cu¹ species from the Cu⁰ surface could be a rate-determining step. When less active alkyl halides, such as methyl 2-bromopropionate (MBrP) were used, the activation was ~3 orders of magnitude slower than for EBPA and slower than comproportionation. This indicates that atom transfer between alkyl halide and Cu⁰ is slower than desorption of Cu¹ from the surface. Under the same conditions (solvent, ligands) rates of activation by Cu⁰ are significantly slower than those by Cu^I. Rate coefficients of comproportionation in MeCN were 10 and more times higher than in DMSO and DMF, respectively, and much larger than those of disproportionation. These results indicate that Cu⁰ acts as a supplemental activator of alkyl halides and also as a reducing agent for Cu^{II} through comproportionation, consistent with the supplemental activator and reducing agent (SARA) ATRP mechanism, as opposed to single electron transfer living radical polymerization (SET-LRP).

^{*}Work in this section was published: <u>**TG Ribelli**</u>, P Krys, Y Cong, K Matyjaszewski. "Model Studies of Alkyl Halide Activation and Comproportionation Relevant to RDRP in the Presence of Cu⁰." *Macromolecules*. **2015**. 48, pp 8428-8436 © 2015 American Chemical Society
3.2.2 Introduction

Reversible deactivation radical polymerization (RDRP) techniques have provided for the control over polymer architectures previously only achievable by the traditional ionic polymerization methods but with additional tolerance to monomer functionalities and reaction conditions known from conventional radical polymerization.¹⁻² Initially referred to as controlled or living radical polymerization (CRP or LRP), RDRP techniques gain their control via an equilibrium between propagating radicals and end-capped dormant species.³⁻⁵ This leads to a steady, low radical concentration and the concurrent growth of all chains, resulting in well-controlled molecular weights (MW) and narrow molecular weight distributions (MWD).⁶ The three most commonly utilized RDRP techniques are nitroxide-mediated polymerization (NMP),⁷ reversible-addition fragmentation chain transfer polymerization (RAFT),⁸⁻⁹ and atom transfer radical polymerization (ATRP).¹⁰

In ATRP, the control is obtained through a reversible redox reaction between a transition metal complex in the lower oxidation state (Mⁿ) and (pseudo)alkyl halide to generate a propagating radical and a metal complex in the higher oxidation state (X-Mⁿ⁺¹). The latter (deactivator complex) quickly traps radicals, resulting in a halogen-capped chain ends and regeneration of the metal complex in the lower oxidation state.¹⁰⁻¹¹ Historically, high concentrations of transition metal catalyst with stabilizing/solubilizing ligands, most commonly copper complexed by polydentate amines and pyridines, were required to achieve high monomer conversion. Due to unavoidable radical termination reactions, a gradual buildup of the X-Cu^{II}/L deactivator species occurred, consistent with the persistent radical effect (PRE).¹²⁻¹⁴

Recent advances in ATRP systems have allowed for the decrease of catalyst loadings to 100 parts per million (ppm) and lower.¹⁵ In these systems, the retardation due to PRE is overcome by continuous (re)generation of the activator complex. ATRP systems based on low ppm Cu catalysts that are commonly utilized include: activators regenerated by electron transfer (ARGET) ATRP,¹⁶⁻¹⁷ which uses chemical reducing agents such as ascorbic acid, Sn^{II} compounds and most recently Ag^{0,18} initiators for continuous activator regeneration (ICAR) ATRP¹³ with traditional thermal radical initiators for activator regeneration; photoATRP which uses UV-Vis irradiation in the presence of an electron donor to reduce Cu^{II} through reductive quenching; *e*ATRP which utilizes electrical current.¹⁸⁻¹⁹ The procedure that is the focus of the current study, supplemental activator and reducing agent (SARA) ATRP, uses zero valent metals such as Cu⁰ to reduce the formed Cu^{II} complex, while also acting as a direct activator of alkyl halides.²⁰⁻²⁴ SARA ATRP is an excellent synthetic method to prepare various well defined polymers.²⁵⁻³³ **Scheme 3.1** presents ATRP mechanism in the presence and absence of activator regeneration.





Recently, the mechanism of RDRP in the presence of Cu⁰ has been the subject of considerable debate in the literature, stemming from two different proposed mechanisms of polymerization, supplemental activator and reducing agent (SARA) ATRP and single electron transfer living radical polymerization (SET-LRP).²¹ Both mechanisms employ exactly the same reagents and reaction conditions but differ only in the respective contribution of involved reactions to the overall polymerization: namely whether Cu⁰ or Cu¹ is the major activating species and the major role of the Cu¹ species (activation of alkyl halides or disproportionation). In SARA ATRP, alkyl halides are activated primarily by the Cu¹/L activator complex *via* innersphere electron transfer (ISET) and comproportionation dominates disproportionation. However, in SET-LRP, the proposed mechanism is that alkyl halides are activated exclusively by

Cu⁰ via an outer-sphere electron transfer (OSET) and that Cu¹ instantaneously disproportionates into nascent Cu⁰ and the Cu^{II}-X deactivator complex. Both mechanisms are presented on **Scheme 3.2**.



Scheme 3.2 Proposed mechanisms of SARA ATRP (top) and SET-LRP (bottom). The relative contributions to the overall mechanism with regards to the Cu species are shown by the thickness of the arrow (bold – major; regular – contributing; dashed – negligible). Propagation and termination reactions as well as stoichiometric balance are omitted for clarity. Cu¹X/L and Cu¹¹X₂/L represent all Cu¹ and Cu¹¹ species, without any particular speciation. Reproduced from ref. [²³] with permission from The Royal Society of Chemistry.

Recent mechanistic studies using either model compounds or polymeric species revealed that in both aqueous and organic media the polymerization in the presence of Cu⁰ obeys the SARA ATRP mechanism. Also, activation by either Cu¹ or Cu⁰ proceeds much faster by ISET then by OSET.

Model studies showed that activation of methyl 2-bromopropionate (MBrP) by Cu¹ complexed by tris[2-(dimethylamino)ethylamine] (Me₆TREN) is much faster ($k_{a1} = 3.2 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$) than activation by Cu⁰ ($k_{a0} = 1.8 \times 10^{-4} \text{ cm s}^{-1}$) in DMSO. Although the dimensions of the rate coefficients are different, it was shown that to achieve the same rate of activation as at 1mM concentration of [Cu¹/Me₆TREN], 2 km of Cu⁰ (diameter, d = 0.25 mm) in 10 mL of dimethyl sulfoxide (DMSO) would be required. It must be noted that this comparison refers to

activation of alkyl halides by particular Cu species, not to overall rate of polymerization. Furthermore, the comproportionation reaction between Cu⁰ and Cu^{II}Br₂/Me₆TREN in the presence of excess ligand showed that in DMSO both comproportionation ($k_{comp} = 9.0 \times 10^{-4}$ cm s⁻¹) and disproportionation ($k_{disp} = 1.9 \times 10^{-5}$ cm s⁻¹) are slow, but comproportionation is much faster due to the low concentration of Cu^{II} species during polymerization. Cu^{II} acts as the main activator of alkyl halides and does not instantaneously disproportionate, as claimed in SET-LRP. Overall, Cu⁰ acts as a supplemental activator of alkyl halides but also a reducing agent for Cu^{II} through the comproportionation reaction. These model experiments confirm the SARA ATRP mechanism over that of SET-LRP.

In the current study we performed a wide array of activation and comproportionation model experiments using three ligand: Me₆TREN, tris(2-pyridylmethyl)amine (TPMA) and N,N,N',N",N"-pentamethyldiethylenetriamine (PMDETA), three solvents: DMSO, dimethyl formamide (DMF) and acetonitrile (MeCN), and three alkyl halides: ethyl α-bromophenylacetate (EBPA), ethyl α-bromoisobutyrate (EBiB) and MBrP. The reagents used in this study are illustrated in **Figure 3.1**. These reaction conditions utilized alkyl halides with a wide range of activities with the most active alkyl halide, EBPA, being 10⁴ times more active than MBrP for activation by Cu¹ in MeCN.^{13, 34} Similarly, for various ligands, catalyst activity spans over 6 orders of magnitude in activation by Cu¹ (eg. MBrP/PMDETA/MeCN *vs*. EBPA/Me₆TREN/MeCN).¹³ Finally, solvent effects were also examined since DMSO and DMF stabilizes stronger Cu^{II} while MeCN stabilizes Cu¹.³⁵⁻³⁶ Accurate kinetic data will also help to more precisely model RDRP in the presence of Cu⁰.^{33, 37-41} Gaining further insight into the reactions occurring at the Cu⁰ surface may allow for new mechanistic conclusions to be drawn.



Figure 3.1 Structures of ligands and alkyl halides used in this study. Abbreviation explanations in text.

3.2.3 Experimental

Materials. Tris(2-(dimethylamino)ethyl)amine (Me₆TREN) was synthesized as reported in the literature.⁴² Tris(2-pyridylmethyl)amine (TPMA) was synthesized as reported in the literature.⁴² Dimethylsulfoxide (DMSO, Fisher, 99.9%), dimethylformamide (DMF, Fisher, 99.9%), and acetonitrile (MeCN, Fisher, 99.9%) were bubbled with nitrogen gas for 30 minutes prior to use. Copper(II) bromide (Cu^{II}Br₂, Acros Organics, >99%), copper(II) trifluoromethanesulfonate (Cu(OTf)₂, Sigma-Aldrich, 98%), Cu⁰ wire (Fisher, 99.8%) ethyl α-bromophenylacetate (EBPA, Sigma-Aldrich, 97%), N,N,N',N'', – pentamethyldiethylenetriamine (PMDETA, Sigma-Aldrich, 99%), ethyl 2-bromoisobutyrate (EBiB, Sigma-Aldrich, 98%), and methyl 2-bromopropionate (MBrP, Sigma-Aldrich, 98%) were used as received.

Instrumentation. *UV-Visible Spectroscopy*: All characterizations were performed using a Varian Cary 5000 UV/Vis/NIR spectrometer.

Experimental Procedure for Activation Experiments

A stock solution of alkyl halide (0.077 mmol) and ligand (0.105 mmol) were placed in 7 mL of solvent. This solution was charged into a Schlenk flask and subjected to three freeze-pump-thaw cycles and then backfilled with nitrogen. In another Schlenk flask capped with an air-tight UV-Vis cuvette (pathlength = 1 cm) and stir bar was placed 4 cm of Cu⁰ wire (diameter = 0.1 cm) which was pre-treated in a solution of HCI:MeOH = 1:2 for 10 minutes. This flask was placed under vacuum and purged with nitrogen gas 3 times. The stock solution containing alkyl halide, ligand and solvent was charged into the flask containing the Cu⁰ wire using an air-tight syringe upside-down to ensure that the solution does not come in contact with the Cu⁰ wire. This was used as a baseline UV-Vis-NIR spectra. The flask was inversed to allow the solution to come in contact with the Cu⁰ wire and was stirred vigorously. Samples were taken at various time intervals to monitor the increase in [Cu^{II}] vs. time. Initial conditions were as follows: [RX]₀:[L]₀ = 1:1.35 in 7 mL of solvent in the presence of 4 cm Cu⁰ wire (S/V = 0.18 cm⁻¹) with [RX]₀ = 11 mM, $T = 22^{\circ}$ C.

RX = EBPA, EBiB or MBrP L = Me_6TREN , TPMA or PMDETA Solvent = DMSO, DMF or MeCN

Note: All activation reactions conducted in DMSO were reproduced in triplicate. The rate coefficients of activation by Cu^0 , k_{a0} , were calculated and were found to be within 10% marginal error of each other. This further adds to the reproducibility of this experimental setup.

Prediction of k_{a0} for MBrP/PMDETA/MeCN

Despite numerous trials, activation experiment in MeCN with PMDETA and MBrP did not result in significant and consistent increase of [Cu^{II}/L] but only a slight initial increase in [Cu^{II}/L] followed by a steady increase in [Cu^I/L]. Upon opening of the flask to air, the solution quickly changed color to green due to oxidation of Cu^I/L present in the reaction mixture. Therefore, the corresponding Cu⁰ activation rate coefficient could not be determined experimentally with the applied method. Predicted value has been calculated based on the observed ca. 1 order of magnitude decrease in rates between EBiB/PMDETA and MBrP/PMDETA in both DMSO and DMF. The predicted value of 1.8×10^{-5} cm s⁻¹ is ca. 700 times smaller than comproportionation rate coefficient for PMDETA in MeCN ($k_{comp} = 1.3 \times 10^{-2}$ cm s⁻¹). It is therefore likely, that comproportionation dominated activation of alkyl halide and thus no buildup of Cu^{II}/L species can be observed, preventing the use of spectrophotometry to evaluate activation rate coefficient.

Experimental Procedure for Comproportionation Experiments

A stock solution of Cu^{II}X₂ (X = Br or OTf) (0.015 mmol) and ligand (0.0315 mmol) were placed in 7 mL of solvent. This solution was charged into a Schlenk flask and subjected to three freezepump-thaw cycles and then backfilled with nitrogen. In another Schlenk flask capped with an air-tight UV-Vis cuvette (pathlength = 1 cm) and stir bar was placed 4 cm of Cu⁰ wire (diameter = 0.1 cm) which was pre-treated in a solution of HCI:MeOH = 1:2 for 10 minutes. This flask was placed under vacuum and purged with nitrogen gas 3 times. The stock solution containing CuX₂ and L was charged into the flask containing the Cu⁰ wire using an air-tight syringe upside-down to ensure that the solution does not come in contact with the Cu⁰ wire. This solution was subjected to UV-Vis-NIR to determine the initial concentration of CuX₂/L. The flask was then inversed and allowed to come into contact with the Cu0 wire and was stirred vigorously. Samples were taken at various time intervals to monitor the decrease in [Cu^{II}] vs. time. Initial conditions were as follows: $[CuX_2]_0:[L]_0 = 1:2.1$ in 7 mL of solvent in the presence of 4 cm Cu⁰ wire (*S*/*V* = 0.18 cm⁻¹) with $[Cu^{II}X_2]_0 = 2.14$ mM, T = 22°C. Solvents and ligands used in comproportionation experiments were the same as noted above.

3.2.4 Results and Discussion

3.2.4.1 Activation of Alkyl Halides by Cu⁰

RDRP in the presence of Cu⁰ involves several different reactions. Of these, activation of alkyl halides at the Cu⁰ surface introduces radicals into a polymerization system. However, to

what extent this reaction occurs has been up for debate. Previous reports have shown that activation by Cu^0 depends on the surface area of Cu^0 to solution volume (*S*/*V*), alkyl halide concentration, and k^{app}_{a0} as shown in **Equations 3.1 and 3.2**.

$$-\frac{d[RX]}{dt} = \frac{d[Cu^{II}]}{dt} = \frac{S}{V} k_{a0}^{app} [RX]$$
(Eq. 3.1)

$$\ln(\frac{[RX]_0}{[RX]_0 - 2[Cu^{II}]}) = \frac{S}{V} k_{a0}^{app} t$$
(Eq. 3.2)

Thus, the rate coefficient of activation could be accurately measured by monitoring the evolution of Cu^{II}/L with time. It was shown that once the initial activation by Cu⁰ occurs, the subsequent activation by formed Cu^I is much faster.⁴³ Therefore, the formation of one equivalent of Cu^{II}/L results in two radicals which can either be reversibly trapped by X-Cu^{II}/L deactivator species or terminate. Termination causes a gradual buildup of Cu^{II} according to the PRE. Additionally, at the beginning of the reaction, comproportionation is slow due to low concentration of Cu^{II} species and disproportionation is negligible due to both low Cu^{II} concentration and excess of free ligand in solution. Activation rate coefficients of MBrP or EBIB by Cu⁰ in the presence of different ligands were on the order of $k^{app}_{a0} = 10^{-4}$ cm s⁻¹.⁴³ The rate coefficient of activation by Cu⁰, k^{app}_{a0} , was determined either by plotting initial evolution of [Cu^{II}] *vs.* time (**Equation 3.1**) or plotting the semi-logarithmic plot as shown in **Equation 3.2**. Both methods gave similar values of k^{app}_{a0} at low alkyl halide conversions.

Previously, Nicolas *et al.* monitored the conversion of alkyl halide by NMR to calculate $k^{app}{}_{a0}$.³⁷⁻⁴¹ Using the method described above, under conditions which force radical termination reactions, i.e. high concentrations of RX and high surface area to volume ratio (*S/V*), the kinetics of the two methods fit to each other within experimental error.⁴³ Moreover, comparing the semilogarithmic plots of alkyl halide conversion (ln([RX]₀/[RX]_t) *vs.* time as monitored by NMR to those reactions where the evolution of Cu^{II}/L was monitored by UV-Vis, with [RX]_t = [RX]₀ – 2[Cu^{II}]_t from the same reaction flask, gave the same kinetic rate coefficients.⁴³ Therefore, for all activation experiments, monitoring the evolution of [Cu^{II}] *vs.* time was chosen due to the simpler setup and lower experimental error of the UV-Vis spectrometer. The rate coefficients of

activation by Cu^0 , k_{a0} were calculated from this plot via internal first-order kinetics, according to **Equation 3.1**. To sufficiently compare reactions, the same initial conditions were used. The effect of concentrations of all reagents on the external order as well as the overall rate will be the subject of a forthcoming study.

A series of experiments was conducted in order to gain further insight into the mechanism of alkyl halide activation by Cu⁰. Previous reports used only MBrP with Me₆TREN in DMSO⁴³ or EBiB and PMDETA in a variety of solvents³⁸ and solvent mixtures. In this report, three different alkyl halides were used with k_{a1} values following the trend: EBPA >> EBiB > MBrP and three ligands with k_{a1} values: Me₆TREN > TPMA > PMDETA in three different solvents, DMSO, DMF and MeCN.³⁴

A rate coefficient of activation of MBrP by Cu⁰ in the presence of Me₆TREN in DMSO at T = 25 °C, $k^{app}_{a0} = 1.8 \times 10^{-4}$ cm s⁻¹ was previously reported.⁴³ In this study, similar results were obtained in DMSO at T = 23 °C with a calculated value of $k^{app}_{a0} = 1.5 \times 10^{-4}$ cm s⁻¹, showing the reproducibility of this experimental setup. When the more active alkyl halides EBPA and EBiB were utilized, the rate increased one order of magnitude to give $k^{app}_{a0} = 1.2 \times 10^{-3}$ cm s⁻¹ and $k^{app}_{a0} = 1.5 \times 10^{-3}$ cm s⁻¹, respectively. Interestingly, as indicated in **Figure 3.2A**, the rate of activation of EBiB and EBPA by Cu⁰ are nearly the same, which is surprising due to the much lower C-Br bond dissociation energy (BDE) of EBPA in comparison to EBiB.^{34, 44-45} When TPMA was used as a ligand, the rates of activation for all three alkyl halides were very similar to those obtained with Me₆TREN, although k_{a1} values with Me₆TREN are 10 times larger than with TPMA. When PMDETA was used, the rate of activation remained similar to Me₆TREN and TPMA for EBPA but decreased one and two orders of magnitude when EBiB and MBrP were used, respectively as shown in Figure 3.2B. PMDETA was the only ligand that showed the expected trend of reactivity for the three alkyl halides chosen, i.e. EBPA > EBiB > MBrP. This would indicate that when using TPMA and Me₆TREN in DMSO, the rate of activation becomes independent of a catalyst after certain activity is reached. Potential explanations for these results will be provided later in this manuscript.

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Figure 3.2 Evolution of $[Cu^{II}/L]$ vs. time for a) Me₆TREN (solid) and TPMA (unfilled) and b) PMDETA. All experiments were conducted under the following conditions: $[RX]_0:[L]_0 = 1:1.5$ in 7 mL DMSO using 4 cm Cu⁰ wire (d = 1 mm) (S/V = 0.18 cm⁻¹) with $[RX]_0 = 11$ mM.

While most Cu⁰ mediated RDRP are conducted in DMSO, to understand the system to a greater degree, activation experiments were also conducted in DMF and MeCN. DMF is an even more disproportionating solvent than DMSO for Cu¹ salts⁴⁶ but the DMF effect on activation by Cu⁰ was not yet fully explored.⁴⁷ Activation for EBPA in DMF was faster ca. 2 times when compared to DMSO. Similar to DMSO, rates decreased with decreasing activity of the alkyl halide.

Finally, MeCN was investigated as a solvent for alkyl halide activation by Cu⁰. The activation of MBrP in the presence of Me₆TREN as a ligand occurs twice faster in MeCN than in DMSO in contrast to Cu¹ systems.³⁵⁻³⁶ This increase in rate was observed for most alkyl halides and ligand systems used which would indicate that solvent is involved in the rate determining step of the activation reaction. The effect of solvent on the activation of EBPA for Me₆TREN, TPMA and PDMETA is shown in **Figure 3,3**. The decrease in [Cu^{II}] observed in MeCN for PMDETA and Me₆TREN is associated with comproportionation reaction becoming significant at high RX conversions. **Table 3.1** summarizes all rate coefficients.



Figure 3.3 Evolution of $[Cu^{II}/L]$ vs. time for a) Me₆TREN (solid) and TPMA (unfilled), and b) PMDETA in three solvents: DMSO, DMF and MeCN. All experiments were conducted under the following conditions: $[EBPA]_0:[L]_0 = 1:1.5$ in 7 mL of solvent using 4 cm Cu⁰ wire (d = 1 mm) (S/V= 0.18 cm⁻¹) with $[RX]_0 = 11$ mM.

Solvent	RX	<i>k^{app}</i> a0 Me ₆ TREN	<i>k^{арр}</i> а0 ТРМА	<i>k^{app}</i> a0 PMDETA
DMSO	EBPA	1.2E-03	2.0E-03	1.9E-03
	EBiB	1.0E-03	1.6E-03	2.0E-04
	MBrP	1.5E-04	2.6E-04	2.0E-05
DMF	EBPA	2.0E-03	5.0E-03	6.0E-03
	EBiB	9.0E-04	8.0E-04	1.0E-04
	MBrP	1.4E-04	7.0E-05	1.5E-05
MeCN	EBPA	1.1E-02	1.1E-02	7.7E-03
	EBiB	5.0E-03	2.1E-03	1.4E-04
	MBrP	3.1E-04	6.2E-05	1.8E-05 ^a

Table 3.1	Activation	rate	coefficients	k ^{app} a0
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Calculated from **Eq. 3.1** for RX = EBPA, EBiB or MBrP in the presence of three different ligands L = Me₆TREN, TPMA or PMDETA in DMSO, DMF or MeCN. Reactions were monitored by the evolution of $[Cu^{II}/L]$ with respect to time. All experiments were conducted under the following standard conditions: $[RX]_0:[L]_0 = 1:1.5$ in 7 mL DMSO using 4 cm Cu⁰ wire (d = 1 mm) (S/V = 0.18 cm⁻¹) with $[RX]_0 = 11$ mM. Rate coefficients have dimensions of cm s⁻¹. ^{*a*} predicted value, see supporting information for details

To summarize, we conducted model studies of various alkyl halide activation by Cu⁰ in the presence of three different ligands in three different solvents. It was observed that the rate coefficients of activation by Cu⁰ span three orders of magnitude, even though the analogous rate coefficients for Cu¹/L span almost 8 orders of magnitude.³⁴ The most active systems were observed in MeCN with EBPA or EBiB in the presence of Me₆TREN or TPMA, while the least active systems involved MBrP and PMDETA. Interestingly, the rate coefficients were highly dependent on the solvent and nearly independent of ligand for the more reactive alkyl halides EBPA and EBiB. PMDETA was the only ligand to show the expected trend of EBPA > EBiB > MBrP. Furthermore, the maximum rates were dependent upon solvent. In comparison, activation rate coefficients by Cu¹/L do not show a maximum rate, but correlate linearly with K_{ATRP} . **Figure 3.4** shows that for more active system, represented by larger K_{ATRP} ,³⁴ the rate coefficients of activation by Cu¹, k_{a1} , increase linearly but for Cu⁰, there's only a weak correlation and they reach a maximum value of k_{a0} . This would indicate that for less active systems such as MBrP, atom transfer should be the rate determining step but for more active systems such as EBPA, the rate determining step could no longer be atom transfer.



Figure 3.4 Plot of $\ln(k_{a1})$ (filled) or $\ln(k_{a0})$ (unfilled) vs. $\ln(K_{ATRP})$ showing a linear increase in k_{a1} with more active systems while k_{a0} reaches a maximum rate due to possible desorption as the rate determining step. Rate coefficients, k_{a1} , were either directly measured or scaled, according to refs.³⁴⁻³⁶

3.2.4.2 Comproportionation Studies

One important mechanistic difference between SARA ATRP and SET-LRP is the dynamics and equilibrium between comproportionation and disproportionation. SET-LRP claims instantaneous and complete disproportionation of the Cu¹ species, however recent studies have shown that while both reactions are slow, comproportionation dominates disproportionation in DMSO,⁴⁸⁻⁴⁹ in agreement with the SARA ATRP mechanism.

Solvated Cu^IX ions in the absence of chelating ligands undergo disproportionation to give a Cu^{II}X₂ solvated complex and insoluble Cu⁰, as shown in **Equations 3.3 and 3.4** with stability constants β^{I} and β^{II} .

$$\mathbf{Cu^{I}X + Cu^{I}X} \xrightarrow{\mathbf{K_{disp}}} \mathbf{Cu^{II}X_{2} + Cu^{0}}$$
(Eq. 3.1)
$$K_{disp} = \frac{[Cu^{II}]}{[Cu^{I}]^{2}} = \frac{\beta^{II}}{(\beta^{I})^{2}}$$
(Eq. 3.4)

The solvent effects on this reaction have been well studied. Water highly favors disproportionation ($K_{disp} = ~10^{6} \text{ M}^{-1}$) while MeCN favors comproportionation ($K_{disp} ~ 10^{-21} \text{ M}^{-1}$).⁴⁷ The solvent influence originates in the coordination ability of the solvent molecule to Cu atoms in the particular oxidation state. For example, H₂O being a highly polar solvent stabilizes Cu^{II} due to the more charged nature of Cu^{II} relative to Cu^I. On the other hand, MeCN has a greater affinity for the Cu^I center than does H₂O. K_{disp} is related to the stability constants β^{I} and β^{II} that take into account coordination ability to the respective oxidation state. However, in ATRP systems, ligands are always used (typically N-based) which changes both the redox potential and β^{I} and β^{II} , in turn affecting the extent of disproportionation. In all cases when a ligand is present, the new disproportionation equilibrium (**Equation 3.5**) is defined as K^{L}_{disp} (**Equation 3.6**).

$$CuI/L + CuI/L \xrightarrow{K^{L}_{disp}} CuII/L + Cu0 + L$$
(Eq. 3.5)

$$K_{\rm disp}^{\rm L} = \frac{[{\rm Cu}^{\rm I}/{\rm L}][{\rm L}]}{[{\rm Cu}^{\rm I}/{\rm L}]^2} = \frac{\beta^{\rm II}}{(\beta^{\rm I})^2[{\rm L}]} K_{\rm disp}$$
(Eq. 3.6)

 K^{L}_{disp} can be defined the same way as K_{disp} but with an additional term for the concentration of ligand that is dissociated from one Cu¹ species which was reduced to insoluble Cu⁰. Therefore, the extent of disproportionation can be predicted using the stability constants, as well as the concentration of free ligand if the equilibrium constant is known. Moreover, according to **Equation 3.6**, increasing the concentration of free ligand suppresses disproportionation.

RDRP systems in the presence of Cu⁰ are commonly conducted using Me₆TREN in DMSO. In this system, comproportionation dominates disproportionation in both pure DMSO and polymerization media with monomers such as MA. However, such model studies have not been conducted using different ligands and solvent combinations. As discussed above, different solvents and ligands strongly affect β^{I} , β^{II} and K^{L}_{disp} .

Three ligands (Me₆TREN, TPMA and PMDETA) and three solvents (DMSO, DMF and MeCN) were chosen because they offer a wide range of stability constants for the Cu¹ species. Comparing the three solvents used, DMF should show the highest degree of disproportionation, followed by DMSO and MeCN. Furthermore, TPMA is known to stabilize Cu¹ more strongly than Me₆TREN and PMDETA. To monitor the kinetics and equilibrium of comproportionation, all experiments were conducted under the same initial conditions with the concentration of Cu^{II}/L monitored via UV-Vis spectroscopy. It should be noted that to calculate k^{app}_{comp} , internal first order kinetics were followed. External orders, as well as well as the effect of concentration of all reagents on rates of comproportionation, are currently being studied and are the subject of a later publication.

It was previously shown that the apparent rate coefficient of comproportionation, k^{app}_{comp} , could be calculated using **Equation 3.7** at Cu^{II} conversions less than 50%.⁴⁸ Using this value of k^{app}_{comp} one can calculate k_{disp} from the equilibrium constant of disproportionation in the presence of ligand, K^{L}_{disp} which can be calculated using **Equation 3.8**. It was assumed that

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equilibrium was reached once the concentration of Cu^{II}/L remained constant for 6 hours. This maximum conversion, *conv*_{eq}, was taken to calculate K^{L}_{disp} where $r = [L]_0/[Cu^{II}]_0.^{48}$

$$f(conv) = \int_0^{conv} \frac{dconv}{(1 - conv) - 4K_{disp}^L conv^2 / (r - 1 - conv)} = (S/V)k_{comp}^{app}t$$
(Eq. 3.7)

$$K_{\rm disp}^{\rm L} = \frac{(1 - conv_{eq})(r - 1 - conv_{eq})}{4conv_{eq}^2}$$
(Eq. 3.8)

To compare the effect of ligand on both the kinetics and equilibrium of comproportionation, studies were initially conducted in DMSO with 2.1 equivalents of ligand relative to $[Cu^{II}Br_2]_0$. This was done to ensure that even at complete conversion of Cu^{II}, all Cu species should be complexed by ligand. The results from the comproportionation experiments of Cu^{II}Br₂/L (L = Me₆TREN, TPMA or PMDETA) in the presence of Cu⁰ wire are presented in **Figure 3.5A**.



Figure 3.5 a) Conversion of Cu^{II}Br₂/L (L = Me₆TREN, TPMA or PMDETA) as a function of time and b) fitting of f(conv) vs. time using **Equation 7**. All experiments were conducted under the conditions: $[Cu^{II}Br_2]_0:[L]_0 = 1:2.1$ in 7 mL DMSO in the presence of 4 cm of Cu⁰ wire (d = 1 mm) ($S/V = 0.18 \text{ cm}^{-1}$) at 25°C with $[Cu^{II}Br_2]_0 = 2.14 \text{ mM}$

The initial rates of Cu^{II} conversion using TPMA and PMDETA as ligands were similar, which was unexpected, due to the drastic differences in relative stabilities of Cu^{II} and Cu^{II} for the two ligands. At equilibrium, the reaction reached a maximum Cu^{II} conversion of 90% for TPMA and 87% for PMDETA, yielding equilibrium constants $K^{L}_{disp} = 6.1 \times 10^{-3}$ and $K^{L}_{disp} = 1 \times 10^{-2}$, respectively. When using Me₆TREN, the reaction reached a maximum conversion of 79% after 22 hours, which is in agreement with previous studies,⁴⁸ showing $K^{L}_{disp} = 3 \times 10^{-2}$.

Fitting the conversion of Cu^{II} to **Equation 3.7** yields the plots shown in **Figure 3.5B** with the slope of f(conv) vs. time to be equal to $(S/V)k^{app}_{comp}$. The apparent rate coefficients of comproportionation using TPMA and PMDETA were similar. This could indicate that electron transfer from Cu⁰ to soluble Cu^{II} species is not involved in the rate-determining step, since redox potentials of Cu^{II} complexes are quite different. On the other hand, the rate decreased by a factor of two with Me₆TREN, compared to TPMA and PDMETA.

Next, a process in a more disproportionating solvent such as DMF was studied. Interestingly, the rate coefficients of comproportionation increased but were still independent of ligand. **Figure 3.6** shows the initial apparent rate of comproportionation in DMF for Me₆TREN (**3.6a**), TPMA (**3.6b**) and PDMETA (**3.6c**). These values were 2-2.5 times larger than in DMSO, although disproportionation is more favored in DMF.

Figure 3.6 shows that at equilibrium, the maximum conversion was higher in DMF than in DMSO for Me₆TREN and TPMA but was lower when using PMDETA. For example, when using Me₆TREN in DMSO, the maximum conversion was 79% while in DMF it increased to 90%. The calculated equilibrium constant in DMF was lowered by a factor of 5 than that obtained in DMSO. This indicated that DMF was less disproportionating for Cu¹ complexes, contrary to Cu¹ salts without ligands. A similar decrease in K^{L}_{disp} was observed for TPMA. Conversely, when using PMDETA, K^{L}_{disp} increased by a factor of 4 in DMF compared to DMSO. This indicates that with PMDETA, DMF was more disproportionating than DMSO. Since the rate of comproportionation was about the same for all three ligands in the respective solvents, it would indicate that K^{L}_{disp} was more influenced by k^{app}_{disp} and was not affected by k^{app}_{comp} , since the latter had a fairly constant value.



Figure 3.6 Conversion of a) Cu^{\parallel}/Me_6TREN b) $Cu^{\parallel}/TPMA$ and c) $Cu^{\parallel}/PMDETA$ as a function of time in DMF, DMSO or MeCN; $[Cu^{\parallel}Br_2]_0:[L]_0 = 1:2.1$ in 7 mL of solvent in the presence of 4 cm of Cu^0 wire (d = 1 mm) (S/V = 0.18 cm⁻¹) at 25 °C with $[Cu^{\parallel}Br_2]_0 = 2.14$ mM

Finally, comproportionation experiments were conducted in MeCN which highly stabilizes Cu¹ and almost completely suppress disproportionation. All reactions conducted in MeCN were an order of magnitude faster than in DMSO but once again were independent of ligand. In MeCN the calculated apparent rate coefficient of comproportionation was $k^{app}_{comp} =$ ~1 × 10⁻² cm s⁻¹ for all three ligands. At equilibrium, reactions employing TPMA showed that >99% of Cu^{II} converted to Cu^I which gave an equilibrium constant $K^{L}_{disp} < 2.2 \times 10^{-4}$. Due to the limitations of the UV-Vis spectrometer, conversions greater than 98% could not be calculated to an accurate degree and these limited values of K^{L}_{disp} are likely to be larger than the actual value. Furthermore, since k^{app}_{disp} is calculated from this limited value of K^{L}_{disp} , the value of k^{app}_{disp} for reactions reaching >98% conversion, is likely to be higher than the reported limited value. With Me₆TREN, 96% conversion was reached at equilibrium, corresponding to $K^{L}_{disp} = 1.4 \times 10^{-3}$ which was an order of magnitude less than in DMSO. Interestingly, PMDETA showed 98% conversion at equilibrium. PMDETA was the only ligand that showed the expected trend with respect to disproportionation, i.e. DMF > DMSO > MeCN. This can be explained by the speciation of the Cu¹ and Cu¹¹ complexes.⁵⁰ Cu¹ generally prefers a four coordinate geometry with the majority of Cu¹/L species present in solution involving a dissociated halide when complexed by PMDETA and Me₆TREN in DMSO.⁵⁰ Depending on the structure of the ligand, possible coordination of solvent to the Cu¹ center may affect K^{L}_{disp} . This could potentially explain the trend observed with PMDETA compared to TPMA and Me₆TREN. All rate coefficients and equilibrium constants calculated in this study are summarized in **Table 3.2**. It should be stressed that these are only apparent rate coefficients and are a combination of all possible elementary reactions for all species present in solution.

Table 3.2 Maximum conversion of Cu^{II} species, rate coefficients of comproportionation (k^{app}_{comp}) and disproportionation (k^{app}_{disp}) and equilibrium constant of disproportionation (K^{L}_{disp}) in DMSO, DMF and MeCN.

Solvent	Ligand	conversion	K^{L}_{disp}	$k^{\sf app}{}_{\sf comp}$	$k^{\sf app}{}_{\sf disp}$
			(M ⁻¹)		
DMSO	Me ₆ TREN	79%	3.0E-02	1.4E-03	4.1E-05
	TPMA	90%	6.1E-03	2.1E-03	1.3E-05
	PMDETA	87%	1.0E-02	2.2E-03	2.1E-05
DMF	Me ₆ TREN	90%	6.8E-03	3.6E-03	2.5E-05
	TPMA	>98%	<2.2E-04	5.5E-03	<1.2E-06
	PMDETA	73%	4.3E-02	4.1E-03	1.8E-04
MeCN	Me ₆ TREN	96%	1.4E-03	1.0E-02	1.4E-05
	TPMA	>98%	<2.2E-04	1.4E-02	<3.1E-06
	PMDETA	>98%	<2.2E-04	1.3E-02	<2.9E-06

Rate coefficients have dimensions of cm s⁻¹. For all experiments, initial conditions were as follows: $[Cu^{II}Br_2]_0:[L]_0 = 1:2.1$ in 7 mL of solvent in the presence of 4 cm of Cu^0 wire (d = 1 mm) (S/V = 0.18 cm⁻¹) at 25 °C with $[Cu^{II}Br_2]_0 = 2.14$ mM. These conditions are similar to those from REF 22a.

Finally, a comproportionation experiment was conducted using the

[Cu^{II}(Me₆TREN)][OTf]₂ complex in the absence of halide anions. The [Cu^{II}(Me₆TREN)][OTf]₂

complex ($E_{1/2} = -0.215$ V vs saturated calomel electrode, SCE) has a more positive reduction potential compared to [Cu^{II}(Me₆TREN)Br][Br] ($E_{1/2} = -0.347$ V vs. SCE) in DMSO.⁵¹ Therefore, if comproportionation proceeds via a pure OSET process, the rate should be increased for the Cu(OTf)₂/L complex according to Marcus Theory.²³ Interestingly, when using [Cu^{II}(Me₆TREN)][OTf]₂ the rate actually decreases relative [Cu^{II}(Me₆TREN)Br][Br]. This would indicate an ISET mechanism and/or accelerated desorption of surface bound Cu^I in the presence of halides.

3.2.4.3 Mechanistic Considerations

The results presented in this paper are summarized in **Figure 3.7**. One surprising observation is that values of k^{app}_{comp} are always larger than k^{app}_{a0} except for the most active system, which uses EBPA. When using EBPA, the values of k_{a0} are nearly identical to those of k_{comp} for the same ligand/solvent combination but do not exceed k_{comp} . This could indicate that for systems using highly active alkyl halides, the rate determining step for comproportionation and activation by Cu⁰ are the same. Furthermore, for comproportionation and activation experiments, the magnitude of rate coefficients followed the trend of MeCN > DMF > DMSO which is opposite of the trend observed for k_{a1} . Generally, TPMA showed similar rates of activation to Me₆TREN, once again opposite of k_{a1} for which Me₆TREN has a value 10 times larger than TPMA. For active systems in DMF and DMSO, PMDETA showed faster rates of activation compared to Me₆TREN, but slightly slower in MeCN, which could be due to various species existing in solution. However, for all ligand/solvent combination, rates of activation were fastest with EBPA followed by EBiB and MBrP, consistent with the trend observed for k_{a1} . Interestingly for Cu¹ activation, these three alkyl halides span 4 orders of magnitude when using the same ligand/solvent system while they only span ~1.5 orders of magnitude for Cu⁰ activation. This would indicate that atom transfer is not always the rate-determining step for activation by Cu⁰ and it could involve adsorption/desorption equilibria at the surface.



Figure 3.7 Rate coefficients of activation by Cu^0 (k_{a0}) and comproportionation (k_{comp}) using Me₆TREN, TPMA or PMEDTA as a ligand in DMSO, DMF or MeCN.

With regards to initial setup, the only difference between activation and comproportionation experiments were the presence of alkyl halides in the former. As stated earlier, values of k_{comp} and k_{a0} for EBPA are the same while k_{a0} for EBIB and MBrP are smaller by one and two orders of magnitude, respectively. This suggests that for less active systems atom-transfer is the rate-determining step, but for more active systems desorption of Cu¹ becomes rate determining. **Figure 3.7** shows a slight dependence on ligand for both k_{a0} and k_{comp} , however the dependence is more pronounced for solvent. This would indicate solvent-assisted desorption of the Cu¹ due to increased rate of both comproportionation and activation in MeCN relative to DMSO. Indeed, MeCN coordinates to Cu¹ much more readily than DMSO or DMF. It is possible that coordination of MeCN to surface bound Cu¹ facilitates and accelerates Cu¹ dissolution which in turn would explain the large increase of rate coefficient in MeCN as compared to DMSO. The fact that the rate of comproportionation decreases by a factor of two in the absence of halides.

Figure 3.8 shows that activation of alkyl halides by Cu⁰ does not occur faster than comproportionation in the systems considered in this article. As the ratio of two rate coefficients approaches 1, the rate of activation by Cu⁰ can become controlled by desorption of Cu¹ from the Cu⁰ surface. For less active systems, the activation of the alkyl halides is chemically controlled by atom transfer and is slower than desorption.



Figure 3.8 Plots of k_{a0}/k_{comp} vs. $\ln(k_{a1})$. The most active alkyl halides have higher values of $\ln(k_{a1})$. The ratio k_{a0}/k_{comp} was calculated from the experiments presented in this manuscript.

3.2.5 Conclusions

Model studies of comproportionation and Cu⁰ mediated activation experiments were conducted using different ligand/solvent systems for different alkyl halides and quantified by the respective apparent rate coefficients k_{comp} and k_{a0} . In all model comproportionation experiments, comproportionation dominated disproportionation with the rate of comproportionation predominantly defined by the choice of solvent. Comproportionation conducted in MeCN was 10 and 5 times faster than in DMSO and DMF, respectively. Furthermore, rates of activation by Cu⁰ were much slower than activation by Cu¹ under comparable conditions. Rates of activation by Cu⁰ increased for more active systems but were unable to reach faster rates than comproportionation. For more active systems, the ratedetermining step for activation and comproportionation could involve desorption of newly formed Cu¹ from the Cu⁰ surface, while atom transfer should be the rate-determining for less active systems. The results presented here further show that comproportionation dominates disproportionation and that the overall rate of activation of alkyl halides by Cu¹ is much faster than by Cu⁰. The findings presented in this paper further support the SARA ATRP mechanism, as opposed to SET-LRP.

3.3 Activation of Alkyl Halides at the Cu0 Surface in SARA ATRP: An Assessment of Reaction Order and Surface Mechanisms

3.3.1 Preface

The external order in reagents for the activation of alkyl halides by Cu⁰ was investigated in supplemental activator and reducing agents (SARA) ATRP. Using methyl 2-bromopropionate (MBrP) or ethyl α -bromophenylacetate (EBPA) and tris(2-(dimethylamino)ethyl)amine (Me₆TREN) in DMSO and MeCN, it was determined that the rate of activation scaled with (S/V)^{0.9} in both solvents. For MBrP, the rate was first order with respect to [MBrP]₀ until a saturation in the rate was observed around 33 and 110 mM in DMSO and MeCN, respectively. For EBPA, the reaction was also first order until a maximum rate was observed at 33 mM in DMSO, whereas an inverse order was observed for concentrations above 66 mM in MeCN. At saturated concentrations of EBPA, it was found that the rate increased linearly with respect to [Me₆TREN]₀ for all systems but became asymptotic with a maximum rate of 2 × 10⁻⁶ and 4 × 10⁻⁵ M s⁻¹ in DMSO and MeCN, respectively. Model polymerizations in the absence of ligand showed slow reaction rates, indicating the necessity for ligand. The results allow more accurate modeling and understanding of SARA ATRP under a large range of initiator concentrations.

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3.3.2 Introduction

Reversible deactivation radical polymerization (RDRP) has emerged as an effective technique for the versatile preparation of polymers with controllable molecular weights and architectures, once only accessible through ionic polymerization.¹ The three most commonly utilized RDRP techniques are nitroxide-mediated polymerization (NMP),⁷ reversible addition-fragmentation chain transfer (RAFT)^{8, 52} polymerization, and atom transfer radical polymerization (ATRP).¹¹

ATRP provides control over the polymerization by using a reversible equilibrium usually involving a transition metal catalyst. Typically, the L/Cu^I (L = ligand) complex activates a (macro)alkyl halide resulting in the oxidized metal complex (L/Cu^{II}–X) and a radical. The radicals are allowed to propagate once or a few times before being quickly deactivated by deactivator complex thus completing the catalytic cycle and reforming L/Cu^I and the P_n–X dormant species.⁵³⁻⁵⁵

Traditionally, ATRP required large amounts of copper catalyst (> 1000 ppm) to account for the conversion of the L/Cu^I activator to the L/Cu^{II}–X deactivator complex due to termination reactions.⁵⁶ Recently, ATRP with activator regeneration has been developed, which allows controlled polymerizations to be carried out using as low as 5 ppm of Cu complex. In these systems, various reducing agents slowly and continuously reduce L/Cu^{II}–X, built up from unavoidable radical termination, back to the L/Cu^I activator. Some common activator regeneration systems use conventional radical initiators in a process termed initiators for continuous activator regeneration (ICAR) ATRP^{17-18, 57}; light in photochemical ATRP⁵⁸⁻⁶⁰; and electrical current in electrochemically mediated ATRP (eATRP)^{19, 61}. Shown in **Scheme 3.3** is the basic mechanism for ATRP with activator regeneration.

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Scheme 3.3 Mechanism of Cu-Mediated ATRP with activator regeneration (purple box).

Another form of activator regeneration is the use of zerovalent metals²², most commonly Cu⁰.^{20, 47, 62} The heterogeneous nature of this system offers promise due to the ability to recycle the catalyst while having a relatively facile experimental setup. Since the use of Cu⁰ in ATRP was first demonstrated in 1997, great developments have been made with regards to reaction scope and mechanistic understanding. It has successfully been utilized in the polymerization of acrylates^{22, 63}, methacrylates⁶⁴⁻⁶⁵, styrenes²⁹, acrylonitrile⁶⁶, and acrylamides⁶⁷ with varying macromolecular architectures⁶⁸⁻⁶⁹. This widespread control⁷⁰ has been achievable in a broad range of reaction media including both aqueous and organic solvents.⁷¹

Mechanistically, it was determined that Cu⁰ acts as both a supplemental activator (SA) of alkyl halides and reducing agent (RA) for Cu^{II}, and thus the process was aptly named SARA ATRP.^{24,} ⁷²⁻⁷⁴ Although Cu⁰ was indeed found to activate alkyl halides, during a typical polymerization 99% of activation occurs from the highly active L/Cu^I catalyst^{43, 74}. Furthermore, comproportionation between Cu⁰ and L/Cu^{II} was shown to dominate disproportionation even in polar organic solvents such as DMSO^{37-38, 75}. **Scheme 3.4** shows the interplay between all of the reactions in a typical SARA ATRP in which activation by L/Cu^{II} and deactivation by L/Cu^{II}-X kinetically dominate all other reactions.



Scheme 3.4 Proposed Mechanism of SARA ATRP. Stoichiometric balance was omitted for clarity. Cu^IX/L and Cu^{II}X₂/L represent all Cu^I and Cu^{II} species, respectively, without particular speciation. Reproduced from ref. ⁷⁴

Recently, we quantified Cu⁰ activation and comproportionation reactions using model studies in the presence of three different ligands: tris(2-dimethylamino)amine (Me₆TREN), tris(2-pyridylmethyl)amine (TPMA), and *N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine (PMDETA), with three different alkyl halides (RX): methyl 2-bromopropionate (MBrP), ethyl α -bromoisobutyrate (EBiB), and ethyl α -bromophenylacetate (EBPA), in MeCN, DMF, and DMSO. These ligands and solvents offer vastly different properties with respect to activities and stabilization of Cu^{1/II} oxidation states.⁷⁶

It has been observed that increasing the activity of the L/Cu¹ catalyst (lower reduction potential, $E_{1/2}$) results in a linear increase of the activation rate coefficient in solution, k_{a1} .^{34, 77} A similar effect was observed for the activation of the less active L & RX systems by Cu⁰. This behavior is expected in surface reactions where the chemical step (i.e. atom transfer reaction, k_{a0}) is the rate determining step (RDS). The same effect, however, was not observed for the surface activation of the most active L & RX system. For such active systems the activation rate "saturated", i.e. the rate gradually increased with RX activity but eventually reached the same value for all of the most active substrates. This behavior is typical of heterogeneous reactions where physical adsorption/desorption reactions, as opposed to chemical reactions, determine the rate. Interestingly, in each case, activation rate gradually reached, but never surpassed, the rate of comproportionation. This observed common maximum rate of comproportionation and

RX activation (for very active RX) suggested that the two reactions had the same RDS. The possible common RDS between comproportionation ($L/Cu^{II} + Cu^0 + L = 2L/Cu^I$) and activation (RX + $Cu^0 + L = L/Cu^I + R^{\bullet} + X^-$) is either adsorption of the ligand or desorption of L/Cu^I from the surface. The latter appeared to be more likely the RDS because of the high energy required to remove a Cu^I atom from the Cu^0 lattice, as opposed to the typically small barriers of non-dissociative adsorption.⁷⁸⁻⁷⁹ For example, the activation energy of Cu^IBr desorption from Cu(111) is very high (62 kcal/mol under ultra-high vacuum),⁸⁰ which further suggests the need of a ligand for efficient surface "cleaning". Cu^0 wire has shown to be formed of predominately either the Cu(111) or Cu(001) lattice⁸¹ and a difference in reactivity between the two cannot be ruled out.

In order to better understand the mechanism of RX activation at the surface, model studies were conducted using two alkyl halides: i) the less active MBrP, which mimics poly(methyl acrylate)-Br chain end and whose activation rate should be limited by the surface atom transfer assisted by L, and ii) the very active EBPA, which is a common ATRP initiator and whose reaction rate could be limited by physical reactions such as adsorption or desorption. Model studies of activation were carried out with Me₆TREN as ligand in both DMSO and MeCN. Results were divided into three categories: effect of [RX]₀, [L]₀, and Cu⁰ surface area on the activation rate.

3.3.3 Experimental

Materials. Acetonitrile (MeCN, Fisher, 99.9%), dimethylsulfoxide (DMSO, Fisher, 99.9%), tris(2-(dimethylamino)ethyl)amine (Me₆TREN, Alfa Aesar, 99+%), ethyl α -bromophenylacetate (EBPA, Sigma-Aldrich, 98%), and methyl 2-bromopropionate (MBrP, Sigma-Aldrich, 98%) were used as received. Methyl acrylate (MA, Sigma-Aldrich, 99+%) was purified by passing through a column packed with basic alumina to remove inhibitor.

Characterization. All absorbance measurements were recorded using a Varian Cary 5000 UV/Vis/NIR Spectrometer. Monomer conversions were determined by ¹H nuclear magnetic resonance spectroscopy (NMR, Bruker Advance 300 MHz). Polymer samples were analyzed by gel permeation chromatography (GPC) with Polymer Standards Services (PSS) columns (guard,

10⁵, 10³, and 10² Å) with THF eluent at 35 °C, flow rate = 1.00 mL/min and differential refractive index (RI) detector (Waters 2410). The apparent molecular weights and molecular weight distributions (MWD or M_w/M_n) were determined with a calibration based on a linear poly(methyl methacrylate) (PMMA) standard. GPC samples were diluted in THF and passed through a 0.2 µm poly(tetrafluoroethylene) (PTFE) membrane filter before injecting into the GPC column (inject volume: 40 µL) with a toluene flow marker.

Cyclic Voltammetry. Cyclic voltammetry (CV) was performed by using an Autolab PGSTAT30 potentiostat (Eco-Chimie, Utrecht, The Netherlands). A three-electrode cell with a glassy carbon (GC) or Cu working electrode and a Pt counter electrode was used. The surfaces of working electrodes were polished with silicon carbide paper (1000, 2500, and 4000 grit) and then with diamond paste (3, 1, and 0.25 μ m), with ultrasonic rinsing between each step. The reference electrode was a Ag|AgI|0.1 M *n*-Bu₄NI in CH₃CN, separated from the working solution by a glass frit and a salt bridge. The reference electrode was calibrated against the ferrocenium/ferrocene couple (Fc⁺/Fc), which allowed converting all potentials to the aqueous saturated calomel electrode (SCE) scale by using $E^{\circ}_{Fc+/Fc} = 0.449$ V vs. SCE in DMSO.⁵¹

Procedure for Activation Experiments

A stock solution of alkyl halide and ligand were mixed in 7 mL of solvent. Cu^0 wire (d = 1 mm) was pre-treated in a solution of HCI:MeOH = 1:2 for 10 minutes, washed with MeOH, dried under N₂ stream, and placed in a Schlenk flask equipped with a stir bar and capped with an airtight UV-Vis cuvette (path length = 1 cm). This flask was placed under vacuum and back-filled with nitrogen gas 3 times. The stock solution containing alkyl halide, ligand, and solvent was charged into the flask containing the Cu⁰ wire using an air-tight syringe with the flask upsidedown to ensure that the solution did not come in contact with the Cu⁰ wire but instead fell directly into the cuvette. This was used as the baseline UV-Vis-NIR spectra. The flask was then inversed to allow the solution to come into contact with the Cu⁰ wire and stirred vigorously, therefore starting the reaction. Spectra were recorded at various time intervals to monitor the increase in [Cu^{II}] vs. time. Activation experiments employed one of the two following conditions:

1) Constant [Me₆TREN]₀ (16.5 mM) in the presence of changing [RX] and/or Cu⁰ wire length (d = 1 mm), or 2) constant [EBPA]₀ (88 mM) in the presence of changing [Me₆TREN]₀ and 4 cm of Cu⁰ wire (d = 1 mm, $S/V = 0.18 \text{ cm}^{-1}$), T = 22 °C.

Procedures for Polymerization Experiments

A stock solution of MA (3.5 mL), alkyl halide (0.077 mmol), was mixed with 3.5 mL of solvent in a Schlenk flask. This solution was subjected to three freeze-pump-thaw cycles and then backfilled with nitrogen. Cu⁰ wire (d = 1 mm) was pre-treated in a solution of HCI:MeOH = 1:2 for 10 minutes, washed with MeOH, dried, and placed in a separate Schlenk flask with a stir bar. This flask was placed under vacuum and back-filled with nitrogen gas 3 times. The stock solution containing alkyl halide, monomer, and solvent was charged into the flask containing the Cu⁰ wire using an air-tight syringe. Monomer conversion was monitored by NMR spectroscopy and molecular weights were analyzed by GPC. Initial conditions were as follows: [MA]:[RX]_0:[Me_6TREN]_0 = 300:1:0, [MA]_0 = 5.5 M, MA/solvent = 1/1 (v/v), $V_{total} = 7$ mL, in the presence of 4 cm Cu⁰ (d = 1 mm, S/V = 0.18 cm⁻¹), T = 22 °C.

3.3.4 Results

3.3.4.1 Model Polymerizations

To first probe the necessity of ligand for activation by Cu⁰, model polymerizations of methyl acrylate (MA) were conducted in the absence of ligand. Without ligand, neither L/Cu¹ nor L/Cu¹¹ can be formed and the polymerization proceeded by a conventional radical polymerization (RP) pathway. By measuring the rate of polymerization, the rate of alkyl halide activation in the absence of ligand can be estimated. Assuming that activation results in one radical which undergoes RP and that termination mode is exclusively via conventional radical termination, k_{a0} can be estimated applying the steady-state assumption, according to **Equations 3.9 & 3.10**.

$$\frac{d[R^{\bullet}]}{dt} = k_{a0}[RX]\frac{S}{V} - 2k_t[R^{\bullet}]^2 = 0$$
(Eq. 3.9)

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$$k_{a0} = \frac{2k_{t}[R^{\bullet}]^{2}}{[RX]\frac{S}{V}}$$
(3.10)

Using the slopes from the semi-logarithmic plots of polymerization to calculate [R[•]], rate coefficients of activation of EBPA by Cu⁰ in the absence of ligands were determined to be 1.1×10^{-7} cm s⁻¹ in MeCN and 1.6×10^{-6} cm s⁻¹ in DMSO at room temperature ($k_p = 13,180 \text{ M}^{-1} \text{ s}^{-1,82}$ $k_t = 3 \times 10^8 \text{ M}^{-1} \text{ s}^{-1} \text{ s}^3$). These rate coefficients were $\approx 10^4$ times smaller than previously reported values in the presence of Me₆TREN⁷⁶. When MBrP was used as a model initiator, no polymerization was observed after 24 hours further demonstrating the need for ligand. The activation of EBPA in the absence of ligand, however, demonstrated the catalytic effect of the Cu⁰ surface towards RX activation.

When SARA ATRP was conducted under analogous conditions (MBrP, Me₆TREN, and Cu⁰), the rate of polymerization increased 3-fold, according to prior literature results.⁴³ This further demonstrated the necessity of ligand for efficient Cu⁰ activation. Although SARA ATRP is usually conducted in the presence of initially added Cu^{II}Br₂/L to facilitate deactivation and achieve better control, this was omitted so that radicals were only initially introduced to the system via activation by Cu⁰ and not via comproportionation.

The activity of specific copper species has previously been assessed by analyzing the overall rates of polymerization using different activators (Cu⁰ vs. L/Cu¹).⁸⁴ However, polymerization rate does not directly correlate to activity of Cu^{0/1} since RDRP in the presence of Cu⁰ exhibits steady-state kinetics while L/Cu¹ follows the persistent radical effect (PRE).⁸⁵ As with all SARA ATRP systems, once enough soluble copper was built up, ATRP activation by L/Cu¹ and deactivation by L/Cu¹¹-X dominated the system and the polymerization was well-controlled.

3.3.4.2 Dependence of Activation Rate on Alkyl Halide Concentration

Previous model studies on activation and comproportionation were carried out at constant initial concentrations of 3 common alkyl halides (MBrP, EBPA and EBiB, $[RX]_0 = 11 \text{ mM}$), three different ligands (PMDETA, Me₆TREN and TPMA, $[L]_0 = 15 \text{ mM}$) in three different solvents (MeCN, DMSO and DMF).⁷⁶ These studies showed that the activation of alkyl halides by Cu⁰

followed an external first order with respect to Cu^0 surface area and a linear first order internal dependence, i.e. the initial plot $In([RX]_0/([RX]_t)$ vs. time was linear. This plot was non-linear only for activation reactions in solvents that promoted comproportionation (e.g. MeCN), due to auto-acceleration. However, to date there have been no studies examining the external order (m, n) with respect to alkyl halide and ligand, i.e. $R_{a0} \sim [Cu^0] [RX]^m [L]^n$, where R_{a0} is rate of activation of alkyl halides by Cu^0 . Using EBPA and MBrP in both DMSO and MeCN, the external order with respect to $[RX]_0$ was determined using "standard" conditions: Me₆TREN as a ligand ([L]₀= 16.5 mM) and copper wire with surface area of 0.18 cm² in 7 mL of solvent. The apparent rate of activation by Cu^0 , R_{a0}^{app} can be obtained by measuring the increase in $[L/Cu^{II}-X]$ in time via UV-Vis spectroscopy. In all cases, only the initial slope of the reaction was considered to avoid comproportionation that occurs as $[L/Cu^{II}-X]$ increases with time.

To assess the reproducibility of previously published work, "standard" conditions were chosen to measure rate coefficients of activation, k_{a0} , for EBPA and MBrP in both MeCN and DMSO. R_{a0} of EBPA in MeCN was faster than in DMSO by a factor of \approx 5. As expected, R_{a0} of MBrP was 100 times slower than EBPA in MeCN and 10 times slower in DMSO. Rate coefficients, k_{a0}^{app} were calculated to be 1.7×10^{-2} cm s⁻¹ and 3×10^{-3} cm s⁻¹ for EBPA in MeCN and DMSO, respectively, and 2×10^{-4} cm s⁻¹, and 3×10^{-4} cm s⁻¹ for MBrP in MeCN and DMSO, respectively. These are in good agreement with previously published values.⁷⁶ Furthermore, it is worthy to note the linearity of the semilogarithmic plots in DMSO indicating an internal first order reaction in [RX]. For MBrP in MeCN, however, a concave slope was observed, attributed to auto acceleration due to comproportionation, a phenomenon which has previously been reported by Harrisson *et al.*³⁸

After the reproducibility of this system was confirmed, the external rate order with respect to $[RX]_0$ was determined. For these experiments, the "standard" conditions from previous experiments were utilized with the exception of initial alkyl halide concentration. $[RX]_0$ was varied from 1 mM to 200 mM for both MBrP and EBPA in DMSO or MeCN, while keeping a constant $[Me_6TREN]_0 = 16.5$ mM. The initial concentrations of alkyl halides correlated to targeted degrees of polymerization (DP) of about 25 to 5000, which are not extraordinary for SARA ATRP.

As the $[MBrP]_0$ was increased, the overall rate of activation also increased in both solvents, as shown in **Figure 3.9A**. At a certain initial alkyl halide concentration, a maximum rate was reached, i.e. the rate plateaued. Saturation rates and concentrations are listed in **Table 3.3**. Interestingly, in DMSO this saturation concentration occurred when $[MBrP]_0 = 33 \text{ mM}$ while in MeCN this occurred at a higher $[MBrP]_0 = 110 \text{ mM}$. This suggests some degree of solvent-dependent saturation, such as a larger number of available active sites in MeCN or a higher degree of competition for the available Cu⁰ surface in DMSO.

Conveniently, by plotting $\log(R_{a0}^{app})$ vs. $\log([RX]_0)$ one can calculate the external order in $[RX]_0$ simply from the slope, as shown in **Figure 3.9B**. In both solvents at low concentrations of alkyl halide, the order was approximately 1 in $[RX]_0$. However, moving towards higher concentrations the reaction rate plateaued, or even slightly decreased with $[RX]_0$.



Figure 3.9. A) Apparent rate of activation of alkyl halides by $Cu^0 (R_{a0}^{app})$ vs. initial concentration of MBrP and B) plot of $log(R_{a0}^{app})$ vs. $log([MBrP]_0)$ with slope, *m*, representing external order $[MBrP]_0^m$. $[MBrP]_0 = 1-200 \text{ mM}$, $[Me_6 \text{TREN}]_0 = 16.5 \text{ mM}$, with 4 cm of Cu^0 wire (*d* = 1 mm, *S/V* = 0.18 cm⁻¹) in 7 mL of MeCN (black) or DMSO (gray) at room temperature.

Table 3.2. Alkyl Halide Saturation Concentration (CRX,sat) and Rat	te (R_{sat}) at Constant [L] ₀ = 16.5
mM, $S/V = 0.18 \text{ cm}^{-1}$, and $T \approx 22 \text{ °C}$.	

Solvent			RX	RX		
	MBrP			EBPA		
	C _{RX,sat} (mM)	log R _{sat}	C _{RX,sat} (mM)	log R _{sat}		
MeCN	110	-5.41	66 ^a	-4.33		

DMSO	33	-5.96	33	-5.18

 ${}^{a}R_{a0}{}^{app}$ sharply decreased for higher RX concentrations

When EBPA was used as the initiator, the reaction rate increased linearly at lower concentrations of [EBPA]₀ in both DMSO and MeCN, showing that the rate of activation was first order at low [EBPA]₀. Rate saturation for EBPA in DMSO occurred at the same [EBPA]₀ = 33 mM, as compared to MBrP. Similar to MBrP, as the concentration of EBPA increased, the order in [EBPA]₀ began to approach 0 in DMSO (if not slightly negative), however it became < -1 in MeCN (**Figure 3.10B**). Due to the high [RX]₀ used, it could be hypothesized that a relatively faster buildup of [L/Cu^{II}] could lead to a faster onset of comproportionation. However, PREDICI simulations indicated that this was not the case and the inverse order in [EBPA]₀ must be due to reactions occurring at the Cu⁰ surface.

A rate dependence of $[EBPA]^{-1}$ would indicate an inhibitory effect, which could result from a competitive adsorption of L and RX at the Cu⁰ surface. High (or even complete) surface coverage is possible at high [RX] and/or [L]. In fact, the number of molecules in solution always exceeds the number of available sites on copper. Under standard reaction conditions ([RX] = [L] = 15 mM, *S/V* = 0.18 cm⁻¹), the amount of reactant molecules is > 1.1×10^4 times larger than the number of surface Cu atoms (see detailed calculation in the SI). Considering that likely adsorption of both RX and L requires many more than one single copper atom, the excess should be even larger.



Figure 3.10 A) Apparent rate of activation of alkyl halides by $Cu^0 (R_{a0}^{app})$ vs. initial concentration of EBPA and B) plot of $log(R_{a0}^{app})$ vs. $log([EBPA]_0)$ with slope, *m*, representing external order

 $[EBPA]_0^m$. $[EBPA]_0 = 1-200 \text{ mM}$, $[Me_6TREN]_0 = 16.5 \text{ mM}$ with 4 cm of Cu⁰ wire (d = 1 mm, $S/V = 0.18 \text{ cm}^{-1}$) in 7mL MeCN (black) or DMSO (gray) at room temperature.

3.3.4.3 Dependence of Activation Rate on Ligand Concentration

To determine the effect that ligand concentration had on the rate of activation, studies similar to those analyzing alkyl halide dependence were conducted by varying ligand concentration between 1 - 135 mM. All initiator/solvent systems exhibited rate saturation at $[RX]_0 \approx 88$ mM (or below) and thus this was chosen as the initial concentration of alkyl halide for each case.

For MBrP, as shown in **Figure 3.11A**, when varying L concentration R_{a0}^{app} did not exhibit the plateau observed when varying RX concentration. Instead, the rate gradually increased reaching maximum values of 2 × 10⁻⁶ and 4 × 10⁻⁵ M s⁻¹ in DMSO and MeCN, respectively. This corresponded to a fractional external order of 0.3 - 0.4 (**Figure 3.11B**). The 20-fold increase in rate from DMSO to MeCN is consistent with model experiments previously conducted under "standard" conditions.



Figure 3.11. Apparent rate of activation of MBrP by $Cu^0 (R_{a0}^{app})$ vs. initial concentration of Me₆TREN (A) and log(R_{a0}^{app}) vs. log([Me₆TREN]₀) (B), where the slope indicates the order in [Me₆TREN]₀ under the initial conditions [MBrP]₀ = 88 mM, [Me₆TREN]₀ = 1-135 mM with 4 cm of Cu^0 wire (d = 1 mm, S/V = 0.18 cm⁻¹) in 7mL MeCN (black) or DMSO (gray) at room temperature.

Table 3.4. Ligand Saturation Concentration ($C_{L,sat}$) and Rate (r_{sat}) at Constant [RX]₀ = 88 mM, S/V = 0.18 cm⁻¹, and $T \approx 22$ °C.

Solvent			RX		
	MBrP			EBPA	
	C _{L,sat} (mM)	log R _{sat}		C _{L,sat} (mM)	log r _{sat}
MeCN	n/a (>135)ª	n/a		60	-4.06
		(>-5.33) ^b			
DMSO	n/a (>135)ª	n/a		30	-5.10
		(>-5.81) ^b			

^a Limit of investigated concentration. ^b R_{a0}^{app} at the highest investigated concentration (135 mM).

For EBPA, (Figure 3.12A) at lower concentrations of ligand the rate of activation increased linearly until a saturation was reached at $[Me_6TREN]_0 \approx 30-60 \text{ mM}$ in both solvents (see also **Table 3.4**). Until this saturation limit, the rate of activation scaled approximately linearly with $[Me_6TREN]_0$ as shown by the slopes in **Figure 3.12B**. However, in MeCN the rate decreased at $[Me_6TREN]_0 > 60 \text{ mM}$. It should be noted that even at low initial concentrations of ligand, the amount of free Me₆TREN was always in excess as compared to soluble copper species when the apparent rate was measured. It has previously been reported that under "standard" conditions, i.e. $[MBrP]_0 = 15 \text{ mM}$ in DMSO with Me₆TREN as a ligand, the initial concentration of ligand had little effect on the rate of activation but affected the final comproportionation equilibrium.⁷⁶



Figure 3.12. Apparent rate of activation of EBPA by $Cu^0 (R_{a0}^{app})$ vs. initial concentration of Me₆TREN (A) and log(R_{a0}^{app}) vs. log([Me₆TREN]₀) (B), where the slope indicates the order in [Me₆TREN]₀ under the initial conditions [EBPA]₀ = 88 mM, [Me₆TREN]₀ = 1-135 mM with 4 cm of Cu⁰ wire (d = 1 mm, $S/V = 0.18 \text{ cm}^{-1}$) in 7 mL MeCN (black) or DMSO (gray) at room temperature. In (A), different scales were used due to the large reactivity difference between the two solvents.

3.3.4.4 Dependence of Activation Rate on Cu⁰ Surface Area

The dependence of Cu⁰ (represented by the surface area to volume ratio, *S/V*) was previously examined in both model studies of activation as well as in SARA ATRP systems. In model activation studies it was directly determined that activation scaled linearly with *S/V* for MBrP with Me₆TREN as ligand in DMSO. The dependence of polymerization rate on the *S/V* has also been extensively measured. In most cases the external dependence was between (*S/V*)^{0.44-0.5 86-88} with the theoretical prediction of (*S/V*)^{0.5}.³⁸ Assuming bimolecular nature of the radical termination reactions, this implies that Cu⁰ activation is approximately first order in *S/V* (although Cu^{0 89} or Cu^{1 90-92} mediated termination may dominate). To confirm that this was the case in the more active EBPA system, experiments were conducted in DMSO and MeCN with varying lengths of Cu⁰ wire, therefore modifying the *S/V* parameter. Indeed, a near linear dependence of (*S/V*)^{0.9}.



Figure 3.13. A) Apparent rate of activation of EBPA by $Cu^0 (R_{a0}^{app})$ vs. initial surface area to volume ratio (*S/V*) and B) plot of $log(R_{a0}^{app})$ vs. log(S/V) for the activation of EBPA in 7mL MeCN (black) or DMSO (gray) under the initial conditions [EBPA]₀ = 11 mM, [Me₆TREN]₀ = 16.5 mM with 1-8 cm of Cu⁰ wire (*S/V* = 0.045-0.36 cm⁻¹) at room temperature.
3.3.5 Discussion

3.3.5.1 Evidence for Adsorption of Reagents

Literature reports and experimental data both suggest that RX can adsorb on Cu⁰, while L can assist the activation reaction either from solution or from the surface. Previously, it was shown that RBr adsorption on copper from the gas phase drastically reduced the activation energy required for C-Br bond cleavage (down to only ~11 kcal/mol, or 15% of the bond dissociation energy in the gas phase).⁹³ It was also demonstrated that the molecularly adsorbed alkyl halide lied approximately flat on the surface with a trans conformation of the C₁-C₂ bond. This flat-lying adsorption geometry was maintained in the transition state for carbon-halogen bond dissociation. This conformation offers minimum steric hindrance, which can provide access of the amine ligand to promote the activation reaction and then remove the oxidized Cu¹ atom from the surface. Under vacuum, however, alkyl halides spontaneously desorbed from Cu(111) well below room temperature. Therefore, RX adsorption behavior in solution was studied.

The first strong evidence for RX adsorption from solution came from polymerization of MA in the presence of Cu wire but in the absence of ligand: the Cu⁰ surface could catalytically activate the weak C-Br bond of EBPA, as previously observed in the gas phase at low temperature, generating radicals that triggered polymerization. However, no MA polymerization was observed in the presence of MBrP without the ligand, which could result from a too strong C-Br bond that can only be activated with ligand assistance. Therefore, adsorption of MBrP on Cu⁰ (in the absence of L) was investigated through cyclic voltammetry.

Cu⁰ showed good electrocatalytic properties towards the reductive cleavage of MBrP in DMSO (RX + e^- = R + X⁻, where electron transfer and bond breaking are concerted reactions⁹⁴). The electrocatalytic behavior of Cu⁰ was revealed by the position of the reduction peak, which shifted ca. 0.5 V towards less negative potential when MBrP was reduced on Cu electrode, compared to the reduction on an inert glassy carbon electrode (**Figure 3.14**). Such electrocatalytic processes occur through adsorption of reagents, intermediates and products on the metal surface, mostly driven by the high affinity of copper toward the halides, which reduce the activation energy required for bond cleavage.⁹⁵⁻⁹⁶ In conclusion, Cu⁰ behaves as a so-called

"inner-sphere" electrode towards RX reductive cleavage.⁹⁷⁻⁹⁸ Moreover, the overall process underlying the reduction peak was kinetically controlled by diffusion, which indicated that adsorption and desorption of reagents, intermediates and products were fast processes compared to diffusion and bond cleavage.



Figure 3.14. Cyclic voltammetry of 1 mM MBrP in DMSO + 0.1 M Et₄NBF₄ on a glassy carbon (GC) disk electrode (area $\approx 0.07 \text{ cm}^2$) and on a Cu disk electrode (area $\approx 0.03 \text{ cm}^2$). Scan rate = 0.2 V s⁻¹, *T* = 25 °C.

A final conclusive evidence towards RX adsorption come from the experiments at different [RX]₀ (**Figure 3.10-3.11**), which showed a clear saturation (and in some cases inhibition) of the reaction rate with increasing concentration. This should be due to complete occupation of the available active sites on Cu⁰, which prevents ligand access to assist activation.

Regarding ligand adsorption, it was reported that tertiary amines (e.g. trimethylamine) could adsorb on Cu⁰ via the nitrogen lone pair, with at least two of the C-N bonds pointing away from the surface.⁹⁹ Tertiary amines can also adsorb onto acidic defects of the surface (Lewis or Brønsted acidic sites such as oxides and hydroxides). Such sites can be present on Cu⁰ after the "surface activation" treatment in aqueous HCl/methanol. Primary amines adsorb even stronger than tertiary amines on Cu⁰, forming irreversible bonds in acetonitrile, stable enough to resist washing and ultrasonic rinsing.¹⁰⁰ Experiments at various [L] (**Figure 3.12-3.13**) showed a saturation rate was observed for strongly adsorbing EBPA. In conclusion, both L and RX should adsorb on Cu⁰ and they may compete for the available sites on the Cu⁰ surface.

3.3.5.2 Possible Mechanisms of R-X Activation

While there is strong evidence for RX adsorption, L may react either from an adsorbed adjacent site (Langmuir-Hinshelwood (LH) mechanism) or from solution (Eley-Rideal (ER) mechanism) (**Scheme 3.5**). There are however cases of reactions occurring simultaneously via ER mechanism on some sites and via LH mechanism on other sites.¹⁰¹⁻¹⁰²



Langmuir-Hinshelwood Mechanism

Scheme 3.5 Possible mechanism of surface activation. Two scenarios are possible in the ER mechanism, in which alkyl halide (RX) adorbs and Me₆TREN (L) reactions from solution (middle) or Me₆TREN adsorbs and RX reacts from solution (bottom). In some cases (RX = EBPA), the rate determining step may be solvent/ligand assisted desorption of Cu¹.

The four specific systems studied (two alkyl halides in two solvents) show complexity of the reactions occurring at the surface of Cu⁰ in SARA ATRP. Different alkyl halides, ligands and solvents could have quite different adsorption/desorption equilibrium and rate constants as well

as rate constants of the activation step, which could affect the overall kinetics of activation of alkyl halides on the surface of Cu⁰.

Activation of alkyl halides *formally* involves the concerted reductive cleavage of the C-X bond (RX + $e^- = R^+ + X^-$), which can proceed either via inner sphere or outer sphere electron transfer (ISET or OSET).⁹⁴ However, an OSET activation pathway could not efficiently generate radicals from the activation reaction of an adsorbed RX. Indeed, if the process was to proceed via OSET, the Cu surface should have a very negative reduction potential to overcome the high intrinsic barrier of RX reduction. However, a Cu surface with such negative redox potential would immediately reduce the adsorbed R⁺ to R⁻, since OSET reduction of R⁺ is a much faster process than OSET reduction of RX (because redox potentials of the processes are similar¹⁰³ but the activation energy is much smaller for R⁺ reduction as it does not involve any bond breaking). Thus, ligand-assisted RX activation must occur via an ISET process, in which favorable interactions between RX and the Cu⁰ centers, assisted by L, lead to a bonded transition state with low activation free energy, in agreement with previous literature reports.^{93, 104}

3.3.6 Conclusions

In conclusion, kinetics of activation of alkyl halides by Cu⁰ was investigated to determine the external order with respect to [RX], [L], and Cu⁰ *S/V* in model SARA ATRP systems. A first order with respect to both RX and L was observed at low reactant concentrations (both [RX]₀ and [L]₀), while at high concentrations the order approached zero or even < 0 in some cases. This should be taken into account in SARA ATRP when targeting low degree of polymerization (i.e. using high [RX]₀) or when using small Cu⁰ area. Ligand is needed to assist the activation process and to efficiently remove Cu¹ from the surface. However, increasing [L] above certain concentration does not increase the activation rate, since it may prevent access of RX to the surface. Nevertheless, without ligand, activation rate was ca. 3 orders of magnitude slower for EBPA, and no reaction was observed in the case of MBrP. Lastly, rate dependence on Cu⁰ surface area was determined to be first order in systems of high and low activities (EBPA and MBrP, respectively).

RX adsorbs on the Cu⁰ surface even in polar organic solvents, facilitating C-X bond cleavage. This was demonstrated by: i) the electrocatalytic behavior of Cu⁰ surfaces towards

MBrP reduction; ii) the activation of EBPA on Cu⁰ in the absence of any ligand; and iii) by the saturation (or even inhibition) of RX activation rate observed at high [RX], which is typical of reaction involving adsorbed substrates. Furthermore, ligand can also adsorb on the Cu⁰ surface. Electrochemical and kinetic data suggests that alkyl halide activation proceeds via an ISET mechanism.

3.4 A Silver Bullet: Elemental Silver as an Efficient Reducing Agent for Atom Transfer Radical Polymerization of Acrylates

3.4.1 Preface

Elemental silver was used as a reducing agent in the atom transfer radical polymerization (ATRP) of acrylates. Silver wire, in conjunction with a $CuBr_2/TPMA$ catalyst, enabled the controlled, rapid preparation of polyacrylates with dispersity values down to D = 1.03. The silver wire in these reactions was reused several times in sequential reactions without a decline in performance, and the amount of copper catalyst used was reduced to 10 ppm without a large decrease in control. A poly(n-butyl acrylate)-block-poly(tert-butyl acrylate) diblock copolymer was synthesized with a molecular weight of 91 400 and D = 1.04, demonstrating good retention of chain-end functionality and a high degree of livingness in this ATRP system

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3.4.2 Introduction

Since the conception of reversible deactivation radical polymerization (RDRP) in the 1990s, these methodologies have revolutionized polymer chemistry.^{3-4, 105} Particularly, RDRP techniques have allowed for the synthesis of polymers with very narrow molecular weight distributions, predetermined molecular weights, and remarkable conservation of chain-end functionality, previously only achievable via ionic polymerization.¹⁰⁶⁻¹⁰⁷ Atom transfer radical polymerization (ATRP) is among the most commonly utilized RDRP methods.^{6, 10, 108-112} In addition to nitroxide mediated polymerization (NMP)¹¹³⁻¹¹⁶ and reversible addition-fragmentation chain transfer polymerization (RAFT),¹¹⁷⁻¹²⁴ ATRP achieves its control of polymer chain growth and architecture through a transition metal catalyzed activation/deactivation redox cycle of alkyl halides and alkyl radicals, respectively.^{11, 125} Traditionally, a large concentration of transition metal catalyst was required to successfully conduct an ATRP due to unavoidable radical termination resulting in a buildup of deactivator species, consistent with the persistent radical effect (PRE).^{11, 126} However, within the last decade the use of reducing agents have allowed for a decrease in the initial amount of metal catalyst necessary for an efficient ATRP down to the ppm level.¹⁵ Regeneration of the activator species from a deactivator complex is facilitated through a variety of different methods, including the addition of azo radical initiators (Initiators for Continuous Activator Regeneration, ICAR ATRP)¹²⁷ or chemical reducing agents (Activator Regenerated by Electron Transfer, ARGET ATRP),^{57, 128} use of electrical current (*e*ATRP ATRP)¹⁹ or light (photoATRP),^{59, 129-133} or addition of zero-valent metals (Supplemental Activator and Reducing Agent, SARA ATRP) (Scheme 3.6).^{24, 134-135} Zero-valent metals were first applied to ATRP processes in 1997,¹³⁶ where Cu⁰ (or Fe⁰) was used both to reduce Cu^{II} deactivator complexes to Cu¹ activator species via comproportionation and directly activate alkyl halide species in solution. In SARA ATRP (aka SET-LRP), Cu⁰ plays an active role in radical generation and plausible radical termination.^{24, 74, 137} Therefore, a reducing agent that acts via single-electron transfer and is inert to radical generation and termination has long been sought after, but other metals such as Fe⁰, Mg⁰, or Zn⁰ operate via a SARA mechanism.¹³⁸ We report here the use of Ag⁰ as a previously unexplored ARGET reagent.



Scheme 3.6. Proposed mechanism of ATRP in the presence of Ag⁰.

3.4.3 Experimental

General. All manipulations were carried out under an inert atmosphere of dry N2 unless otherwise noted. *n*-Butyl acrylate (BA), *tert*-butyl acrylate (tBA), methyl acrylate (MA), ethyl α bromoisobutyrate (EBiB) and copper (II) bromide (CuBr₂) were purchased from various suppliers. Monomers were passed through basic alumina to remove inhibitors and stored at 0 °C before use. Dimethylformamide (DMF) was purchased from Fisher and used without any purification, and silver wire (Alfa, Strem) was used without prior treatment unless otherwise noted. Tris(2-pyridylmethyl)amine (TPMA) was synthesized as according to literature procedures.^{42, 139} All solvents and monomers were bubbled with dry N₂ gas for 30 minutes prior to use unless otherwise noted. Monomer conversion was determined by ¹H NMR in CDCl₃ using a Bruker Avance 300 MHz spectrometer with DMF (δ = 2.96, 2.88, (CH₃)₂NCOH) as the internal standard.¹⁴⁰ Number average molecular weight (M_n) and M_w/M_n values were determined by gel permeation chromatography (GPC) using PSS columns in THF at an eluent at a flow rate of 1 mL/min at 35 °C, calibrated to PMMA using DPE or toluene as an internal standard. The GPC system was composed of Waters 515 HPLC Pump and Waters 2414 Refractive Index Detector. Each sample was filtered over neutral alumina prior to analysis. A Mark-Houwink correction was applied to all samples to obtain the MW of PBA, tBA, or PMA

with respect to the PMMA standard. UV-Visible Spectroscopy was performed on a Varian Cary 5000 UV-Vis-NIR spectrometer.

Experimental Procedures (General)

- a) A 10 mL Schlenk flask was charged with Ag^0 wire (d = 2 mm, l = 5 cm) and stir bar, sealed, and evacuated and refilled with N_2 three times. Excess DMF and BA were independently deoxygenated by bubbling with N_2 for a minimum of 30 min, and 5.0 mL of each were added to the Schlenk flask via syringe. A stock solution of CuBr₂/TPMA (140 µL of 0.05 M CuBr₂ and 0.10 M TPMA in DMF, 0.007 mmol CuBr₂ and 0.014 mmol TPMA), then EBiB (26 µL, 0.17 mmol), was added via syringe. The flask was again sealed and heated to 50 °C, and the reaction was monitored by GPC and ¹H NMR spectroscopy.
- b) A 10 mL Schlenk flask was charged with Ag^0 wire (d = 2 mm, l = 5 cm) and stir bar, sealed, and evacuated and refilled with N_2 six times. A solution of $CuBr_2/TPMA$ (168 µL of 0.05 M $CuBr_2$ and 0.10 M TPMA in DMF, 0.008 mmol $CuBr_2$ and 0.017 mmol TPMA), EBiB (41 mg, 0.21 mmol), DMF (6.0 mL), and BA (6.0 mL, 42 mmol) was prepared and degassed via four freeze-pump-thaw cycles, and 10 mL of this solution was added to the reaction flask under N_2 via syringe. The flask was sealed and heated to 50 °C, and the reaction was monitored by GPC and ¹H NMR spectroscopy.
- c) **PBA-b-PtBA Block Copolymerization.** A PBA-Br macroinitiator ($M_n = 6,600$ g/mol, D = 1.08) was synthesized according to procedure (a) above and purified by precipitation in methanol/water (85/15 by v/v) three times, separating the polymer from the solution by centrifugation. The product was collected and dried under vacuum for 1 day. Silver wire (d = 2 mm, l = 5 cm) was placed in a Schlenk flask under N₂. The synthesized PBA-Br (320 mg, 0.0419 mmol) was dissolved in DMF (7 mL) and transferred to the reaction flask and bubbled with N₂ for 30 minutes. Excess *t*BA was deoxygenated by bubbling with N₂ for 30 min and 7.0 mL (49 mmol) was added to the Schlenk flask via syringe, then the solution of CuBr₂/TPMA (195 μ L of 0.05 M CuBr₂ and 0.1 M TPMA in DMF, 0.01 mmol CuBr₂ and 0.02 mmol TPMA) was added. The flask was sealed and heated to 50 °C, and the reaction was monitored by GPC and ¹H NMR spectroscopy.

3.4.4 Results and Discussion

The use of elemental silver as a reducing agent possesses many attractive characteristics. Silver has only two readily attainable oxidation states (0, +1), so reduction with Ag⁰ would likely be a single-electron process.¹⁴¹⁻¹⁴² Both Ag⁰ and the proposed oxidized species (Ag^IX) are insoluble in most reaction media, which would simplify purification processes and lessen product contamination by transition metals, as well as open the possibility of application on an industrial scale.¹⁴³ Lastly, Ag⁰ is relatively inert towards typical polymerization reagents, which could minimize or eliminate undesirable radical generation or termination events that are commonly observed in SARA ATRP and other reduced-catalyst techniques.²⁴ Herein, we report the first use of Ag⁰ as a heterogeneous reducing agent for copper-mediated ATRP.

The rate-determining step in many ATRP processes with low catalyst loading is the (re)generation of a low-valent activator species.¹²⁷ Therefore, it is of great importance to determine the efficiency of this (re)generation process in new ATRP systems. To achieve this, the heterogeneous reduction of $Cu^{II}Br_2/TPMA$ (TPMA = tris(2-pyridylmethyl)amine)^{42, 139} by Ag⁰ in polymerization media was monitored as a function of time. Alkyl halide initiator was excluded from these reactions to allow for simple and quantitative determination of reduction rates. As one of the most commonly used ligands for Cu-mediated ATRP, TPMA was chosen for the high activity and stability of its copper complexes under these reaction conditions. It was observed that Ag⁰ readily reduced Cu^{II}Br₂/TPMA to the Cu^I activator species, which could then enter into the ATRP equilibrium in the presence of alkyl halide initiator (Scheme 3.6).¹²⁷ In the absence of initiator, equilibrium between Ag⁰/Cu^{II} and Ag^I/Cu^I was achieved after 90 min. It should be noted that copper complexes with both Me₆TREN and PMDTA as ligands (Me₆TREN = tris[2-(dimethylamino)ethyl]amine; PMDTA = N, N, N', N', N''-pentamethyldiethylenetriamine) were successfully reduced by Ag⁰ as well, highlighting the large scope of this new methodology. To establish the efficacy of Ag⁰ as a heterogeneous reducing agent for ATRP, the polymerization of *n*-butyl acrylate (BA) was carried out at 50 °C. Under these conditions, 62% monomer conversion was observed after 2 h at 200 ppm initial CuBr₂/TPMA catalyst loading. Molecular weight was in very good agreement with theoretical values throughout the reaction, increasing linearly with conversion, and at 62% monomer conversion, GPC analysis revealed a very low value of D = 1.03,

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among the lowest reported for copper-mediated ATRP of acrylates. At higher conversion, a decrease in reaction rate was observed, but good control over polymerization was maintained at all reaction times. This low dispersity value likely indicates that Ag⁰ is not active in the generation or termination of radicals, and rather acts solely as a reducing agent. Accordingly, polymerization of BA in the absence of CuBr₂ did not occur over 2 h whereas, in the presence of CuBr₂/TPMA, 50% monomer conversion was attained after 2 hours. Thus, if activation occurred with Ag⁰, it was slow enough relative to Cu¹ activation to be kinetically negligible. Additionally, although radical-radical termination reactions are unavoidable in any RDRP, it is possible that the presence of Ag⁰ may suppress alternative termination pathways such as Cu¹ catalytic radical termination (CRT), which has been shown to be a dominant mode of radical termination in some Cu-based ATRP reactions of acrylates.¹³⁷



Figure 3.15. (a) Kinetics and (b) evolution of M_n and M_w/M_n with conversion in the ATRP of BA with various SA/V of silver. Reaction conditions: [BA]₀:[EBiB]₀: [CuBr₂]₀:[TPMA]₀ = 200 : 1 : 0.04 : 0.08 with [BA]₀ = 3.49 M in DMF at 50 °C, in the presence of 0.5-10 cm Ag⁰ wire (d = 2 mm, SA = 0.4 – 6.4 cm²; V_{tot} = 10 mL; SA/V = 0.04 – 0.64 cm⁻¹).



Figure 3.16. (a) Kinetics and (b) evolution of M_n and M_w/M_n with conversion in the ATRP of BA with the same silver wire in five sequential reactions. Reaction conditions: [BA]₀:[EBiB]₀:[CuBr₂]₀:[TPMA]₀ = 200 : 1 : 0.04 : 0.08 with [BA]₀ = 3.49 M in DMF at 50 °C, in the presence of 5 cm Ag⁰ wire (d = 2 mm, SA = 3.2 cm²; V_{tot} = 10 mL).

Because silver is a relatively expensive reducing agent as compared to alternatives such as copper or ascorbic acid, the minimization of Ag^0 wire used is highly desired. Five separate experiments were conducted with varying amounts of silver wire: 10, 5, 2, 1, and 0.5 cm (silver surface area to solution volume ratio = 0.64, 0.32, 0.13, 0.07 and 0.04 cm⁻¹, respectively). **Figure 3.15a** illustrates the polymerization kinetics of these five reactions. As the surface area of silver was decreased, the rate of polymerization similarly declined, suggesting the involvement of silver in the rate-determining step of the reaction. Molecular weight increased linearly with conversion (**Figure 3.15b**) and was nearly identical to theoretical molecular weight. Molecular weight distributions were independent of silver surface area and remained low, with D = 1.02 at 75% monomer conversion (2 cm Ag⁰ wire). Importantly, because reaction rate was dependent on the silver surface area to reaction volume ratio (SA/V) and not on total amount of silver used, reaction rate could be feasibly increased by either increasing the surface area of silver or decreasing total reaction volume.

Fortunately, use of large amounts of silver is still experimentally reasonable due to the high reusability of the metal. Indeed, one of the greatest advantages of a heterogeneous system is the potential reusability of the reagents,¹⁴³ as demonstrated below. A single piece of silver wire was used without treatment in five sequential polymerizations of BA, and results are

illustrated in **Figure 3.16**. The rate of polymerization does not change significantly over each cycle, and molecular weight values match up well to theoretical values over all cycles. Most importantly, a high degree of control over polymerization was consistently maintained, with D = 1.05 in all reactions. This result suggests that coating of the silver surface by either polymer or initial reagents is minimal and does not notably affect subsequent reactions.

It is also desirable to decrease the amount of catalyst necessary for reaction, so five different polymerizations were run with various initial CuBr₂/TPMA catalyst loadings (Figure 3).¹⁴⁴⁻¹⁴⁵ As observed previously,¹⁴⁶ decrease of catalyst concentration resulted in a reduction of reaction rate and a slight broadening of MWD. However, at all catalyst concentrations linear increase of M_n with conversion was observed, with experimental values matching up well to theoretical. Additionally, with catalyst loadings of down to 10 ppm Cu^{II}Br₂, at 62% monomer conversion $\mathcal{D} = 1.27$, indicating remarkably good control relative to comparable low-catalyst systems.



Figure 1.17. (Left) Kinetic data and (right) evolution of M_n and M_w/M_n with conversion in the ATRP of BA with various initial concentrations of Cu^{II}Br₂. Reaction conditions: [BA]₀:[EBiB]₀: [CuBr₂]₀:[TPMA]₀ = 200 : 1 : x : 2x (x = 0.04, 0.02, 0.01, 0.005, 0. 002) with [BA]₀ = 3.49 M in DMF at 50 °C, in the presence of 5 cm Ag⁰ wire (d = 2 mm, SA = 3.2 cm²; V_{tot} = 10 mL).

To expand the scope of this methodology, polymerizations of tert-butyl acrylate (*t*BA) and methyl acrylate (MA) were carried out and for both acrylates 60% monomer conversion was achieved in under 2 h (**Figure 3.17**). Molecular weight was in good agreement with theoretical

values, indicating a high degree of livingness and preservation of chain-end functionality. A sample of ptBA (M_n = 3,600; D = 1.17) was further studied by ¹H NMR spectroscopy and indicated approximately 97% retention of chain end functionality. This result suggested the possibility of facile and precise block copolymer synthesis, so chain extension from poly(*n*-butyl acrylate) (PBA) was carried out. PBA-Br (M_n = 6,600, D = 1.08) was synthesized and purified according to the procedure given in the supporting information and used as a macroinitiator in the subsequent polymerization of *t*BA. Monomer conversion as a function of time revealed pseudo-first-order kinetics, suggesting that a constant concentration of radicals was maintained throughout the reaction. Additionally, a linear increase in molecular weight with conversion was observed while maintaining very narrow MWD, with D = 1.04. The GPC traces of chain extension shown in **Figure 3.18** reveal very narrow MWD with minor low molecular weight tailing at higher conversions, typical for this type of chain extension.¹⁴⁷ However, it should be noted that at lower monomer conversion (> 50%), D actually decreased upon chain extension from the PBA-Br macroinitiator, from D = 1.07 to D = 1.02 at 40% conversion. Thus, copper-catalyzed ATRP with Ag⁰ is a very powerful method for the preparation of highly defined block copolymers.



Figure 3.18. GPC traces for the chain extension from PBA-Br with *t*BA. Reaction conditions: $[tBA]_0:[PBA-Br]_0:[CuBr_2]_0: [TPMA]_0 = 1000 : 1 : 0.2 : 0.4 with <math>[tBA]_0 = 3.49$ M in DMF at 50 °C, in the presence of 5 cm Ag⁰ wire (d = 2 mm, SA = 3.2 cm²; V_{tot} = 10 mL).

3.4.5 Conclusions

In conclusion, a new copper-catalyzed ATRP system with elemental silver as the reducing agent was developed. Good control over polymerization of BA, *t*BA and MA was demonstrated with this methodology, with MW dispersity down to D = 1.03. Monomer conversions of 60% were

achieved in 1.5 - 2 h with 200 ppm CuBr₂/TPMA catalyst loading, and molecular weight of the resulting polymers were in good agreement with theoretical values. The same silver wire could be used for several sequential polymerizations without adverse effects on the polymer produced, and treatment of the silver was not required between each reaction. The amount of silver wire used in each reaction could be reduced to l = 0.5 cm, corresponding to a surface area-to-volume ratio of 0.04 cm⁻¹, without decrease in control. Polymerization of BA with 10 ppm CuBr₂/TPMA catalyst loading afforded PBA with MW in excellent agreement with theoretical values and D = 1.29. Chain extension of a PBA-Br macroinitiator with *t*BA exhibited high chain-end functionality, and a PBA-*b*-P*t*BA-Br diblock copolymer was synthesized with D = 1.02.

The use of silver as a reducing agent in ATRP represents a significant advance: as a oneelectron heterogeneous reductant, the side reactions that often hinder the efficacy of conventional ARGET ATRP reactions are minimized, and in contrast to the Cu⁰ used in traditional SARA ATRP reactions, the use of Ag⁰ does not engender a buildup of reactive Cu¹ through the course of reaction. As evidenced by the low D values and high livingness observed here, silver likely neither acts to generate nor terminate radicals in the system, thereby eliminating the side reactions observed in other ATRP processes which have previously led to some loss of chain-end functionality. As such, silver is an excellent reducing agent for highly controlled ATRP.

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Chapter 4.

Kinetic Simulations of Normal vs. Low ppm ATRP

4.1 Preface

Mechanistic studies have been published on various low ppm systems which commonly use incorrect assumptions with regards to the kinetics of the system. Specifically, the rate of supplemental activator and reducing agent (SARA) ATRP was investigated by Haddleton *et al* in organic media. They compared the rate of SARA to the rate of normal ATRP, the main difference being the presence of Cu⁰ in the former while being absent in the latter. Not surprisingly, the rate of SARA was significantly faster than the rate of normal ATRP which lead the authors to conclude that Cu⁰ was more active than L/Cu¹ complexes. Unfortunately, these two systems cannot be directly compared based on the overall polymerization rate. This is because they follow two different kinetic regimes. As discussed in **Section 1.2.5.1** and **Section 1.2.5.2**, normal ATRP is subjected to the persistent radical effect (PRE) while SARA overcomes the PRE due to slow and continuous activator regeneration. The fact that this was neglected warranted a separate study which explains how the rate of activation of alkyl halides is related to the overall rate of polymerization. Through the use of kinetic simulations, it was shown for that rate of activation cannot be directly related to the overall rate of polymerization.

The simulations for the paper were conducted by Dr. Pawel Krys. I was involved with the detailed discussions about the simulations and analysis of the results as well as preparation of the manuscript.

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4.2 Relation between Overall Rate of ATRP and Rates of Activation of Dormant Species

4.2.1 Preface

The rate of atom transfer radical polymerization (ATRP) depends on the rate constant of propagation (k_p) and concentration of growing radicals. The latter is related to the ATRP equilibrium constant (K_{ATRP}) and concentrations of alkyl halides, activators and deactivators. Activation of alkyl halides by Cu^I/L and deactivation of radicals by X-Cu^{II}/L are vital processes providing good control in ATRP. Rates of these reactions are typically identical throughout polymerization, since the ATRP equilibrium is maintained in essentially all ATRP systems. There are new ATRP processes carried out with ppm of Cu catalysts, such as activators regenerated by electron transfer (ARGET), initiators for continuous activator regeneration (ICAR), supplemental activators and reducing agents (SARA), electrochemically or photochemically mediated ATRP (eATRP, photoATRP). In these processes, as in conventional radical polymerization (or in RAFT), concentration of radicals is established by balancing rates of radical generation (e.g. from thermal initiators, reduction rate or supplemental activation) and radical termination (i.e. reaching steady state). However, in these processes, the rate of activation of alkyl halides by Cu^I/L is still equal to the rate of deactivation of radicals by X-Cu^{II}/L. Can the rates of activation of alkyl halides (by Cu^I or by Cu⁰) be directly related to the overall rate of ATRP? This report aims to clarify that rate of activation of alkyl halides by Cu^I species cannot be directly related to the overall rate of polymerization. There are many cases with the same rate of ATRP but dramatically different rates of activation and cases with similar activation rates but very different overall ATRP rates. Thus, both analytical approach and PREDICI simulations clearly show that rates of normal ATRP with high catalyst loadings as well as rates of low ppm ATRP systems, such as ICAR ATRP and SARA ATRP, cannot be directly related with rates of activation of alkyl halides by Cu¹. In SARA ATRP, the activation of alkyl halides by Cu¹ is always much faster than by Cu⁰.

4.2.2 Introduction

In the past two decades, the field of radical polymerization has been redefined by various reversible-deactivation radical polymerization (RDRP) methods. These processes provide control over polymer molecular weight and architecture comparable to living ionic polymerization, with concurrent tolerance to functional groups and impurities known from radical polymerization. It is worth noting that equilibria between radicals and dormant species are essential not only in RDRP but also in biological systems.¹ The three most commonly used RDRP techniques are nitroxide-mediated polymerization (NMP),² reversible addition-fragmentation chain transfer polymerization (RAFT),³ and atom transfer radical polymerization (ATRP).⁴⁻⁸ In ATRP, control over polymer structure is achieved by fast activation-deactivation processes between dormant and propagating species. A dormant (macro)alkyl halide (PnX) is activated by a transition metal catalyst in lower oxidation state, typically Cu^I/L, generating a halide complex in higher oxidation state (X-Cu^{II}/L) and a radical (P_n[•]). Quickly, typically after one or several monomer additions, the propagating (macro)radical is deactivated back to the dormant (macro)alkyl halide. Efficient activation and deactivation are crucial in ATRP for obtaining polymers with predefined molecular weight and with narrow molecular weight distributions (MWD). This manuscript investigates relationship between rate of polymerization and rate of activation of dormant species by Cu¹ in several ATRP systems and shows that such direct relation does not exist.

In normal ATRP, typically high catalyst loadings are required (over 1000 parts-per-million (ppm)) due to unavoidable radical termination reactions and persistent radical effect (PRE).⁹ Several methods have been implemented to significantly decrease catalyst concentrations through continuous regeneration of the Cu¹/L activator species. This was achieved with chemical reducing agents (e.g. Sn^{II}R₂, ascorbic acid, or Ag⁰) in activators regenerated by electron transfer (ARGET) ATRP,¹⁰⁻¹² radical initiators (e.g. azobisisobutyronitrile, AIBN) in initiators for continuous activator regeneration (ICAR) ATRP,¹³ zerovalent metal (e.g. Cu⁰, Fe⁰) in supplemental activator and reducing agent (SARA) ATRP,¹⁴⁻¹⁷ electric current in electrochemically mediated ATRP (*e*ATRP),¹⁸⁻¹⁹ or light in photochemically mediated ATRP (photoATRP).²⁰⁻²²

The basic reaction scheme for ATRP is shown in **Scheme 4.1**. The upper part refers to normal ATRP, with rate constants of radical propagation (k_p) , termination (k_t) and

activation/deactivation (k_{a1}/k_{d1}). The bottom part describes systems carried out in the presence of ppm Cu catalyst and with activator regeneration. This is necessary to compensate for loss of catalyst in its deactivated state due to unavoidable radical termination.



Scheme 4.1 Mechanism of Cu-mediated ATRP without (top) and with (bottom) activator regeneration.

In principle, faster activation could increase concentration of radicals and enhance polymerization rate. However, after brief ATRP initiation period, rate of activation equals that of deactivation. Thus, can the rates of activation of alkyl halides (by Cu¹ or by Cu⁰) be related with the overall rate of ATRP? This will be analyzed for three systems: traditional (normal) ATRP carried out with high concentration of Cu catalyst,⁴ and two systems with ppm level of Cu catalyst: ICAR ATRP in the presence of radical initiators¹³ and SARA ATRP in the presence of Cu⁰ wire.¹⁶⁻¹⁷ As will be shown, both analytical approach and PREDICI²³ simulations clearly indicate that rates of normal ATRP, ICAR ATRP or SARA ATRP cannot be directly related to the rates of activation of alkyl halides. There are cases with the same rate of ATRP but dramatically different rates of activation and cases with similar activation rates but very different overall ATRP rates.

4.2.3 Determination of Rate Constants of ATRP Relevant Reactions

The overall rate of polymerization (R_p) can be conveniently measured by monitoring monomer conversion in time. R_p depends on the rate constant of propagation (k_p) and

concentration of radicals ([R[•]]) (**Eq. 4.1**). It should be noted that in all following equations [R[•]] represents concentration of all radicals (R[•] and $P_n^{•}$) and [RX] represents concentration of alkyl halides and dormant polymer chains (RX and P_nX).

$$R_{\rm p} = -\frac{d\ln[M]}{dt} = k_{\rm p}[M][R^{\bullet}]$$
 (Eq. 4.1)

Since k_p values are known from literature,²⁴⁻²⁶ [R[•]] can easily be determined (Eq. 4.2).

$$[\mathbf{R}^{\bullet}] = -\frac{d\ln[\mathbf{M}]}{dt} \frac{1}{k_{p}[\mathbf{M}]}$$
 (Eq. 4.2)

ATRP equilibrium (cf. Scheme 4.1) is maintained in essentially all ATRP systems.⁷ Thus, determination of equilibrium constants is straightforward when relatively high concentration of [Cu^I], [Cu^{II}] and [RX] are used, which do not change due to small extent of termination (**Eq. 4.3**).²⁷

$$K_{\rm ATRP} = \frac{[X - Cu^{\rm II}/L][R^{\bullet}]}{[Cu^{\rm I}/L][RX]}$$
 (Eq. 4.3)

A large collection of data for K_{ATRP} measured this way is available.²⁸⁻²⁹ Otherwise, it is also possible to determine K_{ATRP} using persistent radical effect (PRE).²⁸⁻³⁰

Rate coefficients of activation of alkyl halides by Cu^I/L species (k_{a1}) were determined using several chromatographic and spectroscopic techniques, including high-performance liquid chromatography (HPLC), gas chromatography (GC), size exclusion chromatography (SEC), UV-Vis spectroscopy, or nuclear magnetic resonance (NMR).³¹⁻³⁶ This was typically carried out in the presence of radical traps, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), to prevent contribution of deactivation process. For fast reactions, stopped flow or electrochemical techniques have been successfully used.^{15, 37-40} Rate coefficients were determined either by following consumption of alkyl halides or Cu^I/L species, or by evolution of Cu^{II}/L species. Estimation of rate coefficients was also performed using regression analysis.⁴¹⁻⁴²

Large variety of data is available for various alkyl halides, copper(I) complexes and different solvents and temperatures.^{28, 35-36, 43-44} k_{a1} values span several orders of magnitude from as low as 10⁻⁵ M⁻¹s⁻¹ to 10⁵ M⁻¹s⁻¹.²⁸ Values of rate coefficients of deactivation of radicals by X–Cu^{II}/L species (k_{d1}) can be assessed as a ratio of k_{a1}/K_{ATRP} . They are much larger and typically in the range of 10⁷ M⁻¹s⁻¹ to 10⁸ M⁻¹s⁻¹. They have been also measured using radical clock reactions, initial degrees of polymerization (DP), electrochemical methods, or with single laser pulse-pulsed laser polymerization coupled with electron paramagnetic resonance (SP-PLP-EPR).^{33, 45-48}

Rates of activation and deactivation can be defined according to **Equations** Error! Reference source not found.**.4 and 4.5**, based on the relevant rate coefficients and concentration of the involved reagents.

 $R_{a1} = k_{a1} [Cu^{I}/L] [RX]$ (Eq. 4.4)

 $R_{\rm d1} = k_{\rm d1} [\rm X - Cu^{II} / L] [\rm R^{\bullet}]$ (Eq. 4.5)

Recently, rate coefficients of activation of alkyl halides by Cu⁰ were determined for several alkyl halides (RX), ligands (L), and solvents.⁴⁹ Variations in values of rate coefficients of activation of RX by Cu⁰ with structures of RX, L and solvent are much smaller than the corresponding values determined for Cu¹. The largest values of k_{a0} for most reactive alkyl halides (such as EBPA) approach but do not exceed rate coefficients determined for comproportionation of Cu¹¹/L species under similar conditions (L, solvent). Due to the heterogeneous nature of the activation (and comproportionation) process, rate coefficients have different dimensions, related to the surface area of Cu⁰ and solvent volume ratio (*S*/*V*). They are in the range of 10⁻⁴ cm s⁻¹ to 10⁻² cm s⁻¹ (note two orders of magnitude range for Cu⁰ vs. ten orders for Cu¹).

Rates of activation of alkyl halides by Cu^0 and comproportionation were determined according to **Equations 4.6 and 4.7**, based on the relevant rate coefficients, concentration of alkyl halides or Cu^{II}/L , and surface area of Cu^0 to solvent volume ratio.

$$R_{a0} = k_{a0} \frac{S}{V} [RX]$$
 (Eq. 4.6)
 $R_{comp} = k_{comp} \frac{S}{V} [Cu^{II}/L]$ (Eq. 4.7)

4.2.4 Kinetics of Polymerization and Activation in Normal ATRP of Methyl Acrylate in DMSO

Kinetics of normal ATRP and evolution of [Cu^I]/[Cu^{II}] ratio is shown in **Figure 4.1a** for two different initial ratios and also 3 different absolute concentration of Cu species, using methyl 2-bromopropionate (MBP) as initiator. **Figures 4.1b**, **c** illustrate the rates of propagation, termination and activation/deactivation for these systems as a function of monomer conversion. **Figure 1a** clearly shows that in normal ATRP, the overall rate of monomer consumption depends on the initial ratio of [Cu^I]/[Cu^{II}] but does not depend on absolute concentration of Cu species, if they are sufficiently large. This very well agrees with **Eq. 4.1**, where concentration of radicals was defined by **Eq. 4.3**.





Figure 4.1. (a) Kinetics of normal ATRP and evolution of $[Cu^{I}]/[Cu^{II}]$ ratio, and (b) and (c) rates of propagation, activation, deactivation, and termination as a function of monomer conversion. Conditions: [MA]:[MBP]:[Cu^{II}Br]:[Cu^{II}Br₂]:[Me₆TREN] = 200:1:(x):(y):(x+y); 66% (v/v) MA in DMSO, T = 25 °C, where x/y = 2.3 (b) or 0.8 (c) and x+y = 1, 3, or 10.

Small deviation in kinetics can be noted at high monomer conversions when higher $[Cu^{I}]/[Cu^{II}]$ ratio and the lowest catalyst concentration were used. This results from the radical termination irreversibly converting Cu^I to Cu^{II} (due to the persistent radical effect, PRE⁹). At even smaller concentrations of Cu catalyst, ATRP would become very slow (or even stop) since termination of only a small percentage of chains would significantly decrease concentration of activator. Thus, activator regeneration methods have to be applied (*vide infra*).

Figures 1b, c show that rates of activation and deactivation for each particular system are very well balanced indicating maintenance of ATRP equilibrium throughout the polymerization. These rates depend on absolute concentrations of Cu^I and Cu^{II}, according to **Equations 4.4 and 4.5**, but not on the rates of polymerization. Thus, the overall rate of polymerization in ATRP can be lower but the rate of activation higher and vice versa. There is no direct relation between overall ATRP rates and activation rates. However, faster polymerization leads to faster termination.

In all simulations tris[2-(dimethylamino)ethyl]amine (Me₆TREN) was used as a ligand. Generally, such active ligands with very active initiators (e.g. ethyl 2-bromoisobutyrate (EBiB), or ethyl 2-bromophenylacetate (EBPA)) do not perform well in normal ATRP, due to very large values of k_{act} and K_{ATRP} .⁵⁰ Normal ATRP, with high initial concentration of [Cu¹/L]₀ results in a high concentration of radicals and therefore in fast termination.⁵¹ This fast termination at the onset of the reaction causes a quick decrease in the [Cu^I]/[Cu^{II}] ratio, resulting in a loss of chain end functionality and slower polymerization. To illustrate the effect of catalysts in normal ATRP, PREDICI simulations were conducted with constant values of deactivation rate coefficients and with varying values of activation rate coefficients, k_{a1} , mimicking Cu complexes with different ligands. For slow activation, such as $k_{a1} = 1 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ (resembling e.g. benzyl bromide/2,2′bipyridine/acetonitrile system) a slow, but well-controlled polymerization was observed. When moving towards larger values of k_{a1} , first polymerization was faster (i.e. for $k_{a1} = 1 \text{ M}^{-1} \text{ s}^{-1}$, mimicking e.g. MBP/N,N,N',N",N"-pentamethyldiethylenetriamine (PMDETA)/DMSO). Then, rates decreased (i.e. for $k_{a1} = 1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$, mimicking e.g. EBiB/Me₆TREN/DMSO). This is due to the higher concentration of radicals and higher rates of termination observed in normal ATRP using highly active catalytic systems.⁵¹⁻⁵³ For even higher K_{ATRP} and k_{a1} values, essentially all chains terminate to halt the reaction after only 5% monomer conversion.

4.2.5 Kinetics of polymerization and activation in ICAR ATRP of methyl acrylate in DMSO

Initiators for continuous activator regeneration (ICAR) ATRP is a method of activator regeneration that utilizes conventional thermal initiators (e.g. AIBN) to slowly and continuously reduce excess Cu^{II} resulting from radical termination reactions. ICAR ATRP was chosen for simplicity in modeling, however similar conclusions can be applied to other activator regeneration methods (photoATRP, *e*ATRP, ARGET ATRP).

Kinetics of ICAR ATRP resembles that of conventional radical polymerization (RP) and RAFT. In RP, steady state concentration of radicals is determined from the equal rates of radical generation and termination, as illustrated in **Eq. 4.8**.

$$[\mathbf{R}^{\bullet}] = \sqrt{\frac{fk_{dc}[\mathbf{I}_2]}{k_t}}$$
 (Eq. 4.8)

where k_{dc} is decomposition rate coefficient, [I₂] is concentration of initiator and f is initiator efficiency.

Rates of polymerization in ICAR ATRP (or RAFT) depend on the rate of radical generation from thermal initiators, such as AIBN (k_{dc} is defined by the initiator structure and temperature)

and its concentration (**Eq. 4.9**). These rates do not depend on concentration of Cu species until it reaches very high values. In such a case, ICAR ATRP crosses to reverse ATRP or simultaneous reverse and normal initiation (SR&NI) ATRP regimes.⁵⁴⁻⁵⁶

$$R_{\rm p} = k_{\rm p} [{\rm M}] \sqrt{\frac{fk_{\rm dc} [{\rm I}_2]}{k_{\rm t}}}$$
 (Eq. 4.9)

Nevertheless, ATRP equilibrium is well maintained and $[Cu^{I}]/[Cu^{II}]$ can be still calculated from **Eq. 4.3**, knowing K_{ATRP} , [RX], and [R[•]]. The latter is defined according to **Eq. 4.8**.

Early stages of ICAR ATRP include induction periods due to lack of Cu¹ activator. Throughout this phase Cu^{II} is progressively reduced to Cu¹ until a "steady" concentration of radicals and the related [Cu^I]/[Cu^{II}] ratio is reached. Higher initial [Cu^{II}] leads to longer induction periods, also depending on the rate of radical generation. It should be noted that during the initial period, radicals generated from the thermal initiator and corresponding dormant species (IX) may have a very different value of K_{ATRP} than that of used alkyl halide (RX) and growing polymeric species (P_nX). This can affect the equilibration between all radicals, dormant species and Cu species. They can also add to monomer with lower rate coefficients than k_p . This can influence kinetics in the initial periods, similarly to "initialization" observed in RAFT.⁵⁷

The kinetics of ICAR ATRP and evolution of $[Cu^{I}]/[Cu^{II}]$ ratio are shown in **Figure 4.2a** for two different $[I_2]_0$ values and two varied absolute concentration of Cu^{II} species. **Figure 4.2b**, **c** illustrates the rates of propagation and activation/deactivation for these systems as a function of monomer conversion. **Figure 4.2a** clearly shows that the overall rate of monomer consumption in ICAR ATRP depends on the initial $[AIBN]_0$ but does not depend on absolute concentration of Cu species if they are sufficiently small.⁵⁸ An initial induction period is due to reduction of Cu^{II} to reach a steady $[Cu^{I}]/[Cu^{II}]$ ratio. This ratio adjusts according to **Equation 4.3**. It depends on K_{ATRP} and thus the choice of ligand in ICAR ATRP is important for maintaining narrow MWD. However, rate of polymerization is independent of ligand.



Figure 4.2. (a) Kinetics of ICAR ATRP and evolution of $[Cu^{I}]/[Cu^{II}]$ ratio, and (b) and (c) rates of propagation, activation, deactivation, and termination as a function of monomer conversion. Conditions: $[MA]:[MBP]:[Cu^{II}Br_2]:[Me_6TREN]:[AIBN] = 200:1:(x):0.05:(y); 66% (v/v) MA in DMSO, T = 25 °C, where x = 0.002 or 0.006 and y = 0.3 (b), or 0.05 (c).$

Figures 4.2bc show that rates of activation and deactivation for each particular system are very well balanced, again indicating maintenance of ATRP equilibrium. They depend on absolute concentration of Cu species, according to **Equations 4.4 and 4.5**, but not on the rate of polymerization. Thus, ICAR ATRP can be slower but rate of activation higher and vice versa. There is no direct relation between overall ATRP rate and activation rate, similar to the case of normal ATRP. It is worth noting that faster polymerization leads to faster termination.

4.2.6 Kinetics of polymerization and activation in SARA ATRP of methyl acrylate in DMSO
In supplemental activator and reducing agent (SARA) ATRP a zerovalent metal, typically Cu⁰, is used for activator regeneration. This is achieved by slow and continuous reduction of Cu^{II} via comproportionation process and by slow activation of alkyl halides.^{17, 59}

Similar to ICAR ATRP, the kinetics of SARA ATRP also resembles that of conventional RP. The steady state concentration of radicals is determined from the balance of rates of radical generation (i.e. supplemental activation by Cu⁰ and comproportionation) and radical termination, according to **Eq. 4.10**.

$$[\mathbf{R}^{\bullet}] = \sqrt{\frac{k_{a0}(S/V)[\mathbf{RX}] + k_{comp}(S/V)[\mathbf{Cu}^{II}/\mathbf{L}]}{k_{t}}}$$
(Eq. 4.10)

which resembles Eq. 4.8 but supplements it with Eq's. 4.6 and 4.7.

Thus, rates of polymerization in SARA ATRP depend on the rate of radical generation and *S/V* parameter (**Eq. 4.11**) as reported in the literature.⁶⁰⁻⁶¹

$$R_{\rm p} = k_{\rm p}[{\rm M}] \sqrt{\frac{k_{\rm a0}(S/V)[{\rm RX}] + k_{\rm comp}(S/V)[{\rm Cu}^{\rm II}/{\rm L}]}{k_{\rm t}}} \qquad \text{(Eq. 4.11)}$$

Nevertheless, ATRP equilibrium is well maintained and $[Cu^{I}]/[Cu^{II}]$ ratio can be still calculated from **Eq. 4.3**, knowing K_{ATRP} , [RX], and [R[•]]. The latter is defined according to **Eq. 4.10**.

In SARA ATRP, presence of soluble Cu species at the start of reaction is not required as they are formed *in situ*. However, Cu^{II} species can be added to prevent initial loss of control and to reduce dispersity of the formed polymers.⁶² This also increases the concentration of soluble Cu species (both Cu^{II} and Cu^I) in the system but does not significantly affect polymerization rate.

The kinetics of SARA ATRP and evolution of the [Cu^I]/[Cu^{II}] ratio are shown in **Figure 4.3a** for two different *S/V* values and with a sufficient amount of ligands to complex Cu^I and Cu^{II} species. **Figures 4.3b,c** illustrate rates of propagation and activation/deactivation for these systems as a function of monomer conversion.



Figure 4.3 (a) Kinetics of SARA ATRP and evolution of $[Cu^I]/[Cu^II]$ ratio, and (b) and (c) rates of propagation, activation, deactivation, termination and Cu^0 activation as a function of monomer conversion. Conditions: $[MA]:[MBP]:[Cu^{II}Br_2]:[Me_6TREN] = 200:1:x:0.1; 66\% (v/v) MA in DMSO, T = 25 °C, where x = 0 or 0.01, with (b) I = 10 cm or (c) I = 1 cm of d = 0.25 mm Cu⁰ wire (S = 0.79 cm² or 0.08 cm²), V_{total} = 10 cm³.$

Figure 4.3a shows that the overall rate of monomer consumption in SARA ATRP depends on the *S/V* ratio, and the [Cu^I]/[Cu^{II}] ratio adjusts according to **Eq. 4.3**. The initially added Cu^{II} does not affect polymerization rate but leads to short induction periods, similar to ICAR ATRP (cf. Figure 4.2a).

Figure 4.3b,c show that rates of activation of alkyl halides by Cu^I and deactivation of radicals by Cu^{II} are very well balanced and thus ATRP equilibrium is maintained. The rates of activation by Cu⁰ and comproportionation are much lower. The sum of these two rates is equal

to the rate of radical termination. The initially added Cu^{II} does not affect overall polymerization rate but increases rates of activation/deactivation by Cu^I/Cu^{II}. The added Cu^{II} also increases rate of comproportionation but does not affect activation by Cu⁰. Thus, polymerization rate in SARA ATRP can be lower but rate of activation by Cu^I higher and vice versa. Rates of activation by Cu⁰ are always much smaller than activation by Cu^I. They could be hypothetically increased by increasing surface area (i.e. nano-sized Cu⁰). However, this would inevitably result in a loss of control due to the concurrent increase of radical termination rate.

Figure 4.3a shows that 10 times larger surface area of Cu wire results in ca. 3 times faster polymerization (since $R_p \propto \sqrt{S/V} = \sqrt{10} \approx 3.16$, cf. **Eq. 4.11**). To maintain the ATRP equilibrium, this also leads to larger [Cu¹]/[Cu^{II}] ratio (according to **Eq. 4.3**, since [RX] remains constant). Interestingly, higher R_{a0} generates more soluble Cu species in the system and accelerates rates of activation of alkyl halides by Cu¹ activation (and equally rate of deactivation of radicals by Cu^{II}). These rates are well balanced but also continuously increase during polymerization, due to increasing concentration of soluble Cu species. Therefore, in SARA ATRP, an increase in the rate of activation of alkyl halides by Cu⁰ results in the concurrent increase of the rate of activation by Cu^I.

Similar conclusions can be drawn for aqueous systems.¹⁵ Rates of activation and deactivation by Cu¹/Cu^{II} were balanced and were much higher than activation by Cu⁰ and comproportionation. Despite thermodynamic favorability of disproportionation of Cu¹/L complexes in water, under polymerization conditions its kinetic contribution is negligible. This is due to the exceptional activity of Cu¹ towards activation of alkyl halides, which significantly reduces [Cu¹]. Since rate of disproportionation depends on [Cu¹]², low concentration of Cu¹ leads to very low disproportionation rate.

4.2.7.1 A Unifying Kinetic Picture of Normal ATRP, ICAR ATRP and SARA ATRP of Methyl Acrylate in DMSO

Figure 4.4a shows kinetic plots of normal ATRP, ICAR and SARA ATRP along with $[Cu^{I}]/[Cu^{II}]$ ratio. In all systems, regardless of the mechanism of regeneration or initially set ratios, the same polymerization rate (i.e. the same concentration of propagating radicals) is

accompanied by essentially the same [Cu^I]/[Cu^{II}], although their absolute concentrations can be dramatically different and also can change during polymerization.



Figure 4.4. (a) Kinetics of Normal ATRP, ICAR ATRP, and SARA ATRP and evolution of $[Cu^{1}]/[Cu^{11}]$ ratio, and (b) rates of propagation, activation, deactivation, termination and Cu⁰ activation as a function of monomer conversion. Conditions: Normal ATRP:[MA]:[MBP]:[Cu¹¹Br]:[Cu¹¹Br₂]: $[Me_{6}TREN] = 200:1:0.7:0.3:1;$ ICAR ATRP: $[MA]:[MBP]:[Cu^{11}Br_{2}]:[Me_{6}TREN]:[AIBN] = 200:1:0.002:0.05:0.3;$ SARA ATRP: $[MA]:[MBP]:[Cu^{11}Br_{2}]:[Me_{6}TREN] = 200:1:0:0.1$ with I = 10 cm of d = 0.25 cm Cu⁰ wire (S = 0.79 cm²). All reactions 66% (v/v) MA in DMSO, T = 25 °C, V_{total} = 10 cm³.

Interestingly, in spite of the same overall polymerization rates, activation rates are dramatically different, depending on the concentration of soluble Cu species, as shown in **Figure 4.4b**. Overall concentrations of soluble Cu species and related rates of activation/deactivation stay essentially constant in normal ATRP and ICAR ATRP but continuously increase in SARA ATRP, due to their progressive and irreversible generation from Cu⁰. Nevertheless, in SARA ATRP, rates of activation of alkyl halides by Cu¹ are always much larger than by Cu⁰. In order to match the fast rates of activation by 1 mM Cu¹/Me₆TREN, an unrealistic length of Cu⁰ wire of 2 km (with diameter 0.25 mm) is needed in 10 mL of DMSO/MA solution. It should be stressed that this comparison relates to respective activation rates by Cu¹ and Cu⁰, not to overall polymerization rates in the presence or absence of Cu⁰.

The rates of activation/deactivation by Cu^I/Cu^{II} are defined by their concentrations and related rate constants (**Eq's. 4.4 and 4.5**). In normal ATRP, catalyst concentrations are much

larger than in ICAR or SARA ATRP. The ratio of the rate of deactivation (equal to activation by Cu^I) to that of propagation defines the basic control over dispersity. Dispersity depends on number of monomer units added in each intermittent activation step and amount of dead chains, as shown in **Eq. 4.12**.⁶³ Very low concentration of Cu species leads to broader MWD. Therefore, in SARA ATRP, dispersities are usually quite high at the beginning of the reaction, unless Cu^{II} species are initially added. However, they progressively decrease with conversion, especially due to the buildup of soluble Cu species.

$$\frac{M_{w}}{M_{n}} = 1 + \frac{1}{DP_{n}} + \left(\frac{k_{p}[RX]_{0}}{k_{d}[Cu^{II}/L]}\right)\left(\frac{2}{p} - 1\right) + \left(\frac{k_{t}k_{a}[Cu^{I}/L]_{0}}{4k_{p}k_{d}[Cu^{II}/L]_{0}}\right)p \quad \text{(Eq. 4.12)}$$

4.2.7.2 A case of similar activation rates but different ATRP rates

In a recently published paper, Alsubaie et al. investigated the mechanism of reversibledeactivation radical polymerization (RDRP) in the presence of Cu⁰ in organic media.⁶⁴ They showed that disproportionation does not happen to any significant extent in DMSO and that nascent Cu⁰ has very low activity, consistent with previous reports, in support of SARA ATRP mechanism^{16-17, 40, 65-66} and against single electron transfer living radical polymerization (SET-LRP) mechanism,⁶⁷ as clearly stated in their conclusions. However, on page 5523 it was stated that "only 5 cm of copper wire resulted in a faster polymerization rate when compared with 9.4 mM of CuBr" as well as "According to the previous report, in order to match the activity of CuBr with Cu(0) approximately 19 km of copper wire would be required". In addition, in the graphical abstract, "18.8 km" was crossed and replaced by a phrase in red color "Only 5 cm". This could induce the reader to understand that activation by Cu⁰ is faster than by Cu¹, in contrast with previous reported results.^{40, 65} It should be noted that the authors used the previously reported values of relative rates of activation of alkyl halides by Cu¹ and Cu⁰ but applied them to compare the overall rates of polymerization of normal ATRP and SARA ATRP in the presence of Cu wire. As shown above, it is not possible to assess activity of a specific Cu species based on the overall rate of polymerization and one must determine the activation rates apart from polymerization rates.

PREDICI simulations were conducted to compare rates of polymerization with rates of activation in both normal ATRP and SARA ATRP. For consistency with the experiments in ref. ⁶⁴, in both systems EBiB was chosen as the initiating alkyl halide. As seen in **Figure 4.5**, in normal ATRP, the rate of activation by Cu^I/L and rate of deactivation were exactly the same and were faster than the rate of polymerization.



Figure 4.5 (a) Kinetics of normal ATRP and evolution of $[Cu^{I}]/[Cu^{II}]$ ratio, and (b) rates of respective reactions as a function of monomer conversion. Conditions: [MA]:[EBiB]:[Cu^{II}Br₂]:[Me₆TREN] = 60:1:0.1:0:0.6; 50% (v/v) MA in DMSO, *T* = 25 °C.

In the presence of Cu⁰ (**Figure 4.6**), rates of activation by Cu¹/L and deactivation by X-Cu¹¹/L were initially lower than rate of polymerization but quickly increased due to buildup of soluble copper species that entered solution from Cu⁰ activation and comproportionation. After this initial period, rate of activation by Cu⁰ was 4 orders of magnitude lower than activation by Cu¹/L. As soon as Cu¹/L was generated (at very early reaction stages, <1% monomer conversion), it took the role of a major activator of alkyl halides (>99%). Note that rate of disproportionation is much smaller than rate of comproportionation ($R_{disp} << R_{comp}$) and that rate of activation by Cu⁰ is very close to the rate of radical termination ($R_{a0} \approx R_t$). Increasing R_{a0} by e.g. increasing surface area of Cu⁰ will increase rate of ATRP, but it will also increase contribution of termination (loss of control) and produce more soluble Cu species (further increase of rate of activation by Cu¹).



Figure 4.6 (a) Kinetics of SARA ATRP and evolution of $[Cu^{i}]/[Cu^{ii}]$ ratio, and (b) rates of respective reactions as a function of monomer conversion. Conditions: [MA]:[EBiB]:[CuⁱBr]:[CuⁱBr₂]:[Me₆TREN] = 60:1:0:0:0.12; 50% (v/v) MA in DMSO, T = 25 °C, Cu⁰ wire: I = 5 cm, d = 0.25 mm (S = 0.39 cm²), $V_{\text{total}} = 4$ cm³.

Figure 4.7 shows comparison of normal ATRP with SARA ATRP. Despite much faster polymerization in SARA ATRP and slower normal ATRP, rates of activation by Cu¹ and deactivation by Cu¹¹ were similar in both systems. However, activation of alkyl halides by Cu⁰ was still 3 orders of magnitude slower than activation by Cu¹ in the normal ATRP.



Figure 4.7 (a) Kinetics of Normal ATRP and SARA ATRP and evolution of [Cu¹]/[Cu^{II}] ratio, and (b) rates of propagation, activation, deactivation, termination and Cu⁰ activation as a function of monomer conversion. Conditions: Normal ATRP [MA]:[EBiB]:[Cu^IBr]:[Cu^{II}Br₂]:[Me₆TREN] = 60:1:0:0.6; SARA ATRP [MA]:[EBiB]:[Cu^IBr]:[Cu^{II}Br₂]:[Me₆TREN] = 60:1:0:0:0.12, Cu⁰ wire: *I* =

5 cm, d = 0.25 mm (S = 0.39 cm²), $V_{\text{total}} = 4$ cm³. All reactions 50% (v/v) MA in DMSO, T = 25 °C;

While normal ATRP can be slower than SARA ATRP (or any low ppm Cu ATRP systems), this observation cannot be directly related to relative rates of activation of alkyl halides by Cu¹ vs. Cu⁰. The activation rates must be determined independently and such a comparison clearly showed that the activation of alkyl halides is at least 100 times faster by Cu¹ than by Cu⁰.

4.2.8 Conclusions

In summary, it was demonstrated that there is no direct relation between an overall rate of polymerization in normal ATRP and low ppm Cu ATRP systems such as ICAR ATRP and SARA ATRP with the rates of activation of alkyl halides by Cu¹. Faster polymerization may be accompanied by slower activation and vice versa. Regardless, in SARA ATRP, the activation of alkyl halides by Cu¹ is always much faster than by Cu⁰.

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Chapter 5.

Development of Active ATRP & ATRA Catalysts

5.1 Preface

The copper catalyst is at the heart of ATRP in that it both activates dormant alkyl halides but also deactivates propagating radicals to gain control. Although many metals have been used in ATRP, copper has shown to be the most versatile in large part because of the ability to tune reaction conditions. As discussed in **Section 1.3**, a large part of this tunability comes from a wide range of ligands that have been employed in ATRP. The activity of a L/Cu complex in ATRP can be conveniently assessed by measuring the redox potential, $E_{1/2}$, of the L/Cu^{1/11} redox couple. More reducing L/Cu¹ complexes (more negative $E_{1/2}$) lead to a more active catalyst due to a thermodynamic drive force to stabilize the cupric species. One method of decreasing $E_{1/2}$ is by increasing electron density at the Cu center by addition of electron donating groups (EDG) to the ligand. This was previously shown using relatively simple bipyridine (bpy) ligands for which the pyridine ring was substituted with various EDG such as aliphatic hydrocarbons, methoxy and dimethylamino groups. Tris(pyridylmethyl)amine (TPMA) is a tetradentate bridged pyridine-based ligand which is 3000 times more active than bpy. This chapter will discuss the synthesis, characterization and utilization of substituted TPMA-based ligands which are over 1 billion times more active than seminal ATRP catalysts.

^{*}Work in this section was published:

A Kaur, <u>TG Ribelli</u>, K Schröder, K Matyjaszewski, T Pintauer. "Properties and ATRP Activity of Copper Complexes with Substituted Tris(2-pyridylmethyl)amine Based Ligands." *Inorg. Chem.* 2015, 54 (4), pp 1474-1486 © 2015 American Chemical Society

 <u>TG Ribelli</u>, M Fantin, R Poli, JC Daran, KF Augustine, K Matyjaszewski. "Synthesis, Characterization of the Most Active ATRP Catalyst Based on tris[(4dimethylaminopyridyl)methyl]amine." J. Am. Chem. Soc. 2018, 140 (4), pp 1525 © 2018 American Chemical Society

Each pyridine arm of TPMA was substituted with 3,5-dimethyl-4-methoxypyridine to make three new ligands named TPMA^{*1}, TPMA^{*2} and TPMA^{*3} where the number denotes the number of substituted arms. These ligands were complexed to copper and fully characterized in the solid-state for both the cuprous and cupric complexes. Solution studies were also conducted to assess ATRP activity. It was found that substitution of each arm led to a catalyst that was 10 times more active i.e. TPMA^{*3} is 10 times more active than TPMA^{*2} which is 10 times more active than TPMA^{*1}. These catalysts were used in activator regenerated by electron transfer (ARGET) ATRP.

It was then of interest to move towards even more electron donating groups, thus each pyridine was substituted with 4-dimethylamino to form the fully substituted TPMA^{NMe2} ligand. The [Cu^{II}(TPMA^{NMe2})Br][Br] complex was characterized in the solid-state and in solution. It was shown that this catalyst is 50,000 times more active than the unsubstituted TPMA ligand and over 100 million times more active than bpy-based catalysts. Initiators for continuous activator regeneration (ICAR) ATRP and Ag⁰ ATRP were conducted using as little as 10 ppm of catalyst while still exhibiting a well-controlled polymerization. It is of great hope that the activity of this complex is such that less activated monomers such as vinyl acetate can be polymerized by ATRP.

This chapter was a collaborative effort between many people. Initially, Dr. Kristin Schroder synthesized the TPMA^{*3} ligand. Myself and Dr. Aman Kaur synthesized the other ligands and/or made more of TPMA^{*3}. Dr. Kaur and Prof. Tomislav Pintauer characterized the copper complexes in the solid state. The electrochemistry and assessment of thermodynamic parameters was conducted by myself or Dr. Kaur. I aided in manuscript preparation and experimental design. For the TPMA^{NMe2} project, I synthesized the ligand and complex as well as conducted the polymerizations. I would like to thank Prof. Rinaldo Poli and Dr. Jean-Claude Daran for help with X-ray diffraction studies and EPR. A special thanks to Dr. Marco Fantin which helped me tremendously with the electrochemistry, specifically the simulations of activation.

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5.2 Properties and ATRP Activity of Copper Complexes with Substituted Tris(2pyridylmethyl)amine-Based Ligands

5.2.1 Preface

Synthesis, characterization, electrochemical studies and ATRP activity of a series of novel copper(I and II) complexes with TPMA based ligands containing 4-methoxy-3,5-dimethyl substituted pyridine arms were reported. In the solid state, Cu¹(TPMA^{*1})Br , Cu¹(TPMA^{*2})Br and Cu¹(TPMA^{*3})Br complexes were found to be distorted tetrahedral in geometry and contained coordinated bromide anions. Pseudo coordination of the aliphatic nitrogen atom to copper(I) center was observed in Cu¹(TPMA^{*2})Br and Cu¹(TPMA^{*3})Br complexes, whereas pyridine arm dissociation occurred in Cu^I(TPMA^{*1})Br. All copper(I) complexes with substituted TPMA ligands exhibited high degree of fluxionality in solution. At low temperature, Cu^I(TPMA^{*1})Br was found to be symmetrical and monomeric, while dissociation of either unsubstituted pyridine and/or 4methoxy-3,5-dimethyl substituted pyridine arms was observed in Cu¹(TPMA^{*2})Br and Cu^I(TPMA^{*3})Br. On the other hand, the geometry of the copper(II) complexes in the solid state deviated from ideal trigonal bipyramidal, as confirmed by a decrease in τ values $([Cu^{\parallel}(TPMA^{*1})Br][Br] (\tau=0.92) > [Cu^{\parallel}(TPMA^{*3})Br][Br] (\tau=0.77) > [Cu^{\parallel}(TPMA^{*2})Br][Br] (\tau=0.72)).$ Furthermore, cyclic voltammetry studies indicated a nearly stepwise decrease ($\Delta E^{\sim}60 \text{ mV}$) of $E_{1/2}$ values relative to SCE (TPMA (-240 mV)>TPMA^{*1} (-310 mV) > TPMA^{*2} (-360 mV) > TPMA^{*3} (-420 mV)) on going from [Cu^{II}(TPMA)Br][Br] to [Cu^{II}(TPMA^{*3})Br][Br], confirming that the presence of electron donating groups in the 4 (-OMe) and 3,5 (-Me) positions of the pyridine rings in TPMA increases the reducing ability of the corresponding copper(I) complexes. This increase was mostly the result of a stronger influence of substituted TPMA ligands towards stabilization of the copper(II) oxidation state ($\log \beta = 13.4 \pm 0.2$, $\log \beta^{I} = 19.3$ (TPMA^{*1}), 20.5 (TPMA^{*2}) and 21.5 (TPMA^{*3})). Lastly, ARGET ATRP kinetic studies show that with more reducing catalysts an induction period is observed. This was attributed to slow regeneration of Cu^I species from the corresponding Cu^{II}.

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5.2.2 Introduction

Tris(2-pyridylmethyl)amine (TPMA)¹⁻² is a widely used neutral tripodal nitrogen based ligand that has been complexed to a wide variety of transition metals. Currently, the Cambridge Crystallographic Database contains over 360 structures of TPMA complexes with metals spanning from group 1 to 13 of the periodic table, including many cases from the lanthanide and actinide series. TPMA contains both σ -donating tertiary amine and π -accepting pyridyl groups and is an excellent chelator that typically coordinates to a metal center in a tetradentate fashion.³⁻⁵ However, in some cases, tridentate coordination resulting from pyridyl arm dissociation has also been observed.^{3, 6-7}

Over the past two decades, TPMA has received a considerable attention as a ligand of choice for many transition metal catalyzed reactions. For example, it is widely used as a chelator in copper and/or iron complexes that mimic certain metalloenzymes of relevance to oxygen activation.^{5, 8-17} Furthermore, a number of metal complexes with TPMA have also been shown to be active in C-H and O-O activation of small molecules,^{18-19 20-24} as well as [3+2] azide-alkyne cycloaddition.²⁵⁻³⁰ Lastly, copper complexes with TPMA are currently among the most active catalysts in atom transfer radical addition (ATRA)³¹⁻³³ and polymerization (ATRP) reactions.³⁴⁻³⁶ Both processes originated from well-known Kharasch addition in which polyhalogenated compounds were added to alkenes via free-radical means.³¹⁻³³ Recent studies have also indicated that TPMA is a superior complexing ligand in ATRA^{25, 32-33, 37-47} and ATRP^{42, 48-51} that utilize reducing agents. The role of a reducing agent in both systems is to continuously regenerate the activator species (copper(I) complex) from the corresponding deactivator (copper(II) complex). The latter one accumulates in the system as a result of unavoidable and often diffusion controlled radical-radical termination reactions. As a result, both processes can be conducted very efficiently using ppm amounts of the catalyst.⁴² As indicated in **Scheme 5.1**, the ATRP equilibrium $(K_{ATRP}=k_a/k_d)$ is controlled by a fast and reversible homolytic cleavage of a C-(pseudo)halogen bond in a redox reaction with the copper(I) catalyst, yielding well-defined halogen-capped polymers. Consequently, ATRP provides a very versatile synthetic tool for the preparation of polymers with predefined functionalities, compositions and architectures.⁵²⁻⁵⁶



Electrochemical measurements are commonly used to predict the activity of copper complexes in atom transfer radical processes, namely ATRA and ATRP.^{4, 43, 54, 57-61} Generally, for a given alkyl halide, the equilibrium constant for atom transfer ($K_{ATRP}=k_a/k_d$) can be directly correlated with $E_{1/2}$ values provided that the halidophilicity of the metal complex ($X^-+[Cu^{II}L_m]^{2+} \rightleftharpoons [Cu^{II}L_mX]^+$, K_X , X=Br or Cl) remains constant. As a result, for copper complexes with neutral nitrogen-based ligands commonly used in ATRA and ATRP, a linear correlation between $\ln(K_{ATRP})$ and $E_{1/2}$ values is typically observed.^{59, 62-63} Another method of predicting the activity of copper catalysts in ATRP is to directly compare the stability constants of Cu^{II} and Cu^I complexes with the particular ligand (β^{II} and β^{I} , respectively, **Eq 5.1**). Both β^{II} and β^{I} should be large in order to eliminate or suppress possible concurrent reactions such as coordination of monomer and/or polymer, which are typically present in large excess relative to the catalyst.

$$b^{m} = \frac{[Cu^{m}L_{n}]}{[Cu^{m}][L]^{n}}; m=I \text{ or } II, n=1 \text{ or } 2$$
 [1]

Generally, a copper complex with a low reduction potential should be more stable in its oxidized form (i.e. Cu^{II} should be more stable than Cu^I) in order to achieve high catalytic activity.⁶⁰⁻ ⁶¹ Indeed, as indicated in **Figure 5.1** more reducing copper(I) complexes have higher values for both K_{ATRP} and the ratio of the stability constants (β^{II}/β^{I}). Furthermore, an increase in β^{II}/β^{I} ratio for a particular ligand is mostly the result of an increase in the stability constant of the copper(II) relative to copper(I) complex.^{60, 62-67}



Figure 5.1. Correlations between K_{ATRP} , redox potential $(E_{1/2})$ and stability constants (β and β^{II}) for copper complexes with neutral nitrogen based ligands commonly used in ATRP. Generally, more reducing copper(I) complexes have higher values for K_{ATRP} and β^{II}/β^{I} ratio, as a result of greater ligand stabilization towards copper(II) oxidation state. All values were taken from Ref. ⁶⁰. Stability constants (β and β^{II}) were measured in aqueous medium. K_{ATRP} values were determined in CH₃CN at 22±2 °C for ethyl-2-bromoisobutyrate. $E_{1/2}$ values were measured in CH₃CN and are relative to SCE.

With the recent discovery indicating that the reducing agents can significantly reduce the amount of copper complexes in ATRP,⁴² a significant effort has been devoted towards development of more active catalysts that could be used at even lower concentrations, and potentially enable controlled radical polymerization of α -olefins. The research in this area is significantly focused on ligand design, which can be used to tailor electronic properties of the copper(I) center. One way to increase the reduction potential of copper(I) complex is through systematic incorporation of electron donating groups (EDGs) to ligands that are already active in ATRP. This approach indeed seems to be justified, as demonstrated in a recent study which showed that EDGs in the para-substituted 2,2'-bipyridine ligands can significantly enhance catalytic activity in ATRP.⁶⁸ In a related work, inspired by the synthetic modifications of TPMA ligand for copper catalyzed oxygen activation⁶⁹ and iron mimicking site for methane monooxygenase,⁷⁰ even more active Cu^{II}X₂/TPMA^{*3} (X=Br or Cl, TPMA^{*3}= tris((4-methoxy-3,5dimethylpyridin-2-yl)methyl)amine) in situ system was discovered containing a total of nine EDGs.⁷¹ This catalyst attained excellent polymerization results in photoATRP⁷²⁻⁷⁴ of acrylates and emerged as one of the most active ATRP systems nowadays. Furthermore, it also elucidated the interplay between ATRP, organometallic mediated radical polymerization (OMRP) and catalytic termination pathways for the first time.⁷⁵



Scheme 5.2. Substituted Tris(2-pyridylmethyl)amine Ligands Investigated in the present study.

As evident from the discussion above, further development and catalytic activity of transition metal complexes containing modified TPMA ligands could provide invaluable and

important information to various research fields ranging from inorganic, bioinorganic to organic/polymer chemistry. In this article, we report on the synthesis, characterization, electrochemical studies and ATRP activity of a series of novel copper(I and II) complexes with TPMA based ligands containing 4-methoxy-3,5-dimethyl substituted pyridine arms (**Scheme 5.2**).

5.2.3 Experimental

General. All chemicals were purchased from commercial sources, and used as received if not stated otherwise. Tris(2-pyridylmethyl) amine (TPMA)³⁸ and tris((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amine⁷⁰⁻⁷¹ were synthesized according to previously published literature procedures. Butyl acrylate (BA) was passed through a column filled with basic alumina to remove inhibitor prior to use. All procedures for atom transfer radical polymerizations and cyclic voltammetry were performed under argon or nitrogen. Solvents were degassed by at least three freeze-pump-thaw cycles. All manipulations involving copper(I) complexes were performed under argon in the drybox (<1.0 ppm O₂ and <0.5 ppm H₂O) or using standard Schlenk line techniques. Copper(II) complexes were synthesized under ambient conditions.

Instrumentation and Equipment. ¹H NMR spectra were obtained using Bruker Avance 300, 400 and/or 500 MHz spectrometers and chemical shifts are given in ppm relative to residual solvent peaks [CDCl₃ δ 7.26 ppm; (CD₃)CO δ 2.05 ppm; CD₃CN δ 1.96 ppm]. iNMR and KaleidaGraph 4.1 software were used to generate images of NMR spectra. IR spectra were recorded in the solid state using Nicolet Smart Orbit 380 FT-IR spectrometer (Thermo Electron Corporation). Elemental analyses for C, H, and N were obtained from Midwest Microlabs, LLC. UV-Vis spectra were recorded using a Beckman DU-530 spectrometer in 1.0 cm path-length airtight quartz cuvettes. Mass spectra were recorded on a mass spectrometer with a Varian Saturn 2100T MS with 3900 GC using an El source. In each case, characteristic fragments with their relative intensities in percentages are shown. Electrospray mass spectra were measured on a Thermo-Fisher LCQ ESI/APCI Ion Trap containing a quadrupole field ion trap mass spectrometer with electrospray ionization (ESI). All cyclic voltammograms were measured at 25°C with a PARC 263A

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potentiostat. Solutions of CuBr₂ and Cu(OTf)₂ complexes with TPMA based ligands (1.0 mM) were prepared in dry acetonitrile containing 0.1 M NBu₄PF₆ as the supporting electrolyte. Measurements were carried out under N₂ atmosphere at a scanning rate (v) of 0.1 Vs⁻¹, using a platinum disk and platinum mesh as the working and counter electrode, respectively. An Ag|Ag||^T reference electrode was used and potentials were measured relative to a ferrocenium/ferrocene couple (E°_{Fc+/Fc}=0.391 V vs SCE in CH₃CN),⁷⁶ which was used as an internal standard. This has allowed conversion of the potentials to the aqueous saturated calomel electrode (SCE) scale, to which all potentials are referenced. The stability constants for copper complexes (β and β ^{II}) were determined using modified literature procedures,^{57,71,76} as outlined in the supporting information.

X-ray Crystal Structure Determination. The X-ray intensity data were collected at 150 K using graphite-monochromated Mo-K radiation (0.71073 Å) with a Bruker Smart Apex II CCD diffractometer. Data reduction included absorption corrections by the multi-scan method using SADABS.⁷⁷ Structures were solved by direct methods and refined by full matrix least squares using SHELXTL 6.1 bundled software package.⁷⁸ The H-atoms were positioned geometrically (aromatic C-H 0.93, methylene C-H 0.97, and methyl C-H 0.96) and treated as riding atoms during subsequent refinement, with $U_{iso}(H) = 1.2U_{eq}(C)$ or $1.5U_{eq}$ (methyl C). The methyl groups were allowed to rotate about their local threefold axes. Crystal Maker 8.3 was used to generate molecular graphics. For detailed crystallographic data tables refer to supporting information.

Gel Permeation Chromatography (GPC). GPC was used to determine number average molecular weight (M_n) and M_w/M_n values. The GPC was conducted with a Waters 515 HPLC Pump and Waters 2414 Refractive Index Detector using PSS columns (Styrogel 102, 103, 105 Å) in tetrahydrofuran (THF) as an eluent at a flow rate of 1 mL/min at 35 °C. The column system was calibrated with 12 linear polystyrene (PSt, $M_n = 376^{\sim}2,570,000$) and 12 linear poly(methyl methacrylate) (PMMA, $M_n = 800 \sim 2,570,000$) standards. Diphenyl ether (DPE) was used as internal standard. Monomer conversion was determined by ¹H NMR spectroscopy.

Ligand Synthesis.

1-(4-methoxy-3,5-dimethylpyridin-2-yl)-N,N-bis(pyridin-2-ylmethyl)methanamine (TPMA^{*1}). A solution containing 2-chloromethyl-3,5-dimethyl-4-methoxypyridine•hydrochloride (100.0 mg, 0.450 mmol, 1.0 eq.), NaOH (36.0 mg, 0.900 mmol, 2.0 eq.) and 1.0 mL H₂O was added to bis(2-pyridylmethyl)amine (89.7 mg, 0.450 mmol, 1.0 eq.) dissolved in 1.0 mL of CH₂Cl₂ and heated in a pressure tube at 60 °C. After 24 hours, heterogeneous mixture was allowed to cool to room temperature, followed by the addition of 3.0 mL 1.0M NaOH solution. The aqueous layer was then extracted with CH₂Cl₂ (5x5.0 mL). The organic layers were combined and dried over MgSO₄. Following the filtration, yellow solution was concentrated under reduced pressure. Purification over alumina (MeOH/EtOAc, 5:95) yielded 120 mg (76%) of TPMA^{*1} as a yellowish oil. *R_f*: 0.47. ¹H NMR (400 MHz, CDCl₃, 298 K): δ 8.50 (d, *J*=4.7 Hz, 2H), δ 8.14 (s, 1H), δ 7.60 (td, *J*=7.7, 1.9 Hz, 2H), δ 7.43 (d, *J*=7.8 Hz, 2H), δ 7.11 (m, 2H), δ 3.83 (s, 6H), δ 3.69 (s, 3H), δ 2.18 (s, 3H), δ 2.12 (s, 3H). ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 164.1, 159.7, 157.0, 149.0, 148.7, 136.3, 126.4, 125.2, 123.7, 122.0, 60.5, 59.9, 59.3, 13.3, 10.9. MS (ESI) *m/z*: 349.2 [M+H]^{*}.

1-(4-methoxy-3,5-dimethylpyridin-2-yl)-N-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-N-

(pyridin-2-ylmethyl)methanamine (TPMA*2). 2-Picolylamine (1.46 g, 13.5 mmol), 2chloromethyl-4-methoxy-3,5-dimethylpyridine hydrochloride (6.00 g, 27.0 mmol) and Na₂CO₃ (7.25 g, 68.4 mmol) were place in a pressure tube containing 200 mL of HPLC grade CH₃CN. Then, tetrabutylammonium bromide (3.0 mg, 9.3×10^{-3} mmol) was added to the stirred solution under nitrogen. The mixture was heated at 80 °C for 48 h, allowed to cool to room temperature, and poured into 150 mL 1.0 M NaOH. After extraction with CH₂Cl₂ (3x10.0 mL), the combined organic fractions were dried over Na₂SO₄, filtered, and the solvent evaporated under reduced pressure to give an orange/brown crude product. Purification over alumina (MeOH/EtOAc, 5:95) yielded 5.1 g (92%) of a yellowish, crystalline solid. R_{f} : 0.55. ¹H NMR (400 MHz, CDCl₃, 298 K): δ 8.44 (d, *J*=4.7 Hz, 1H), δ 8.15 (s, 2H), δ 7.54 (td, *J*=7.8, 1.8 Hz, 1H), δ 7.20 (d, *J*=7.8 Hz, 1H), δ 7.09 (m, 1H), δ 3.78 (s, 6H), δ 3.68 (s, 6H), δ 2.20 (s, 6H), δ 1.91 (s, 6H). ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 164.1, 159.7, 157.2, 148.7, 148.5, 136.0, 126.5, 125.2, 124.4, 121.9, 60.5, 59.8, 59.3, 13.3, 10.5. MS (ESI) *m/z*: 407.2 [M+H]⁺.

Synthesis of Copper Complexes.

Cu'(TPMA^{*1})Br. A solution of TPMA^{*1} (228 mg, 0.655 mmol) in 1.0 mL of methanol was added to a suspension of Cu^IBr (94.0 mg, 0.655 mmol) in 2.0 mL of methanol, resulting in the formation of a yellow solution. After stirring for 5 min at ambient temperature, Cu^I(TPMA^{*1})Br was precipitated as yellow powder by the slow addition of diethyl ether (yield=231 mg, 72%). X-ray quality crystals were obtained by crystallization in acetone via slow diffusion of diethyl ether. ¹H NMR ((CD₃)₂CO, 400 MHz, 220 K): δ 9.07 (s, 2H), δ 8.72 (s, 1H), δ 7.78 (pt, *J*=7.5 Hz, 2H), δ 7.39 (pd, *J*=7.6 Hz, 2H), δ 7.32 (m, 2H), δ 3.92 (m, 6H), δ 3.62 (s, 3H), δ 2.12 (s, 6H). Anal. Calcd. for C₂₁H₂₄BrCuN₄O (491.89): C, 51.28; H, 4.92; N, 11.39. Found: C, 51.98; H, 4.99; N, 12.01.

Cu'(TPMA^{*2})Br. The complex was prepared using the procedure for Cu'(TPMA^{*1}) except that Cu'Br (94.0 mg, 0.655 mmol) and TPMA^{*2} (266 mg, 0.655 mmol) were used. Yield=331 mg (89%). X-ray quality crystals were obtained by crystallization in methanol via slow diffusion of diethyl ether. ¹H NMR ((CD₃)₂CO, 400 MHz, 188 K): δ 9.03 (m, 1H), δ 8.72 (s, 1H), δ 8.51 (m, 2H), δ 8.19 (s, 3H), δ 7.78 (m, 3H), δ 7.39 (m, 2H), δ 3.93(s, 2H), δ 3.90 (s, 1H), δ 3.67 (s, 6H), δ 2.19(s, 6H), δ 2.14(s, 6H) δ 1.80(s, 6H). Anal. Calcd. for C₂₄H₃₀BrCuN₄O₂ (549.97): C, 52.41; H, 5.50; N, 10.19. Found: C, 52.46; H, 5.47; N, 11.01.

Cu'(TPMA^{*3})Br. The complex was prepared using the procedure for Cu'(TPMA^{*1}) except that Cu^IBr (94.0 mg, 0.655 mmol) and TPMA^{*3} (330 mg, 0.655 mmol) were used. Yield=331 mg (83%). X-ray quality crystals were obtained by crystallization in methanol via slow diffusion of diethyl ether. ¹H NMR ((CD₃)²CO, 400 MHz, 188 K): δ 8.68 (s, 2H), δ 8.22 (s, 1H), δ 8.51 (m, 2H), δ 3.67(s, 4H), δ 3.61 (s, 2H), δ 3.67 (s, 6H), δ 2.19(s, 9H), δ 2.14(s, 9H) δ 2.08(s, 9H). Anal. Calcd. for C₂₇H₃₆BrCuN₄O₃ (608.04): C, 53.33; H, 5.97; N, 9.21. Found: C, 53.42; H, 5.94; N, 9.41.

[Cu^{II}(TPMA^{*1})Br][Br]. A solution of TPMA^{*1} (425 mg, 1.21 mmol) in 5.0 mL of methylene chloride was added to a round-bottom flask containing Cu^{II}Br₂ (273 mg, 1.22 mmol). The reaction mixture

was stirred at room temperature for 15 min and the product precipitated by the slow addition of *n*-pentane (ca. 20 mL). The supernatant liquid was decanted and the green powder was washed with 3×5.0 mL of *n*-pentane and dried under vacuum to yield 519 mg (75%) of $[Cu^{II}(TPMA^{*1})Br][Br]$. X-ray quality crystals were obtained by crystallization in dichloromethane via slow diffusion of *n*-pentane. UV-Vis (CH₃CN): λ_{max} = 983 nm, ε_{max} = 176.5 Lmol⁻¹cm⁻¹. FT-IR (solid): ν (cm⁻¹) = 3053(w), 2998(s), 1605(s) 1574(w), 1475.8(w), 1433(s), 1263(s), 1078(s), 733(s), 704(s), 610(s) Anal. Calcd. for C₂₁H₂₄Br₂CuN₄O (571.79): C, 44.11; H, 4.23; N, 9.80. Found: C, 43.92; H, 4.29; N, 9.34.

[**Cu^{II}(TPMA^{*2})Br**][**B**r]. The complex was prepared using the procedure for [Cu^{II}(TPMA^{*1})Br][Br] except that Cu^{II}Br₂ (326 mg, 1.46 mmol) and TPMA^{*2} (593 mg, 1.46 mmol) were used. Yield=791 mg (86%). X-ray quality crystals were obtained by crystallization in dichloromethane via slow diffusion of *n*-pentane. UV-Vis (CH₃CN): λ_{max} = 980 nm, ε_{max} = 185 Lmol⁻¹cm⁻¹. FT-IR(Solid): *v*(cm⁻¹) = 3053(w), 2998(w), 1600(s), 1578 (w), 1475(s), 1427(s), 1400(w), 1265(s), 1074(s), 994(s), 733(s), 704(s), 611(s). Anal. Calcd. for C₂₄H₃₀Br₂CuN₄O₂ (629.87): C, 45.76; H, 4.80; N, 8.89. Found: C, 45.38; H, 4.69; N, 8.02.

[**Cu^{II}(TPMA^{*3})Br**][**B**r]. The complex was prepared using the procedure for [Cu^{II}(TPMA^{*1})Br][Br] except that Cu^{II}Br₂ (326 mg, 1.46 mmol) and TPMA^{*3} (678 mg, 1.46 mmol) were used. Yield=844 mg (84%). X-ray quality crystals were obtained by crystallization in dichloromethane via slow diffusion of *n*-pentane. UV-Vis (CH₃CN): λ_{max} = 981 nm, ε_{max} = 191 Lmol⁻¹cm⁻¹. FT-IR(Solid): *v*(cm⁻¹) =3370(w), 2942(b), 1709(s) 1598(w), 1477(s), 1419(w), 1401(s), 1270(s), 1113(s), 1076(s), 997(s), 881(w). Anal. Calcd. for C₂₇H₃₆Br₂CuN₄O₃ (687.95): C, 47.14; H, 5.27; N, 8.14. Found: C, 45.52; H, 5.09; N, 8.02.

General Procedure for ARGET ATRP reactions. ATRP reactions were performed in 10 mL Schlenk flasks. In a typical experiment, *n*-butyl acrylate (BA) (30 mmol, 4.2 mL) and ethyl 2-bromoisobutyrate (EBiB) (0.184 mmol, 27 μ L) was dissolved in 1.1 mL of anisole. After the addition of Cu^{II} complex, ([Cu^{II}Br₂]_o:[TPMA^{*} ligand]_o =1:3.75; [Cu^{II}Br₂]_o:[alkene]_o= 1:10,000), the

reaction mixture was degassed by three freeze pump thaw (FPT) cycles. Sn(EH)₂ (182 uL of 0.1M stock solution in anisole, 0.018 mmol) was charged into the flask using an airtight syringe and the reaction mixture was placed under nitrogen atmosphere. The flask was placed in the oil bath at 60°C with samples taken periodically to be measured for conversion and molecular weight. The conversion of the monomer was determined by ¹H NMR spectroscopy using anisole as the internal standard.

5.2.4 Results and Discussion

5.2.4.1 Solid-State Structural Studies of Copper(I) Complexes.

Cu¹(TPMA^{*1})Br, Cu¹(TPMA^{*2})Br and Cu¹(TPMA^{*3})Br complexes were synthesized by reacting Cu¹Br with the stoichiometric amounts of substituted TPMA based ligand (Scheme 5.2). Crystals suitable for X-ray analysis were obtained in acetone (Cu^I(TPMA^{*1})Br) or methanol (Cu¹(TPMA^{*2})Br and Cu¹(TPMA^{*3})Br) by slow diffusion of diethyl ether. The corresponding molecular structures are shown in Figure 5.2, with selected bond distances and angles summarized in **Table 5.1**. In the solid state, Cu^I(TPMA^{*1})Br complex was found to be distorted tetrahedral in geometry, with the complexation to the copper(I) center occurring through nitrogen atoms from both unsubstituted (Cu1-N2=2.001(5) Å) and 4-methoxy-3,5-dimethyl substituted (Cu1-N1=2.036 Å) pyridine rings, aliphatic nitrogen atom (Cu-N4=2.316(6) Å) and a bromine anion (Cu1-Br=2.3511(10) Å). The remaining pyridine arm was dissociated from the copper(I) center (Cu1-N3=3.494 Å). In the case of previously isolated and structural characterized Cu^I(TPMA)Br³⁸ and Cu^I(TPMA)Cl³⁹ complexes, ligand arm dissociation from TPMA was not observed in the solid state, unless bulky auxiliary ligands such as PPh₃ or 4,4'bipyridine were used.³ In the latter two complexes, the distance between the copper(I) center and dissociated TPMA arm was much smaller than in Cu^I(TPMA^{*1})Br (3.258 and 2.523 Å, respectively). As indicated in **Table 5.1**, Cu^I-Br and Cu^I-N(aliphatic) bonds in Cu^I(TPMA^{*1})Br complex were significantly longer (~0.313(6) Å) than the Cu^I-N(pyridine) ones. This is the primary reason for significant distortions from ideal tetrahedral geometry, as manifested in relevant bond angles (Br1-Cu1-N4=132.36(13)°, and Br1-Cu1-N2=125.68(15)°). Interestingly,

Cu^I-N bond lengths from substituted and unsubstituted pyridine arms were found to be very similar (d(Cu^I-N_{OMe,Me-py})-d(Cu^I-N_{py})=0.035(8) Å). Lastly, the crystal structure of Cu^I(TPMA^{*1})Br was stabilized by a series of weak C-H---C (2.774(3)-3.039(5) Å) and dipole C-H---Br (3.021(3) Å) interactions. Additionally, π - π stacking between 4-methoxy-3,5-dimethyl substituted pyridine rings (3.561(7) Å) was observed.



Figure 5.2. Molecular structures of Cu¹(TPMA^{*1})Br (a), Cu¹(TPMA^{*2})Br (b) and Cu¹(TPMA^{*3})Br (c) shown with 30% probability displacement ellipsoids. H-atoms have been omitted for clarity.

Complex	[Cu ^l (TPMA)Br] ^b	[Cu ^l (TPMA ^{*1})Br] ^c	[Cu ^l (TPMA ^{*2})Br] ^c	[Cu ^l (TPMA ^{*3})Br] ^c
Cu1-N1	2.0709(15)	2.036(6)	2.0837(17)	2.092(3)
Cu1-N2	2.1024(15)	2.001(5)	2.0886(19)	2.116(3)
Cu1-N3	2.0753(15)	3.494	2.0452(17)	2.086(3)
Cu1-N4	2.4397(14)	2.316(6)	2.4190(19)	2.406(3)
Cu1-Br1	2.5088(3)	2.3511(10)	2.5025(3)	2.5045(6)
N1-Cu1-N2	112.40(6)	118.53(2)	114.40(7)	110.07(10)
N1-Cu1-N3	120.51(6)	/	122.31(7)	122.73(10)
N1-Cu1-N4	75.37(5)	79.24(19)	74.83(7)	75.76(10)
N2-Cu1-N3	107.61(6)	/	105.62(7)	108.22(10)
N3-Cu1-N4	74.84(5)	/	77.46(7)	75.29(10)
N4-Cu1-N2	74.80(5)	80.5(2)	75.39(6)	74.63(10)
Br1-Cu1-N1	105.25(4)	110.50(15)	101.59(5)	103.53(9)
Br1-Cu1-N2	105.43(4)	125.68(15)	103.06(5)	105.99(8)
Br1-Cu1-N3	104.28(4)	/	108.53(5)	104.91(7)
Br1-Cu1-N4	179.14(3)	132.36(13)	173.97(4)	179.22(7)
Cu1-LSP _{N,Py} d	0.538(3)	/	0.508(3)	0.534(8)

Table 5.1. Structural Comparision of Copper(I) Complexes with Substituted TPMA Ligands.^a

^aBond lengths are given in angstroms (Å) and angles in degrees (deg). ^bRef ³⁸. ^cN4 corresponds to aliphatic nitrogen atom in all complexes. Nitrogen atom in 4-methoxy-3,5-dimethyl substituted pyridine ring is labeled as N1 (Cu¹(TPMA^{*1})Br), N1 and N2 (Cu¹(TPMA^{*2})Br) and N1, N2 and N3 (Cu¹(TPMA^{*3})Br). ^dDistance between copper(I) atom and LSP derived from nitrogen atoms in pyridine rings.

In the solid state, copper(I) halide complexes with TPMA ligand can be best described as formally being distorted tetrahedral in geometry, with the coordination to the copper(I) center occurring through a halide anion and three nitrogen atoms from pyridine rings.^{3, 32, 38-39} The remaining copper(I)-aliphatic nitrogen bond at approximately 2.4 Å is much more elongated

when compared to typical Cu¹-N bond length (2.0-2.1 Å).⁴ Similar structural features were also observed in Cu¹(TPMA^{*2})Br complex (**Figure 5.2b**). The copper(I) center was coordinated by a nitrogen atom from unsubstituted pyridine arm (Cu1-N3=2.0452(17) Å), two nitrogen atoms from 4-methoxy-3,5-dimethyl substituted pyridine arms (Cu1-N1=2.0837(17) Å and Cu1-N2=2.0886(19) Å) and a bromine atom (2.5025(3) Å). The remaining Cu¹-N(aliphatic) bond distance (2.4190(19) Å) was slightly shorter than in Cu¹(TPMA)Br complex (2.4397(14) Å).³⁸ Furthermore, the copper(I) atom was positioned 0.508(3) Å below the least-squares plane derived from N1, N2 and N3 atoms towards the bromide anion, consistent with Cu¹ preferring a tetrahedral geometry. The main Br1-Cu1-N4 axis (173.97(4)°) in Cu¹(TPMA^{*2})Br was slightly bent when compared to Cu¹(TPMA)Br (179.14(3)°). As a result, Cu^{II}(TPMA^{*2})Br complex does not possess near (non-crystallographic) three-fold symmetry with respect to Cu1-N4 vector and N1, N2 and N3 atoms. Lastly, the crystal structure of Cu¹(TPMA^{*2})Br was stabilized by weak C-H---C (2.800(2) Å) and dipole C-H---N (2.746(3) Å) and C-H---Br (2.892(7)-2.970(3) Å) interactions.

The structural features of Cu¹(TPMA^{*3})Br complex (**Figure 5.2c**) were very similar to previously reported Cu¹(TPMA)Br.³⁸ The copper(I) center exhibited a distorted tetrahedral geometry and was coordinated by three nitrogen atoms from 4-methoxy-3,5-dimethyl substituted pyridine arms (Cu1-N1=2.093(3) Å, Cu1-N2=2.116(3) Å and Cu1-N3=2.086(3) Å) and a bromine atom (Cu1-Br1=2.5045(6) Å). Similar to Cu¹(TPMA^{*2})Br, the remaining Cu¹-N(aliphatic) bond length (2.406(3) Å) was slightly shorter than in Cu¹(TPMA)Br complex (2.4397(14) Å). The copper(I) atom was positioned 0.534(8) Å below the least-squares plane derived from N1, N2 and N3 atoms towards the bromide anion. With respect to Br1-Cu1-N4 vector and nitrogen atoms from substituted pyridine arms, Cu¹(TPMA^{*3})Br was nearly C₃-symmetric. However, as indicated in the space filling model (**Figure 5.3**), the presence of methoxy and methyl groups in the pyridine rings caused significant twisting of the ligand arms when compared to previously characterized Cu¹(TPMA)Br complex. Hence, viewing along Br1-Cu1-N4 axis, Cu¹(TPMA^{*3})Br appeared to be much closer to T-shaped rather than trigonal planar as observed in Cu¹(TPMA)Br. This cannot be attributed to the packing forces in the crystal structure because the only significant interactions in the unit cell were weak C-H---Br dipoles (2.780(4)-2.818(3) Å).



Figure 5.3. Space filling models (bottom view) of Cu^I(TPMA)Br (a) and Cu^I(TPMA^{*3})Br (b) indicating twisting of 4-methoxy-3,5-dimethyl substituted pyridine arms. H-atoms have been omitted for clarity.

In summary, Cu^I(TPMA^{*1})Br , Cu^I(TPMA^{*2})Br and Cu^I(TPMA^{*3})Br complexes were found to be distorted tetrahedral in the solid state and contained coordinated bromide anions (Cu^I-Br=2.3511(10) Å, 2.5025(3) Å and 2.5045(6) Å, respectively). Pseudo coordination of the aliphatic nitrogen atom to copper(I) center was observed in Cu^I(TPMA^{*2})Br (Cu^I-N=2.4190(19) Å) and Cu^I(TPMA^{*3})Br (Cu^I-N=2.406(3) Å) complexes, similarly to previously isolated Cu^I(TPMA)Br (Cu^I-N=2.4397(14) Å).³⁸ On the other hand, pyridine arm dissociation occurred in Cu^I(TPMA^{*1})Br complex (Cu^I-N_{py}= 3.494(3)) Å). Regardless of the number of 4-methoxy-3,5-dimethyl substituted pyridine arms in TPMA^{*2} and TPMA^{*3} complexes, two of the Cu^I-N_{py} bonds were nearly identical (2.083±0.012 Å), whereas the third one either increased (TPMA^{*3}: Cu^I-N_{py}=2.116(3) Å) or decreased (TPMA^{*2}: Cu^I-N_{py}=2.0452(17) Å). Lastly, significant ligand arm twisting was observed in Cu^I(TPMA^{*3})Br complex when compared to Cu^I(TPMA)Br, which was found to be nearly C₃-symmetric in the solid state.

5.2.4.2 Solution Studies of Copper(I) Complexes.

Variable temperature ¹H NMR spectroscopy was used to probe the structural features of copper(I) complexes with substituted TPMA based ligands in solution. Previously, this technique has been shown to be useful in examining structures of Cu^I(TPMA)Br³⁸ and Cu^I(TPMA)Cl^{39, 79}

complexes, which were found to be highly symmetrical and monomeric in solution, consistent with the solid-state studies. Shown in **Figure 5.4** are the aromatic and methylene regions of the variable temperature ¹H NMR spectra of Cu^I(TPMA^{*1})Br complex in (CD₃)₂CO. The proton resonances at ambient temperature were very broad, indicating a fluxional system very typical for d¹⁰ transition metal complexes containing neutral ligands.⁸⁰



Figure 5.4. Variable temperature ¹H NMR spectra (400 MHz, $(CD_3)_2CO$) of Cu^I(TPMA^{*1})Br complex in the aromatic and methylene regions.

However, on cooling to 220 K, the resonances due to the coordinated TPMA^{*1} became relatively well resolved. Only one set of resonances for the aromatic protons in TPMA^{*1} ligand were observed, which is not consistent with the solid-state structure of Cu^I(TPMA^{*1})Br in which one pyridine arm was dissociated from the copper(I) center (vide supra). The hydrogen atoms next to the nitrogen atoms in unsubstituted (H¹, Figure 5.4) and 4-methoxy-3,5-dimethyl substituted (H², Figure 5.4) pyridine arms at 220 K moved approximately 0.60 ppm downfield relative to free TPMA^{*1}. Such downfield shift between 0.50 and 0.70 ppm is typically observed in copper(I) complexes containing nitrogen-based ligands.⁸¹⁻⁸⁴ Similarly, downfield shift for the methylene protons in TPMA^{*1} (H⁶ and H⁷, Figure 5.3) by 0.10 ppm also indicated coordination. Much smaller shift for methylene protons (H⁶ and H⁷) in TPMA^{*1}, when compared to pyridine protons (H¹ and H²), clearly points to a weaker interaction between the aliphatic nitrogen atom and copper(I) center. Exactly the same trend was observed in previously characterized Cu^I(TPMA)Br and Cu^I(TPMA)Cl.^{39, 79} In latter complexes, TPMA was coordinated to the copper(I) center in a nearly C₃-symmetric fashion with Cu^I-N(aliphatic) bond distance being on average 0.360 Å longer than the corresponding distances with nitrogen atoms from pyridine rings. Therefore, taking into account the presence of only one set of resonances for the aromatic protons in TPMA^{*1} and similarity with the spectra of Cu^I(TPMA)Br and Cu^I(TPMA)Cl, the structure of Cu^I(TPMA^{*1})Br is most likely symmetrical and monomeric in solution as shown in Figure 5.4.

Similar to Cu^I(TPMA^{*1})Br, the proton resonances in Cu^I(TPMA^{*2})Br at room temperature were broad indicating highly fluxional system (**Figure 5.5**). On cooling to 188 K, distinct resonances for protons associated with coordinated unsubstituted (H², δ 9.03, δ - δ_{free} =0.59 ppm) and 4-methoxy-3,5-dimethyl substituted (H¹, δ 8.72, δ - δ_{free} =0.53 ppm) pyridine arms were observed. Interestingly, separate proton resonances for corresponding dissociated arms also appeared (pyridine: H^{2'}, δ 8,51, δ - δ_{free} =0.07 ppm and 4-methoxy-3,5-dimethyl pyridine: H^{1'}, δ 8.19, δ - δ_{free} =0.06 ppm). The spectrum at 188 K was not consistent with commonly encountered dimerization that is easily observed by ¹H NMR spectroscopy due to inequivalence of methylene protons,^{3, 85} but rather the presence of two different complexes each containing uncomplexed pyridine (35%) and 4-methoxy-3,5-dimethyl substituted pyridine (65%) arms, respectively. Therefore, the proposed structures shown in **Figure 5.5** are not consistent with the solid state in which TPMA^{*2} was coordinated to the copper(I) center through bromide anion and three nitrogen atoms from pyridine rings (vide supra).



Figure 5.5. Variable temperature ¹H NMR spectra (400 MHz, $(CD_3)_2CO$) of Cu^I(TPMA^{*2})Br complex in the aromatic region.

Lastly, ligand arm dissociation was also observed in Cu^I(TPMA^{*3})Br complex (**Figure 5.6**). At 188 K, proton resonances for complexed and uncomplexed 4-methoxy-3,5-dimethyl substituted pyridine rings resolved in the integration ratio of 2:1. This clearly indicates that Cu^I(TPMA^{*3})Br adopts tetrahedral geometry in solution with copper(I) center being coordinated by two nitrogen atoms from pyridine arms, one aliphatic nitrogen atom, and a bromine atom. Therefore, the structure of Cu¹(TPMA^{*3})Br in solution is not consistent with the solid state, but rather resembles Cu¹(TPMA^{*1})Br in the solid state as discussed above (**Figure 5.2a**).

In summary, Cu¹(TPMA^{*1})Br, Cu¹(TPMA^{*2})Br and Cu¹(TPMA^{*3})Br complexes were found to be more fluxional in solution than previously investigated Cu¹(TPMA)Br and Cu¹(TPMA)Cl.^{39, 79} Furthermore, the structures of all three complexes were not consistent with the solid-state discussed above. At low temperature, Cu¹(TPMA^{*1})Br was found to be symmetrical and monomeric. Lastly, dissociation of either unsubstituted pyridine and/or 4-methoxy-3,5-dimethyl substituted pyridine arms was observed in Cu¹(TPMA^{*2})Br and Cu¹(TPMA^{*3})Br complexes.



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Figure 5.6. Variable temperature ¹H NMR spectra (400 MHz, $(CD_3)_2CO$) of $Cu^{I}(TPMA^{*3})Br$ complex in the aromatic and methylene regions.

5.2.4.3 Solid-State Structural Studies of Copper(II) Complexes.

Copper(II) complexes that are generated during ATRA and ATRP processes are essential for the deactivation step (i.e. reversible halogen atom abstraction from a copper(II) complex by radicals to generate dormant alkyl halide species and a copper(I) complex, (**Scheme 5.1**).^{4, 42-43} [Cu^{II}(TPMA^{*1})Br][Br], [Cu^{II}(TPMA^{*2})Br][Br] and [Cu^{II}(TPMA^{*3})Br][Br] complexes were synthesized by reacting Cu^{II}Br₂ with the stoichiometric amounts of substituted TPMA based ligand. Crystals suitable for X-ray analysis were obtained in dichloromethane by slow diffusion of *n*-pentane. The corresponding molecular structures are shown in **Figure 5.7**, and selected bond distances and angles summarized in **Table 5.2**.



Figure 5.7. Molecular structures of $[Cu^{II}(TPMA^{*1})Br][Br]$ (a), $[Cu^{II}(TPMA^{*2})Br][Br]$ (b) and $[Cu^{II}(TPMA^{*3})Br][Br]$ (c) shown with 30% probability displacement ellipsoids. H-atoms and bromide counterion have been omitted for clarity.

Complex	[Cu ^{ll} (TPMA)Br] ^{+b}	[Cu ^{ll} (TPMA ^{*1})Br] ^{+c}	[Cu ^{ll} (TPMA ^{*2})Br] ^{+c}	[Cu ^{ll} (TPMA ^{*3})Br] ^{+c}
Cu1-N1 _{eq}	2.073(15)	2.062(2)	2.028(5)	2.059(3)
$Cu1-N2_{eq}$	2.073(15)	2.0400(19)	2.072(5)	2.149(3)
$Cu1-N3_{eq}$	2.073(15)	2.064(2)	2.136(4)	2.044(3)
Cu1-N4 _{ax}	2.040(3)	2.0411(19)	2.025(4)	2.028(3)
Cu1-Br1	2.3836(6)	2.3852(3)	2.3814(7)	2.3740(5)
N1-Cu1-N2	80.86(5)	117.74(8)	133.26(19)	115.63(12)
N1-Cu1-N3	80.86(5)	111.04(8)	114.07(18)	132.39(12)
N1-Cu1-N4	80.86(5)	80.61(8)	82.74(17)	81.07(12)
N2-Cu1-N3	117.53(3)	124.60(8)	105.58(18)	104.99(12)
N3-Cu1-N4	117.53(3)	81.01(8)	81.36(17)	82.81(12)
N4-Cu1-N2	117.53(3)	82.51(7)	79.66(18)	79.82(11)
Br1-Cu1-N1	99.14(5)	99.23(6)	98.72(12)	97.27(8)
Br1-Cu1-N2	99.14(5)	97.73(5)	97.19(12)	100.99(8)
Br1-Cu1-N3	99.14(5)	98.89(6)	100.71(12)	98.35(8)
Br1-Cu1-N4	180.00(5)	179.76(5)	176.64(13)	178.33(9)
Cu1-LSP _{N,Py} d	0.329	0.307	0.303	0.329
τ ^e	1.0	0.92	0.72	0.77

Table 5.2. Structural Comparision of Copper(II) Complexes with Substituted TPMA Ligands.^a

^aBond lengths are given in angstroms (Å) and angles in degrees (deg). ^bRef ³⁸. ^cN4 corresponds to aliphatic nitrogen atom in all complexes. Nitrogen atom in 4-methoxy-3,5-dimethyl substituted pyridine ring is labeled as N1 ([Cu^{II}(TPMA^{*1})Br][Br]), N1 and N2 ([Cu^{II}(TPMA^{*2})Br][Br]) and N1, N2 and N3 ([Cu^{II}(TPMA^{*3})Br][Br]). ^dDistance between copper(I) atom and LSP derived from nitrogen atoms in pyridine rings. ^e τ parameter is calculated as τ =(ϕ_1 - ϕ_2)/60 where ϕ_1 and ϕ_2 are the largest and second largest N-Cu^{II}-N(Br) bond angles, τ =1 (regular trigonal bipyramidal geometry) and τ =0 (regular square pyramidal geometry).
All three complexes deviated from the ideal trigonal bipyramidal geometry observed in previously characterized [Cu^{II}(TPMA)Br][Br].³⁸ This can easily be seen from the corresponding τ values (τ =1 for regular trigonal bipyramidal geometry and τ =0 for regular square pyramidal geometry),⁸⁶⁻⁸⁷ which generally decreased in the order [Cu^{II}(TPMA)Br][Br] (τ =1) > $[Cu^{II}(TPMA^{*1})Br][Br](\tau=0.92) > [Cu^{II}(TPMA^{*3})Br][Br](\tau=0.77) > [Cu^{II}(TPMA^{*2})Br][Br](\tau=0.72)).$ The average Cu^{II}-Neg bond distances increased on going from [Cu^{II}(TPMA^{*1})Br]Br] (2.055(3) Å) to [Cu^{II}(TPMA^{*2})Br][Br] (2.078(8) Å) and [Cu^{II}(TPMA^{*3})Br][Br] (2.084(5) Å) complexes, and were not equal when compared to [Cu^{II}(TPMA)Br][Br] (2.073(15) Å). Generally, two Cu^{II}-N_{eq} bond lengths were either longer (TPMA^{*1}: 2.063(3) Å vs. 2.040(2) Å) or shorter (TPMA^{*2}: 2.050(7) Å vs. 2.136(4) Å and TPMA^{*3}: 2.052(4) Å vs. 2.149(3) Å). Furthermore, Cu^{II}-Br bond length in [Cu^{II}(TPMA^{*1})Br]Br] (2.3852(3) Å) and [Cu^{II}(TPMA^{*2})Br][Br] (2.3814(7) Å) were similar to [Cu^{II}(TPMA)Br][Br] (2.3836(6) Å), but slightly decreased in [Cu^{II}(TPMA^{*3})Br][Br] (2.3740(5) Å). Additionally, particularly in the case of [Cu^{II}(TPMA^{*2})Br][Br] and [Cu^{II}(TPMA^{*3})Br][Br], the presence of methoxy and methyl groups in the pyridine rings caused significant ligand arm twisting, as indicated in the space filling model (Figure 5.8). Lastly, the crystal structures of copper(II) complexes with substituted TPMA based ligands were stabilized by π - π stacking interactions between pyridine rings (TPMA^{*1}: 3.722(4) Å) and a series of weak C-H---C (TPMA^{*2}: 2.756(4) Å, TPMA^{*3}: 2.877*6) Å) and dipole C-H---O (TPMA^{*1}: 2.375(7) Å, TPMA^{*2}: 2.325(3)-2.674(5) Å, TPMA^{*3}: 2.657(2)-2.700(4) Å) and C-H---Br (TPMA^{*1}: 3.030(3)-3.042(3) Å, TPMA^{*2}: 2.882(4)-3.006(3) Å, TPMA^{*3}: 2.962(7)-3.020(5) Å) interactions.



Figure 5.8. Space filling models (top view) of [Cu^{II}(TPMA)Br][Br] (a), [Cu^{II}(TPMA^{*1})Br][Br] (b), [Cu^{II}(TPMA^{*2})Br][Br] (c) and [Cu^{II}(TPMA^{*3})Br][Br] (d) indicating twisting of 4-methoxy-3,5-dimethyl substituted pyridine arms. H-atoms and bromide counterion have been omitted for clarity.

With the exception of TPMA^{*1}, the structural feature of copper(I and II) complexes with TPMA^{*2} and TPMA^{*3} ligands appear to be rather similar. In Cu^I(TPMA^{*2})Br and Cu^I(TPMA^{*3})Br complexes, the average Cu-N_{eq} bond lengths are 0.0100 Å and 0.0140 Å longer than in [Cu^{II}(TPMA^{*2})Br][Br] and [Cu^{II}(TPMA^{*3})Br][Br], respectively. The N_{eq}-Cu-N_{aq} bond angles are very similar in both Cu^I and Cu^{II} complexes, while the average angle in the plane N_{eq}-Cu-N_{eq} is slightly larger in [Cu^{II}(TPMA^{*2})Br][Br] (117.63(2)°) and [Cu^{II}(TPMA^{*3})Br][Br] (117.67(2)°) when compared to Cu^I(TPMA^{*2})Br (114.11(12)°) and Cu^{II}(TPMA^{*3})Br (113.67(18)°), respectively. The only more pronounced difference in TPMA^{*2} and TPMA^{*3} coordination to the copper center can be seen in shortening of Cu-N_{ax} bond length by approximately 0.400 Å on going from Cu^I(TPMA^{*2} or ³)Br to

[Cu^{II}(TPMA^{*2 or 3})Br][Br]. Similar conclusions were also reached in the case of previously isolated Cu^{II}(TPMA)Br and Cu^{II}(TPMA)Br][Br] complexes.³⁸

5.2.4.4 Solution Studies of Copper(II) Complexes.

Apart from electrospray ionization mass spectrometry (ESI-MS), copper(II) complexes with substituted TPMA based ligands were also characterized in solution using UV-Vis spectroscopy (Figure 5.9). The corresponding λ_{max} and ε_{max} values are summarized in Table 5.3. Data for previously reported [Cu^{II}(TPMA)Br][Br],³⁸ [Cu^{II}(Me₆TREN)Br][Br]⁸⁸ (Me₆TREN=tris[2-(dimethylamino)ethyl]amine) and [Cu^{II}(bpy)₂Br][Br]^{4, 89} (bpy=2,2'-bipyridine) complexes are included for comparison. The absorption spectra in the Vis/NIR region for copper(II) complexes with TPMA^{*1}, TPMA^{*2} and TPMA^{*3} ligands can be characterized in terms of the absorption bands centered around 754 and 980 nm. These bands are typically observed in [CuN₄X]⁺ (X=Br or Cl) chromophores that have trigonal bipyramidal geometry, and correspond to $d_{xz} \approx d_{yz} \rightarrow d_{z^2}$ and $d_{x^2-y^2} \approx d_{xy} \rightarrow d_{z^2}$ transitions, respectively.^{4, 90-92} Furthermore, all spectra are consistent with previously characterized copper(II) complexes containing TPMA, Me₆TREN and bpy ligands, which were found to be trigonal bipyramidal in geometry. Therefore, solution structures of [Cu^{II}(TPMA^{*1})Br][Br], Cu^{II}(TPMA^{*2})Br][Br] and [Cu^{II}(TPMA^{*3})Br][Br] are consistent with the solid state discussed above.



Figure 5.9. Absorption spectra (Vis/NIR) of $Cu^{II}Br_2$ complexes with TPMA, TPMA^{*1}, TPMA^{*2} and TPMA^{*3} ligands in acetonitrile at ambient temperature ([Cu^{II}]₀=5.0×10⁻³ M).

Complex	λ_{\max} (nm) / $arepsilon_{\max}$ (Lmol ⁻¹ cm ⁻¹)	Ref.
[Cu ^{II} (TPMA ^{*1})Br][Br]	983 (195), 754 (89)	this work
[Cu ^{II} (TPMA ^{*2})Br][Br]	982 (193), 754 (83)	this work
[Cu ^{ll} (TPMA ^{*3})Br][Br]	979 (187), 756 (78)	this work
[Cu ^{ll} (TPMA)Br][Br]	981 (178), 759 (75)	38
[Cu ^{ll} (Me ₆ TREN)Br][Br]	973 (170), 757 (73)	88
[Cu ^{ll} (bpy) ₂ Br][Br]	984 (230), 750 (346)	4

Table 5.3. Summary of λ_{max} and ε_{max} Values in Acetonitrile for Cu^{II}Br₂ Complexes with TPMA and TPMA^{*1-3} Ligands.

5.2.4.5 Electrochemical Studies

As mentioned in the introduction section, electrochemical measurements are commonly used to predict the activity of copper complexes in atom transfer radical processes, namely ATRA and ATRP.^{4, 43, 54, 57-61} Generally, for a given alkyl halide, the equilibrium constant for atom transfer ($K_{ATRP}=k_a/k_d$) can be directly correlated with $E_{1/2}$ values provided that the halidophilicity of the metal complex $(X^{-+}[Cu^{II}L_m]^{2+} \rightleftharpoons [Cu^{II}L_mX]^+, K_X, X=Br \text{ or CI})$ remains constant. As a result, for copper complexes with neutral nitrogen-based ligands commonly used in ATRA or ATRP, a linear correlation between $\ln(K_{ATRP})$ and $E_{1/2}$ values is typically observed.^{59, 62-63} The basic hypothesis behind the work presented in this article was that the systematic incorporation of electron donating groups to pyridine rings in TPMA scaffold will result in more reducing and consequently more active ATRA/ATRP copper catalysts. Shown in Figure 5.10 are cyclic voltammograms of [Cu^{II}(TPMA^{*1})Br][Br], [Cu^{II}(TPMA^{*2})Br][Br] and [Cu^{II}(TPMA^{*3})Br][Br] complexes in acetonitrile. The electrochemical data relative to SCE are given in Table 5.4. Values for previously reported [Cu^{II}(TPMA)Br][Br]³⁸ and [Cu^{II}(Me₆TREN)Br][Br]⁶³ are included for comparison. All copper complexes displayed a single quasireversible redox behavior with i_{pa}/i_{pc} varying from 0.95 to 1.18 and peak separations of less than 90 mV at a scan rate of 100 mV/s. Interestingly, a nearly stepwise decrease ($\Delta E^{\sim}60 \text{ mV}$) of $E_{1/2}$ values (TPMA (-240 mV) > TPMA*1

(-310 mV) > TPMA*2 (-360 mV) > TPMA*3 (-420 mV)) was observed on going from $[Cu^{II}(TPMA)Br][Br]$ to $[Cu^{II}(TPMA^{*3})Br][Br]$, clearly indicating that the presence of electron donating groups in the 4 (-OMe) and 3,5 (-Me) positions of the pyridine rings in TPMA increases the reducing ability of the corresponding copper(I) complexes. Similar trends were observed previously in the case of copper complexes containing tris-4-substituted (-^tBu, -Me, -MeO and -NMe₂) TPMA⁶⁹ and 4,4'-subsituted (-Me, -MeO and -NMe₂) bipyridine⁶⁸ based ligands. Furthermore, cyclic voltammograms for the copper(II) triflate complexes with substituted TPMA based ligands also followed the similar trend, with the exception that the $E_{1/2}$ values were less negative by ~250-275 mV (**Table 5.4**). The diminished reducing potential originates from the differences in Cu^{II} stability constants as discussed below.^{38, 65-66, 76}



Figure 5.10. Cyclic voltammograms of $Cu^{II}Br_2$ complexes with TPMA^{*1}, TPMA^{*2} and TPMA^{*3} ligands at 25 °C. All measurements were conducted in acetonitrile with 0.1 M TBAPF₆ as a supporting electrolyte at a scan rate of 100 mV/s, [Cu^{II}Br₂]₀:[L]₀=1:1, [Cu^{II}Br₂]₀=1.0 mM.

Table 5.4. Cyclic Voltammetry Data for Copper Complexes with TPMA Based Ligands in Acetonitrile.

Complex ^a	<i>E</i> _{1/2} (mV)	<i>∆E</i> _p (mV)	i _{pa} /i _{pc}	$eta_{\scriptscriptstyle Br}^{\scriptscriptstyle II}$ / $eta_{\scriptscriptstyle Br}^{\scriptscriptstyle I}$	Ref.
[Cu ^l (TPMA)Br][Br]	-240	93	1.08	2.5×10 ⁴	38
[Cu ^l (TPMA ^{*1})Br][Br]	-310	84	0.96	1.2×10 ⁴	this work
[Cu ^l (TPMA ^{*2})Br][Br]	-360	86	0.95	6.9×10 ³	this work

[Cu ^I (TPMA ^{*3})Br][Br]	-420	79	1.18	1.3×10 ⁴	this work
[Cu ^I (TPMA)][OTf] ₂	22	86	0.94		38
[Cu ^I (TPMA ^{*1})][OTf] ₂	-69	104	0.78		this work
[Cu ^I (TPMA ^{*2})][OTf] ₂	-133	120	0.93		this work
[Cu ^I (TPMA ^{*3})][OTf] ₂	-177	108	1.20		this work
[Cu ^l (Me ₆ TREN)Br][Br]	-300	115	0.72		63

^aPotentials are reported relative to SCE and were measured under the same electrochemical cell conditions. b_{Br}^{II} / b_{Br}^{I} ratio was calculated using Eq. [2].

Another method for predicting the activity of copper catalysts in ATRP is to compare the stability constants of the Cu^{II} and Cu^I complexes with the particular ligand (β^{II} : Cu^{II}+mL \rightleftharpoons Cu^{II}L_m and β : Cu^{II}+mL \rightleftharpoons Cu^{II}L_m, respectively), since the equilibrium constant for atom transfer, K_{ATRP} , directly correlates with the ratio β^{II}/β . More importantly, β^{II} and β should be large in order to eliminate or suppress possible concurrent reactions such as coordination of monomer and/or polymer, which are typically present in large excess relative to the catalyst. Generally, more reducing copper complex should be more stable in its oxidized from (i.e. Cu^{II} should be more stable than Cu^I) in order to achieve high catalytic activity.⁶¹ For the case of relatively stable 1:1 copper complexes, the ratio of the stability constants can be calculated from the readily available reduction potentials using Eq. [2], where $E_{Cu^{II}/Cu^{I}}^{o'}$ corresponds to a standard reduction potential for the Cu^{II}/Cu^I couple in the absence of a coordinating ligand.⁹³⁻⁹⁶

$$\ln \frac{b^{II}}{b^{I}} = \frac{F}{RT} (E^{o'}_{Cu^{II}/Cu^{I}} - E^{o'}_{Cu^{II}L/Cu^{I}L})$$
[2]

Unfortunately, Eq. [2] only provides the ratio and not the specific stability constants for the respective oxidation states. While this ratio may increase with more active catalysts, it is not directly known whether this is a result of an increase in β^{I} or a decrease in β^{I} . However, another quantity, namely $\beta^{I}/(\beta^{I})^{2}$ ratio, can be readily obtained from disproportionation studies as previously reported in the literature.^{57,71,76} Due to the scattering effect of the Cu⁰ that is formed during disproportionation on the UV-Vis spectroscopy, comproportionation experiments

between Cu⁰ and [Cu^{II}/L][OTf]₂ (L=complexing ligand) in the presence of excess free ligand were conducted. Once the equilibrium point was reached, i.e. the concentration of [Cu^{II}/L][OTf]₂ was unchanged for 3 hours, the equilibrium constant for disproportionation (K_{disp}) was easily calculated using Eq. [3]. It was assumed that the newly soluble Cu^I complex formed from Cu⁰ was immediately complexed by excess free ligand. Using the experimentally determined value for $K_{disp,Cu}/L$ and the value for the solvated Cu species, $K_{disp,Cu}$ taken from literature, the ratio of $\beta^{II}/(\beta^{I})^{2}$ was then

$$K_{\text{disp,Cu/L}} = \frac{[Cu^{II}/L]_{\text{eq}}[L]_{\text{eq}}}{[Cu^{I}/L]_{\text{eq}}^{2}}$$
[3]
$$\frac{\beta^{II}}{(\beta^{I})^{2}} = \frac{K_{\text{disp,Cu/L}}}{K_{\text{disp,Cu}}}$$
[4]

determined using Eq. [4]. Finally, using the ratios β^{I}/β^{I} from electrochemical studies (Eq. [2]) and $\beta^{I}/(\beta^{I})^{2}$ from the disproportionation equilibrium (Eq. [4]), the individual stability constants β^{I} and β^{II} can be calculated. It is important to note that both the electrochemical and comproportionation studies need to be conducted in the same solvent for accurate and consistent results.

Using Eq. [2], the difference between $E_{Cu^{II}LCu^{IL}}^{o'}$ for TPMA based copper triflate and halide complexes reported in **Table 5.4**, and $E_{Cu^{II}/Cu^{I}}^{o'}$ for CH₃CN, which was determined by potentiometry (1.056 V),⁷⁶ the ratio of stability constants (b_{Br}^{II} / b_{Br}^{I}) for the coordination of Br⁻ anions to copper(I and II) complexes with TPMA^{*1}, TPMA^{*2} and TPMA^{*3} were determined to be 1.2×10⁴, 6.9×10³ and 1.3×10⁴, respectively. These results were in excellent agreement with the previously reported value for TPMA (2.5×10⁴),⁵⁹ and indicate that the degree of ligand arm substitution does not significantly affect halidophilicty. The stability constants (b_{L}^{II} and b_{L}^{I}) for the complexation of TPMA, TPMA^{*1}, TPMA^{*2} and TPMA^{*3} ligands to copper(I and II) triflate complexes in dimethylformamide at 25 °C are summarized in **Table 5.5**.

Table 5.5. Electrochemical Data and Disproportionation and Stability Constants for Copper Triflate Complexes with TPMA Based Ligands in Dimethylformamide at 25 °C.

Ligand ^a	ТРМА	TPMA ^{*1}	TPMA ^{*2}	TPMA ^{*3}
<i>E</i> _{1/2} ^b (mV)	85.0	30.0	-50.0	-90.0
$E_{Cu^{II}/Cu^{I}}^{o'}$ - $E_{Cu^{II}L/Cu^{I}L}^{o'}$ (mV) ^c	295	350	430	470
β^{I}/β^{I}	9.7×10 ⁴	8.3×10 ⁵	1.9×10 ⁷	8.8×10 ⁷
\mathcal{K}_{disp} , Cu/L ^d	1.3×10 ⁻⁴	6.3×10 ⁻⁴	2.1×10 ⁻²	4.7×10 ⁻²
$\beta^{\parallel}/(\beta^{\parallel})^2$	7.3×10 ⁻⁹	3.4×10 ⁻⁸	1.2×10 ⁶	2.6×10 ⁶
eta	1.3×10 ¹³	2.4×10 ¹³	1.6×10 ¹³	3.4×10 ¹³
$eta^{\!$	1.3×10 ¹⁸	2.0×10 ¹⁹	3.0×10 ²⁰	3.0×10 ²¹
$(eta^{\!$	5.0	5.9	7.3	7.9
b_L^I / b_{TPMA}^I	1.0	1.8	1.2	2.6
b_L^{II} / b_{TPMA}^{II}	1.0	15	2.3×10 ²	2.3×10 ³

^aAll calculations were performed using equations derived in the supporting information. ^b $E_{1/2}$ potentials are reported relative to Ag/AgCl electrode. ^c $E_{Cu^{II}/Cu^{I}}^{o'}$ =380 mV. ^d $K_{disp,Cu/L}$ and $K_{disp/Cu}$ =1.82×10⁴ were determined by UV-Vis spectroscopy in DMF by monitoring the comproportionation reaction between Cu^{II}/L or Cu^{II} and Cu⁰, respectively.

The stability constant β remains nearly constant for all ligands, while β^{II} increases nearly 2300 times from TPMA to TPMA^{*3}. Therefore, the trend observed in redox potentials discussed above clearly indicate that the TPMA based ligands induce a stronger influence towards the stabilization of the copper(II) oxidation state (log β^{I} =13.4±0.2, log β^{II} =19.3 (TPMA^{*1}), 20.5 (TPMA^{*2}) and 21.5 (TPMA^{*3})).

Electrochemical data, stability constants and previously established linear correlation between $\ln(K_{ATRP})$ and $E_{1/2}$ values^{43, 63} indicate that copper complexes with TPMA^{*1}, TPMA^{*2} and TPMA^{*3} ligands should have the equilibrium constant for atom transfer (K_{ATRP}) approximately 10, 100 and 1000 times larger than TPMA ($D(E_2^o - E_1^o) = 59 \text{ mV} \rightarrow K_2 / K_1 = 10$). Indeed, for Cu¹(TPMA^{*3})Br complex, the equilibrium constant for atom transfer ($K_{ATRP}=k_a/k_d=8400/2.0\times10^7=4.2\times10^{-4}$) was found to be nearly 1300 larger than for Cu¹(TPMA)Br ($K_{ATRP}=k_a/k_d=3.8 \text{ M}^{-1}\text{s}^{-1}/1.2\times10^7 \text{ M}^{-1}\text{s}^{-1}=3.2\times10^{-7}$). The large difference in K_{ATRP} values can be attributed mostly to an increase in the activation rate constant (k_a , 8400 M⁻¹s⁻¹ vs. 3.8 M⁻¹s⁻¹), indicating that Cu^I(TPMA^{*3})Br should be much more active in ATRP, as confirmed by recently published study.⁷¹

5.2.4.6 Application in Atom Transfer Radical Polymerization (ATRP).

TPMA is a widely used ligand for copper catalyzed ATRP methods ranging from conventional ATRP^{34-35, 97} to improved protocols that require only ppm amounts of the catalyst.^{32-33, 42, 48-51, 98} These enhanced synthetic procedures allow for the use of air stable Cu^{II} complexes, often eliminating the need for deoxygenation, and rely on the continuous reduction of Cu^{II} to Cu^{II} species within the polymerization process. Consequently, additional non-radical (e.g. tin(II) 2-ethylhexanoate = Sn(EH)₂, ascorbic acid or hydrazine) or radical (e.g. AIBN or V-70) reducing agents are employed. The selection of appropriate ATRP conditions is reliant on various factors such as monomer, initiator, ligand, solvent, etc.^{52, 59} Large *K*_{ATRP} values require ATRP methods with constant regeneration of Cu^I complex due to early termination reactions that typical occur under normal ATRP conditions.^{71, 99} Therefore, in the present study, activators regenerated by electron transfer (ARGET) ATRP⁴⁹ of n-butyl acrylate (*n*-BA) was targeted utilizing low amounts of Sn^{II}(EH)₂ as the reducing agent and only 100 ppm of the copper complexes with TPMA, TPMA^{*1}, TPMA^{*2} and TPMA^{*3} ligands. As indicated in **Table 5.6**, all catalysts showed moderate

Complex ^a	Conv. (%)	M n,exp	$M_{ m n,theo}$	$M_{\rm w}/M_{\rm n}$
[Cu ^{II} (TPMA)Br][Br]	67	13600	13721	1.09
[Cu ^{ll} (TPMA ^{*1})Br][Br]	64	13300	13107	1.10
[Cu ^{ll} (TPMA ^{*2})Br][Br]	64	13200	13107	1.09
[Cu ^{II} (TPMA ^{*3})Br][Br]	62	14500	12700	1.09

Table 5.6. Polymerization Results for ARGET ATRP of *n*-Butyl Acrylate Catalyzed by 100 ppm of Copper Complexes with TPMA Based Ligands.

^aConditions: $[nBA]_{0}$: $[EBiB]_{0}$: $[Sn(EH)_{2}]_{0}$: $[TPMA \text{ or } TPMA^{*x}]_{0}$: $[Cu^{II}Br_{2}]_{0}$ =160:1:0.1:0.032:0.008, EBiB=ethyl 2-bromoisobutyrate, $[nBA]_{0}$ =6.65 M, 20% (v/v) anisole, $[Cu^{II}]_{0}$ =100 ppm, T=60 °C, t=24 h. Monomer conversion was determined by ¹H NMR spectroscopy using anisole as an internal standard. conversions and good correlation between experimental $(M_{n,exp})$ and theoretical molecular weights $(M_{n,theo})$, with narrow molecular weight distribution $(M_w/M_n \sim 1.1)$. Kinetic experiments were conducted to further confirm reversible deactivation radical polymerization behavior. At steady-state, a pseudo first order kinetic plot $(\ln([M]_o/[M]_t vs. t))$ was linear, demonstrating constant radical concentration, which is one of the main criteria for a controlled ATRP (see supporting information). Additionally, a linear increase of experimentally determined molecular weight $(M_{n,exp})$ with monomer conversion was observed, as expected. However, $M_{n,exp}$ were slightly higher than the $M_{n,theo}$ values during the polymerization, potentially indicating slow initiation or slow deactivation.

Interestingly, the two most active catalysts, $[Cu^{II}(TPMA^{*2})Br][Br]$ and $Cu^{II}(TPMA^{*3})Br][Br]$, showed approximately a 1-hour induction period. This induction period can be attributed to the more negative reduction potentials of these complexes since the rate of ARGET ATRP scales with a square root dependence on the reduction rate coefficient, k_{red} , as shown in Eq. [5].

Rate
$$\Box \sqrt{\frac{k_{\rm red} [{\rm Cu}^{\rm II}][{\rm RA}]}{k_{\rm t}}}$$
 [5]

A decreased *k*_{red} for more active complexes would decrease the rate of activator generation from Cu^{II} and reducing agent (RA). A slower generation of the Cu^I activating species would therefore decrease the rate of alkyl halide activation and retard the formation of radicals, thus allowing no conversion of monomer to take place. This is consistent with our work showing that more active catalysts prefer the Cu^{II} oxidation state. This rate-dependence is assuming that termination proceeds exclusively through radical-radical coupling or disproportionation. However, it has been well established that in Cu-mediated ATRP reactions, Cu^{II} induced termination processes contribute greatly towards the total number of radical termination reactions, although the mechanism of this process is still under investigation.^{75, 99} Taking into consideration Cu^{II} termination, this rate law (Eq. [5]) becomes much more complex. Due to this complicated process, we are currently in the process of conducting detailed kinetic studies and further exploring the ATRP activity of copper complexes with substituted TPMA based ligands.

5.2.5 CONCLUSIONS

In summary, synthesis, characterization, electrochemical studies and ATRP activity of a series of novel copper(I and II) complexes with TPMA based ligands containing 4-methoxy-3,5dimethyl substituted pyridine arms were reported. In the solid state, Cu¹(TPMA^{*1})Br, Cu^{i} (TPMA^{*2})Br and Cu^{i} (TPMA^{*3})Br complexes were found to be distorted tetrahedral in geometry and contained coordinated bromide anions (Cul-Br=2.3511(10) Å, 2.5025(3) Å and 2.5045(6) Å, respectively). Pseudo coordination of the aliphatic nitrogen atom to copper(I) center was observed in Cu^I(TPMA^{*2})Br (Cu^I-N=2.4190(19) Å) and Cu^I(TPMA^{*3})Br (Cu^I-N=2.406(3) Å) complexes, whereas pyridine arm dissociation occurred in Cu¹(TPMA^{*1})Br complex (Cu¹-N_{py}= 3.494(3)) Å). Regardless of the number of 4-methoxy-3,5-dimethyl substituted pyridine arms in TPMA^{*2} and TPMA^{*3} complexes, two of the Cu¹-N_{py} bonds were nearly identical (2.083±0.012 Å), whereas the third one either increased (TPMA^{*3}: Cu^I-N_{py}=2.116(3) Å) or decreased (TPMA^{*2}: Cu^I- N_{pv} =2.0452(17) Å). In solution, all copper(I) complexes with substituted TPMA ligands were found to be very fluxional. At low temperature, Cu^I(TPMA^{*1})Br was symmetrical and monomeric, while dissociation of either unsubstituted pyridine and/or 4-methoxy-3,5-dimethyl substituted pyridine arms was observed in Cu¹(TPMA^{*2})Br and Cu¹(TPMA^{*3})Br. On the other hand, the geometry of the copper(II) complexes in the solid state deviated from trigonal bipyramidal as confirmed by a decrease in τ values ([Cu^{II}(TPMA^{*1})Br][Br] (τ =0.92) > [Cu^{II}(TPMA^{*3})Br][Br] (τ =0.77) > $[Cu^{II}(TPMA^{*2})Br][Br](\tau=0.72))$. Furthermore, cyclic voltammetry studies indicated a nearly stepwise decrease ($\Delta E^{\sim}60 \text{ mV}$) of $E_{1/2}$ values (TPMA (-240 mV)> TPMA^{*1} (-310 mV) > TPMA^{*2} (-360 mV) > TPMA^{*3} (-420 mV)) on going from $[Cu^{\parallel}(TPMA)Br][Br]$ to $[Cu^{\parallel}(TPMA^{*3})Br][Br]$, confirming that the presence of electron donating groups in the 4 (-OMe) and 3,5 (-Me) positions of the pyridine rings in TPMA increases the reducing ability of the corresponding copper(I) complexes. This increase was mostly the result of a stronger influence of substituted TPMA ligands towards stabilization of the copper(II) oxidation state. Lastly, ARGET ATRP kinetic studies show that with more reducing catalysts an induction period is observed. This is attributed to slow regeneration of Cu^I species from the corresponding Cu^{II}.

5.3 Synthesis and Characterization of the Most Active Copper ATRP Catalyst Based on Tris[(4-dimethylaminopyridyl)methyl]amine

5.3.1 Preface

The synthesis and characterization of tris[(4-dimethylaminopyridyl)methyl]amine (TPMA^{NMe2}) as a ligand for copper catalyzed atom transfer radical polymerization (ATRP) is reported. In solution, the [Cu^I(TPMA^{NMe2})Br] complex shows fluxionality by variable temperature NMR, indicating rapid ligand exchange. In the solid-state, the $[Cu^{II}(TPMA^{NMe2})Br][Br]$ complex exhibits a slightly distorted trigonal bipyramidal geometry ($\tau =$ 0.89). The UV-Vis spectrum of [Cu^{II}(TPMA^{NMe2})Br]⁺ salts is similar to those of other pyridinebased ATRP catalysts. Electrochemical studies of [Cu(TPMA^{NMe2})]²⁺ and [Cu(TPMA^{NMe2})Br]⁺ showed highly negative redox potentials ($E_{1/2}$ = -302 mV and -554 mV vs. SCE, respectively), suggesting unprecedented ATRP catalytic activity. Cyclic voltammetry (CV) in the presence of methyl 2-bromopropionate (MBrP; acrylate mimic) was used to determine activation rate constant $k_a = 1.1 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, confirming the extremely high catalyst reactivity. In the presence of the more active ethyl α -bromoisobutyrate (EBiB; methacrylate mimic), total catalysis was observed and an activation rate constant $k_a = 7.2 \times 10^6 \text{ M}^{-1} \text{s}^{-1}$ was calculated with values of K_{ATRP} \approx 1. ATRP of methyl acrylate showed a well-controlled polymerization using as little as 10 ppm of catalyst relative to monomer while side reactions such as Cu¹ catalyzed radical termination (CRT) could be suppressed due to the low concentration of L/Cu¹ at a steady-state.

^{*}Work in this section was published: <u>**TG Ribelli**</u>, M Fantin, R Poli, JC Daran, KF Augustine, K Matyjaszewski. "Synthesis, Characterization of the Most Active ATRP Catalyst Based on tris[(4dimethylaminopyridyl)methyl]amine." *J. Am. Chem. Soc.* **2018**, 140 (4), pp 1525 © 2018 American Chemical Society

4.3.2 Introduction

Atom transfer radical polymerization (ATRP) has gained widespread use due to its easy setup, tolerance to functional groups, mild conditions and wide range of applications.^{52, 100-102} Since its inception in 1995, when stoichiometric amounts of air-sensitive Cu¹ relative to alkyl halide initiator were used,¹⁰³ many advances have been made to improve the efficiency of this polymerization system.¹⁰⁴ The development of new operating techniques such as initiators for continuous activator regeneration (ICAR) ATRP¹⁰⁵⁻¹⁰⁶, activators regenerated by electron transfer (ARGET) ATRP¹⁰⁷⁻¹⁰⁹, supplemental activators and reducing agents (SARA) ATRP¹¹⁰ as well as photoATRP¹¹¹⁻¹¹⁵, *e*ATRP¹¹⁶ and most recently mechanoATRP¹¹⁷⁻¹¹⁸ have allowed polymerizations to be conducted using ppm levels of catalyst relative to monomer.

As shown in **Scheme 5.3**, the control in ATRP is achieved via a reversible redox equilibrium between a L/Cu^{1/II} couple where L signifies a multidentate nitrogen-based ligand. L/Cu¹ activates a (macro)alkyl halide chain end, resulting in the L/Cu^{II}-X deactivator and a carbon-based radical,¹¹⁹ which propagates by adding to monomer before being trapped by the L/Cu^{II}-X deactivator, regenerating the L/Cu^I species and the dormant polymer chain.⁵² To control the polymerization,¹²⁰ this equilibrium (K_{ATRP}) should lie on the dormant side to diminish the concentration of radicals and retain chain-end functionality (CEF). K_{ATRP} can be expressed as the ratio of activation (k_a) to deactivation (k_d) rate constants and can be tuned over 8-orders of magnitude¹²¹ based on temperature, pressure, solvent,¹²²⁻¹²³ polymer chain-end,¹²⁴ and choice of catalyst.¹²¹ In order to reach even lower catalyst loadings or to polymerize less active monomers such as vinyl acetate (VAc),¹²⁵ higher values of K_{ATRP} must be achieved.



Scheme 5.3 Mechanism of ATRP (boxed) and equilibria involving association of ligand (β^m) and halide (β^m_x) to either the Cu^I (m = I) or Cu^{II} (m = II) ion.

One simple way to tune ATRP is by changing the coordination sphere of copper. Over the years, rational ligand design has allowed for the understanding of how the catalyst structure affects reactivity. The activity of the catalyst in ATRP correlates with ligand denticity, nature of the N-donor atom and electron donating ability through the coordinating nitrogen atom(s).¹²⁶ Indeed, a linear correlation between the redox potential ($E_{1/2}$) and In(K_{ATRP}) has been established where a more negative $E_{1/2}$ results in a larger value of K_{ATRP} .¹²⁷ This strong correlation allows for the prediction of new catalysts' activity based solely on their redox potential. The activity of a catalyst can also be further assessed by comparing the stability constants (binding constants), β , of the L/Cu^{II} and L/Cu^{III} complexes since K_{ATRP} scales with the β^{II}/β^{I} ratio, as shown in **Scheme 5.3**. While both β^{II} and β^{I} should be large, $\beta^{II} > \beta^{I}$ in order to provide a thermodynamic driving force for alkyl halide activation.¹²⁷ Indeed, β^{I} values are rather constant but β^{I} values change significantly with the ligand structures.¹²⁸

To date, the most active ATRP catalyst has used the ligand tris[((4-methoxy-2,5dimethyl)-2-pyridyl)methyl]amine (TPMA*³) which has three electron donating groups on each pyridine ring.¹²⁹⁻¹³⁰ This led to a catalyst that is 5 million times more active than the seminal catalytic system employing the 2,2'-bipyridine (bpy) ligand and 1000 times more active than the commonly used tris(pyridylmethyl)amine (TPMA) ligand (**Scheme 2**). According to Hammett parameters, using the even more electron donating dimethyl amino (–NMe₂) group should further increase the catalyst activity as already observed for bpy derivatives.¹³¹ Therefore, we have considered using tris[(4-dimethylamino-2-pyridyl)methyl]amine (TPMA^{NMe2}) ligand as shown in **Scheme 5.4**.¹³²⁻¹³⁴ This ligand was previously reported by Karlin *et al* where the [Cu^I(TPMA^{NMe2})]⁺ complex was used as an oxygen activation catalyst to mimic various copper containing enzymes¹³⁵⁻¹³⁶ such as amine oxdiases,¹³⁷ multicopper oxidases¹³⁸ (MCOs) and tyrosinases¹³⁹ as well as to study this complex's interactions with carbon monoxide.¹⁴⁰ This new Cu-based ATRP catalyst with TPMA^{NMe2}, in both relevant oxidation states, has been characterized in solution and the solid state and utilized in ATRP systems with low catalyst loadings (down to 10 ppm) and was shown to exhibit unprecedented reactivity with alkyl halides.



Scheme 5.4 Structure of the ligands used in this study.

4.3.3 Experimental

General All chemicals were purchased from Sigma Aldrich and used as received unless otherwise noted. Ag⁰ (d = 1.0 mm) wire was purchased from Fisher Scientific (#A11434). 2,2'-Azobis(isobutyronitrile) (AIBN) was purchased from Wako Chemical. Acetonitrile was taken from a solvent distillation apparatus using argon atmosphere and stored in a flame-dried flask over molecular sieves. Methyl acrylate (MA, Sigma Aldrich, 99%) was passed through a column of basic alumina to remove inhibitor prior to use.

Characterization

Size Exclusion Chromatography (SEC): SEC was conducted using a Waters 515 HPLC Pump and Waters 2412 Refractive Index Detector using PSS columns (Styrogel 10^2 , 10^3 , 10^4 , 10^5 Å) in THF as an eluent at a flow rate of 1 mL/min at 35°C. The system was calibrated with 12 linear polystyrene (PSt, $M_n = 376$ -2,570,000) and 12 linear poly(methyl methacrylate) (PMMA, $M_n = 800$ -2,5700,000) standards. Peak deconvolution was conducted using OriginPro 7.0.

NMR: Monomer conversion was measured using ¹H NMR spectroscopy using a Bruker Avance 500 or 300 MHz spectrometer at room temperature. Variable temperature NMR was conducted on a Bruker Avance 400 MHz NMR spectrometer.

UV-Vis-NIR: Characterization of Cu^{\parallel} complexes were conducted on a Varian Cary 5000 UV/Vis/NIR spectrometer.

EPR: Single crystals from the batch used for the X-ray structural analysis were dissolved in MeCN. The measurement was carried out at 120 K on a Elexsys E500 Bruker spectrometer (X-band) equipped with both a frequencemeter and gaussmeter.

Electrochemistry: Electrochemical measurements were conducted on a Gamry Ref 600 potentiostat in a three-electrode cell. The counter electrode was a Pt ring, the working electrode a GC disk (3 mM diameter, Metrohm), and the reference electrode was Ag|Ag|| 0.1 M *n*-Bu₄NI in DMF. The GC electrode surface was cleaned by polishing with a 2.5 mm diamond paste prior to each experiment, followed by ultrasonically rinsing in ethanol for 5 min. The GC working electrode was connected to a rotating disk electrode (RDE, Metrhom Autolab).

X-Ray Diffraction A single crystal of the [Cu^{II}(TPMA^{NMe2})Br][Br] compound was mounted under inert perfluoropolyether at the tip of a glass fiber and cooled in the cryostream of a Rigaku Oxford-Diffraction Xcalibur Eos Gemini diffractometer.

The structure was solved by using the integrated space-group and crystal structure determination SHELXt software¹⁴¹ and refined by least-squares procedures on F^2 using SHELXL-2014¹⁴². The

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asymmetric unit contains the Cu complex, the counter anion Br and one and a half water solvent molecules. The difference Fourier syntheses revealed weak residual electron densities which could be filled by rather diffuse water molecules. There are 8 cavities located around Wyckoff position 8a (1/8, 1/8, 1/8) with site symmetry 222. It was difficult to model their positions and distribution reliably. Therefore, the SQUEEZE function¹⁴³ of PLATON was used to eliminate the contribution of the electron density in the solvent region. Each cavity of about 153 Å³ contains roughly 22 electrons which is twice what could be expected for a water molecule. However, it is well known that the count of electrons for disordered water molecule could be overestimated. The solvent-free model was employed in the final refinement. Due to the omission of the water molecules from the model, it was not possible to fully analyse the hydrogen-bonding interactions. All H atoms attached to carbon atoms were introduced in the calculation at idealised positions and treated as riding models. The H atoms attached to solvent water molecules were located on difference Fourier syntheses and their coordinates were refined using restraints whereas their isotropic thermal parameters were restrained to 1.5 the value of the equivalent thermal parameter of the O atom to which they are attached. The drawing of the molecules was realized with the help of ORTEP32.¹⁴⁴ Crystal data and refinement parameters are shown in Tables 1. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1579962. Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Procedures

Synthesis of TPMA^{NMe2}

General Consideration: A slightly modified synthetic route taken from reference ¹³² was used in this study. High pressure tubes were purchased from ACE glass (ACE Glass #8648-77) with special chemical resistant O-Ring (ACE glass # 7855-813). 2-Hydroxymethyl-4-chloropyridine (1) was purchased from Frontier Scientific (#C10194). Reactions involving high pressure tubes can be dangerous, always use a blast shield and proper personal protection equipment.



Scheme 5.5 Synthetic pathway for TPMA^{NMe2}.

2-Hydroxymethyl-4-dimethylaminopyridine¹³³ (2): 2.3 g (16.02 mmol) of 2-hydroxymethyl-4chloropyride (1) and 6.53 g (80.1 mmol) of dimethyl amine hydrochloride were added to a 20 mL pressure tube equipped with a stir bar to which 5 mL of ultra-high purity water was added. 3.0 g (75 mmol) of NaOH was quickly added to the pressure tube which was quickly sealed. The reaction mixture was stirred at 150°C for 24 hours. After cooling to room temperature, the yellow-brown reaction mixture was diluted with 30 mL of water and extracted with DCM (4 x 50 mL). The organic layers were combined and dried over Na₂SO₄ and filtered. The solvent was evaporated and placed on a vacuum pump overnight. The brown solid was recrystallized from hot acetone to give a brown crystalline product in an obtained yield of 64%. ¹H NMR (300 MHz, CDCl₃): δ 3.02 (6H, s), 3.92 (1H, s, br), 4.67 (2H, s), 6.5 (1H, d, *J* = 6.0 Hz), 6.7 (1H, s), 8.13 (1H, d, *J* = 6.0 Hz). 2-Chloromethyl-4-dimethylaminopyridine Hydrochloride (**3**): 2.7 g (17.7 mmol) of 2hydroxymethyl-4-dimethylaminopyridine (**2**) was dissolved in 150 mL of DCM. 2.8 g (23 mmol) of thionyl chloride was slowly added. Upon complete addition of thionyl chloride, the reaction mixture was stirred at room temperature for 2 hours and then quenched with a saturated aqueous solution of Na₂CO₃. The organic layer was collected and the aqueous layer was extracted with DCM (4 x 50 mL). The organic layers were combined and dried over Na₂SO₄ and filtered. The DCM was evaporated off and the dark brown product was placed under vacuum overnight to afford a dark brown liquid. The crude product solidified upon standing and was used without further purification. Upon ¹H NMR in *d*₃-MeCN, two species were present which were identified as **3** and **3**•HCl in a 2:1 ratio, respectively. Isolated product gave 2.8 g (90%) of product. ¹H NMR (**3**, 300 MHz, *d*₃-MeCN): δ 3.05 (6H, s), 4.65 (2H, s), 6.62 (1H, dd, *J* = 6.0 Hz), 6.80 (1H, d, *J* = 3.0 Hz), 8.11 (1H, d, *J* = 6.0); (**3**•HCl, 300 MHz, *d*₃-MeCN): δ 3.30 (6H, s), 5.83 (2H, s), 6.91 (1H, dd, *J* = 8.0 Hz), 7.32 (1H, d, *J* = 4.0 Hz), 8.41 (1H, d, *J* = 8.0).

2-Chloromethyl-4-chloropyridine (4): 3.2 g (22 mmol) of 2-hydroxymethyl-4-chloropyridine (1) was dissolved in 200 mL of DCM. 3.4 g (29 mmol) of thionyl chloride was slowly added to the reaction mixture under nitrogen atmosphere and was stirred for 12 hours at room temperature and then quenched with a saturated aqueous solution of Na₂CO₃. The organic layer was collected and the aqueous layer was extracted with DCM (4 x 50 mL). The organic layers were combined and dried over Na₂SO₄ and filtered. The DCM was evaporated off to give a dark brown liquid in 93% yield which was used without further purification. ¹H NMR (300 MHz, CDCl₃): δ 4.71 (2H, s), 7.24 (1H, d, *J* = 6.0 Hz), 7.47 (1H, s), 8.47 (1H, d, *J* = 6.0).

*2-Phthalimidomethyl-4-chloropyridine*¹³¹ (**5**): 3.55 g of 2-chloromethyl-4-chloropyridine (21.9 mmol) (**4**) was dissolved in 75 mL of anhydrous DMF. 4.05 g (21.9 mmol) of potassium phthalimide was added and the reaction was stirred for 5 minutes. 12.67 g (92 mmol) of K₂CO₃ was then added and the reaction was stirred overnight at 85°C. The reaction mixture was

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cooled and a saturated solution of NaHCO₃ was added which resulted in precipitation of a white solid. The solid was filtered, dissolved in DCM, dried over Na₂SO₄ and filtered. The white solid was recrystallized from hot ethanol and resulted in white crystals which were further washed with cold ethanol. The resulting solid was dried overnight under vacuum resulting in 83% yield. ¹H NMR (300 MHz, CDCl₃): δ 4.98 (2H, s), 7.18 (1H, d, *J* = 6.0 Hz), 7.28 (1H, s), 7.75 (2H, dd, *J* = 6.0, *J'* = 3.0),), 7.85 (2H, dd, *J* = 6.0, *J'* = 3.0),), 8.45 (1H, d, *J* = 6.0).

2-Aminomethyl-4-dimethylpyridine (**6**): 3.6 g (13 mmol) of 2-phthalimidomethyl-4chloropyridine (**5**) and 6.5 g (80 mmol) of dimethylamine HCl were added to a 20 mL pressure tube equipped with a stir bar. 10 mL of ultra-high purity water was added to which 3.2 g (80 mmol) of NaOH was added and quickly the tube was quickly closed. The mixture was stirred at 155°C for 24 hours. The resulting mixture was diluted with 50 mL of 1M NaOH and stirred for 2 hours and then extracted with DCM (4 x 50 mL). The organic layers were combined dried over Na₂SO₄, filtered and evaporated giving a pale-yellow oil which was placed under vacuum overnight to give **6** in 42% yield and was used without further purification. ¹H NMR (300 MHz, CDCl₃): δ 2.85 (2H, s, br), 3.02 (6H, s), 3.88 (2H, s), 6.38 (1H, dd, J = 6.0 Hz, J' = 3.0 Hz), 6.48 (1H, d, J = 3.0), 8.16 (1H, d, J = 6.0).

Tris[(4-dimethylamino-2-pyridyl)methyl]amine (TPMA^{NMe2}): 1.96 g (11.5 mmol) of 2chloromethyl-4-dimethyl-pyridine HCl (**3**) and 0.76 g (5 mmol) of 2-aminomethyl-4dimethylaminopyridine (**6**) were added to a flask equipped with a stir bar. 10 mL of DCM and 15 mL of 1 M NaOH was added and the reaction mixture was stirred at 60°C for 4 days. Upon cooling, the organic layer was collected and the aqueous layer was extracted with DCM (4 x 50 mL), dried over Na₂SO₄ and filtered. The solvent was evaporated off resulting in a dark green/brown mixture. Cold acetonitrile was slowly added to this mixture resulting in a light yellow solid. The solid was collected and washed multiple times with cold acetonitrile resulting in the final product, TPMA^{NMe2} in 28% yield and confirmed to be pure by NMR and ESI-MS (**Figure S1-3**). ¹H NMR (300 MHz, CDCl₃): δ 3.00 (18H, s, br), 3.86 (6H, s), 6.38 (3H, d, *J* = 6 Hz), 7.01 (3H, s), 6.48 (1H, d, J = 3.0), 8.16 (3H, d, J = 3.0). ¹H NMR (300 MHz, CDCl₃). High-resolution ESI-MS, m/z calculated for C₂₄H₃₄N₇⁺ 420.28, found 420.29.

Synthesis of [Cu^{II}(TPMA^{NMe2})Br][Br] In a vial, 20 mg of TPMA^{NMe2} (0.047 mmol) and 10.6 mg of CuBr₂ (0.047 mmol) were mixed in 10 mL of MeCN. The solution was mixed for one hour at room temperature. The complexed was precipitated by addition of diethyl ether and the precipitate was collected and dried on a vacuum line overnight yielding [Cu^{II}(TPMA^{NMe2})Br][Br] in 70% yield (21.2 mg). The complex was dissolved in MeCN and slowly diffused with ether to give crystals suitable for X-ray diffraction.

ICAR ATRP Polymerization To a 20 mL vial was added 0.173 mmol (36.6 mg) of ethyl bromoisobutyrate (EBiB), the allotted amount of a 5 mM solution of $[Cu^{II}(TPMA^{NMe2})Br][Br]$ (0.0035 – 0.00035 mmol; 690 – 69 µL) in DMF, 0.0276 mol (4 mL) of methyl acrylate, 0.034 mmol (5.7 mg) of AIBN and 2.2 mL of dry anisole. The mixture was transferred to a Schlenk flask and subjected to three freeze pump thaw cycles. The reaction was placed in an oil bath at 60°C to begin the reaction. Samples were taken periodically and analyzed by NMR for conversion and GPC for molecular weights.

Ag⁰ ARGET ATRP Polymerization To a 20 mL vial was added 0.173 mmol (36.6 mg) of ethyl bromoisobutyrate (EBiB), the allotted amount of a 5 mM solution of $[Cu^{II}(TPMA^{NMe2})Br][Br]$ (0.0035 – 0.00035 mmol; 690 – 69 µL) in DMF, 0.034 mol (3 mL) of methyl acrylate and 3 mL of dry DMF. This mixture was transferred to a Schlenk flask and subjected to 3 freeze pump thaw cycles. In another flask, 10 cm of Ag⁰ wire (d = 0.1 cm; SA/V = 3.15 cm⁻¹) was placed under vacuum and purged with nitrogen 3 times. Using an air-tight syringe, the solution in the first flask was transferred to the flask containing the Ag⁰ wire which was placed in an oil bath at 50°C. Samples were taken periodically and analyzed by NMR for conversion and GPC for molecular weights.

5.3.4 Results and Discussion

TPMA^{NMe2} was prepared by a procedure slightly modified from that used by Karlin *et al*¹³² (**Scheme 5.5**). The synthesis of 2-hydroxymethyl-4-dimethylaminopyridine (**2**; **Scheme 5.5**) was conducted as previously published by Comba *et al*.¹³³ The synthesis of 2phthalimidomethyl-4-chloropyridine (**5**; **Scheme 5.5**) was conducted as previously published by our group.¹²⁹ 2-Aminomethyl-4-dimethylpyridine (**6**; **Scheme 5.5**) was synthesized directly from a basic workup of 2-phthalimidomethyl-4-dimethylaminopyridine. It should be noted that it is very important to use chemical resistant O-Ring (ACE glass # 7855-813) for reactions using high pressure tubes. The ligand has been characterized by ¹H/¹³C NMR and ESI-MS which confirmed the predicted structure.

5.3.4.1 Variable Temperature NMR of Cu¹ complexes

It has been previously shown that L/Cu¹ complexes with multidentate pyridine-based ligands can undergo fast ligand exchange in the presence of excess ligand relative to Cu¹.¹⁴⁵ The solution prepared by addition of TPMA^{NMe2} to CuBr was studied by variable temperature NMR, as shown in **Figure 5.11**.



Figure 5.11 Variable temperature ¹H NMR of the aromatic region of the free TPMA^{NMe2} ligand and its CuBr complex at the molar ratio $[CuBr]_0$:[TPMA^{NMe2}]₀ = 1:3 in d_6 -acetone.

Upon reacting equimolar amounts of TPMA^{NMe2} and CuBr in d_6 -acetone, the reaction initially turned to a pale-yellow color, common for Cu¹ complexes coordinated by pyridinic ligands. However, upon stirring, the reaction mixture turned green along with a dark precipitate indicative that the [Cu¹(TPMA^{NMe2})Br] complex underwent disproportionation to [Cu^{II}(TPMA^{NMe2})Br][Br] and Cu⁰ + TPMA^{NMe2}. Typically, unsubstituted TPMA shows little to no disproportionation. The position of the disproportionation equilibrium, $K_{Disp,LCu}$, depends on the relative stability of LCu^{II} compared LCu^I. Since TPMA^{NMe2} stabilizes Cu^{II} much more than TPMA, disproportionation is possible. This is especially true in a disproportionating solvent such as acetone, which is polar and coordinates weakly to Cu^{1,127} To suppress disproportionation and reform the [Cu¹(TPMA^{NMe2})Br] complex, 2 additional equivalents of TPMA^{NMe2} were added.¹⁴⁶ Indeed, upon further stirring for 30 minutes, the reaction regained its yellow color and the Cu⁰ particles were no longer visible.

The ¹H NMR spectrum shows significant broadening of the aromatic peaks upon complexation, which has been previously been shown for other Cu¹ complexes.¹⁴⁷⁻¹⁴⁹ This broadening indicates a fast exchange between free and coordinated ligand. Upon decreasing the temperature to 240 K, the peaks attributed to coordinated and uncoordinated ligand began to resolve due to the slower rate of exchange. At 180 K, two distinct peaks were observed at 8.05 and 8.5 ppm, attributed to free and coordinated ligand, respectively.^{145, 150-153} The peaks became narrower at lower temperature but were broader than those of previously published TPMA-based Cu¹ complexes at 180 K. This could be due to the presence of small amounts of paramagnetic Cu^{II} formed from disproportionation and plausible self-exchange between the Cu^{III} and Cu¹ complexes. This cannot be avoided due to the disproportionating nature of acetone and the highly reactive [Cu¹(TPMA^{NMe2})]⁺ complex. Although the variable temperature NMR spectra indicate a significant amount of ligand exchange, the total amount of uncoordinated Cu is extremely low due to the large stability constants, β^I, as has been previously observed for substituted TPMA ligands.¹⁴⁵

5.3.4.2 Structural Studies of Cu^{II} Deactivator Complex

The [Cu^{II}(TPMA^{NMe2})Br]⁺ complex was synthesized and crystallized as reported in the Supporting Information. The resulting molecular structure is presented in **Figure 5.12** with selected bond distances and angles summarized in **Table 5.7**.



Figure 5.12 Molecular structure of [Cu^{II}(TPMA^{NMe2})Br][Br] shown (left) with 50% probability displacement ellipsoids. H atoms, counter Br⁻ anion and solvent molecules have been omitted for clarity.

The [Cu^{II}(TPMA^{NMe2})Br]⁺ cation is in a slightly distorted trigonal bipyramidal geometry, indicated by a structural parameter $\tau = 0.89$ ($\tau = 1.00$ for trigonal bipyramidal). Coordination of the tetradentate ligand occurs through three substituted pyridinic nitrogen atoms in the equatorial plane (N_{eq}) and a central anchoring aliphatic nitrogen in the axial plane (N_{ax}). The N_{ax^-} $Cu-N_{eq}$ bond angles are all slightly smaller than 90° which is consistent with a previously reported cupric aqua adduct,¹³⁴ [Cu^{II}(TPMA^{NMe2})(H₂O)]²⁺. The similar N_{ax}-Cu-N_{eq} angles between the two complexes, although with differently sized axial ligands (Br⁻ vs. H₂O), suggests these deviations from 90° are most likely due to the natural bite of the ligand as opposed to steric repulsion from the axial ligand. The previously reported¹⁴⁰ cuprous carbonyl adduct, [Cu¹(TPMA^{NMe2})(CO)]⁺, showed a Cu¹-N_{ax} bond distance of 2.446 Å which is significantly elongated compared to the Cu^{II}-N_{ax} bond distance of 2.05 Å presented in this study. Although the two complexes cannot be directly compared due to the difference in axial ligand, Cu-Nax bond elongation upon reduction of Cu^{II} to Cu^I has been observed in other TPMA-based complexes.¹⁵⁴ This is attributed to Cu^{II} preferring a 5-coordinate environment while the reduced Cu¹ ion prefers 4-coordinate geometries.¹⁵⁵ Thus, the Cu¹-N_{ax} bond is elongated to a non-bonding distance forming a distorted tetrahedral geometry. Furthermore, the crystal structure is stabilized by $\pi - \pi$ stacking interactions between substituted pyridine rings as well as weak C-H---Br (2.84 Å) interactions.

Table 5.7 Selected Bond Distances and Angles of Relevance for L/Cu^{II}-Br Deactivator Species^a

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	[Cu ^{ll} (TPMA)Br][Br] ^b	[Cu ^{ll} (TPMA* ³)Br][Br] ^c	[Cu ^{ll} (TPMA ^{NMe2})Br][Br] ^d
Cu-N1 _{ax}	2.040(3)	2.028(3)	2.047(3)
Cu-N2 _{eq}	2.073(15)	2.059(3)	2.051(2)
Cu-N3 _{eq}	2.073(15)	2.149(3)	2.108(3)
Cu-N4 _{eq}	2.073(15)	2.044(3)	2.046(3)
Cu-Br₁	2.384(6)	2.3740(5)	2.3898(6)
N_1 -Cu- N_2	80.86(5)	81.07(12)	80.59(10)
N ₁ -Cu-N ₃	80.86(5)	82.81(12)	80.60(10)
N ₁ -Cu-N ₄	80.86(5)	79.82(11)	81.42(10)
N ₂ -Cu-N ₃	117.53(3)	132.39(12)	126.78(10)
N ₂ -Cu-N ₄	117.53(3)	115.63(12)	116.34(10)
N ₃ -Cu-N ₄	117.53(3)	104.99(12)	109.40(10)
N_1 -Cu-Br $_1$	180.00(5)	178.33(9)	179.89(9)
N_2 -Cu-Br ₁	99.14(5)	100.99(8)	98.59(8)
N ₃ -Cu-Br ₁	99.14(5)	98.35(8)	99.49(7)
N ₄ -Cu-Br ₁	99.14(5)	97.27(8)	99.32(7)
τ ^e	1.0	0.77	0.89

^aBond lengths are given in angstroms (Å) and angles in degrees (°). ^bFrom Ref 51. ^cFrom Ref 42. ^dThis work. ^e τ parameter is calculated as $\tau = (\phi_1 - \phi_2)/60$, where ϕ_1 and ϕ_2 are the largest (N₁-Cu-Br₁) and second largest (N₂-Cu-N₃) bond angles, $\tau = 1$ (trigonal bipyramidal geometry), and $\tau = 0$ (square pyramidal geometry).

5.3.4.3 Solution Studies of Cu^{II} Complexes

The UV-Vis-NIR spectra were obtained using CuBr₂ to form [Cu^{II}(TPMA^{NMe2})Br]⁺ and also Cu(OTf)₂ to form [Cu^{II}(TPMA^{NMe2})(MeCN)]²⁺, since the OTf⁻ anion coordinates very weakly to the Cu^{II} center in solution. As shown in **Figure 5.13A**, two d→d transitions are observed in the NIR and visible region at 1038 and 776 nm for the [Cu^{II}(TPMA^{NMe2})Br]⁺ and 980 and 725 nm for the [Cu^{II}(TPMA^{NMe2})(MeCN)]²⁺ complex, respectively. These two transitions are typical of d⁹ Cu^{II} possessing trigonal bipyramidal geometry and are attributed to d_{xz} ≈ d_{yz} → d_{z2} and to d_{x2-y2} ≈ d_{xy} → d_{z2}.¹⁵⁶⁻¹⁵⁷ A ligand to metal charge transfer (LMCT) band is apparent in both complexes, centered around 425 and 395 nm for [Cu^{II}(TPMA^{NMe2})Br]⁺ and [Cu^{II}(TPMA^{NMe2})(MeCN)]²⁺, respectively. The absorption spectra of these two complexes are consistent with previously published results for many ATRP deactivator complexes presenting trigonal bipyramidal geometry.^{145, 158}

A sample of $[Cu^{II}(TPMA^{NMe2})Br][Br]$ crystals was also investigated, after dissolution into a dichloromethane (DCM)/toluene mixture, by X-Band EPR spectroscopy at 120 K as shown in **Figure 5.13B**. The spectrum revealed a pattern and g/A parameters rather close to those of the related $[Cu^{II}(TPMA)Br]^+$ complex.¹⁵⁹ On the other hand, a rather uninformative cubit tensor at g = 2.123 and a linewidth of ca. 110 G without observable copper hyperfine coupling was observed in pure MeCN or pure DCM.



Figure 5.13 A) Absorption spectra of the $[Cu^{II}(TPMA^{NMe2})Br]^+$ deactivator complex (red) and $[Cu^{II}(TPMA^{NMe2})(MeCN)]^{2+}$ complex (blue) in MeCN. $[CuX_2]_0 = 1 \text{ mM} (X = Br^- \text{ or OTf}^-) \text{ and } B)$ Experimental (red) and simulated (green) X-band EPR spectra of the $[Cu^{II}(TPMA^{NMe2})Br][Br]$ complex in a 1:1 mixture of DCM:toluene recorded at 120K ($g_1 = 2.173$, $A_1 = 255.3 \text{ MHz}$, $g_2 = 2.198$, $A_2 = 336.5 \text{ MHz}$, $g_3 = 1.95$, $A_3 = 260.1 \text{ MHz}$).

5.3.4.4 Thermodynamic Parameters

As noted above, one method to determine catalyst activity in ATRP is by measuring the stability constants, β^{I} and β^{II} , for the L/Cu^I and L/Cu^{II} complexes.¹⁴⁵ The redox potential of the [Cu(L)]²⁺ complex gives the β^{II}/β^{I} ratio as shown in **Eq 5.6**, where $E_{Cu^{2+}/Cu^{+}}^{\circ}$ and $E_{LCu^{II}/LCu^{I}}^{\circ}$ represent the standard redox potential of solvated Cu and the ligated Cu species, respectively.⁷⁶ Furthermore, according to **Eq 5.7**, it is also possible to obtain the ratio $\beta^{II}_{X,app}/\beta^{I}_{X,app}$ electrochemically, where $\beta^{II}_{X,app}$ and $\beta^{I}_{X,app}$ are the apparent equilibrium constants of halide association to ligated copper, L/Cu^{II}–X or L/Cu^{II}–X, respectively.¹⁴⁵ $\beta^{II}_{X,app}$ considers that addition

of X⁻ do not change the original β^{I} and β^{II} values. For efficient deactivation, β_{X}^{II} values must be high. Values of β_{X}^{I} should be low, since the [Cu^I(L)Br] is an inefficient activator in ATRP.¹⁶⁰

$$\ln \frac{\beta^{\rm I}}{\beta^{\rm I}} = \frac{F}{RT} \left(E^{\rm o}_{{\rm Cu}^{2+}/{\rm Cu}^+} - E^{\rm o}_{{\rm LCu}^{\rm I}/{\rm LCu}^{\rm I}} \right)$$
(Eq. 5.6)

$$\ln \frac{\beta_{X,app}^{II}}{\beta_{X,app}^{I}} = \frac{F}{RT} \left(E_{LCu^{II}/LCu^{I}}^{o} - E_{LCu^{II}-X/LCu^{I}-X}^{o} \right)$$
(Eq. 5.7)

As shown in **Figure 5.14**, both the [Cu(TPMA^{NMe2})(MeCN)]²⁺ and [Cu(TPMA^{NMe2})Br]⁺ complexes exhibit a reversible redox wave at $E_{1/2}$ = -302 mV and -554 mV vs. SCE, respectively, representing the most reducing ATRP catalysts to date. Separation between the anodic and cathodic peaks is ca. 60 mV at a scan rate of 0.2 V s⁻¹, indicating good reversibility. Increasing the scan rate results in the expected increase in current; peak separation also increases, revealing a quasi-reversible nature of the electron transfer. This shows that the TPMA^{NMe2} ligand is able to sufficiently stabilize the electrochemically generated Cu¹, and indicates that these complexes have small rearrangement energies between the Cu^{1/II} oxidation states. Using **Eq 5.6**, the β^{II}/β^{I} ratio was calculated as 1.1 x 10²³ (**Table 5.8**) which is 1500 times larger than the previously reported value for the tris(2-dimethylaminoethyl)amine (Me₆TREN) complex in MeCN.⁷⁶ This large increase may be either due to a more stabilized Cu^{II} or a destabilized Cu^I. However, it was previously shown¹⁴⁵ that stability constants for Cu^I were similar using variously substituted pyridine-based ligands in DMF.¹²⁸

Upon introduction of coordinating bromide anions, the complex $[Cu(TPMA^{NMe2})Br]^+$ is formed, and the redox potential shifts by -252 mV to give $E_{1/2} = -554$ mV vs. SCE. K_{ATRP} increases roughly one order of magnitude for every 59 mV shift of redox potential,¹²⁴ indicating K_{ATRP} should be approximately 140,000 times greater relative to the unsubstituted TPMA-based catalyst, which has $E_{1/2} = -240$ mV vs. SCE,¹⁴⁸ and >10⁹ times greater than the original bpy catalyst, which has $E_{1/2} = +30$ mV vs. SCE.¹⁶¹ Furthermore, using **Eq. 5.7**, the $\beta_{X,app}^{II}/\beta_{X,app}^{I}$ ratio was calculated to be 1.8 x 10⁴, similar to that of other TPMA-based ligands in MeCN.¹⁴⁵



Figure 5.14 Cyclic voltammograms of (A) 1 mM $[Cu(TPMA^{NMe2})(MeCN)]^{2+}$ and (B) 1 mM $[Cu(TPMA^{NMe2})Br]^+ + 20 \text{ mM Et}_4NBr$ in dry MeCN at different scan rates using Et_4NBF4 as a supporting electrolyte and glassy carbon working electrode; $[L/Cu^{II}]_0 = 1 \text{ mM}$.

$$K_{\text{disp,LCu}} = \frac{[\text{LCu}^{\text{II}}]_{\text{eq}}[\text{L}]_{\text{eq}}}{[\text{LCu}^{\text{I}}]_{\text{eq}}^{2}}$$
(Eq. 5.8)
$$\frac{\beta^{\text{II}}}{(\beta^{\text{I}})^{2}} = \frac{K_{\text{disp,LCu}}}{K_{\text{disp,Cu}}}$$
(Eq. 5.9)

Since cyclic voltammetry can only provide the $\beta^{\parallel}/\beta^{l}$ ratio, further analysis was carried out to estimate the individual β values. We previously reported¹⁴⁵ on the disproportionation equilibrium allowing for the calculation of $\beta^{\parallel}/(\beta^{l})^{2}$, as shown in **Eq's 5.8 & 5.9**, where $K_{disp,LCu}$ and $K_{disp,Cu}$ are the equilibrium constants of disproportionation for ligated and solvated copper, respectively.¹⁴⁵ The determination of the disproportionation equilibrium, when coupled with electrochemical measurements, allows for the calculation of individual stability constants.

Analysis of $K_{disp,LCu}$ is difficult in MeCN due to the highly comproportionating nature of this solvent, i.e. very small values of $K_{disp,.}$ In fact, values of $K_{disp,Cu}$ for the solvated Cu^I complex in acetonitrile have previously been estimated on the order of 10^{-21} .¹⁶² Therefore, it was only possible to estimate a limit of $K_{disp,LCu} < 1.0 \times 10^{-4}$. Nonetheless, using this value the lower limits of β^{II} and β^{I} as 3.5 x 10^{29} and 1.9 x 10^{6} were estimated, respectively. These values, although likely underestimated due to uncertainty of $K_{disp,LCu}$, are in good agreement with previously

reported values for other ATRP catalysts.^{76, 145} All thermodynamic parameters obtained in this study, as well as for TPMA and TPMA^{*3}-based complexes, are summarized in **Table 5.8.** It should be noted that values of β^{I} are significantly limited by unattainable values of $K_{disp,LCu}$ in MeCN.

	ΤΡΜΑ	TPMA ^{*3}	TPMA ^{NMe2}
^a <i>E</i> _{1/2,Cu}	1.06	1.06	1.06
<i>E</i> _{1/2,LCu}	-0.030 ^c	-0.177 ^b	-0.302
E _{1/2,LCuBr}	-0.240	-0.420	-0.554
E _{1/2,Cu} -E _{1/2,LCu}	1.090	1.237	1.362
E _{1/2,LCu} -E _{1/2,LCuBr}	0.210	0.243	0.252
^d K _{Disp,Cu}	1.0 x 10 ⁻²¹	1.0 x 10 ⁻²¹	1.0 x 10 ⁻²¹
^е К _{Disp,LCu}	<1.0 x 10 ⁻⁴	<1.0 x 10 ⁻⁴	<1.0 x 10 ⁻⁴
β"/β'	2.7 x 10 ¹⁸	8.1 x 10 ²⁰	1.1 x 10 ²³
β /(β) ²	<1.0x 10 ¹⁷	<1.0 x 10 ¹⁷	<1.0 x 10 ¹⁷
β"	>7.1 x 10 ¹⁹	>6.6 x 10 ²⁴	>1.1 x 10 ²⁹
β ^ı	>2.7 x 10 ¹	>8.1 x 10 ³	>1.1 x 10 ⁶
$\beta_{X,app}^{II}/\beta_{X,app}^{I}$	5.3 x 10 ³	1.3 x 10 ⁴	5.3 x 10 ³
^f K _{ATRP}	≈10 ⁻⁵	≈10 ⁻³	≈10 ⁻¹
k _a (MBrP)	2.2 x 10 ^{2g}	8.4 x 10 ^{3 h}	1.1 x 10 ⁶

Table 5.8 Thermodynamic Properties of the $[Cu(L)(MeCN)]^{2+}$ and $[Cu(L)Br]^{+}$ Complexes in MeCN (L = TPMA, TPMA^{*3}, TPMA^{NMe2})

Redox potentials in V vs. SCE; k_a in M⁻¹s⁻¹. ^aTaken from literature¹⁶³. ^bTaken from Ref¹⁴⁵, ^cTaken from Ref¹⁴⁸ using the conversion factor $E^o(Fc^+/Fc) = 0.390$ V vs. SCE. ^dFrom Ref¹⁶² ^eExperimental limiting value of $K_{\text{Disp,LCu}}$. ^fEstimated for acrylates based on value of $E_{1/2,\text{LCuBr}}$ and the trend of $E_{1/2}$ vs. K_{ATRP}^{145} ^gFrom Ref¹⁶⁴ ^hFrom Ref¹²⁹.

5.3.4.5 Assessment of ATRP Activity

The ability of L/Cu¹ complexes to activate (macro)alkyl halide bonds is paramount to the success of an ATRP system. The bond dissociation free energy (BDFE) of a C-X (X = Cl or Br) has been correlated to values of K_{ATRP} via DFT.^{119, 125} Generally, the activation reaction is faster (larger values of k_a) if the resulting radical is more stabilized either through steric or resonance effects.

Electrochemistry is a useful tool in determining kinetic parameters in ATRP. The use of a rotating disk electrode allowed for measurement of k_a and K_{ATRP} for systems with moderately

high activity ($k_a < 10^4$). For more active processes such as in aqueous media¹⁶⁵ and systems involving highly active catalysts¹⁶⁶, cyclic voltammetry of copper complexes under catalytic conditions (in the presence of RX) can be used to obtain k_a .¹⁶⁶⁻¹⁶⁸ k_a is obtained from the current enhancement or degree of catalysis defined as $I_p/I_{p,0}$, where I_p and $I_{p,0}$ stand for the cathodic peak current of the catalyst measured in the presence and absence of initiator, respectively (**Figure 5.15B**). The procedure is described in the supporting information.



Figure 5.15 Cyclic voltammograms of $[Cu(TPMA^{NMe2})Br]^+$ in the presence of methyl 2bromopropionate (MBrP; acrylate mimic) at (A) varying scan rates and (B) different $[MBrP]_0$ in MeCN at scan rate 0.2 V s⁻¹ at room temperature. In (A) current was normalized by dividing by square root of the scan rate. $[MBrP]_0:[TPMA^{NMe2}]_0:[CuBr_2]_0:[TEMPO]_0 = 0-10:1:1:10; [CuBr_2]_0 = 1$ mM.

As shown in **Figure 5.15A**, cyclic voltammetry of the [Cu(TPMA^{NMe2})Br]⁺ complex was conducted in the presence of methyl 2-bromopropionate (MBrP) and TEMPO. Here, MBrP acted as a small molecule model of acrylate chain-end, while TEMPO was used as a radical trap to prevent the deactivation reaction. The dramatic increase in $I_p/I_{p,0}$, as the scan rate decreased, is consistent with previous reports.^{166, 169} The absence of an oxidation peak indicates that the electrochemically generated Cu¹ was completely consumed in the activation of MBrP, showing the high activity of this catalyst in the activation of acrylates. This gave a rate coefficient of activation, k_a , of $(1.1 \pm 0.4) \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, which is the largest value reported for this initiator with copper-based ATRP catalysts. As will be shown later, values of k_d were calculated to be 5 x 10⁷ $\text{M}^{-1}\text{s}^{-1}$. Thus, K_{ATRP} was estimated on the order of 10⁻¹. This value is consistent with that estimated from the redox potential (**Table 5.8**, $K_{\text{ATRP}} = 1.0 \times 10^{-1}$). This also indicates that studies further indicate that this new complex is the most active copper-based ATRP catalyst to date.

Figure 5.16A shows cyclic voltammetry of [Cu(TPMA^{NMe2})Br]⁺ in the presence of more active ethyl α-bromoisobutyrate (EBiB; methacrylate mimic). With [EBiB]₀ >> [Cu^{II}(TPMA^{NMe2})Br]₀ a large increase of the cathodic current and complete disappearance of the anodic peak was observed, similar to the voltammograms in the presence of the less active MBrP. Cyclic voltammetry under catalytic conditions gave $k_a = (7.2 \pm 2.0) \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ indicating that K_{ATRP} approaches unity. However, at a ratio of [Cu^{II}(TPMA^{NMe2})Br]₀:[EBiB]₀ = 1, an interesting cyclic voltammogram was observed where the cathodic wave splits into two peaks (**Figure 5.16B**). This particular phenomenon is attributed to "total catalysis", which is usually found for extremely efficient catalysts with rate constants for bimolecular reactions > 10⁶ M⁻¹ s⁻¹.¹⁷⁰ Indeed, in this case, only an infinitesimal amount of L/Cu^{II} is required for the complete reduction of RBr, giving a first irreversible peak at $E > E_{1/2,LCuBr}$ due to the very fast catalytic reduction of EBiB. On the other hand, the electrochemical reduction of [Cu(TPMA^{NMe2})Br]⁺ is still reversible since the majority of the catalyst is not involved in the electrocatalytic process. Overall, these results show the extreme reactivity of [Cu(TPMA^{NMe2})Br]⁺, which can be used in ATRP with unprecedentedly low ppm concentrations.



Figure 5.16. Cyclic voltammograms of 1 mM [Cu(TPMA^{NMe2})Br]⁺ in the presence of ethyl α bromoisobutyrate (EBiB; methacrylate mimic) at (A) 5 mM (B) 1 mM concentration in MeCN at room temperature. In (A) current was normalized by dividing by square root of the scan rate. [EBiB]₀:[TPMA^{NMe2}]₀:[CuBr₂]₀:[TEMPO]₀ = 1-5:1:1:10.

5.3.4.6 Low ppm ATRP of Acrylates

To assess the efficiency of the $[Cu(TPMA^{NMe2})Br]^+$ catalyst, various forms of ATRP with activator regeneration were conducted. First, ICAR ATRP was conducted at catalyst loadings ranging from 10 to 100 ppm relative to monomer with 2,2'-azobis(2-isobutyronitrile) (AIBN) as radical initiator.¹⁷¹ As shown in **Figure 5.17**, linear semi-logarithmic plots vs. time were observed at all catalyst loadings. This is consistent with previously established ICAR kinetics with bimolecular termination for which the amount of catalyst does not change the rate of polymerization as shown in **Eq 5.10**, where *f* is initiator efficiency of AIBN, k_{azo} is the decomposition rate coefficient and k_t is the rate coefficient of radical-radical termination.¹⁷²⁻¹⁷³

$$[\mathbf{R}^{\bullet}] = \sqrt{\frac{f k_{azo} [\text{AIBN}]}{k_{t}}}$$
(Eq. 5.10)

$$[\mathbf{R}^{\bullet}] = \frac{f k_{azo} [\text{AIBN}]}{k_{CRT}^{app} [\text{Cu}^{T}]}$$
(Eq. 5.11)

After 4 hours, >90% conversion was achieved for all reactions with a linear increase of molecular weights with conversion, typical of a well-controlled polymerization. While the rate of polymerization was unaffected by the initial amount of catalyst, molecular weight distributions gradually broadened upon decreasing catalyst concentration. This is attributed to decreased rate of deactivation relative to propagation. Although the initial amount of catalyst does not affect the rate of polymerization, at lower catalyst loadings there is less deactivator complex to reversibly trap radicals. This causes more monomer additions per activation cycle and thus a broadening of the molecular weight distribution. (cf. **Eq. 7**)



Figure 5.17 A) Semi-logarithmic plots and B) M_n and D vs. conversion for the ICAR ATRP of *n*butyl acrylate (BA) at different [Cu^{II}(TPMA^{NMe2})Br][Br] loadings under the initial conditions [BA]₀:[EBiB]₀:[L/CuBr₂]₀:[TPMA^{NMe2}]₀:[AIBN]₀ = 160:1:0.016-0.0016:0.2 in anisole at 60 °C; catalyst loadings in ppm vs. monomer; [BA]₀ = 4.5 M.

An interesting point to note is that, according to the kinetic plots presented in **Figure 5.17A** and PREDICI simulations, bimolecular radical termination (RT) should dominate catalytic radical termination (CRT), contrary to previous studies with other ATRP catalysts.¹¹¹ If CRT would significantly contribute to overall termination, the polymerization kinetics would depend on catalyst concentration (**Eq. 5.11**), where k_{CRT}^{app} is the apparent CRT rate coefficient.¹⁷⁴ This is because, as shown in **Scheme 5.6**, CRT requires the coordination of a propagating radical (P_n[•]) to the L/Cu^I complex to form a L/Cu^{II}-P_n organometallic species.¹⁷⁴



Scheme 5.6 Interplay between conventional bimolecular radical termination (RT) and catalytic radical termination via the reactive $L/Cu^{II}-P_n$ intermediate in ATRP of acrylates.

Since the L/Cu¹ concentration in ICAR ATRP is governed by the dynamic ATRP equilibrium¹⁷⁵ (Scheme 5.3), and considering the very high values of $K_{\text{ATRP}} \approx 10^{-1}$ for this system,

the amount of TPMA^{NMe2}/Cu¹ present in solution is calculated to be 9.6 x 10⁻¹⁰ at equilibrium.¹⁷⁵ In other words, a radical will kinetically terminate with a second radical faster than with the trace amounts of TPMA^{NMe2}/Cu¹. This should still happen, even if addition of a radical to TPMA^{NMe2}/Cu¹ occurs at diffusion-controlled rates ($k_{add} = 10^8 \text{ M}^{-1}\text{s}^{-1}$). This is not the case of less active catalysts such as TPMA-based systems ($K_{ATRP} \approx 10^{-5}$)¹⁶⁴ where CRT dominates because of a relatively higher concentration of TPMA/Cu¹ of 1.8 x 10⁻⁶ M. These findings are supported by PREDICI simulations: the much more active TPMA^{NMe2}-based system kinetically suppressed CRT because only a small fraction of TPMA/^{NMe2}/Cu¹ is present in solution, resulting in a relatively larger fraction of living chains compared to less active systems.

Then, $Ag^0 ATRP$, a form of ARGET ATRP, was conducted to further test the scope of the newly synthesized catalyst. $Ag^0 ATRP$ employs silver wire to heterogeneously reduce L/Cu^{II} to L/Cu^{II}, with oxidation of Ag^0 to Ag^1Br .¹⁰⁹ As shown in **Figure 5.18**, the TPMA^{NMe2} catalyst successfully polymerized MA via Ag^0 ARGET ATRP using as little as 10 ppm of catalyst relative to monomer. However, at 5 ppm, the polymerization was no longer living as confirmed by the molecular weights decreasing with conversion and high D values (>1.5). Since the rate of Ag^0 ARGET ATRP depends on the rate of Cu^{II} generation, the linear semi-logarithmic kinetic plots showed that Cu^{III} was still reduced but unable to efficiently deactivate radicals. This is because, at such low catalyst concentrations, the rate of propagation and termination are competing with the rate of deactivation. Thus, it is likely that 10 ppm is around the lowest possible limits to achieve a well-controlled polymerization in copper catalyzed ATRP of acrylates. Nevertheless, unprecedented control was achieved using as little as 10 ppm of catalyst for the polymerization of acrylates. The nearly colorless nature of the polymerization solution at 10 ppm can be seen in **Figure 5.18C**.



Figure 5.18 A) Semi-logarithmic plots and B) M_n and D vs. conversion for the Ag⁰ ATRP of methyl acrylate (MA) at different loadings of [Cu^{II}(TPMA^{NMe2})Br][Br] under the initial conditions [MA]₀:[EBiB]₀:[Cu^{II}(TPMA^{NMe2})Br][Br]₀ = 200:1:0.02-0.002 with 10 cm Ag⁰ wire (SA/V) = 0.53 cm⁻¹ in DMF at 50 °C; catalyst loadings in ppm vs. monomer; [MA]₀ = 5.75M and C) pictures of polymerization solution at decreasing catalyst loadings of [Cu^{II}(TPMA^{NMe2})Br][Br].

Using the results from the two polymerization systems shown in **Figures 5.17 & 5.18**, one can estimate the rate coefficient of deactivation, k_d , according to **Eq 5.12** where DP is the degree of polymerization, k_p is the propagation rate constant,¹⁷⁶ and p is monomer conversion.⁵²

$$M_{\rm w}/M_{\rm n} = 1 + \frac{1}{\rm DP} + \left(\frac{k_{\rm p}[{\rm RX}]}{k_{\rm d}[{\rm LCu}^{\rm II} - {\rm X}]}\right) \left(\frac{2}{p} - 1\right)$$
 (Eq. 5.12)

Due to the negligible amount of termination, it has been assumed that $[RX] = [RX]_0$. Furthermore, since the K_{ATRP} is so large, it can be assumed that essentially all copper is in the
form of L/Cu^{II}-X and therefore $[L/Cu^{II}-X] = [L/Cu^{II}-X]_0$. Using the final dispersity data of the polymerizations, $k_d = (5.4 \pm 1.7) \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ was obtained which gives an estimated value of $K_{\text{ATRP}} = 2.2 \times 10^{-2}$ for acrylate systems. This indicates that the degree of substitution and redox potential of pyridinic-based catalysts have very little effect on k_d . Instead, only the total amount of Cu^{II}-X deactivator, which is regulated by $[Cu^{II}]_0$ and K_{ATRP} , will define the level of control in a particular ATRP system with activator regeneration.

5.3.5 Comparison of TPMA^{NMe2} to Other Ligands in ATRP

As shown in **Figure 5.19**, the redox potential scales linearly with log(K_{ATRP}) for EBiB in MeCN at room temperature for a variety of ligands. Based on $E_{1/2}$ values, the newly synthesized TPMA^{NMe2}-based catalyst ($E_{1/2} = -554$ mV) is almost 10 billion times more active than seminal bpy-based catalyst ($E_{1/2} = +30$ mV). Even looking at catalysts which are widely used for low ppm ATRP, the TPMA^{NMe2}-based system is $\approx 300,000$ and 30,000 times more active than the TPMA ($E_{1/2} = -240$ mV) and Me₆TREN ($E_{1/2} = -300$ mV) based catalysts, respectively. Unfortunately, with such a highly active catalyst as [Cu(TPMA^{NMe2})]⁺, activation of alkyl halides approaches diffusion-controlled limits ($k_a > 10^6$ M⁻¹s⁻¹), and with already diffusion-controlled deactivation rates ($k_d = > 10^7$ M⁻¹s⁻¹), values of K_{ATRP} begin to approach unity. This would mean that for commonly used monomers such as acrylates and methacrylates, this catalytic system may be the upper limit of activity since the only way to further increase K_{ATRP} would be to decrease k_d . This is not best since the control achieved in ATRP is due to fast rates of deactivation. Encouragingly, the high ATRP activity provided by the TPMA^{NMe2}-based catalyst can open the possibility to polymerize less active monomers such as vinyl acetate and *N*-vinylpyrrolidone which have historically fallen victim to too low values of K_{ATRP} .



Figure 5.19 Redox potential ($E_{1/2}$) vs. log(K_{ATRP}) for various ATRP catalysts complexed by multidentate nitrogen-based ligands. Values for $E_{1/2}$ have previously been determined experimentally vs. an SCE electrode in MeCN at room temperature. Values of K_{ATRP} are for ethyl α -bromoisobutyrate (EBiB; methacrylate mimic) in MeCN at room temperature.

5.3.6 Conclusions

The synthesis of a new ATRP catalyst employing the p-dimethylamino substituted TPMA ligand, tris[(4-dimethylaminiopyridyl)methyl]amine (TPMA^{NMe2}), is reported. Variable temperature NMR showed a fluxional Cu¹ complex with rapid ligand exchange. In the solid state, the [Cu^{II}(TPMA^{NMe2})Br]⁺ complex exhibited nearly perfect trigonal bipyramidal geometry. UV-Vis and EPR confirmed that this geometry was retained in solution. Electrochemical measurements showed a quasi-reversible TPMA^{NMe2}Cu^{I/II} couple indicating small geometric rearrangement throughout the redox cycle. Stability constants for Cu¹ and Cu^{II} were comparable to other copper ATRP catalysts in MeCN. Electrochemistry was also utilized to assess the activation of methyl 2-bromopropionate (MBrP; acrylate mimic) and ethyl α -bromoisobutyrate, for which a rate coefficient of activation was measured as $k_a = 1.1 \times 10^6$ M⁻¹s⁻¹ and 7.2 x 10⁶ M⁻¹s⁻¹, respectively. This leads to an estimation of $K_{ATRP} = 2.2 \times 10^{-2}$ and 7.2 x 10⁶ M⁻¹s⁻¹ was calculated this is the most active ATRP catalyst to date. A large value of $k_d > 10^7$ M⁻¹ s⁻¹ was calculated and indicated that the catalyst is also a good deactivator. Both ICAR and Ag⁰ ATRP of acrylates were well-controlled using as little as 10 ppm of catalyst relative to

monomer. Encouragingly, due to the high values of K_{ATRP} and low [TPMA^{NMe2}/Cu¹], unwanted side reactions involving Cu¹ such as catalytic radical termination (CRT) are suppressed leading to higher chain-end functionality. Furthermore, this catalyst can potentially allow for the successful ATRP of less active monomers. Investigations in this direction are currently ongoing in our laboratories.

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Chapter 6.

Understanding the Termination of Acrylate Radicals

6.1 Preface

Any radical polymerization system, living or conventional, inherently involves bimolecular termination events. The rates of bimolecular radical termination (RT) are generally expressed by *Rate*_{RT} = $2k_t[R^*]^2$ for which values of k_t approach diffusion-controlled limits $k_t > 10^8$ M⁻¹s⁻¹. The rate coefficients of termination have been extensively studied and are widely agreed upon. Mechanistically, there are two pathways of bimolecular termination: disproportionation (Disp.) or combination (Comb.). Termination via Disp results in two chains, one with a saturated chain-end and the other with an unsaturated chain-end. On the other hand, termination via Comb results in one chain with a molecular weight that is the summation of the two chains. The pathway of termination relies heavily on the nature of the radical. Generally, methacrylates undergo both Disp and Comb while styrene undergoes predominately Comb. Acrylates, on the other hand have been long debated in the literature and analysis is generally complicated by an additional reaction known as "backbiting," or more formally a 1,5-hydrogen atom transfer. Moreover, in ATRP, acrylates undergo a reaction known as catalyzed radical termination (CRT) with highly active copper catalysts. Indeed, CRT is the predominant pathway of acrylate termination in ATRP with >90% of terminated chains arising from CRT.

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 <u>TG Ribelli</u>, KF Augustine, M Fantin, P Krys, R Poli, K Matyjaszewski. "Disproportionation or Combination? The Termination of Acrylate Radicals In ATRP." *Macromolecules*. 2017. 50, pp 7920-7929. © 2017 American Chemical Society

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This chapter discusses mechanistic studies to elucidate the CRT mechanism with the hopes of developing systems that are able to suppress this unwanted side reaction. First, the nature of uncatalyzed radical termination was investigated i.e. Disp vs. Comb. This investigation took use of kinetically promoting either RT or CRT in a "termination" reaction of an ATRP macroinitiator in the absence of monomer. Studying the resulting terminated chains under different conditions allowed us to conclude that uncatalyzed radical termination proceeds predominately via combination while CRT gives dead-chains that are the same molecular weight as the macroinitiator. Furthermore, kinetic simulations were conducted in order to deduce the contribution of each of the termination pathways as well as to account for the backbiting reaction.

The effect of ligand was then investigated on both the rate and molecular weights of CRT. Using six different ligands with various geometries and electronics, we were able to quantify apparent rate coefficients of CRT, k^{app}_{CRT} . Relating the rates to redox potential, E1/2, of the L/Cu^{1/II} couple allowed us to define parameters for OMRP activity. It was concluded that the more stable the L/CuII-R species, the faster the rate of termination. Density functional theory (DFT) was also used to investigate the stability of the elusive L/CuII-R organometallic species. Even with the most active copper catalysts, the reaction was still more selective for alkyl halide than for radicals. Kinetic analysis was conducted and was used to conclude that the structure of the ligand had a pronounced effect on the rate determining step (RDS) of CRT.

Finally, a previous system used by Yamago *et al* involving organotellurium species was reinvestigated. Using a combination of experimental and theoretical techniques, a novel organometallic pathway was discovered, involving hydrogen atom transfer from a propagating radical (R[•]) to organotellanyl radicals (•TeR) leading to exclusive disproportionated products. DFT revealed the reaction likely proceeds via an organotellurium hydride (H-TeR) species.

The majority of this work has been conducted in close collaboration with Prof. Rinaldo Poli at the Laboratoire de Chemie de Coordination in Toulouse, France with whom I was lucky enough to study for 7 months from October 2015 until April 2016. For the three projects, the experiments were conducted and analyzed myself. All DFT calculations were carried out by Prof. Poli or Dr. Wahidur Rahaman. PREDICI simulations were conducted mostly by Kyle

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Augustine with the help of Dr. Pawel Krys or myself. Dr. Marco Fantin aided in quantifying ATRP parameters for the products of termination.

6.2 Disproportionation or Combination? The Termination of Acrylate Radicals in ATRP

6.2.1 Preface

The termination of acrylate radicals in atom transfer radical polymerization (ATRP) can involve either conventional bimolecular radical termination (RT) or catalytic radical termination (CRT). These processes were investigated using a poly(methyl acrylate)-Br macroinitiator under different initial conditions tuned to change the RT/CRT ratio. The polymers, obtained from alkyl halide chain-end activation by [Cu^I(L)]⁺ (L = tris[2-(dimethylamino)ethyl]amine (Me₆TREN), tris(2pyridylmethyl)amine (TPMA), or tris(3,5-dimethyl-4-methoxy-2-pyridylmethyl)amine (TPMA*3)) in the absence of monomer, were analyzed by size exclusion chromatography (SEC). RTpromoting conditions resulted in the increase of a shoulder with double molecular weight (MW) relative to the macroinitiator distribution, indicating that RT occurred predominantly via radical combination. Conversely, when CRT was promoted, the macroinitiator distribution did not shift, indicating a disproportionation-like pathway. The termination reactions for the TPMA system were further analyzed via PREDICI simulations, which showed the significant impact of mid-chain radicals, arising from backbiting, on the overall termination profile. In all cases, CRT and cross termination between secondary chain-end and tertiary mid-chain radicals contributed the most to the overall amount of terminated chains.

^{*}Work in this section was published: <u>**TG Ribelli**</u>, KF Augustine, M Fantin, P Krys, R Poli, K Matyjaszewski. "Disproportionation or Combination? The Termination of Acrylate Radicals In ATRP." *Macromolecules*. **2017**. 50, pp 7920-7929. © 2017 American Chemical Society

6.2.2 Introduction

Conventional radical polymerization (RP) and the recently developed reversibledeactivation radical polymerization (RDRP) methods have achieved tremendous success.¹⁻⁵ Versatility of the radical-based processes originates from facile experimental setup, wide range of reaction temperatures, and tolerance to functional groups, solvents, and impurities. Throughout the years, elementary reactions occurring in radical polymerizations have been identified and meticulously studied.⁶⁻¹¹ This also led to development of sophisticated techniques allowing for the precise determination of rate coefficients.^{7, 12-13} In conventional RP, propagation and termination rate coefficients can be accurately measured using time-resolved electron paramagnetic resonance (EPR) spectroscopy coupled with single pulse pulsed laser polymerization technique (SP-PLP).¹⁴⁻²⁰ Although the kinetics of termination has been well studied, the mechanism of bimolecular termination is still a topic of some debate.

As shown in Scheme 6.1, bimolecular radical termination can occur via combination (Comb) or disproportionation (Disp), resulting in one chain with doubled molecular weight or two chains with a saturated and unsaturated chain end, respectively. The relative extent of these reactions depends on the nature of the radicals. Styrenes²¹⁻²² and acrylonitrile²³ were suggested to primarily undergo coupling, while methacrylates undergo both Disp and Comb^{22, 24}. Acrylates, however, present a more complex, debated, and yet unresolved case.^{21, 25-26} Recently, using radicals photo-generated from organotellurium macroinitiators, Yamago et al. suggested that acrylate radicals terminate predominantly (99%) by disproportionation at room temperature.²⁷ However, Asua et al. ²⁸ suggested that acrylate radicals terminate via combination, but transfer reactions may explain the surprising results reported by Yamago. Due to the relatively high reactivity of the acrylate radicals, both intermolecular²⁹ and intramolecular (backbiting)³⁰⁻³¹ transfer to polymer can occur.³²⁻³⁵ Such reactions lead to tertiary mid-chain radicals (MCR), which can terminate with another secondary propagating radical (SPR) or MCR.³⁶ At higher temperatures, MCRs undergo radical migration³⁷⁻³⁸ and β -scission leading to macromonomers.³⁹⁻ ⁴¹ Undoubtedly, transfer reactions are important for in-depth understanding of the termination mechanism of acrylates. This also holds true in RDRP techniques, where radical termination is suppressed.

Radical Generation



Scheme 6.1 (Top) Pathways of bimolecular radical termination of two chain—end acrylate radicals ($P_2 \bullet$), proceeding either via disproportionation (blue) or combination (red); (bottom) formation of tertiary mid-chain radicals ($P_3 \bullet$) via backbiting and subsequent termination with another mid-chain radical or secondary chain-end radical, both resulting in disproportionated chains.³⁶

RDRP methods such as reversible addition-fragmentation chain transfer (RAFT) polymerization and atom transfer radical polymerization (ATRP) can successfully control the polymerization of acrylate-based monomers.^{33-34, 42-45} The reactions can be conducted under mild conditions and are typically fast and efficient. However, ATRP systems with highly active catalysts⁴⁶ present an additional side reaction in which acrylate radicals can reversibly coordinate to L/Cu^I resulting in formation of a L/Cu^{II}–P_n complex as shown in **Scheme 6.2**.⁴⁷⁻⁴⁹ This is related to organometallic mediated radical polymerization (OMRP) systems⁵⁰, most common with cobalt complexes.⁵¹⁻⁵⁴ The L/Cu^{II}–P_n species can then react with a second radical, leading to catalytic

radical termination (CRT).⁵⁵⁻⁵⁶ Indeed, CRT has recently been shown to be the dominant mode of termination in ATRP of acrylate monomers.^{48, 57} Despite the low overall amount of terminated chains (<3%) in these reactions, the majority (\approx 90%) of these dead chains originated from CRT reactions, even when low amounts of L/Cu¹ were used.



Scheme 6.2 Catalytic radical termination (CRT) of acrylates in the presence of L/Cu¹ complexes.

Previously, we have reported that CRT gives disproportionation-like products with a tris(2-pyridylmethyl)amine (TPMA) based system.⁴⁸ Interestingly, Yamago *et al.* recently proposed²² that using the tris[2-(dimethylamino)ethyl]amine (Me₆TREN)-based system, termination gave products of doubled molecular weight via a proposed Me₆TREN/Cu^{III}-(pMA)₂ intermediate. Due to the ongoing debate involving the mechanism of bimolecular radical termination and contradicting results of CRT, we sought to obtain a better understanding of these two mechanisms of termination. Using three different L/Cu catalytic systems, L = Me₆TREN, TPMA and tris(3,5-dimethyl-4-methoxy-2-pyridylmethyl)amine (TPMA^{*3}), under controlled conditions, it is possible to reassess the products of CRT as well as obtain valuable information about the mechanism of conventional bimolecular radical termination.

One method of studying termination mechanisms is by generating chain-end radicals via activation of "living" macroinitiators. Using various initial conditions and catalytic systems, we were able to kinetically promote different contributions of conventional radical termination of chain-end radicals (RT) and catalytic radical termination (CRT). By analyzing the kinetics of termination and molecular weights of the resulting polymers, valuable mechanistic insights were obtained. According to **Eq. 6.1**, to increase the fraction of RT relative to CRT one can: a) decrease $[L/Cu^{II}-X]_0$ or b) increase the ATRP equilibrium constant (K_{ATRP}):

$$\frac{Rate_{\rm RT}}{Rate_{\rm CRT}} = \frac{k_{\rm t}[{\rm P}_{\rm n}\cdot]^2}{k_{\rm CRT}[{\rm P}_{\rm n}\cdot][{\rm L}/{\rm Cu}^{\rm I}]} = \frac{k_{\rm t}[{\rm P}_{\rm n}\cdot]}{k_{\rm CRT}[{\rm L}/{\rm Cu}^{\rm I}]} = \frac{k_{\rm t}[{\rm P}_{\rm n}X]}{k_{\rm CRT}[{\rm L}/{\rm Cu}^{\rm II}-{\rm X}]}K_{\rm ATRP}$$
(Eq. 6.1)

Indeed, PREDICI simulations carried out at three different initial conditions confirmed the predictions from Eq 6.1. As shown in Figure 6.1, when using the same catalyst (i.e. same K_{ATRP}), RT₂₂/CRT is higher for a) lower [PMA-Br]:[L/Cu^{II}] ratio (1:1) and b) lower [L/Cu^{III}]. Note that RT₂₂ refers to termination between secondary radicals. Figure 6.1 also shows the large variation of the RT₂₂/CRT ratio with time. RT₂₂/CRT is largest only at the very first instants when radical concentration is highest. Since the bimolecular termination of chain-end radicals depends on [R•]², RT₂₂ dominates only during the very first milliseconds. Once the L/Cu^{II}-X deactivator buildsup via the persistent radical effect (PRE), the [R•] is suppressed, thus significantly decreasing the rate of RT₂₂. After this initial "influx" of radicals, CRT dominates since $[Cu^{I}] >> [R_{I}]$ and thus a radical will preferentially coordinate to L/Cu^I before terminating with a second radical. This is further shown under the most CRT-inducing conditions (green line), where additional deactivator is present from the beginning and a very small RT/CRT is observed, even at the onset of the reaction. This is because the initial influx of radicals can be quickly deactivated before termination. Therefore, since PREDICI confirmed that the RT/CRT ratio can be kinetically controlled by changing the initial conditions, a pMA-Br ATRP macroinitiator with 99% chain end functionality (CEF) was synthesized via Ag⁰ ATRP.⁵⁸ By changing the RT₂₂/CRT ratio, one can analyze the resulting polymer products via SEC to determine the proportion of high MW to low MW polymer and thus obtain invaluable mechanistic information about the products of RT and CRT.



Figure 6.1. PREDICI simulations of termination of radicals generated from a pMA-Br macroinitiator. RT_{22}/CRT ratio vs. time under three different initial conditions [pMA-Br]₀:[L/Cu^{II}-Br]₀ = 1:1:0 (red), 1:2:0 (blue) and 1:2:1 (green) where L = TPMA.

In order to reassess previous contributions, experiments were first conducted under conditions similar to those reported by Yamago *et al.*²² In order to eliminate assumptions which were not accounted for by Yamago, we slightly altered the experimental setup. One significant difference is the choice of copper salt and solvent. [Cu¹(MeCN)₄][PF₆] in acetonitrile was used throughout this study, while Yamago *et al.* used Cu¹Br in toluene. In our study, the use of [Cu¹(MeCN)₄][PF₆] results in the formation of a discrete [Cu¹(Me₆TREN)]⁺ catalyst *in situ*, while the use of Cu¹Br has been shown to form a mixture of [Cu¹(Me₆TREN)]⁺, [Cu¹(Me₆TREN)Br], and Cu¹Br₂⁻, which have different activities in ATRP⁵⁹ and thus could have skewed previously reported conclusions. Secondly, to make sure there was no disproportionation of the L/Cu¹ species, MeCN was chosen as the solvent instead of toluene. Finally, Yamago *et al.* conducted all but one of their termination experiments in the presence of Cu⁰ powder, which has recently⁶⁰ been shown to also catalyze the termination of acrylate radicals and would be indistinguishable from Cu¹ CRT. In addition, avoiding the use of Cu⁰ allows facile monitoring of the extent of termination by the determination of [L/Cu^{II}], since Cu⁰ is able to comproportionate with Cu^{II} to regenerate Cu^I and would not allow for efficient monitoring of [L/Cu^{II}].

6.2.3 Experimental

General All chemicals were purchased from commercial sources and used as received unless otherwise noted. Acetonitrile was taken from a solvent distillation apparatus using argon atmosphere and stored in a flame-dried flask over molecular sieves. Methyl acrylate (MA, Sigma Aldrich, 99%) was passed through a column of basic alumina to remove inhibitor prior to use. Tris(2-pyridylmethyl)amine) (TPMA)⁶¹ and tris(3,5-dimethyl-4-methoxy-2-pyridylmethyl)amine (TPMA*³)⁴⁶ were synthesized according to previously published procedure. Tris[2-(dimethylamino)ethyl]amine (Me₆TREN) was purchased from Alfa Aesar. L/Cu¹ complexes (L = TPMA, TPMA*3, or Me₆TREN) were synthesized in situ under nitrogen atmosphere using standard Schlenk techniques by mixing respective ligand and [Cu¹(MeCN)₄][PF₆] in dry and degassed acetonitrile.

Characterization

Size Exclusion Chromatography (SEC): SEC was conducted using a Waters 515 HPLC Pump and Waters 2412 Refractive Index Detector using PSS columns (Styrogel 10^2 , 10^3 , 10^4 , 10^5 Å) in THF as an eluent at a flow rate of 1 mL/min at 35°C. The system was calibrated with 12 linear polystyrene (PSt, $M_n = 376$ -2,570,000) and 12 linear poly(methyl methacrylate) (PMMA, $M_n = 800$ -2,5700,000) standards. Peak deconvolution was conducted using OriginPro 7.0.

NMR: Monomer conversion was measured using ¹H NMR spectroscopy using a Bruker Avance 500 MHz spectrometer at room temperature.

UV-Vis-NIR: The evolution of $[L/Cu^{II}-Br]$ was monitored using a Varian Cary 5000 UV/Vis/NIR spectrometer. Extinction coefficients for the $[Cu^{II}(TPMA)Br]^+$, $[Cu^{II}(TPMA^{*3})Br]^+$ and $[Cu^{II}(Me_6TREN)Br]^+$ were $\varepsilon_{950} = 190 \text{ M}^{-1}$, $\varepsilon_{979} = 240 \text{ M}^{-1}$, and $\varepsilon_{760} = 210 \text{ M}^{-1}$ in MeCN, respectively. **Electrochemistry:** Electrochemical measurements were conducted on a Gamry Ref 600 potentiostat in a three-electrode cell. The counter electrode was a Pt ring, the working electrode a GC disk (3 mM diameter, Metrohm), and the reference electrode was Ag|AgI| 0.1 M *n*-Bu₄NI in DMF. The GC electrode surface was cleaned by polishing with a 2.5 mm diamond paste prior to each experiment, followed by ultrasonically rinsing in ethanol for 5 min. The GC working electrode was connected to a rotating disk electrode (RDE, Metrhom Autolab).

Synthesis of pMA–Br Macroinitiator

Ag⁰ ATRP was chosen due to the facile setup and high chain-end functionality of obtained polymers, previously demonstrated for acrylates.⁵⁸ A mixture of ethyl α -bromoisobutyrate (EBiB; 0.39g, 2 mmol), Cu^{II}Br₂ (5 mg, 0.022 mmol), TPMA (6.5 mg, 0.024 mmol), 10 mL of MA (9.5 g, 0.111 mol) and 10 mL of dimethylformamide (DMF) were added to a Schlenk flask. The flask was sealed and subjected to three freeze-pump-thaw cycles to remove oxygen. This degassed solution was charged into a second, nitrogen-purged Schlenk flask containing 5 cm of newly purchased Ag⁰ wire (d = 2 mm, SA = 3.2 cm²) and a stir bar. The flask was sealed and placed in an oil bath at 50°C. Samples were taken periodically to measure conversion. The polymerization was stopped by opening the flask to air when monomer conversion reached ~50%. Residual monomer was removed using rotary evaporator. The polymer was precipitated in a mixture of H₂O/MeOH = 9/1 and was then centrifuged for 20 minutes. The polymer was collected and dried overnight in a vacuum oven to give pure pMA–Br macroinitiator.

Termination Reactions in the Absence of L/Cu^{II}Br₂

A 6.6 mM stock solution containing ligand (ligand = TPMA, TPMA^{*3}, or Me₆TREN) was made using degassed, anhydrous MeCN. In a separate flask, $[Cu^{I}(MeCN)_{4}][PF_{6}]$ was weighed out and quickly placed under vacuum. 5 mL of the ligand solution was charged into the flask containing the copper salt using an air-tight syringe. This mixture was stirred for 10 minutes to form the $[Cu^{I}(L)]^{+}$ complex *in situ*. This solution was taken as the baseline for UV-Vis analysis. 100 µL of a pMA-Br macroinitiator solution (0.11 M for TPMA and TPMA*3 reactions or 0.08M for Me₆TREN reactions) was charged into the flask containing the L/Cu^I solution to begin the reaction. Samples were taken on the UV-Vis spectrophotometer.

Termination Reactions in the Presence of L/Cu^{II}Br₂

A 6.6 mM stock solution containing ligand (ligand = TPMA, TPMA^{*3}, or Me₆TREN) was made using degassed, anhydrous MeCN. In a separate flask, $[Cu^{I}(MeCN)_{4}][PF_{6}]$ and $CuBr_{2}$ were weighed out and quickly placed under vacuum. 5 mL of the ligand solution was charged into the

flask containing the copper salt using an air-tight syringe. This mixture was stirred for 10 minutes to form both the $[Cu^{I}(L)]^{+}$ and $[Cu^{II}(L)Br]^{+}$ complexes *in situ*. This solution was taken as the baseline for UV-Vis analysis. 100 µL of a pMA-Br macroinitiator solution (0.11 M for TPMA and TPMA*3 reactions or 0.08M for Me₆TREN reactions) was charged into the flask containing the L/Cu^I solution to begin the reaction. Samples were taken on the UV-Vis spectrophotometer.

6.2.4 Results and Discussion

6.2.4.1. Termination in the Presence of Me₆TREN/Cu¹ Complex

Termination experiments were conducted in the absence of monomer and termination extent could be determined from the increase in [L/Cu^{II}-Br], according to the principle of halogen conservation.⁶² This allowed the amount of termination to be related to the SEC traces of the resulting terminated polymer (**Figure 6.2**). Using the same [pMA-Br]₀:[Me₆TREN/Cu^{II}]₀ = 1:5 as previously reported²², a high molecular weight shoulder accounting for 27% of chains was observed for the polymer recovered after quantitative (>99 %) termination. This is in very good agreement with the Yamago contribution, where 25% of chains were reported to have doubled molecular weight. As predicted by **Eq 6.1**, upon addition of [Me₆TREN/Cu^{II}-Br]⁺ deactivator, the amount of conventional radical termination was kinetically suppressed relative to CRT. Upon addition of 0.5 or 1 equivalents of [Me₆TREN/Cu^{II}-Br]⁺ relative to [pMA-Br]₀, the fraction of high molecular weight polymer decreased from 27% to 9% and 7%, respectively (in all cases, the termination was quantitative after 1 hour according to the [Me₆TREN/Cu^{II}] analysis). These results would indicate that the high molecular weight peak previously attributed to CRT coupling²² is actually the result of non-catalyzed termination (RT), due to the high radical concentration triggered by fast pMA-Br chain-end activation by the [Cu^{II}(Me₆TREN)]⁺ catalyst.



Figure 6.2 (A) SEC traces of the termination products from the pMA–Br macroinitiator recovered after 30 min at different RT/CRT ratios and (B) deconvolution of the of the product of reaction $[pMA-Br]:[Me_6TREN/Cu^{l}] = 1:5$. Conditions: $[pMA-Br]:[Me_6TREN/Cu^{l}]:[Me_6TREN/Cu^{l}-Br] = 1:5:0-1$ in anhydrous MeCN at room temperature; $[pMA-Br]_0 = 1.6$ mM.

In order to assess the products of RT and CRT under more relevant polymerization conditions, termination reactions under $[pMA-Br]_0$: $[Me_6TREN/Cu^{l}]_0 = 1:1-2$ ratios were conducted. The kinetics of termination and the resulting SEC traces of the terminated polymer are presented in **Figure 6.3.** Under the initial conditions [pMA–Br]₀:[Me₆TREN/Cu¹]₀ = 1:1, 81% of chains were terminated after one hour with 38% high molecular weight fraction compared to >99% and 27%, respectively, when this ratio was 1:5. Upon initial addition of 0.5 eq. of deactivator complex [Me₆TREN/Cu^{II}-Br]⁺ relative to [pMA-Br]₀ and doubling [Me₆TREN/Cu^I]₀, the high molecular weight shoulder decreased to 18% while achieving 91% termination. The higher amount of terminated chains is due to the excess of [Me₆TREN/Cu^I]₀ relative to [pMA-Br]₀. The high molecular weight peak was further decreased upon initial addition of 1 eq. of deactivator complex to give only 7% high molecular weight chains at quantitative termination. These results indicate that acrylate radicals terminate via combination, while CRT gives a terminated polymer with the same molecular weight as the pMA-Br macroinitiator, contrary to recent reports.^{22, 27} Due to the high activity of the [Me₆TREN/Cu¹] activator complex, the initial concentration of radicals could not be suppressed efficiently to completely eliminate RT, as evidenced by the small high molecular weight fraction even in the presence of 1 eq. of deactivator complex.



Figure 6.3 (A) evolution of fraction of terminated chains with time and (B) SEC traces of the termination product of pMA–Br macroinitiator recovered after 30 min at different RT/CRT ratios. Reaction conditions: $[pMA-Br]_0:[Me_6TREN/Cu^I]_0:[Me_6TREN/Cu^{II}-Br]_0 = 1:1-2:0-1$, in anhydrous MeCN at room temperature; $[pMA-Br]_0 = 1.6$ mM.

6.2.4.2. Termination in the Presence of TPMA/Cu¹ Complex

The next termination experiments were carried out using the $[Cu^{i}(TPMA)]^{+}(TPMA = tris(2-pyridylmethyl)amine))$ catalyst as shown in **Figure 6.4**. The catalyst was used at two different $[pMA-Br]_{0}:[TPMA/Cu^{i}]_{0}$ ratios. With $[pMA-Br]_{0}:[TPMA/Cu^{i}]_{0} = 1:1$, 67% of chains were terminated after one hour, but only 7% of all chains corresponded to the high molecular weight shoulder, compared to 38% for the Me₆TREN system under the same conditions. The fraction of high molecular weight terminated polymer was further decreased by decreasing the RT/CRT ratio using different concentration of $[TPMA/Cu^{i}]_{0}$ and $[TPMA/Cu^{i}]_{-}Br]_{0}$. Relative to the Me₆TREN system, the lower fraction of doubled molecular weight product is due to the lower ATRP activity of the TPMA catalyst. The rate coefficient of pMA-Br activation is approximately 10x higher for $[Cu^{i}(Me_{6}TREN)]^{+}$ compared to $[Cu^{i}(TPMA)]^{+}$.⁶³ Since the rate of radical termination is proportional to $[R \bullet]^{2}$ and the rate of CRT is proportional only to $[R \bullet]$, a 10-fold increase in radicals leads to a 100 times faster RT and only 10 times faster CRT.



Figure 6.4 (A) Evolution of fraction of terminated chains with time and (B) SEC trace of the termination product of pMA–Br macroinitiator recovered after 1 h at different RT/CRT ratios. Reaction conditions: $[pMA–Br]_0$: $[TPMA/Cu^I]_0$: $[TPMA/Cu^I–Br]_0$ = 1:1-2:0-1, in anhydrous MeCN at room temperature; $[pMA–Br]_0$ = 2 mM.

6.2.4.3. Termination in the Presence of Cu^I/TPMA^{*3} Complex

As noted earlier, the ratio of RT to CRT can be tuned by changing K_{ATRP} (**Eq 6.1**). One way to increase K_{ATRP} is by using more active L/Cu¹ catalysts.^{46, 64} Thus, replacing [Cu¹(TPMA)][PF₆] with the more active [Cu¹(TPMA^{*3})][PF₆] (TPMA^{*3} = tris(3,5-dimethyl-4-methoxy-2pyridylmethyl)amine), should lead to a higher initial concentration of radicals. As alluded to above, this should lead to a faster rate of RT relative to CRT compared to the TPMA system. Therefore, assuming that RT occurs via combination, as suggested by the investigations of the TPMA and Me₆TREN systems above, a larger fraction of high molecular weight peak should be observed when using TPMA^{*3} compared to TPMA under the same conditions.

Indeed, the termination experiment under conditions [pMA–Br]₀:[TPMA*³/Cu¹]₀: = 1:1 (Figure 6.5) confirmed this expectation. After only 5 minutes, 98% of chains were terminated, compared to only 67% after 1 hour for the TPMA system under the same initial conditions. This is due to the much higher activity of the TPMA*³/Cu¹ catalyst. Deconvolution of the resulting SEC traces showed 24% of the chains terminated via combination for TPMA*³ compared to only 7% for TPMA. Under the conditions [pMA–Br]₀:[TPMA*³/Cu¹]₀: = 1:2 all chains were terminated in only 4 minutes and the high molecular weight shoulder accounted for only 12% of all chains, indicating a larger fraction of CRT relative to RT. Upon initial addition of 0.5 or 1 equivalent of TPMA^{*3}/Cu^{II}-Br deactivator, the high molecular weight peak decreased to 7 and 4%, respectively, with >99% of chains terminated. The concurrent decrease of the high molecular weight shoulder with decreasing RT provides further evidence that RT occurs predominantly via combination while CRT gives products with the same molecular weight as the pMA-Br macroinitiator. Like in the Me₆TREN system, a small fraction of high molecular weight product was observed due to the high activity of the TPMA^{*3}/Cu^{II} catalyst.



Figure 6.5 (A) Evolution of fraction of terminated chains with time and (B) SEC traces of the termination product of pMA–Br macroinitiator recovered after 1 h at different RT/CRT ratios. Reaction conditions: $[pMA–Br]_0$:[TPMA*³/Cu^I]_0:[TPMA*³/Cu^{II}–Br]_0 = 1:1-2:0-1, in anhydrous MeCN at room temperature; $[pMA–Br]_0 = 2.5 \text{ mM}$).

An interesting question arises as to why the TPMA^{*3} system did not show as much of a high molecular weight peak as the Me₆TREN system. This is most likely due to much faster association of the pMA radicals to TPMA^{*3}/Cu¹ relative to Me₆TREN/Cu¹. In fact, UV-Vis analysis shows the formation of both the TPMA^{*3}/Cu^{II}-Br and the TPMA^{*3}/Cu^{II}-pMA organometallic species. Since this organometallic species was observed on the time scale of the reaction, this means that TPMA^{*3}/Cu^{II}-pMA is more thermodynamically stable (larger value of K_{OMRP})⁵⁶ than Me₆TREN/Cu^{II}-pMA. Formation of TPMA^{*3}/Cu^{II}-pMA decreases the radical concentration, thus suppressing the rate of bimolecular termination and therefore decreasing the fraction of high molecular weight product in SEC.

The summary of all termination reactions (**Table 6.1**) clearly shows that the RT/CRT ratio can be kinetically altered by changing the [pMA-Br]:[L/Cu^{II}]:[L/Cu^{II}-Br] ratios but also by changing K_{ATRP} . As the RT/CRT ratio was kinetically decreased, the relative fraction of high molecular polymer (Comb/Disp) also decreased. These results indicate that bimolecular radical termination of acrylates operates predominantly via combination while CRT gives predominantly chains with the same molecular weight as the pMA-Br initiator.

Ligand	[pMA-Br]: [L/Cu ^ı]:[L/Cu ^{ıı} -Br]	Terminated (%)ª	Living (%)	Combined (%) ^b	Disp (%) ^c	% Disp. Of All Term ^d
Me ₆ TREN	1:1:0	81	19	38	43	53
	1:2:0.5	91	9	18	73	80
	1:2:1	>99	<1	13	86	86
	1:5:0	>99	<1	27	73	73
	1:5:0.5	>99	<1	9	91	91
	1:5:1	>99	<1	7	93	93
ΤΡΜΑ	1:1:0	67	33	7	60	90
	1:2:0	98	2	5	93	95
	1:2:1	71	29	2	69	97
	1:1:0	98	2	24	74	76
TPMA* ³	1:2:0	>99	<1	12	88	88
	1:2:0.5	>99	<1	7	93	93
	1:2:1	>99	<1	4	96	96

Table 6.1 Experimental product distribution of the termination reactions.

All percentages were calculated at $t = 30 \text{ min (TPMA}^{*3}) \text{ or } 1 \text{ h (TPMA and Me₆TREN); Relative to [pMA-Br]₀ unless otherwise noted. ^a Calculated based on the increase of [L/Cu^{II}–Br]; ^b The High MW from the deconvoluted SEC traces; ^c Calculated from the Low MW fraction of the deconvoluted SEC traces as Low MW = Living + Disp; ^dCalculated as the amount of chains terminated by disproportionation related to all terminated chains.$

6.2.4.4 PREDICI Simulations

To further quantify the termination reactions, PREDICI simulations were conducted. In order to obtain useful mechanistic information, the kinetic model in use must first be validated

by comparing to experimental results. In this case, experimental [L/Cu^{II}-Br] was conveniently monitored by UV-Vis spectroscopy and then compared to the PREDICI simulations.

One major area of debate in the termination of acrylate radicals is the extent of backbiting for which reported rate coefficients, k_{bb} , span 4 orders of magnitude.³⁶ However, backbiting is an important feature of acrylate polymerization and cannot be neglected.³⁰ In fact, setting $k_{bb} = 0$ in the simulation (**Figure 6.6A**) caused a significant underestimation of the experimental [L/Cu^{II}-Br]. Therefore, backbiting was included in the simulation, taking into account the most recent and accurate k_{bb} value at room temperature reported by Buback *et al.*^{16, 31} using the PLP-SEC or PLP-EPR methods (40 < k_{bb} < 250) and Asua *et al*³⁶ using experimental fitting (10 < k_{bb} < 40). With k_{bb} in this range, all simulations agreed better with the experimental data, and the best agreement was obtained for $k_{bb} = 40$ s⁻¹. It should be noted that the value of k_{bb} , within its interval of accuracy, was the only value fitted to the experimental data, whereas all other values were taken directly from the literature or measured in this study.





Figure 6.6 A) Evolution of $[TPMA/Cu^{II}-Br]$ vs. time for different values of k_{bb} (in s⁻¹); B) experimental (squares) and simulated (lines) evolution of TPMA/Cu^{II}-Br vs. time; C) fraction of chains terminated by disproportionation relative to total terminated chains for two cases, where RT and CRT give combination and disproportionation, respectively (bold lines) and vice versa (dashed lines). All squares are experimental data obtained either via UV-Vis or SEC under the specified initial ratio with $[pMA-Br]_0 = 2 \text{ mM}$ in anhydrous MeCN at room temperature.

The remaining simulations were conducted using the value of $k_{bb} = 40 \text{ s}^{-1}$. As shown in **Figure 6.6B**, the fit between the experimental and simulated evolution of TPMA/Cu^{II}-Br for the other two [pMA-Br]:[L/Cu^{II}-Br] ratios remained good, validating this PREDICI model. **Figure 6.6C** shows the fraction of disproportionated chains to total terminated chains vs. time under two different scenarios. In the bold lines, it was assumed that termination between two chain-end radicals (RT₂₂) gives 100% Comb while CRT gives 100% Disp. On the other hand, in the dashed lines, the assumptions were reversed, in which case RT₂₂ gives 100% disproportionation and CRT gives 100% combination, as has been proposed by Yamago.^{22, 27}

The extent of Disp/Comb for the mid-chain radical is not precisely known and has only been taken as the average of RT_{22} and RT_{33} .⁶⁵ In light of this and due to the best fitting between experimental and PREDICI, it was assumed that any termination involving tertiary mid-chain radicals (RT_{23} and RT_{33}) gives 100% disproportionation.^{34, 36} In fact, Asua *et al*²⁸ has proposed that the study conducted by Yamago *et al*²⁷ more accurately models how tertiary mid-chain radicals termination as opposed to chain-end radicals due to [P_3 •] > [P_2 •]. This gives further support of bimolecular termination involving mid-chain radicals terminating by disproportionation at room temperature. The experimental results can only be explained if one assumes that RT_{22} operates via combination while CRT gives products of disproportionation. This further validates the experiments conducted above, in which reactions that were kinetically tuned to promote RT vs. CRT gave a higher molecular weight shoulder.

To quantify the contribution of each reaction toward the decrease in chain-end functionality, the evolution of all products of termination were simulated with respect to time. In the present model, there are four pathways in which radicals can terminate: 1) CRT, the reaction between TPMA/Cu^{II}-P₂ and a chain-end radical, P₂[•]; 2) RT₂₂, the reaction between two chain-end radicals; 3) RT₂₃, the "cross-termination" between a chain-end radical and a mid-chain radical; 4) RT₃₃, the reaction between two mid-chain radicals. Based on the good fit between experimental and simulations in **Figure 6.6C**, the three reactions CRT, RT₂₃ and RT₃₃ were simulated to give disproportionated chains and RT₂₂ was set to give combined chains. **Figure 6.7** shows the distribution of products obtained by these four termination reactions.



Figure 6.7 Simulations of the contribution of CRT (black), RT₂₃ (red), RT₂₂ (green) and RT₃₃ (blue) to total termination vs. time under the initial [pMA-Br]₀:[TPMA/Cu^{II}]₀: [TPMA/Cu^{II}-Br]₀ ratios of (A) 1:1:0 (B) 1:2:0 and (C) 1:2:1 at room temperature.

For the ratio $[pMA-Br]_0:[TPMA/Cu^I]_0:[TPMA/Cu^{II}-Br]_0 = 1:1:0$ (Figure 6.7A), a surprising result is the dominance of the bimolecular "cross termination" between chain-end and mid-chain radicals (RT₂₃). So much, in fact, that after approximately 25 minutes, the majority of terminated chains underwent termination via cross termination. This is because the concentration of tertiary mid-chain radicals (P₃•) was greater than that of secondary chain-end radicals (P₂•) after only 5 minutes. This relatively higher concentration of mid-chain radicals results from the fast rate of backbiting (BB). In fact, backbiting was between 10 and 100 times faster than RT₂₂ due to the unimolecular nature of the reaction. The high abundance of mid-chain radicals in acrylate polymerization has previously been observed via EPR even at room temperature.³⁰ PREDICI simulations showed that after one hour, 50% of all terminated chains were terminated via RT₂₃ while surprisingly only 39% were terminated via CRT. Only within the first millisecond of the reaction, when [P₂•] was highest, did RT₂₂ dominate RT₂₃, as shown in the insert in Figure 6.7A. Finally, due to the slower reaction between two sterically hindered mid-chain radicals, RT₃₃ accounted for only 1% of all terminated chains.

The simulations under the more CRT promoting conditions of [pMA- $Br]_0:[TPMA/Cu^{I}]_0:[TPMA/Cu^{II}-Br]_0 = 1:2:0$ were similar to those using the 1:1:0 ratio, since the initial ratio of RT and CRT rates does not depend on [TPMA/Cu^{II}-Br]₀ (Equation 1). However, relatively more chains were terminated via CRT. This is due to a two-fold effect of the excess TPMA/Cu¹ on the overall rate of termination. Firstly, the faster P₂• trapping by TPMA/Cu¹ suppressed chain-end radical concentration thus slowing down the backbiting reaction and suppressing the rate of cross-termination, RT₂₃, by an order of magnitude. Secondly, this caused a slight initial increase in [TPMA/Cu^{II}-P], which resulted in a faster increase of the CRT rate. Under these initial conditions, CRT accounted for 57% of all terminated chains compared to 39% for the 1:1:0 ratio. Furthermore, at this 1:2:0 ratio, 7% of chains were terminated via RT₂₂ compared to 10% under the 1:1:0 ratio, as expected according to Eq. 6.1. Nonetheless, RT₂₃ still dominated all bimolecular radical-based termination events, accounting for 34% of all terminated chains.

Using the initial ratio [pMA-Br]₀:[TPMA/Cu^I]₀:[TPMA/Cu^{II}-Br]₀ = 1:2:1, only 4% of chains were terminated via RT₂₂. This is because the concentration of chain-end radicals was significantly suppressed by the quick and efficient trapping by the TPMA/Cu^{II}-Br deactivator present from the beginning. After one second, the concentration of chain-end radicals was [P₂•] \approx 7 x 10⁻⁸ M in the presence of the deactivator. In comparison, after one second but in the absence of initially added deactivator, $[P_2^{\bullet}] \approx 3 \times 10^{-7}$ M. Interestingly, the amount of CRT and RT₂₃ were 46% and 48%, respectively. Under these "most CRT promoting conditions," one would have expected the most amount of CRT according to Eq 6.1. This can be rationalized on the basis that the initial rate of CRT is suppressed by a factor of 50 due to the suppression of $[P_2^{\bullet}]$ by the initially added TPMA/Cu^{II}-Br deactivator. Since CRT requires the reaction between TPMA/Cu^{II}-P₂ and [P2[•]], the suppression of the latter will undoubtedly slow down the rate of CRT. Although the "most CRT-promoting conditions" did in fact lead to the most amount of disproportionation, they did not result in the most amount of chains being terminated via CRT. Thus, Eq 6.1 would be better referenced as a way to kinetically suppress RT₂₂ as opposed to kinetically promote CRT. The summary of the distribution of terminated polymer according to our simulations are summarized in Table 6.2. It should be noted that in the case of a polymerization reaction, the mid-chain radicals can also add to acrylate monomer leading to a branching point. The addition of this reaction could potentially change the contribution of mid-chain radical termination (RT₂₃ & RT₃₃) to the overall termination distribution since addition of P₃[•] to monomer regenerates a chain-end radical, P₂•.

[pMA-Br]: [L/Cu ⁱ]:[L/Cu ⁱⁱ -Br]	CRT (%)	RT ₂₃ (%)	RT ₃₃ (%)	RT ₂₂ (%)
1:1:0	39	50	1	10
1:2:0	57	34	2	7
1:2:1	46	48	2	4

Table 6.2 Product distribution of terminated polymer chains.

All percentages were calculated based on total terminated chains $Term_{tot}$ = [CRT]+[RT₂₃]+[RT₃₃]+2*[RT₂₂] since chains undergoing combination comprise two initial pMA-Br macroinitiators. For all cases L = TPMA.
The results presented here indicate that RT₂₂ operates predominately via combination whereas CRT gives products with the same molecular weight as the living chain. This is in contrast to the previous contribution by Yamago *et al.*, which concluded that acrylate chain-end termination occurs predominately (>99%) via disproportionation²⁷ while CRT gives coupling.²² In order to rationalize the results observed with the organotellurium systems studied by Yamago, we hypothesize that the •TeR radical is able to catalyze radical disproportionation via an H-TeR intermediate.⁶⁶

6.2.5 Conclusions

Termination reactions using a pMA-Br ATRP macroinitiator were utilized to shed light on the termination mechanism of polyacrylates in ATRP. Three different catalysts were used under various conditions to change the fraction of bimolecular chain-end radical termination (RT) to copper-catalyzed radical termination (CRT). Wherever the RT/CRT ratio was largest, a high molecular weight shoulder became apparent in the SEC traces. As this ratio was gradually decreased, the relative fraction of high molecular weight polymer decreased significantly. This indicates that the bimolecular radical termination of acrylates operates via combination while CRT gives terminated polymers of unchanged molecular weight. These results are in stark contrast to recent reports; therefore, PREDICI simulations were conducted to support our experimental findings. In fact, very similar results were observed for the experimental and simulated data for the TPMA-based system. It was found that due to the high initial radical concentration, bimolecular termination dominated only at the very first instants. After this initial influx of radicals, catalytic radical termination and backbiting dominated the fate of the secondary chain-end radical. Due to the relatively high concentration of mid-chain radicals relative to chain-end radicals, the amount of cross termination between mid-chain and chainend radicals (RT₂₃) was found to be more dominant than termination via two chain-ends (RT₂₂) and, in some cases, even more kinetically significant than CRT.

6.3 Catalyzed Radical Termination in the Presence of Tellanyl Radicals

6.3.1 Preface

The decomposition of the diazo initiator dimethyl 2,2'-azobis(isobutyrate) (V-601), generating the Me₂C[•](CO₂Me) radical, affords essentially the same fraction of disproportionation and combination in media with a large range of viscosity (C₆D₆, DMSO-*d*₆ and PEG 200) in the 25-100°C range. This is in stark contrast to recent results by Yamago *et al.* on the same radical generated from Me₂C(TeMe)(CO₂Me) and on other X-TeR systems (X = polymer chain or unimer model; R = Me, Ph). The discrepancy is rationalized on the basis of an unprecedented RTe[•]-catalyzed radical disproportionation, with support from DFT calculations and photochemical V-601 decomposition in the presence of Te₂Ph₂.

^{*}Work in this section was published: <u>**TG Ribelli**</u>, SMW Rahaman, R Poli, K Matyjaszewski. "Catalyzed Radical Termination in the Presence of Organotellanyl Compounds." *Chem. Eur. J.* **2017**, 23, pp 13879-13882. © 2017 Wiley

6.3.2 Introduction and Background

The mechanism of radical termination is of fundamental importance in polymer chemistry. Bimolecular radical termination can occur via either disproportionation (Disp) or combination (Comb). Disp results in two chains, one with an unsaturated chain-end and one with a saturated one, while Comb gives a single chain following C-C coupling.⁶⁷ The respective amounts of Disp and Comb highly depend on the nature of the radical species. For example, styrenes^{22, 68} and acrylonitrile⁶⁹ radicals undergo predominately Comb while methacrylates undergo both Disp and Comb.^{22, 70} The termination of acrylates has been of intense, ongoing debate with contrasting evidence in favor of either Comb or Disp.^{26, 68, 71}

Recently, Yamago *et al.* have put forth a few contributions towards the understanding of the radical termination mechanisms using a tellurium-mediated radical polymerization (TERP) system.^{27, 72-73} Various TERP macroinitiators, for instance poly(methyl methacrylate) (pMMA-TeR), poly(methyl acrylate) (pMA-TeR) and polystyrene (pSt-TeR) (R = Ph or Me) species with controlled molecular weight (MW) and narrow MW distribution, as well as corresponding low molar mass models (unimers), were synthesized and used as radical species precursors. The C-Te bonds were photolyzed, resulting in the pair of carbon- (R₀·) and tellurium-based (·TeR) radicals which then underwent spontaneous termination processes. The ·TeR radicals ultimately combine to form the RTe-TeR dimer, whereas the fate of the carbon-based radicals was investigated by NMR, SEC and MS to quantify the respective contributions of Disp and Comb, see **Scheme 6.3 (A and B)**. Furthermore, the generation of radicals via photolysis allowed these termination reactions to be investigated under a wide variety of conditions by varying temperature and solvent.

Scheme 6.3 (top): work using organotellurium initiators to generate carbon-based radicals from (A) TERP macroinitiators and (B) the unimer model of the pMMA-TeMe dormant species.^{27, 72-73} 2 (bottom): activation of the diazo compound V-601 to generate methacrylate radicals in the absence of tellurium compounds.

While the Disp/Comb ratio was as expected on the basis of previous literature reports for the pMMA[•] and pSt[•] radicals,⁷² it was surprisingly found that acrylate radicals resulting from a pMA-TePh macroinitiator terminate almost exclusively (99%) via Disp,²⁷ in contrast with several other previous^{25-26, 74} and subsequent⁷⁵ reports. In the most recent contribution,⁷³ it was shown that the product distribution depends on the reaction medium, a greater viscosity resulting in an increase of the Disp/Comb ratio. For example, 59% Disp was observed for the methacrylate unimer model compound Me₂C(TeMe)CO₂Me at relatively low viscosity ($\eta = 1.1$ mPas), whereas this amount increased significantly to 94% at $\eta = 84$ mPas at room temperature. Even more glaring was the use of the styrene unimer model complex CH₃(TeMe)CHPh in which case 14% Disp was observed at low viscosity ($\eta = 1.1$ mPas) and increased drastically to 99% at $\eta = 84$ mPas at room temperature. In order to rationalize these surprising results, Yamago and coworkers have put forth an "advanced collision model", which rests on the principle that Comb is more viscosity-sensitive than Disp, hence a viscosity increase would result in a more significant retardation of the Comb rate constant (k_c) than of the Disp constant (k_d).

We have also been interested in the termination mechanism of acrylates, particularly in the case when this is catalyzed by a transition metal complex such as certain Cu-based ATRP catalysts.^{48, 76-77} Initial studies have given strong indications that the Cu-catalyzed radical termination (CRT) overwhelmingly leads to Disp-type products in the ATRP of acrylates.⁴⁸ In addition, a more recent analysis of the termination products of acrylate radicals led to the conclusion that pMA radicals spontaneously terminate predominantly by Comb, in contrast to the recent report by Yamago *et al.*²⁷ These results, which will be reported separately,⁷⁸ led us to hypothesize that the presence of RTe[•] radicals may promote Disp. In order to verify this hypothesis, it was necessary to first investigate the fate of radicals related to those of the investigation by Yamago *et al.*, but obtained in the absence of RTe[•], and then to rationalize any observed differences.

We report here the use of the diazo initiator dimethyl 2,2'-azobis(isobutyrate) (V-601) as a radical precursor to study radical termination.⁷⁹ This compound, by either thermal or photochemical activation, yields a radical identical to one of those studied by Yamago *et al.*, see Scheme 6.8C. We show that the viscosity effects reported for the termination using the

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 $Me_2C(TeMe)-CO_2Me$ initiator are not observed in the absence of tellurium. Furthermore, introduction of Te_2Ph_2 in the photochemical V-601 decomposition in C_6D_6 increases the Disp/Comb ratio, indicating the action of PhTe[•] as a Disp catalyst, which was further supported by DFT calculations We propose a simpler model, based on a viscosity effect on the radical diffusion away from the solvent cage, to rationalize the previously reported results.

6.4.3 Results and Discussion

The Me₂C[•](CO₂Me) radical terminations, generated from V601, were carried out under conditions as close as possible to those used by Yamago *et al.* for the Me₂C(TeMe)CO₂Me decomposition. The reactions were carried out in the same media, except for PEG 200 instead of PEG 400 because of better NMR spectral resolution (however, the viscosity range of these two solvents partially overlap), and in a wider temperature range (25-100°C). The % Disp and Comb obtained in all our experiments are in **Figure 6.8**. Examination of these results shows quite clearly that the temperature and the solvent nature have little effect, if any, on the relative proportions of Disp and Comb, thus questioning the validity of the previous proposed "advanced collision model".⁷³

Figure 6.8. Fraction of disproportionation vs. (A) temperature and (B) viscosity for the isobutyryl radical in benzene (squares), DMSO (circles) or PEG 200/400 (triangles). Both the results obtained in this work from the V601 diazo initiator (filled symbols) and those reported by Yamago *et al.*⁷³ using the MMA-TeMe initiator (unfilled symbols) are shown for comparison. [V601]₀ = 10 mM (DMSO & C₆D₆) or 100 mM (PEG 200) heated or irradiated for 24 hours. Colored figures can be seen in Figure S12.

A possible way to rationalize the different outcome of the two decomposition experiments is suggested by the analysis of the termination reaction as a stepwise process: (*i*) formation of the Me₂C[•](CO₂Me) radical and a second partner radical within a solvent cage, (*ii*) escape from the cage and (*iii*) termination by Disp and/or Comb. For V-601, both isobutyryl radicals needed for the termination events are formed within the same solvent cage, hence

bimolecular termination may occur either within the solvent cage or after cage escape. For the tellurium-based system, on the other hand, cage escape is necessary for bimolecular radical termination between two isobutyryl radicals to occur. Thus, the observed difference in product distribution may result from the presence of side reactions between the Me₂C[•](CO₂Me) and tellanyl radicals within the cage.⁸⁰

Scheme 6.4. Proposed mechanism for C-based radical disproportionation catalyzed by RTe[•]. (*i*) Radical pair generation; (*ii*) solvent cage escape; (*iii*) bimolecular radical termination

A possible side reaction is β -H abstraction⁸¹ from the C-based radical by RTe[•], resulting in RTe-H and an alkene (R = Me, Ph), as shown in **Scheme 6.4**, step (a). This process has been previously shown for Cr⁸² and Co⁸³ complexes and can also be envisaged for any β -H-containing alkyl chains, such as pMMA, pMA, pSt and their unimolecular models. The RTe-H intermediate may then transfer the H atom to a second radical, yielding the saturated Disp product with regeneration of RTe[•] as shown in **Scheme 6.4** step (b). Note that the tellanyl radical produced in step (b) may dimerize but may also induce disproportionation of additional radicals that have already escaped from their solvent cages.

The feasibility of this catalytic disproportionation has been analyzed by DFT calculations on both steps (a) and (b) of the catalytic cycle proposed in **Scheme 6.4**, using the same MeTe[•] and Me₂C[•](CO₂Me) radicals of the experimental investigation presented in **Figure 6.8**. The DFT results are summarized in **Figure 6.9**. The unrestricted optimization of the MeTe[•] + Me₂C[•](CO₂Me) radical pair, carried out under the broken symmetry approach (total spin S = 0) yielded a loose van der Waals minimum (**vdW1**), the shortest contact being 4.68 Å between the Te atom and one Me H atom. This adduct is slightly stabilized (-0.8 kcal/mol) relative to the sum of the two separate radicals on the gas-phase electronic energy scale (ΔE_{gas}), but destabilized on the Gibbs energy scale after corrections for dispersion and solvation in MeCN ($\Delta G_{D3,MeCN}$ = (+3.5 kcal/mol). In this adduct, each partner maintains its full spin density (1.000 for MeCH[•](CO₂Me), of which 0.788 on the unsaturated C atom; -1.000 for MeTe[•], all on the Te atom). Step *a* is exoergic by 23.0 kcal/mol from the separated MeTe[•] + Me₂C[•](CO₂Me) reagents. We failed to locate the transition state for this step (**TS1**) but our attempts prove that this must be located very near the **vdW1** minimum and that the barrier is nearly non-existent. Likewise, step *b* starts from a very loose van der Waals minimum (**vdW2**, shortest contact of 5.5 Å), slightly stabilized on the ΔE_{gas} scale (-0.7 kcal/mol) but destabilized on the $\Delta G_{D3,MeCN}$ scale (+0.6 kcal/mol) relative to the sum of the two separate species. The transformation is again exoergic through a very low energy and relatively "early" transition state **TS2** with the Te-H bond stretched to 1.738 Å (relative to 1.676 Å in **vdW2**), an H…C distance of 1.852 Å, and a low imaginary frequency of 177i cm⁻¹. In **TS2**, the spin density is still mostly localized on the C atom (0.657), though a significant amount is already transferred to the Te atom (0.200), whereas the H atom being transferred has a very low spin density of -0.036.



Figure 6.9. Results of the DFT calculations for steps *a* and *b* of **Error! Reference source not found.**. (A) R = Me, R₁ = Me and (B) R = Ph, R₁ = H. The gas-phase electronic energies (ΔE_{gas}) and the solvation- and dispersion-corrected free energies ($\Delta G_{D3,MeCN}$, bold characters in parentheses) are in kcal/mol.

The above computations show the likelihood of the mechanism proposed in **Scheme 6.5** for the MMA model radical. Thus, the same process may also take place for the other organotellurium reagents, in particular for the controversial case of the pMA[•] radical. This was

further suggested by an analogous investigation on the PhTe[•]/MeCH[•](CO₂Me) radical pair, giving similar results (**Figure 6.9B**). At this point, a reasonable interpretation of the results published in the contribution by Yamago and coworkers⁷³ rests on the hypothesis that the solvent viscosity affects the rate of step (*ii*) (solvent cage escape). A viscosity increase slows down the radical diffusion away from the cage, providing a bias in favour of the RTe[•]-catalyzed Disp. As the solvent viscosity is lowered and thus radical escape from the cage becomes more efficient, a greater contribution of Comb is observed for all radicals generated from organotellurium compounds, approaching the "true" uncatalyzed fraction of Disp to Comb.^{27, 72-73} The presence of "in-cage" radical reactions has previously been shown using alkoxy radicals.⁸⁰

It is also noteworthy that the PSt[•] radical, known to lead preferentially to Comb,^{22, 68} was also forced to dramatically shift preference to yield a Disp/Comb ratio of 97/3 when generated from PSt-TePh under very high viscosity conditions.⁷³ We propose that this result can more easily be rationalized by the combination of a viscosity-dependent solvent cage escape and the PhTe[•]- catalyzed Disp process, than by the "advanced collision model" proposed by Yamago *et al.*⁷³

In order to substantiate the proposed tellanyl radical-catalyzed disproportionation, the V-601 photochemical decomposition at room temperature in C₆D₆ was carried out in the presence of variable amounts of Ph₂Te₂, known to generate PhTe[•] under irradiation. In this case, the putative PhTe[•]-catalyzed disproportionation may only occur after the V-601-generated radical pair has escaped from the solvent cage. Indeed, the Disp/Comb ratio increased from 50/50 in the absence of PhTe[•] radicals to 68/32 in the presence of 10 eq. of Te₂Ph₂ relative to V-601.

As a final remark, the Disp/Comb fraction obtained from organotellurium initiators appears to be much more skewed for pMA than for pSt and pMMA compared to generally accepted Disp/Comb ratios. This could be related to the trend of RTe-alkyl bonds bond strengths (*i.e.* the energy associated to the homolytic C-Te bond cleavage, step (*i*) in **Scheme 6.4**). Radicals forming a weaker bond presumably have a greater recombination barrier (Hammond principle) and may be able to escape faster from the cage and thus be less susceptible to undergo the catalyzed Disp process. The DFT calculations support this view (**Table 6.3**). For acrylate radicals, the occurrence of transfer reactions such as backbiting must also be carefully considered.^{75, 78}

Table 6.3. Homolytic bond strength calculated by DFT for a variety of organotellurium systems.

Alkyl radical	•TeR	ΔE_{gas} ,	$\Delta G_{D3,MeCN}$
		kcal/mol	kcal/mol
Me ₂ C•(CO ₂ Me)	•TeMe	41.4	31.7
Me ₂ C•(CO ₂ Me)	•TePh	37.4	33.8
MeCH•(Ph)	•TePh	37.1	34.3
MeCH•(CO ₂ Me)	•TePh	43.3	37.3

6.3.4 Conclusion

In conclusion, the V-601 diazo initiator was used to thermally or photochemically generate isobutyryl radicals, which were allowed to undergo bimolecular termination. The resulting fractions of disproportionated (Disp) and combined (Comb) products were found to remain essentially unchanged over a wide range of temperatures and solvent viscosities, contrary to recent reports using organotellurium initiators. In-depth DFT studies demonstrated that a previously undiscovered RTe[•] catalysed radical disproportionation reaction is viable, providing a likely interpretation of the previously published experimental results.^{27, 72-73} The proposed mechanism occurs via a β -H abstraction from the carbon-based radical forming an unsaturated chain end and a RTe-H intermediate. The latter species can then transfer the hydride to a second radical forming the saturated species and completing the catalytic cycle. At higher solvent viscosities, the alkyl/tellanyl radical pair diffuses more slowly out of the solvent cage and thus more time is available for the catalysed disproportionation to occur.

6.4 Effect of Ligand Structure on the L/Cu^{II}-R OMRP Dormant Species and its Consequences for Catalytic Radical Termination in ATRP

6.4.1 Preface

The kinetics and mechanism of Catalytic Radical Termination (CRT) of *n*-butyl acrylate (BA) in MeCN in the presence of Cu complexes with tridentate and tetradentate ligands was investigated both theoretically and experimentally. The tetradentate TPMA, TPMA*1, TPMA*2, TPMA*³ and the newly synthesized tridentate N-propyl-N,N-bis(4-methoxy-3,5-dimethylpyrid-2ylmethtyl)amine (BPMA^{*Pr}) as well as tridentate BPMA^{Me} were used as ligands. L/Cu^{II}X₂ (X = Cl or OTf) complexes were characterized by cyclic voltammetry (CV), UV-Vis-NIR and X-ray diffraction. Polymerization of *n*-butyl acrylate (BA) initiated by azobisisobutylnitrile (AIBN) MeCN in the presence of a L/Cu^I complex showed higher rates of CRT for more reducing L/Cu^I complexes. The ligand denticity (tri- vs. tetradentate) had a minor effect on the relative polymerization kinetics but affected the molecular weights in a way specific for ligand denticity. Quantification of the apparent CRT rate coefficients, k_{CRT}^{app} , showed larger values for more reducing L/Cu^I complexes, which correlated with the L/Cu^{II}-R (R = CH(CH₃)(COOCH₃)) bond strength, according to DFT calculations. The bond strength is mostly affected by the complex reducing power and to a lesser degree by the ligand denticity. Analysis of kinetics and molecular weights for different systems indicates that, depending on the ligand nature, the ratedetermining step of CRT may be either the radical addition to L/Cu^{1} to form the L/Cu^{1} -R species or the reaction of the latter species with a second radical.

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6.4.2 Introduction

Reversible deactivation radical polymerization (RDRP) has changed the scope of polymer science over the past two decades. At the heart of all RDRP methods is the concomitant growth of all chains through a reversible deactivation equilibrium between propagating radical and dormant species with retention of chain-end functionality. In atom transfer radical polymerization (ATRP), chain-end functionality of the dormant species is usually an alkyl halide (P_n-X). Through a reversible redox process with a transition metal, most commonly copper, polymer chain ends are repetitively activated by the reduced complex, *e. g.* by Cu¹/L, to form the propagating radicals which are quickly deactivated by the oxidized complex, *e. g.* X-Cu¹¹/L. The equilibrium L/Cu¹ + RX radical is characterized by the equilibrium constant K_{ATRP}, which corresponds to the k_a/k_d ratio (Scheme 6.5).⁸⁴ Several parameters, including solvent, temperature, pressure, alkyl halide chain-end and ligand, affect the value of K_{ATRP}.^{13, 85-92}



Scheme 6.5. Mechanism of normal ATRP showing conventional radical termination by combination or disproportionation

In order to polymerize less active monomers with higher R-X bond dissociation energies, complexes with larger values of K_{ATRP} should be used. This can be accomplished through appropriate ligand design. Over the past 20 years, a wide array of ligands has been synthesized which allow K_{ATRP} to be varied over 10 orders of magnitude. A linear correlation between redox potential, $E_{1/2}$, and K_{ATRP} is well-established.⁹³ This understanding has allowed for the development of the most active ATRP catalyst to date, TPMA*³, which efficiently polymerized acrylates utilizing only 5 ppm of Cu in ICAR ATRP.⁹⁴ **Figure 6.10** shows examples of four ligands that form very active ATRP catalysts with respective values of k_a in parenthesis. They can be applied to various low ppm Cu ATRP systems.^{11,12}



Figure 6.10. TPMA-based ligands that form very active ATRP catalysts when complexed to Cu. Activity (larger K_{ATRP} and k_a) increases from left to right correlating to a more negative reduction potential, $E_{1/2}$. Values in parenthesis are the activation rate coefficients, k_a , in M⁻¹s⁻¹ for methyl 2-bromopropionate (MBrP) either a) measured in MeCN at 25°C^{91, 94} or b) estimated from previously published electrochemical data.⁹³

While highly active Cu¹ catalysts permitted polymerization of a large range of monomers, they can also react with propagating radicals to form L/Cu^{II}-R species⁹⁵⁻⁹⁶, akin to organometallic meditated radical polymerization (OMRP).^{51, 97-98} The resulting L/Cu^{II}-R dormant species can terminate through catalytic radical termination (CRT), especially in the polymerization of acrylates.⁴⁷⁻⁴⁹ Initially, the dNbpy₂/Cu^I complex was shown to retard the rate of free radical polymerization (FRP) of acrylates.⁴⁹ Later, it was reported that the FRP of methyl acrylate in the presence of the most active TPMA*³/Cu^I complex required 30 hours to reach ~75% conversion, while in the absence of the Cu^I complex the same conversion was reached in ~30 minutes.⁴⁷ This retardation was attributed to Cu^I-promoted CRT, which has since been shown to be the dominant radical termination mechanism in acrylate ATRP systems.⁹⁹⁻¹⁰⁰

$$\frac{Rate_{t,Cu}}{Rate_{t,R}} = \frac{k_{t,Cu(II)} [L/Cu^{I}][R \cdot]}{k_{t,R} [R \cdot]^{2}} = \frac{k_{t,Cu(II)} [L/Cu^{I}]}{k_{t,R} [R \cdot]}$$
(Eq. 6.2)

Using **Eq. 6.2**, one can calculate the ratio of chains terminated via CRT to those terminated by conventional radical termination. This can be illustrated by analysis of two systems, a

traditional ATRP and a low ppm ATRP, using the following parameters: $[R^{\bullet}] = 1 \times 10^{-8}$ M; $k_{tR} = 3 \times 10^{8}$ M⁻¹s⁻¹ ⁹; $k_{t,Cu(II)} = 4 \times 10^{4}$ M⁻¹s^{-1 48}. Thus, in traditional ATRP where $[Cu^{I}] = 5.5 \times 10^{-3}$ M (1000 ppm vs monomer), CRT should account for 98.7% of total termination. However, even in the presence of 100 ppm of Cu^I, CRT should still account for 88% of terminated chains. Therefore, due to the high contribution of CRT in the ATRP of acrylates, it is important to understand this unwanted side reaction in order to learn how to suppress it or decrease its importance.

As shown in **Scheme 6.5**, various mechanisms may be conceived for CRT. The organometallic species, L/Cu^{II}-R, were proposed to be involved in the unimolecular β -H elimination⁴⁷ (a) and in the reaction with another radical to form a L/Cu^{III}-R₂ species, followed by reductive elimination¹⁰¹ (d). Other possibilities include direct β -H abstraction from the L/Cu^{II}-R dormant species by a propagating radical (b) or direct attack of the metal-bonded C atom in L/Cu^{II}-R (c) by a propagating radical (c). While routes (a) and (b) lead to the radical disproportionation products, routes (c) and (d) lead to radical coupling. The recent DFT study for the Cu/TPMA system suggest that β -H elimination pathway (a), leading to L/Cu^{II}-H and olefin, has an unrealistically high activation energy and its contribution should be neglected.¹⁰² Therefore pathways (b-d) should be responsible for CRT process and their contributions may depend on reaction conditions and ligand structure.



Scheme 6.6. Possible mechanisms of Cu-mediated CRT involving unimolecular reaction (route a) and bimolecular reactions (routes b-d), all proceeding through the L/Cu^{II}-R species.

Typical OMRP systems operating via a reversible deactivation mechanism undergo a radical addition to a metal in a low oxidation state, Mⁿ, resulting in an oxidized organometallic complex, Mⁿ⁺¹-R.^{52, 103} In order to maintain control over the polymerization, the equilibrium should be shifted to the side of dormant species, as shown in **Scheme 6.6**. The metal-carbon bond strength defines the value of K_{OMRP} and is greatly affected by the choice of ligand,⁵³ solvent, and nature of the radical.⁵⁴ While cobalt based systems have been the most extensively studied and successfully applied in OMRP, copper-based systems have seen no success in OMRP. This could be attributed to the high reactivity of the L/Cu^{II}-R dormant species and its ability to undergo catalytic radical termination (CRT).



Scheme 6.7. Mechanism of copper mediated OMRP operating under a reversible deactivation mechanism and the addition of catalytic radical termination (CRT) where a radical terminates with the L/Cu^{II} -R dormant species with rate coefficient $k_{tCu(II)}$.

Many OMRP reactions are initiated by thermal decomposition of diazo initiators such as AIBN to generate radicals which are quickly trapped by L/Mⁿ to form the L/Mⁿ⁺¹-R dormant species. This methodology has previously been carried out for copper-based systems where L/Cu¹ acts as a radical trap to form the L/Cu^{II}-R dormant species.⁴⁷ Kinetic and molecular weight analyses showed significant CRT when using TPMA^{*3} as a ligand. While the mechanistic understanding of Cu-mediated CRT is still inadequate, one can imagine the impact of ligand electronics and geometry on L/Cu^{II}-R reactivity. Thus, in the present study, various L/Cu^I complexes were used as OMRP trapping complexes in order to determine the effect that ligand structure has on CRT.

Both electronic and steric/geometrical properties of the ligand can significantly affect the L/Cu^{II}-R bond strength as well as the possible CRT mechanism. Unfortunately, little is known about L/Cu^{II}-R species¹⁰⁴⁻¹⁰⁸ due to their instability/high reactivity¹⁰⁹ although they have been discussed as possible intermediates in various systems.¹¹⁰⁻¹¹⁵ Thus, indirect methods such as those used in the present study must be conducted to better understand this elusive species. The results of experimental and computational studies presented here could pave the way for better understanding of catalytic cycles involving copper organometallic species not only in polymerizations but also in other systems.

6.4.3 Results

6.4.3.1 Ligand and complex syntheses and characterization

The L/Cu^I complexes used in the CRT studies were generated *in situ* from [Cu^I(MeCN)₄][BF₄] and the ligands from the tetradentate TMPA-based family (TPMA, TPMA^{*1}, TPMA^{*2}, TPMA^{*3})⁹³⁻⁹⁴ the tridentate BPMA^{Me116} and the new BPMA^{*Pr} (see **Scheme 6.8** for ligand structure). BPMA^{Me 116} and the TPMA-based ligands⁹³⁻⁹⁴ were prepared according to previously published procedures while BPMA^{*Pr} is reported for the first time here. The tridentate ligands have also been used to generate a few well-defined Cu^{II} derivatives (**Scheme 6.8**) although these

were crystallized for electrochemical characterization and to ensure correct ligand synthesis and are otherwise not used in this study. Complex **1** has already been reported¹¹⁷ but its X-ray structure has now been obtained with greater precision, whereas [Cu(BPMA^{Me})(MeCN)(OTf)][OTf] (**2**) and [Cu(BPMA^{*Pr})(H₂O)(OTf)][OTf] (**3**) are reported here for the first time.



 $[Cu^{II}(BPMA^{*Pr})(H_2O)(OTf)][OTf] (3)$

Scheme 6.8. Synthesis and X-ray structures of Cu^{II} complexes with the BPMA^{Me} and BPMA^{*Pr} ligands. The ligand H atoms in the structures of **2** and **3** have been omitted for clarity.

2 has a quasi-reversible reduction wave with $E_{1/2} = +113$ mV vs. SCE. Substituting the pyridine rings with the electron donating methoxy and methyl groups, as in **3**, causes a negative shift in the reduction potential, $E_{red} = 0$ mV, consistent with previous results using the tetradentate TPMA ligand scaffold. The latter complex shows a wave with reduced intensity of the return oxidation peak even at higher scan rates when using a Pt-disk working electrode. However, when a glassy carbon electrode was used, a pseudo-symmetric reversible wave was obtained with $E_{1/2} = +70$ mV. Compound **1** has a drastic negative shift in the half-wave potential ($E_{1/2} = -220$ mV) due to a more stable Cu^{II} species because of the stronger coordination of the Cl⁻ anions compared to weakly coordinating OTf⁻ anions. All electrochemical data for newly and previously synthesized complexes used in this report are presented in **Table 6.4**.

Table 6.4. Electrochemical data of copper complexes used in this study at 25°C. All measurements were conducted in MeCN with 0.1 M TBAPF₆ as a supporting electrolyte at a scan rate of 100 mV/s with $[Cu^{II}X_2]_0 = 1$ mM. All potentials are vs. SCE.

Complex ^a	E _{red} (mV)	E _{ox} (mV)	E _{1/2} (mV)	$\Delta E_p(mV)$	ref
1	-300	-145	-220	155	This work
2	61	174	174	113	This work
3	0	140	70	140	This work
[Cu(TPMA)][OTf] ₂	-25	69	22	94	118
[Cu(TPMA*1)][OTf] ₂	-130	-12	-69	118	118
[Cu(TPMA* ²)][OTf] ₂	-206	-60	-133	146	118
[Cu(TPMA*3)][OTf] ₂	-255	-100	-177	155	118

6.4.3.2 Polymerization Studies

To experimentally probe the effect of ligand denticity and its electron donating power on Cu-promoted CRT, OMRP reactions mediated by various L/Cu¹ complexes were conducted. Primary radicals were generated by thermal dissociation of azobisisobutyronitrile (AIBN). The propagating radical chains were then intercepted by the L/Cu¹ complex (L = BPMA^{Me}, BPMA^{*Pr}, TPMA and TPMA^{*n}; n = 1, 2, 3), promoting CRT. The monomer conversion and polymer molecular weights were analyzed in order to gain mechanistic insight into the CRT process.

OMRP reactions were first carried out at three different concentrations of TPMA/Cu¹. As shown in **Figure 6.11A**, after a short induction period, linear semi-logarithmic monomer conversion plots were observed at all [L/Cu¹]₀, indicating the establishment of a steady-state concentration of radicals. To reach monomer conversion of ~25%, it took 20, 45, 120 and 145 minutes for 0, 100, 500, 1000 ppm of Cu¹/TPMA. This is consistent with a higher concentration of dormant species and higher rate of CRT in the presence of greater amounts of L/Cu¹, as previously reported.⁴⁸ **Figure 6.11B** shows that, in the absence of L/Cu¹, the molecular weight decreases with conversion, consistent with FRP. Upon introduction of Cu¹/TPMA to the system, the molecular weights decreased dramatically as compared to FRP. At 25% monomer conversion, FRP gave polymers with molecular weights of ~1.5 x10⁶ while the reactions in the presence of L/Cu¹ gave polymers with molecular weights < 5x10⁵, indicating faster radical termination due to CRT. Interestingly, upon increasing the amount of L/Cu¹ in the system, molecular weights only

slightly decreased. At catalysts loadings of 100, 500 and 1000 ppm, the molecular weights were 4.7, 3.7, and 3.3 x 10^5 at ~30% conversion, respectively.



Figure 6.11 (A) Kinetics and (B) molecular weight data of the polymerization of n-butyl acrylate (BA) initiated by AIBN in the presence (OMRP) and absence (FRP) of TPMA/Cu¹ at 60°C. Initial molar ratios of reagents were [nBA]:[AIBN]:[TPMA]: [Cu¹(MeCN)₄][BF₄] = 160:0.2:2x:x (x = 0-0.16) at 60°C in 50% MeCN; [nBA]₀ = 3.48 M; 100 ppm = 0.016.

Next, the TPMA^{*n} ligand family was employed using the same amount of L/Cu¹ (500 ppm) to further assess the effect of reduction potential on the overall rate of Cu-promoted CRT. The overall rate of polymerization decreased progressively upon using more reducing L/Cu¹ complexes, as shown in **Figure 12.A**. Furthermore, using higher-activity catalysts, polymers with lower molecular weights were obtained. These two results show that CRT activity correlates with reducing power of the L/Cu¹ complex.



Figure 6.12 (A) Kinetics and (B) molecular weight data of *n*-butyl acrylate (BA) polymerization initiated by AIBN in the presence (OMRP) and absence (FRP) of L/Cu¹ (L = TPMA, TPMA^{*1}, TPMA^{*2}, TPMA^{*3}) at 60°C. Initial molar ratios were [BA]:[AIBN]:[L]: [Cu¹(MeCN)₄][BF₄] = 160:0.2:0.16:0.08 at 60°C in 50% MeCN; [BA]₀ = 3.48 M

Finally, analogous reactions were conducted using the tridentate BPMA ligand scaffold to determine the effect of denticity on CRT. Using BPMA^{Me}/Cu^I at a 1000 ppm loading, a slow and gradual increase in the rate was observed during the first hour, indicating some interactions between radical and BPMA^{Me}/Cu^I. The rate gradually increased over 60 minutes until the steady-state rate was the same as in FRP. Moreover, the molecular weights were lower than in FRP, indicating that this complex is mildly active in CRT.

The BPMA^{*Pr}/Cu¹ complex (reducing power similar to TPMA/Cu¹), resulted in a much more pronounced decrease in the polymerization rate compared to BPMA^{Me}/Cu¹, as shown in **Figure 6.13**. This complex also showed progressively decreasing rates upon increasing [L/Cu¹]₀, similar to the TPMA system. However, a strong decrease in molecular weights was observed upon increasing [L/Cu¹]₀ with *M*_n values of 1.3, 0.56 and 0.25 x 10⁶ at ~30% conversion when using 100, 500 and 1000 ppm of L/Cu¹, respectively. Interestingly, the kinetic data for BPMA^{*Pr}/Cu¹ was similar to those using TPMA, while molecular weight trends were quite different. This difference will be discussed later in the discussion section. Molecular weight analysis of all polymerization systems showed broad molecular weight distributions and little to no increase in molecular weight with conversion. This further indicates that the L/Cu¹ complexes used in this study are inefficient OMRP mediators and primarily act as catalysts for CRT.



Figure 6.13 (A) Kinetics and (B) molecular weight data of n-butyl acrylate (BA) initiated by AIBN in the presence (OMRP) and absence (FRP) of BPMA^{*Pr}/Cu^I at 60°C. Initial molar ratios were [nBA]:[AIBN]:[BPMA^{*Pr}]: [Cu^I(MeCN)₄][BF₄] = 160:0.2:2x:x (x = 0-0.16) at 60°C in 50% MeCN; [nBA]₀ = 3.48 M; 100 ppm = 0.016

The apparent rate constants of polymerization and molecular weights as a function of the reduction potential of the L/Cu^{II} complex are illustrated in **Figure 6.14**. This **plot** shows that the rate of CRT increases for more reducing L/Cu^{II} complexes.



Figure 6.14. Relationship between measured values of $E_{1/2}$ and both molecular weights (red) and rate of polymerization (blue). All values are for reactions using 500 ppm of L/Cu¹. The molecular weights for BPMA^{Me}/Cu¹ were measured using 1000 ppm L/Cu¹.

6.4.3.3 DFT Investigation of the OMRP Trapping Equilibrium

The above kinetic investigations discussed above pointed towards radical trapping by L/Cu^I to yield a L/Cu^{II} organometallic intermediate. The question can be asked whether the CRT activity correlates with the Cu^{II}-C bond strength. Thus, the Bond Dissociation Free Energies (BDFE) for all L/Cu^{II}-R species studied were estimated by DFT calculations. The ligands BPMA^{Me}, TPMA, TPMA^{*1-3} were used for all systems except for BPMA^{*Pr}, where the Pr group was simplified to an electronically similar Me group, BPMA^{*Me}. The calculations were carried out using BP86-D3 with the 6-311G(d,p) basis set for the light atoms (O,N,C,H) and the LANL2DZ(f) basis for Cu. Additional thermal and solvation corrections (in MeCN solution) were applied (see computational details). This is the same level of theory used by us recently for the exploration of the [(TPMA)Cu^{II}-H]⁺ formation by direct β-H atom transfer from a free radical.¹⁰²

Since the experimental CRT studies were carried out in MeCN, a stabilization of the L/Cu¹ species by solvent coordination (**Eq. 6.3**), affecting the OMRP equilibrium, is possible. This was confirmed by X-ray structural study of the [Cu¹(TPMA)(MeCN)][BPh₄] salt.¹¹⁹⁻¹²⁰ The MeCN coordination stabilizes [Cu¹(TPMA)]⁺ by 2.4 kcal/mol at the used level of theory, suggesting that the L/Cu¹ species should be coordinated by MeCN. The optimized geometry for the acetonitrile adduct [Cu¹(TPMA)(MeCN)]⁺ is in good agreement with the structure determined by X-ray.

$$[CuI(L)]+ + MeCN \rightleftharpoons [CuI(L)(MeCN)]+$$
(Eq. 6.3)

In order to give these calculations quantitative merit, the activation of the CH₃CH(Br)COOCH₃ ATRP initiator by the [Cu^I(TPMA)]⁺ system was investigated, because the K_{ATRP} of this equilibrium has been experimentally determined ($K_{ATRP} = 3.2 \times 10^{-7}$; $\Delta G_{ATRP} = 8.8$ kcal/mol) in MeCN at 22°C.⁸⁶ The computed ΔG_{ATRP} values are 10.2 and 7.8 kcal/mol with (**Eq 6.4**) and without (**Eq 6.5**) MeCN coordination to Cu^I, respectively. Both values are in good agreement with the experimentally determined value of 8.8 kcal/mol, confirming the suitability of this level of theory.

$$[CuI(TPMA)(MeCN)]^{+} + R-Br \rightleftharpoons [CuIIBr(TPMA)]^{+} + R^{\bullet} + MeCN$$
(Eq. 6.4)
$$[CuI(TPMA)]^{+} + R-Br \rightleftharpoons [CuIIBr(TPMA)]^{+} + R^{\bullet}$$
(Eq. 6.5)

 $R = CH(CH_3)COOCH_3$

Given the experimental and theoretical evidence of MeCN coordination to $[Cu^{I}(TPMA)]^{+}$, the free energy of MeCN addition (ΔG_{MeCN}) was also calculated for all other $[Cu^{I}(L)]^{+}$ complexes (Eq. 6.3). The Cu^{II}-R (R = CH(CH₃)COOCH₃) bond dissociation free energy (BDFE; Eq. 6.6) was combined with the MeCN coordination to yield Eq 6.7 as the operating OMRP equilibrium. The results are shown in Table 6.5.

$$[CuI(L)]+ + {}^{*}R \rightleftharpoons [CuIIR(L)]^{+}$$
(Eq. 6.6)
$$[CuI(L)(MeCN)]^{+} + {}^{*}R \rightleftharpoons [CuIIR(L)]^{+} + MeCN$$
(Eq. 6.7)

Table 6.5 Calculated ΔG values (in kcal/mol) for processes related to the $^{\circ}CH(CH_3)COOCH_3$ trapping by $[L/Cu^{l}]^{+}$. The values are corrected for solvation in MeCN.

L	BDFE ^a	ΔG_{MeCN}^{b}	$\Delta G_{\rm OMRP}^{\rm c}$
BPMA ^{Me}	14.1	-4.9	-9.2
BPMA* ^{Me}	16.1	-5.3	-10.8
ΤΡΜΑ	14.3	-2.4	-11.9
TPMA*1	15.1	-2.1	-13.0
TPMA* ²	15.8	-2.4	-13.4
TPMA* ³	17.6	-2.9	-14.7

^a ΔG associated to the reverse of **Eq. 6.5** (bond dissociation). ^b ΔG associated to **Eq. 6.3**. ^c ΔG associated to **Eq. 6.7**.

The values of BDFE for the TPMA^{*n} series correlate well with the CRT activity, each substitution of a py by a py^{*} donor resulting in a BDFE increase. This effect is electronic, not steric, because the increase of steric bulkiness upon py/py^{*} modification would lead to bond weakening. The CRT activity correlates better with ΔG_{OMRP} than with BDFE. In fact, the [Cu^I(L)]⁺ stabilization by MeCN coordination is ca. twice stronger for tridentate BPMA and BPMA^{*} systems than for the tetradentate TPMA^{*n} systems. In terms of correlation with E_{1/2}, the experimentally measured 199 mV decrease on going from the TPMA to the TPMA^{*3} system translates into an

expected ΔG_{OMRP} increase of ca. 4.1 kcal/mol under the assumption of constant "carbophilicity". This is in rather good agreement with the calculated ΔG_{OMRP} increase of 2.8 kcal/mol.

6.4.4 Discussion

Kinetically, a steady-state radical concentration should be defined by the balance of the rates of radical generation and termination, as shown by **Eq 6.8**, assuming that termination is a bimolecular reaction between Cu^{II}-R organometallic species and propagating radicals. Furthermore, the molecular weights should be defined by the ratio between the propagation and termination rates, as shown in **Eq 6.9**.

$$[R \cdot] = \frac{fk_{azo}[AIBN]}{k_{tCu(II)}[L/Cu^{II} - R]}$$
(Eq. 6.8)

$$DP = \frac{M_n}{MW_{nBA}} = \frac{Rate_p}{Rate_{CRT}} = \frac{k_p[M][R\cdot]}{k_{tCu(II)}[Cu^{II} - R][R\cdot]} = \frac{k_p[M]}{k_{tCu(II)}[Cu^{II} - R]}$$
(Eq. 6.9)

CRT should dominate relative to conventional (non-catalyzed) radical termination and therefore the latter can be neglected, due to the large amounts of L/Cu^I used. Until more kinetic data are available on the specific rates of addition, dissociation and termination (Scheme 3), only overall rate coefficients of CRT, k_{CRT}^{app} , can be estimated. Thus taking $k_{CRT}^{app} = k_{tCu(II)}[Cu^{II}-R]$, Eq 6.8 & 6.9 can be rearranged to give Eq 6.10 & 6.11, which were used to calculate apparent rate coefficients of Cu-mediated termination, as summarized in Table 6.5.

$$k_{CRT}^{app} = \frac{fk_{azo}[AIBN]}{[R \cdot]}$$
(Eq. 6.10)

$$k_{CRT}^{app} = \frac{k_p[M]}{[DP]}$$
 (Eq. 6.11)

Average values of k_{CRT}^{app} from eq. 9 and 10 were calculated at L/Cu^I loading of 500 ppm ([L/Cu^I]₀ = 1.74 mM). The redox potentials, values of K_{OMRP} and values of K_{ATRP} are also presented

in **Table 6.6**, in order to gain insight into the relationship between catalyst structure and reactivity.

Table 6.6. Values of $E_{1/2}$ (mV vs. SCE) and calculated BDE (kcal/mol) of the Cu^{II}-R bond for MBrP in MeCN at 25°C. Estimated overall rate coefficients of CRT, k_{CRT}^{app} (M⁻¹ s⁻¹), from kinetics and molecular weight data are also included.

Ligand	E _{1/2}	Komrp ^c	KATRP	Average k_{CRT}^{app} f
BPMA ^{Me}	174 ^a	5.6 x 10 ⁶	7.3 x 10 ^{-10d}	1.2 x 10 ¹
BPMA* ^{Pr}	70 ^a	8.3 x 10 ⁷	4.7 x 10 ^{-8d}	2.0×10^{1}
TPMA	22 ^b	5.3 x 10 ⁸	3.2 x 10 ^{-7e}	2.9 x 10 ¹
TPMA*1	-69 ^b	3.4 x 10 ⁹	5.9 x 10 ^{-6d}	4.5×10^{1}
TPMA* ²	-133 ^b	6.7 x 10 ⁹	1.5 x 10 ^{-4d}	5.5 x 10 ¹
TPMA* ³	-177 ^b	6.0 x 10 ¹⁰	4.2 x 10 ^{-4e}	9.6 x 10 ¹

^a This work. ^b From ref. ⁹³. ^c Calculated from ΔG_{OMRP} in Table 2 ^d Estimated from the β^{II}/β^{I} ratio (see text below) obtained from electrochemistry according to a modified version of the Nernst equation presenting in Ref 66. ^e Calculated.^{94 f} Averaged value of k_{CRT}^{app} estimated from kinetics (Eq 9) and molecular weight data (Eq 10) at 500 ppm [Cu^I]₀.

Table 6.6 shows that the more reducing the L/Cu¹ complexes have larger values of K_{OMRP}. Indeed, Cu^{II} species with more negative reduction potential should be relatively more stable. This is also the reason for the increase in K_{ATRP} for more active catalysts. Also, the rate of Cu-mediated termination increases with more ATRP active catalysts. Interestingly, the magnitude by which these three parameters are affected by the redox potential is dramatically different. It has been reported that ln(K_{ATRP}) increases linearly with the reduction potential with an overall increase by 6 orders of magnitude for the six complexes studied. On the other hand, K_{OMRP} should increase only by four orders of magnitude, according to the DFT calculations. However, the apparent rate coefficients of CRT, k_{CRT}^{app} , increased only by one order of magnitude. Thus, termination is less sensitive to the electronic properties of the L/Cu¹ complex than the two K parameters. It is worthy to note that although the calculated values of K_{OMRP} at room temperature are large, the fraction of Cu^{II}-R relative to total copper should be small (for BPMA and TPMA systems), due to the small concentration of radicals ([R[•]] ~ 1 x 10⁻⁹ M). This fraction should further decrease upon increasing temperatures due to a decrease in K_{OMRP}. A comparison of the overall rates of Cu mediated termination with K_{OMRP} and K_{ATRP} with respect to redox potential is shown in **Figure 6.15**.



Figure 6.15 Relationship between reduction potential and K_{ATRP} (red) for MBrP in MeCN at 25°C, K_{OMRP} for acrylate radical (blue) and apparent rate coefficient of Cu mediated termination, k_{CRT}^{app} (green). The y-axis values were arbitrarily scaled to zero for the BPMA^{Me} system (E_{1/2} = 174 mV) after natural In were taken in order to emphasize the relative slopes of the three parameters.

All of the data presented in this study are consistent with the formation of a L/Cu^{II}-R intermediate which reacts with another radical, resulting in termination. However, as alluded to above, the formation of the L/Cu^{II}-R intermediate does not imply that termination must happen, i.e. the trapping process could be reversible. Recent experiments showed that dissociation of L/Cu^{II}-R may be fast at temperatures above $0^{\circ}C.^{55}$

According to **Eq 6.8 & 6.9**, the rates of polymerization and molecular weights should scale as $1/k_{tCu(II)}[L/Cu^{II}-R]$ but, due to the intermediacy of the organometallic species, its concentration at this stage can only be estimated by DFT calculations. As shown in **Scheme 6.7**, two limiting scenarios can be envisaged; one in which the OMRP equilibrium is established and one in which it is not. The establishment of the OMRP equilibrium depends on whether the L/Cu^{II}-R species is able to dissociate back to the radical and L/Cu^{II} before the complex undergoes CRT with a second radical. If equilibrium cannot be established because of fast termination, the rate limiting step may be the addition of a radical to L/Cu^{II}, followed by a fast reaction of L/Cu^{II}-R with growing radicals. Conversely, when the equilibrium can be established, the termination of a second radical with L/Cu^{II}-R, leading to CRT, becomes the rate determining step. Under these conditions, the radical concentration (rate of polymerization) and molecular weights will be differently defined, by two limiting expressions presented in **Eq 6.12-6.15**, as derived in the Supporting Information.

If, $k_{tCu(II)}[R^{\bullet}] >> k_{dis}$

$$DP = \frac{M_n}{MW_{nBA}} = \frac{k_p[M]}{k_{add}[L/Cu^I]}$$
(Eq. 6.12)

$$[R \cdot] = \frac{fk_{azo}[AIBN]}{k_{add}[L/Cu^{I}]}$$
(Eq. 6.13)

If, $k_{dis} \gg k_{tCu(II)}[R^{\bullet}]$

$$DP = \frac{M_n}{MW_{nBA}} = \frac{k_p[M]}{k_{tCu(II)}[L/Cu^I][R \cdot]K_{OMRP}}$$
(Eq. 6.14)
$$[R \cdot] = \sqrt{\frac{fk_{azo}[AIBN]}{k_{tCu(II)}[L/Cu^I]K_{OMRP}}}$$
(Eq. 6.15)

In the case of $k_{tCu(II)}[R^{\bullet}] \gg k_{dis}$, both rate of polymerization and molecular weights will scale inversely with $[L/Cu^{I}]$. However, for the scenario in which $k_{dis} \gg k_{tCu(II)}[R^{\bullet}]$, molecular weights could scale with $1/k_{tCu(II)}K_{OMRP}$ and rates will scale with $1/(k_{tCu(II)}K_{OMRP}[L/Cu^{I}])^{1/2}$. Indeed, when $[L/Cu^{I}]_{0}$ was increased 10 times, the molecular weights obtained in the presence of BPMA*^{Pr}/Cu^I, decreased by a factor of 10 but only by a factor of 1.4 for TPMA/Cu^I. This indicates that these two complexes operate under two different kinetic regimes. This suggests that BPMA*^{Pr}/Cu^I undergoes faster CRT relative to dissociation, with MW defined by **Eq 6.12**. On the other hand, for the TPMA/Cu^I system, an OMRP equilibrium can be established and therefore the molecular weights should follow **Eq 6.14**. Hence, increasing $[L/Cu^{I}]_{0}$ will produce more L/Cu^{II}_{-} R but the $[L/Cu^{I}][R^{\bullet}]$ product could stay approximately constant, effectively showing little dependence of the molecular weight on $[L/Cu^{I}]_{0}$. For all systems, increasing $[L/Cu^{I}]_{0}$ showed a decrease in rate of polymerization since rates will scale with either $1/[L/Cu^{I}]$ or $1/[L/Cu^{I}]^{1/2}$. It was recently proposed that CRT may proceed by radical coupling via a L/Cu^{III}R₂ intermediate .¹⁰¹ The [Cu^{II}(BPMA*^{Pr})(R)] complex has a weakly coordinated MeCN ligand which decreases the steric hindrance at the Cu^{II}-R bond. This makes the complex more susceptible to accept a second incoming radical, as shown in the top of **Scheme 6.9**. On the other hand, for the [Cu^{II}(TPMA)(R)] complex to accept another radical, ligand rearrangement (arm opening) may be necessary and this would effectively slow down the CRT process, as shown in the bottom of **Scheme 6.9**. The termination in this case may also proceed by the direct reaction of a L/Cu^{II}-R complex with an incoming radical by H-abstraction or addition to the metal bonded chain.

Scenario 1: $[R\bullet]k_{tCu(II)} > k_{dis}$



Scenario 2: k_{dis}>[R]k_{tCu(II)}



Scheme 6.9. Two possible scenarios in which the OMRP equilibrium is not established (top) and one in which it is (bottom). Arrow thickness corresponds to relative rates. For each scenarios, the radical in the second step may attack either the β -H atom, the metal-bonded C atom or the metal, according to pathways (b), (c) and (d) in Scheme 2, respectively

When analyzing the results related to the geometrically similar TPMA^{*n} family of ligands the more reducing L/Cu¹ complexes yields both a slower rate of polymerization and lower molecular weights, as shown in **Figure 6.13**. At the same $[Cu^1]_0 = 500$ ppm, the measured molecular weights are ~ 40, 32, 21, and 13 x 10⁴ for TPMA, TPMA^{*1}, TPMA^{*2} and TPMA^{*3}, respectively. These systems, structurally similar to the parent TPMA system, may also operate according to scenario 2, (bottom of **Scheme 6.7** and **Eq's 6.14 & 6.15**), hence the molecular weights should depend on $1/k_{tCu(II)}[Cu^1][R^*]K_{OMRP}$ with rates depending on $1/(k_{tCu(II)}[L/Cu^1]K_{OMRP})^{1/2}$. As shown in **Table 6.6**, K_{OMRP} increases moving from TPMA to TPMA^{*3} which would explain the lower molecular weights. Furthermore, since MW also varies with $1/k_{tCu(II)}$, it is possible that the observed molecular weight decrease is due to a change both in K_{OMRP} and $k_{tCu(II)}$.

The termination in ATRP of acrylates can proceeds by either coupling or disproportionation. There is a debate in recent reports if the preference for disproportionation (supported by computations) can originate from tertiary radicals formed by backbiting.²⁷⁻²⁸ In the presence of L/Cu¹ or Cu⁰, experiments show preference for disproportionation-like or coupling-like products, depending on reaction conditions and ligands.^{18,24} To better understand the mechanism of Cu-induced CRT, it is important to understand the termination mechanism of acrylate radicals. Thus, our future efforts will focus on further probing the CRT mechanism via a combination of experimental and computational work.

6.4.5 Conclusions

A new, electron rich tridentate ligand, BPMA^{*Pr} was synthesized and compared with the less electron-rich BPMA^{Me} ligand and with several tetradentate TPMA^{*n} (n = 0-3 ligands). The complexes were characterized by cyclic-voltammetry, UV-Vis and X-ray diffraction. L/Cu¹ complexes were formed in situ and studied as CRT catalysts in the polymerization of n-butyl acrylate. The complexes with more negative redox potentials and higher ATRP activity show higher activity in CRT, while the ligand denticity (tridentate *vs.* tetradentate) may determine the rate limiting step of CRT. The effect of E_{1/2} of Cu complexes on K_{ATRP} is larger than on k_{CRT}^{app} . The calculated K_{OMRP} values correlate well with the apparent rates of CRT. The molecular weight and kinetic analyses show that two different kinetic regimes are possible, depending on the relative

rates of dissociation of the OMRP dormant species vs. its reaction with a second radical. If $k_{tCu(II)}[R^{\bullet}] > k_{dis}$, then the rate of termination depends on $k_{add}[Cu^{I}][R^{\bullet}]$ and molecular weights decrease for larger values of $[L/Cu^{I}]_{0}$. However, if $k_{dis} > k_{tCu(II)}[R^{\bullet}]$, then the OMRP equilibrium can be established and the rate of termination depends on $k_{tCu(II)}K_{OMRP}$ and molecular weights do not depend on $[L/Cu^{I}]$. The details of the intimate mechanism leading from the $L/Cu^{II}R$ species to the regeneration of the L/Cu^{I} catalyst and the terminated chains, however, remain elusive. Additional investigations aimed at clarifying these details are in progress and will be reported in due course.

6.5 Mechanistic Studies of Copper-Catalyzed Termination of Acrylates

6.5.1 Preface

The mechanism of copper(I) catalyzed radical termination (Cu¹-CRT) of acrylates was examined in both stock (i.e. wet) and dry acetonitrile (MeCN or d_3 -MeCN) or dimethylformamide (DMF). Two macroinitiators, one with a hydrogenated poly(methyl acrylate) backbone, pMA-Br, and one with a deuterated backbone, p(d_3)MA-Br, were synthesized *via* Ag⁰-mediated ARGET ATRP and fully characterized *via* MALDI-TOF-MS and NMR. Under Cu¹-CRT promoting conditions i.e. [L/Cu¹]₀ > [pMA-Br]₀ and in stock solvents, the terminated pMA-Br macroinitiator had saturated chain ends (pMA-H) without observation of an unsaturated alkene end group. However, in carefully dried solvents, a second, smaller distribution corresponding to coupled products was observed. Model studies using the small molecule methyl 2-bromopropionate (MBrP) as an acrylate mimic indicate a slower overall rate of termination. NMR analysis revealed that the majority of the product is the coupled dimer while formation of the saturated species is formed later in the reaction. All of the synthesis, termination reactions and analysis were conducted by myself other than the MALDI-TOF-MS which was conducted with the help of Logan Plath.

6.5.2 Introduction

Controlled radical polymerization techniques have revolutionized polymer science over the past two decades due to their ability to synthesize polymers with predetermined and tunable molecular weights and architectures.^{5, 121} One of the most commonly used techniques is atom transfer radical polymerization (ATRP).^{4, 122-123}Generally, ATRP uses a copper catalyst in the reduced L/Cu^I state to activate a dormant (macro)alkyl halide, P_n-X, generating a free radical, P_n[•], and the oxidized deactivator complex, L/Cu^{II}-X. The radical can propagate with a few monomer units before being deactivated by the L/Cu^{II}-X complex, thus regenerating the dormant alkyl halide and reduced L/Cu^I species, as shown in **Scheme 6.10A**.

Since ATRP's inception in 1995, various studies have been conducted in order to better understand the mechanism of atom transfer⁵⁹ and also side reactions occurring at the metal center.¹²⁴ One of these side reactions involves interaction of the L/Cu^{II}-Pn, as shown in **Scheme 6.10B**. The oxidative association and reductive dissociation of radicals at metal centers is the premise of organometallic mediated radical polymerization (OMRP) operating *via* a reversible termination mechanism.^{51, 98, 125-126} OMRP has been successful for both conjugated and unconjugated monomers with various cobalt complexes.^{51, 54, 127-128} Copper complexes, however, have so far been unable to successfully mediate OMRP. This arises, at least in part, from the aptitude of the L/Cu^{II}-Pn organometallic species to undergo catalytic radical termination (CRT), which results in dead polymer chains and regeneration of the L/Cu^{II} complex, as shown in **Scheme 6.10C**. Indeed, CRT has been shown to be the prevalent termination mechanism in ATRP of acrylates with very reactive Cu complexes.^{47, 129-130} Thus, there has been a need to understand and quantify various aspects of the OMRP and CRT mechanisms with copper catalysts.

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Scheme 6.10 A) ATRP equilibrium with copper catalysts B) organometallic mediated radical polymerization (OMRP) equilibrium operating *via* a reversible termination mechanism (Mtⁿ = Co^{II}, Fe^{II}, Cu^{II}, Mo^{III}, Cr^{II}, Os^{II} and Ti^{III}) and C) copper catalyzed radical termination (CRT) in which the L/Cu^{II}-P_n organometallic intermediate can react with solvent or a second radical to give terminated chains and regenerate L/Cu^I.

Many of the previous studies on CRT have been conducted in the presence of Cu⁰, either in the form of wire, powder, or *in situ* generation *via* disproportionation of L/Cu^{1,22,49} A recent contribution has shown that Cu⁰ also catalyzes the termination of radicals and indeed dominates both Cu¹-CRT and conventional bimolecular radical termination in supplemental activator and reducing agent (SARA) ATRP.⁶⁰ Thus, in the presence of Cu⁰, it is difficult to differentiate between Cu⁰- and Cu¹-CRT, which could operate *via* different mechanisms. In order to analyze solely the Cu¹-CRT, we previously examined "termination" reactions of a pMA-Br macroinitiator in acetonitrile (MeCN), a solvent known to suppress the catalyst redox disproportionation. Subsequent GPC and kinetic analyses revealed that conventional radical termination of acrylates occurred predominantly *via* combination while Cu¹-CRT resulted in dead-chains with a molecular weight similar to the initial macroinitiator, and thus were deemed "disproportionation-like." Furthermore, Yamago *et al* conducted similar experiments in toluene and found that the chain-ends were completely saturated, although the possibility of Cu⁰-CRT could not be ruled out.²²

6.5.3 Experimental

Synthesis of pMA-Br

A mixture of ethyl α -bromoisobutyrate (EBiB; 0.390 g, 2 mmol), Cu^{II}Br₂ (2.23 mg, 0.02 mmol), TPMA (3.2 mg, 0.022 mmol), 5 mL of MA (4.75 g, 0.05 mol) and 5 mL of dimethylformamide (DMF) were added to a Schlenk flask. The flask was sealed and subjected to three freeze-pump-thaw cycles to remove oxygen. This degassed solution was charged into a second, nitrogen-purged Schlenk flask containing 10 cm of newly purchased Ag⁰ wire (d = 2 mm) and a stir bar. The flask was sealed and placed in an oil bath at 50°C. Samples were taken periodically to measure conversion. The polymerization was stopped by opening the flask to air when monomer conversion reached ~80%. Residual monomer was removed using a rotary evaporator. Polymer was precipitated in a mixture of H₂O:MeOH = 4:1 and the solvent was decanted. The polymer was then washed with water to remove any residual copper. The polymer was taken up in THF and dried with MgSO₄, filtered, and the THF was then evaporated. The remaining polymer was dried under vacuum at 60°C for 24 hours to give pure pMA–Br macroinitiator. Characterization via ¹H NMR (**Figure 6.16**) and MALDI-TOF-MS (**Figure 6.17**) reveal a pMA-Br macroinitiator with >99% chain-end functionality.





Figure 6.16 ¹H NMR (500 MHz; CDCl₃) spectrum of the pMA-Br ATRP macroinitiator with assigned peaks.

Figure 6.17. MALDI-TOF-MS mass spectrum of the synthesized pMA-Br macroinitiator: full mass spectrum and zoomed inset for n =16-18 (m/z range 725-3800) and selected peak (n = 17) showing the experimental isotopic distribution (black) against the simulated isotopic distribution (red).

Synthesis of $p(d_3)MA$ -Br

Due to the high price of d_3 -MA, a slightly modified procedure was used. A mixture of ethyl α -bromoisobutyrate (EBiB; 0.195g, 0.22 mmol), Cu^{II}Br₂ (0.5 mg, 0.0022 mmol), TPMA (0.7 mg, 0.0025 mmol), 1.05 mL of MA (1 g, 0.011 mol) and 1 mL of dimethylformamide (DMF) were added to a Schlenk flask. The flask was sealed and subjected to three freeze-pump-thaw cycles to remove oxygen. This degassed solution was charged into a second, nitrogen-purged Schlenk flask containing 2 cm of newly purchased Ag⁰ wire (d = 2 mm) and a stir bar. The flask was sealed and placed in an oil bath at 50°C for 2 hours. The polymerization was stopped by opening the flask to air when monomer conversion reached ~50%. Residual monomer was removed using rotary evaporator. Polymer was precipitated in a mixture of H₂O:MeOH = 4:1 and the solvent was decanted. The polymer was then washed with water to remove any residual copper. The polymer was taken up in THF and dried with MgSO₄, filtered, and the THF was then evaporated. The remaining polymer was dried under vacuum at 60°C for 24 hours to give pure p(d_3)MA–Br macroinitiator. Characterization via ¹H NMR (**Figure 6.18**) and MALDI-TOF-MS (**Figure 6.19**) reveal a pMA-Br macroinitiator with C-Br chain-end and approximately 97% deuterium incorporation.



Figure 6.18. ¹H NMR (500 MHz; CDCl₃) spectra of the $p(d_3)$ MA-Br ATRP (DP_{avg} = 24) macroinitiator with assigned peaks showing residual proton in the polymer backbone resulting from incomplete

deuterium incorporation with an average number of hydrogen in the backbone equal to 2.1. This correlates to \approx 97% deuterium incorporation in monomer.



Figure 6.19. A) Full MALDI-TOF-MS mass spectrum of $p(d_3)$ MA-Br with insert showing a difference of 89.04 Da between peaks, corresponding to the molecular weight of d_3 -MA and B) comparison between the simulated and experimental mass spectra for the $p(d_3)$ MA-Br (DP = 24) isotopic envelope.

Termination Reaction of pMA-Br or p(d₃)MA-Br

Cu^IBr (0.029 g, 0.2 mmol) and TPMA (0.064 g, 0.22 mmol) were added to a Schlenk flask under nitrogen. The flask was sealed and placed under vacuum for 15 minutes and then purged with nitrogen. This process was repeated three times. 5 mL of degassed, dry solvent (MeCN or d_3 -MeCN) was charged into the flask using an airtight syringe to give a 40 mM solution of [Cu^I(TPMA)Br]. The macroinitiator solution (pMA-Br, $M_n = 3200$ or p(d_3)MA-Br, $M_n = 2500$) was prepared by first taring a glass pipette on a balance, gathering the maximum amount of macroinitiator in the pipette, and measuring the mass transferred to the Schlenk flask by difference. This was done until 0.32 g of pMA-Br or 0.27 g of p(d_3)MA-Br were transferred to the Schlenk flask. This flask was then placed under vacuum for 15 minutes and purged with nitrogen. This process was repeated three times. 5 mL of degassed, dry solvent (MeCN or d_3 -MeCN) was charged into the flask using an airtight syringe to give a 20 mM solution of macroinitiator. The solution containing the copper complex was then added to the macroinitiator solution to begin the reaction. The reaction was placed in an oil-bath at 25°C for 24 hours. Upon 24 hours, the reaction was exposed to air and quenched with CDCl₃ which was subjected to NMR analysis.
Termination Reaction for methyl 2-bromopropionate (MBrP)

Cu^IBr (0.029 g, 0.2 mmol) and TPMA (0.064 g, 0.22 mmol) were added to a Schlenk flask under nitrogen. The flask was sealed and placed under vacuum for 15 minutes and then purged with nitrogen. This process was repeated three times. 5 mL of dry, degassed solvent (MeCN, d_3 -MeCN or d_7 -DMF) was then charged into the flask using an air-tight syringe to give a 40 mM solution of [Cu^I(TPMA)Br]. Then, 11.1 uL of methyl 2-bromopropionate (MBrP; 16.7 mg, 0.1 mmol) was added to a second flask equipped with a stir bar and an airtight, quartz cuvette under nitrogen. 5 mL of dry, degassed solvent (MeCN, d_3 -MeCN or d_7 -DMF) was then charged into the flask using an air-tight syringe to give a 20 mM solution of MBrP. This was used as the solvent baseline for UV-Vis. The solution containing the copper complex was then added to the MBrP solution to begin the reaction. The increase in [Cu^{II}(TPMA)Br]⁺ was monitored via UV-Vis-NIR spectroscopy.

6.5.4 Results and Discussion

The residual moisture in the reaction media has been proposed to be most contributing factor towards chain-saturation by Yamago.²² This was seemingly confirmed by the purposeful addition of MeOD to the termination reaction in toluene. MALDI-TOF-MS analysis revealed pMA-D chain-ends as opposed to pMA-H chain-end in the absence of MeOD.²²

6.5.4.1 Termination of pMA-Br in Stock Solvents

The termination of pMA-Br was first investigated in "dry" solvents purchased directly from Sigma Aldrich. As shown in **Figure 6.20**, the product distribution of the termination reaction was independent of the solvent used. All reactions gave saturated chain ends, pMA-H, with very few <3% of coupled chains. In MeCN, a small species attributed to the [K⁺] adduct was observed while this peak was not observed in *d*₃-MeCN or DMF and is likely attributed to preparation of the sample for MALDI-TOF-MS. Nevertheless, even in deuterated solvent, the lack of a deuterium chain-end indicates the hydrogen is not arising from solvent.



Figure 6.20 MALDI-TOF-MS spectra of the termination of pMA-Br in (top) MeCN, (middle) d_3 -MeCN) or (bottom) DMF and experimental peak (black) in d_3 -MeCN (DP = 17) and simulation (red) under the initial conditions [pMA-Br]:[CuBr]:[TPMA] = 1:2:2.1 at 25°C; [pMA-Br]_0 = 10 mM.

These results are consistent with previously published results by Yamago²² and Whittaker et al¹³¹ who used [Cu^I(Me₆TREN)Br] in toluene and Cu⁰/Me₆TREN in DMSO, respectively for which fullysaturated chains were observed with little to no evidence of combined or disproportionated products. Whittacre attributed the saturation to chain-transfer to ligand while Yamago proposed hydrolysis of the L/Cu^{II}-R intermediate. In these experiments, only a slight excess of TPMA relative to CuBr was used which would give a maximum number of chains terminated by transfer to ligand at 10%. It is unlikely that transfer to [Cu^{II}(TPMA)Br]⁺ occurs since UV-Vis indicates only one species is present in solution. However, in these solvents, the water content was in excess of 200 ppm which is in excess of [pMA-Br]₀. Thus, the termination reactions were conducted in carefully dried solvents.

6.5.4.2 Termination of pMA-Br in Dry Solvents

MeCN, d_3 -MeCN and DMF were refluxed over CaH₂, distilled and stored over activated molecular sieves for 24 hours. A notable difference arises changing from stock MeCN to dry MeCN (Figure 6.21 Top). While 80% of chains were still saturated, a noticeable peak arises at approximately 2-times the molecular weight of the macroinitiator indicating 20% of chains underwent termination via combination. Indeed, this was simulated to have ethyl α isobutyrate (EiB) initiating fragments to give EiB-pMA-EiB. There was also the slight occurrence of potassium ionized chains. The reaction in d_3 -MeCN gave > 99% saturated chain ends. The second, smaller species is the [pMA-H Cu⁺] ionized chains. The termination reaction in "dried" DMF showed slightly more coupled chains than stock DMF but still > 95% of chains were saturated. A new peak was observed consistent with either the loss of 16.05 or gain of 69.99 Da compared to the monoisotopic peak of pMA-H. Although this peak cannot be definitely determined, this is consistent with a loss of CH₄. To assess the impact of residual moisture, even in a dried solvent, a larger concentration of macroinitiator was used. At $[pMA-Br]_0 = 30$ mM, the fraction of residual moisture should be significantly less than the number of total chains (previously [pMA-Br]₀ = 10 mM). Interestingly, this reaction also gave saturated chain ends with little evidence of coupling or disproportionated products.



Figure 6.21 MALDI-TOF-MS spectra of the termination of pMA-Br in dry solvents (top) MeCN, (middle) d_3 -MeCN) or (bottom) DMF and experimental peak (black) in d_3 -MeCN (DP = 17) and

simulation (red) under the initial conditions [pMA-Br]:[CuBr]:[TPMA] = 1:2:2.1 at 25°C; [pMA-Br]₀ = 10 mM.

The kinetics of the termination reactions can be conveniently tracked via the accumulation of L/Cu^{II}-Br with time analyzed via UV-Vis-NIR spectroscopy. As shown in **Figure 6.22A**, the most termination occurred in MeCN followed by d_3 -MeCN and then DMF. This is surprising since K_{ATRP} is largest in DMF and therefore, [R[•]] should be largest resulting in the fastest rate of radical termination. The accumulation of L/Cu^{II}-X with time was fit to the F(Y) or G(Y) function for conventional radical termination or catalyzed radical termination, respectively. As shown in **Figure 6.22B**, the reactions in MeCN or d_3 -MeCN had a slight upward curvature when fitting the data to F(Y) indicating radicals are terminating faster than expected by conventional radical termination. Contrary, the reaction in DMF exhibited a linear F(Y) vs. time fitting for the first 7 hours which then turned concave down. It is notable that there was no observable kinetic isotope effect or formation of pMA-D chains (**Figure 6.22B** showed G(Y) vs. time plots for MeCN and d_3 -MeCN indicating catalyzed radical termination with the rate law: $Rate_{CRT} = k_{CRT}[L/Cu^I][R[•]]$ is dominating the termination pathways.



Figure 6.22 (A) Evolution of $[Cu^{II}(TPMA)Br]^+$ with time for the termination of pMA-Br and the fitting to the (B) F(Y) function for conventional radical termination or (C) G(Y) function for catalyzed radical termination in dry MeCN, d_3 -MeCN or DMF under the initial conditions [pMA-Br]:[CuBr]:[TPMA] = 1:2:2.1 at 25°C; [pMA-Br]_0 = 10 mM.

6.5.4.3 Model termination with MBrP

The small molecule mimic to acrylate radicals, methyl 2-bromopropionate (MBrP), was then investigated in a termination reaction under otherwise identical conditions in the same dry solvents. As with the pMA-Br macroinitiator, the accumulation of L/Cu^{II}-X was monitored via UV-Vis-NIR. Surprisingly, the termination was slower than with pMA-Br, reaching \approx 80% after 48 hours for all reactions (**Figure 6.23A**). Furthermore, the F(Y) function was linear for the three solvents although a slight upward curvature is observed at longer times in d_3 -MeCN (**Figure 6.23B**). The plots for the G(Y) exhibit downward curvature within the first quarter of the reaction indicating reactions are terminating slower than expected by CRT, likely due to conventional radical termination.



Figure 6.23 (A) Evolution of $[Cu^{II}(TPMA)Br]^+$ with time for the termination of MBrP and the fitting to the (B) F(Y) function for conventional radical termination or (C) G(Y) function for catalyzed radical termination in dry MeCN, d_3 -MeCN or DMF under the initial conditions [pMA-Br]:[CuBr]:[TPMA] = 1:2:2.1 at 25°C; [pMA-Br]_0 = 10 mM.

The reaction in d_3 -MeCN was also simultaneously tracked via ¹H NMR as shown in **Figure 6.24**. The three main species, MBrP starting material, the coupled dimer (MP-MP) and saturated product (MP) were observed. It was found that 80% of the dimer (m δ 2.75 2H ppm and dd δ 1.12 ppm 6H) was formed within the first 15 minutes of the reaction with the remaining 20% formed slowly over the next 24 hours. The coupling reaction can produce either the R,R/S,S or the R,S/S,R stereoisomers as illustrated by the complex splitting patterns. After the initial 15 minutes, the majority of the terminated species are saturated (q, δ 2.28, 3H and t δ 1.07 ppm 2H). After 24 hours, there \approx 15% MBrP remained (q δ 4.51 1H and d δ 1.77 3H) which is in good agreement with UV-Vis (20%).



Figure 6.24 (Top) ¹H NMR and (bottom) percentage of species for the termination reaction of MBrP in d_3 -MeCN under the initial conditions [pMA-Br]:[CuBr]:[TPMA] = 1:2:2.1 at 25°C; [pMA-Br]_0 = 10 mM.

One possible explanation for the difference between pMA-Br and MBrP is the difference in conventional radical termination rate coefficients, k_t . Values of k_t for small molecules are typically in the range of 1-4 x 10⁹ M⁻¹s⁻¹ while values of k_t for polymers have been measured to be 1-3 x 108 M-1s-1 for polymers of this size length.¹³² The potential for a competitive process between RT and CRT is plausible. Since the termination of MBrP can between 10-40 times faster, it is possible that at the onset of the reaction when [R•] is highest, conventional radical termination dominates. In the pMA-Br system, conventional radical termination is 30 times slower so CRT dominates from the beginning. Kinetic simulations may be useful to quantitate these reactions.

6.5.5 Current Mechanistic Understanding and Future Outlook

For all of the reactions studied, the dominate products of termination are saturated chains, pMA-H. There is seemingly no effect of solvent on the distribution of the products whether dry or used as received. There was also no observable kinetic isotope effect. These results would indicate that solvent is unlikely to be the source of the hydrogen atom which is further supported by the lack of products containing the acetonitrile radical (°CH₂CN) as the acetonitrile dimer (succinonitrile) or °CH₂-CN terminated chain ends.

The effect of backbiting seems to be negligible under these reaction conditions due to the absence of any disproportionated chains via ¹H NMR or MALDI-TOF-MS. Of course, this is under the assumption that mid-chain radicals terminate via disproportionation. The condition which promoted the most chain combination was using dry MeCN. The reaction conducted at higher initial macroinitiator concentration seemingly ruled out residual moisture being the main source of hydrogen, although hydrolysis most likely occurs to a certain extend.

There are several possible sources of hydrogen atoms in the reaction mixture, all of which will be investigated separately. Since solvent and residual moisture in the solvent have been effectively ruled out, the likely hydrogen atom donor could be polymer or catalyst. Free ligand is unlikely since $[CuBr]_0$: $[TPMA]_0 = 1:1.05$ and thus could only account for 20% of saturated chains. Intra- or intermolecular C-H hydrogen atom transfer/abstraction from

coordinated ligand could be imagined, although one would expect a change in the absorption spectra of the [Cu^{I/II}(•TPMA)] complex which does not seem to occur.

Reactions are currently being conducted in order to investigate these possibilities. Namely, reaction of organotin radicals with the alkyl halide as shown in **Scheme 6.11**. R₃Sn[•] species irreversibly abstract bromines which will generate the acrylate chain-end radical. The product distribution will be analyzed and compared to the above reactions to assess the effect of copper on the termination.



Scheme 6.11 Proposed reaction using tin radicals to understand the effect of copper.

Upon understanding the formal mechanism of copper catalyzed radical termination, we hope to synthesize new catalysts which can suppress the formation of the L/Cu^{II}-R intermediate or avoid the subsequent radical termination. However, reaction conditions can currently be set such that, under activator regeneration conditions, the concentration of L/CuI at steady-state is $\approx 10^{-9}$ with the most active, [Cu(TPMA^{NMe2})Br] catalyst which should significantly suppress Cu^I catalyzed side-reactions such as CRT. Nonetheless, it is of fundamental importance to understand termination mechanisms in both conventional radical polymerization and RDRP methods such as ATRP.

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Chapter 7.

Conclusions and Outlook

7.1 Conclusions

The goal of this thesis was to understand, more intimately, mechanisms occurring in ATRP processes with activator regeneration and to synthesize, characterize, and assess novel, highly active copper catalysts. While the activity of these complexes is unprecedented for halogen atom transfer, they can also interact with radicals resulting in chain-breaking reactions via catalyzed process. **Chapter 1** reviewed the state-of-the-art in the area of ATRP catalysis. An in-depth discussion of reactions occurring in ATRP were examined and quantified. Various ligands and coordination chemistry of the copper complexes were also discussed as well as a history of initiation systems in ATRP. Finally, new systems in aqueous media, dispersed media and even oxygen tolerant techniques were examined.

Chapter 2 focused on photochemical methods in ATRP, specifically the elucidation of the activator regeneration mechanism in *photo*ATRP. It was found that, using violet irradiation (392 nm), over 90% of activator regeneration results from a reductive quenching mechanism between excited-state deactivator complex and aliphatic amine donors. Other photochemical radical generation methods were quantified and added to the overall kinetic model of the system. Furthermore, the effect of photochemistry on ICAR ATRP was quantified in which it was found that irradiation only contributes significantly at low rates of AIBN decomposition.

Chapter 3 focused on the mechanistic studies and development of zero-valent metals in ATRP. RDRP in the presence of Cu^0 , more correctly known as SARA ATRP, has shown to be a complex system both kinetically and mechanistically since Cu^0 can act as a supplemental activator of alkyl halides (k_{a0}) and as a reducing agent via comproportionation (k_{comp}). k_{a0} and k_{comp} were measured for a variety of different ligands and alkyl halides in various solvents. It was found that the rates did not increase linearly with increasing activity, as observed for L/Cu¹, but rather reached a plateau for which rate saturation was observed. This was attributed to a physical rate-limiting process such as adsorption or desorption, as opposed to a chemically limiting step. The "most active" systems were ones which best stabilized Cu¹ species i.e. TPMA

and MeCN. These initial studies were further complimented by analyzing the external order on activation to gain further understanding of mechanisms occurring at the Cu⁰ surface. Both alkyl halide and ligand could adsorb and either an Eley-Rideal or Langmuir-Hinshelwood mechanism could not be ruled out. ATRP in the presence of Ag⁰ was also developed since Ag⁰ acts as a true one electron reducing agent. Indeed, the polymerization of acrylates gave fast and efficient polymerization with D < 1.03 and > 99% chain-end functionality making it one of the most well-controlled ATRP systems to date.

Chapter 4 was centered around the kinetics of ATRP. Specifically, the differences between normal ATRP and ATRP with activator regeneration. A misconception that the rate of alkyl halide activation was directly related to the rate of polymerization in SARA ATRP was the driving force for this simulative study. Indeed, it was found that normal ATRP can be correlated with alkyl halide activation due to the rate dependence on K_{ATRP} . This is not the case for low ppm systems such as ICAR and SARA for which the [L/Cu^{II}-X]/[L/Cu^I] ratio is dynamic and the rate of polymerization depends on ratio of radical generation to radical termination, the former typically involving an external mediator, such as AIBN decomposition or photochemical processes.

Chapter 5 discussed the synthesis, characterization, and utilization of novel copper complexes as ATRP catalysts. The TPMA ligand scaffold was substituted with electron donating -OMe groups. The Cu^I and Cu^{II} complexes were studied both in the solid state and in solution. It was found that substitution of each pyridine arm resulted in a 10-fold increase in ATRP activity resulting in a catalyst that was 1000 times more active than TPMA. The pyridine ring was then substituted with even more electron donating NMe₂- groups. Similarly, the complexes were characterized in the solid-state and in solution. To date, the [Cu(TPMA^{NMe2})Br]⁺ complex is the most active ATRP catalyst with activity over 100,000,000 times higher than seminally used bpy-based catalysts. It was an efficient catalyst for both ICAR and Ag⁰ ATRP of acrylates down to a catalyst loading of 10 ppm.

Finally, **Chapter 6** discusses recent advancements made in understanding the termination mechanism of acrylate radicals, which has long been debated. Adding to the complexity is the ability of active L/Cu¹ complexes to catalyze acrylate radical termination. It

was found that conventional radical termination proceeds via combination while catalyzed termination gives saturated chain-ends. Reassessment of previously use tellurium-mediated systems reveled a novel pathway for which organotellanyl radicals can catalyzed termination via hydrogen atom transfer. The effect of ligand structure on the kinetics of copper catalyzed radical termination were assessed. It was found that, depending on the geometry of the ligand, the rate-limiting reaction can be switched. Furthermore, more active complexes were found to undergo faster catalyzed termination although selectively for halogen atom transfer increased at a faster rate.

7.2 Outlook

Since the initial reports on ATRP in 1995, this controlled radical polymerization method has expanded significantly. Polymers with complex and novel architectures such as block copolymers, brushes, stars, hybrid materials and bioconjugates can now synthesized with ease. The biggest advantage over other RDRP methods is that ATRP is catalytic and involves a relatively inert, colorless and odorless alkyl halide chain-end which can be easily modified. With the in-depth understanding of reactions occurring in ATRP, reaction conditions can be easily tuned in order to prepare the desired material.

The scope of ATRP is now broader than ever with newly developed externally regulated systems such as *photo*ATRP, *mechano*ATRP and *e*ATRP, it is now possible to obtain both temporal and spatial control over the polymerization. Furthermore, ATRP can now be conducted in ionic-liquids, supercritical CO₂ and dispersed media. Recently, acidic monomers were polymerized by ATRP which historically were "challenging" monomers. ATRP has also been conducted using organic-photoredox catalysts. Despite these significant advances in the last 5 years, many challenges are still present in ATRP.

Perhaps, the biggest challenge of ATRP compared to RAFT is the monomer scope. Less active monomers such as vinyl acetate and N-vinylpyrrolidone are currently unable to be polymerized by ATRP. This comes from the very strong C-Br bond which requires very reactive catalysts. However, initial studies have indicated that the [Cu(TPMA^{NMe2})]⁺ complex can activate this chain-end providing promise for the future. Unfortunately, with this extreme

reactivity comes detrimental side reactions like catalyzed radical termination which may be even more prevalent for nucleophilic radicals such as vinyl acetate compared to acrylates. While our understanding of CRT has improved significantly over the past 5 years, much work is still needed. Specifically, accurate quantification of the kinetics of organometallic formation and dissociation are required as well as the intimate mechanism. Preliminary work has indicated a hydrogen atom transfer mechanism. Isolation of a discrete [CuII(L)(R)]+ complex is also of great interest. With knowledge of kinetics and mechanism, it may be possible to design a ligand or reaction conditions which can suppress this detrimental side reaction.

Along the same lines of quantification, it is paramount to obtain accurate values of all kinetic and thermodynamic parameters in ATRP. These include, k_a , k_d , k_{add} , k_{dis} , k_{CRT} , K_{OMRP} , K_{ATRP} , K^I_X , and K^{II}_X . One issue that has been exhaustively discussed in the competitive complexation of X⁻ to L/Cu^I which forms an inactive complex. Thus, much of the data in the literature present actually apparent parameters and not true parameters. In order to obtain the clearest mechanistic picture, as well as accurately model ATRP for scale-up purposes, these parameters need to be accurately known. As the new techniques improve, namely electrochemical methods, an encyclopedia of these parameters may not be far off.

With the increasingly growing interest in RDRP methods, especially industrially, ATRP will continue to grow and become a household method. As monomer scope and initiation systems expand, unprecedented materials can be imagined with endless opportunities.

Appendix

A-1. List of Published Papers

- 6. *TG Ribelli, D Konkolewicz, S Bernhard, K Matyjaszewski. "How are Radicals (Re)Generated in photoATRP." J. Am. Chem. Soc. 2014, 136, pp 13303-13312.
- 7. *TG Ribelli, D Konkolewicz, X Pan, K Matyjaszewski. "Contribution of Photochemistry to Activator Regeneration in ATRP." *Macromolecules*, **2014**, 47, pp 6316-6321.
- *A Kaur, <u>TG Ribelli</u>, K Schröder, K Matyjaszewski, T Pintauer. "Properties and ATRP Activity of Copper Complexes with Substituted Tris(2-pyridylmethyl)amine Based Ligands." *Inorg. Chem.* 2015, 54 (4), pp 1474-1486
- *VA Williams, <u>TG Ribelli</u>, P Chmielarz, S Park, K Matyjaszewski. "A Silver Bullet: Elemental Silver as an Efficient Reducing Agent for Atom Transfer Radical Polymerization of Acrylates." *J. Am. Chem. Soc.* 2015, 137 (4), pp 1428-1431
- A Kaur, E Gorse, <u>TG Ribelli</u>, C Jerman, T Pintauer. "Atom Transfer Radical Addition (ATRA) Catalyzed by Copper Complexes with N,N,N',N' – tetrakis(2-pyridylmethyl)ethylenediamine (TPEN) Ligand." *Polymer*, 2015, 72, pp 246-252
- *TG Ribelli, P Krys, Y Cong, K Matyjaszewski. "Model Studies of Alkyl Halide Activation and Comproportionation Relevant to RDRP in the Presence of Cu⁰." *Macromolecules.* 2015. 48, pp 8428-8436
- 12. *P Krys, <u>**TG Ribelli**</u>, K Matyjaszewski, A Gennaro. "Relation between Overall Rate of ATRP and Rates of Activation of Dormant Species." *Macromolecules.* **2016.** 49, pp 2467-2476
- *TG Ribelli, SMW Rahaman, P Krys, K Matyjaszewski, R Poli. "Effect of Ligand Structure on the Cu^{II}-R OMRP Dormant Species and its Consequences for Catalytic Radical Termination." *Macromolecules*. 2016. 49, pp 7749-7757
- *KF Augustine, <u>TG Ribelli</u>, M Fantin, P Krys, K Matyjaszewski. "Activation of Alkyl Halides at the Cu⁰ Surface in SARA ATRP: An Assessment of Reaction order and Surface Mechanism." *J. Polym. Sci.*, *Part: A.* **2017** 55, pp 3048-3057. (Special Invitation in Celebration of Prof. Robert Grubbs' 75th Birthday)
- 15. *TG Ribelli, SMW Rahaman, R Poli, K Matyjaszewski. "Catalyzed Radical Termination in the Presence of Organotellanyl Compounds." *Chem. Eur. J.* 2017, 23, pp 13879-13882.
- *<u>TG Ribelli</u>, KF Augustine, M Fantin, P Krys, R Poli, K Matyjaszewski. "Disproportionation or Combination? The Termination of Acrylate Radicals In ATRP." *Macromolecules*. **2017**. 50, pp 7920-7929.

^{*}Denotes that paper is discussed in this thesis

- 17. *TG Ribelli, M Fantin, R Poli, JC Daran, KF Augustine, K Matyjaszewski. "Synthesis, Characterization of the Most Active ATRP Catalyst Based on tris[(4-dimethylaminopyridyl)methyl]amine." J. Am. Chem. Soc. 2018, 140 (4), pp 1525*
- H Li, CR Collins, <u>TG Ribelli</u>, K Matyjaszewski, GJ Gordon, T Kowalewski, DJ Yaron. "Tuning the Molecular Weight Distribution from Atom Transfer Radical Polymerization Using Deep Reinforcement Learning." Accepted.
- 19. <u>**TG Ribelli**</u>, SMW Rahaman, K Matyjaszewski, R Poli, "Catalyzed Radical Termination (CRT) in the Metal-Mediated Polymerization of Acrylates: Experimental and Computational Studies." ACS Symp. Ser. *Accepted*.
- 20. G Xie, M Martinez, WFM Daniel, AN Keith, <u>TG Ribelli</u>, M Fantin, SS Sheiko, K Matyjaszewski. "Fast and High-Yield Synthesis of Polyacrylate Molecular Brushes Facilitated by Catalytic Radical Termination." *Submitted*.
- 21. <u>**TG Ribelli**</u>, K Matyjaszewski, R Poli. "The Interaction of Organic Radicals with Copper(I) and Alkylcopper(II) Complexes." Review. *Submitted.*
- 22. *TG Ribelli, LD Plath, G Withers, ME Bier, R Poli, K Matyjaszewski. "Copper(I) Catalyzed Termination of Acrylate Radicals in Acetonitrile." *In Preparation*.*
- 23. G Xie, X Pan, M Olszewski, <u>TG Ribelli</u>, M Fantin, K Matyjaszewski. "The Crucial Role of Active Catalytic System in the Synthesis of Complex Molecular Architecture by Photo-mediated Atom Transfer Radical Polymerization." *In Preparation*.

A-2. List of Abbreviations

1-PECI	1-phenylethyl chloride
4-MeOPh-PTZ	10-(4-methoxyphenyl)-phenothiazine
AA	Ascorbic Acid
AIBN	2,2'-Azobis(2-methylpropionitrile)
AGET	Activators generated by electron transfer
ANDC	acrylonitrile dithiocarbamate
ARGET	Activators regenerated by electron transfer
ATRA	Atom transfer radical addition
ATRP	Atom transfer radical polymerization
β ^ı	Stability constant of ligand association to Cu ^I (L + Cu ^I \leftarrow \rightarrow L/Cu ^I)
β"	Stability constant of ligand association to Cu ^{II} (L + Cu ^{II} $\leftarrow \rightarrow$ L/Cu ^{II})
BA	Butyl acrylate
BDE	Bond dissociation energy
BiTiO₃	Barium titanate
BPMEA	N,N'-bis(2-pyridylmethyl)ethanolamine
BPMOA	N,N-bis(2-pyridylmethyl)octylamine
BPMODA	N,N'-bis(2-pridylmethyl)octadecylamine
BPMODA*	N,N'-bis(2-(4-methoxy-3,5-
	dimethyl)pyridylmethyl]octadecylamine
bру	Bipyridine
ССТ	Catalytic chain transfer
CDTB	Cumyl dithiobenzoate
CRP	Controlled radical polymerization
CRT	Catalyzed Radical Termination
СТ	Charge-transfer
СТА	Chain-transfer agent
CV	Cyclic Voltammetry
Cyclam-B	4,11-Dimethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane
Ð	Polydispersity
Da	Dalton
dHbpy	4,4'-n-heptyl bipyridine
dNbpy	4,4'-dinonyl bipyridine
DP	Degree of polymerization
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DT	Degenerative transfer
dTbpy	4,4'-tert-butyl bipyridine
E _{1/2}	Redox potential or half-wave potential
eATRP	Electrochemically mediated atom transfer radical polymerization
EBiB	Ethyl bromoisobutyrate
EBPA	Ethyl bromophenylacetate

EBrP	Ethyl 2-bromopropionate
EDG	Electron donating group
EMADC	Ethyl methacrylate dithiocarbamate
EPR	Electron paramagnetic resonance
ER	Eley-Rideal Mechanism for surface reactions
ESI-MS	Electrospray ionization mass spectroscopy
EtOAc	Ethyl acetate
EWG	Electron withdrawing group
EXAFS	Extended X-ray Absorption Fine Structure
GOx	Gluxose Oxygenase
GPC	Gel permeation chromatography
HAA	Hydrogen atom abstraction
HEA	Hydroxyethyl acrylate
HEBiB	Hydroxyethyl bromoisobutryate
HMTETA	1,1,4,7,10,10-hexamethyltriethylenetetramine
ICAR	Initiators for continuous activator regeneration
ICP-MS	Inductively coupled plasma mass spectroscopy
ISC	Intersystem crossing
ISET	Inner sphere electron transfer
ITP	Iodine transfer polymerization
I-M-X	Initiating fragment formed by radical initiator (I) which adds to
	monomer (M) and is then trapped by L/Cu ^{II} -X
I-X	Initiating fragment formed by radical initiator (I) and is then
	trapped by L/Cu ^{II} -X
ka	Rate coefficient of alkyl halide activation by L/Cu ^I
k _{a0}	Rate coefficient of alkyl halide activation by Cu ⁰
<i>k</i> _{add}	Rate coefficient of initiating radical to monomer
KATRP	Equilibrium constant of ATRP (RX + L/CuI $\leftarrow \rightarrow$ R [•] + L/Cu ^{II} -X)
k _{azo}	Rate coefficient of diazo initiator decomposition
$k_{ m bb}$	Rate coefficient of intramolecular transfer to polymer
	"backbiting"
<i>k</i> _{comp}	Rate coefficient of comproportionation (L/Cu ^{II} + Cu ⁰ + L \rightarrow 2 L/Cu ^I)
<i>k</i> _{CRT}	Rate coefficient of catalyzed radical termination
<i>k</i> _{dc}	Rate coefficient of radical initiator decomposition
K _{disp}	Equilibrium constant of disproportionation of solvated
	Cu^{I} (2 $Cu^{I} \leftarrow \rightarrow Cu^{II} + Cu^{0}$)
<i>K</i> ^L disp	Equilibrium constant of disproportionation of liganted L/Cu ^I
	$(2 \operatorname{Cu}^{\scriptscriptstyle I} \leftarrow \rightarrow \operatorname{Cu}^{\scriptscriptstyle II} + \operatorname{Cu}^{\scriptscriptstyle 0})$
<i>k</i> ^L disp	Rate coefficient of disproportionation of ligated L/Cu ^I
	$(2 L/Cu' \rightarrow L/Cu'' + Cu^0 + L)$
<i>k</i> p	Rate coefficient of monomer propagation
<i>k</i> _{red}	Rate coefficient of reduction of L/Cu ^{II} -X by reducing agent
<i>k</i> t	Rate coefficient of conventional radical termination
k _{tr,L}	Rate coefficient of radical transfer to ligand

$k_{ m tr,EBiB}$	Rate coefficient of radical transfer to EBiB
Κx ^I	Equilibrium constant of halide association to L/Cu ^I (L/Cu ^I + X ⁻ $\leftarrow \rightarrow$
	L/Cu ^I -X)
κ _{x^{II}}	Equilibrium constant of halide association to L/Cu ^{II} (L/Cu ^{II} + X ⁻ $\leftarrow \rightarrow$ L/Cu ^{II} -X)
L	Ligand
LH	Langmuir-Hinshelwood mechanism for surface reactions
LED	Light emitting diode
Μ	Monomer
M ⁿ	Metal in oxidation state n
M ⁿ⁺¹	Metal in oxidation state n+1
<i>M</i> _n	Number average molecular weight
M _w	Weight average molecular weight
MA	Methyl acrylate
MAA	Methacrylic acid
MANDC	Methacrylonitrile dithiocarbamate
MBrP	Methyl 2-bromopropionate
MCIAc	Methyl 1-chloroacetate
MCIP	Methyl 2-chloropropionate
Me ₄ Cyclam	1,4,8,11-Tetramethyl-1,4,8,11-tetraaacyclotetradecane
Me ₆ TREN	Tris[2-(dimethylamino)ethyl]amine
<i>mechano</i> ATRP	Mechanical or ultrasound mediated atom transfer radical
	polymerization
MeCN	Acetonitrile
MeOH	Methanol
MET	Mechanically induced electron transfer
MgSO ₄	Magnesium Sulfate
NHC	N-heterocyclic carbene
MMA	Methyl methacrylate
MPADC	Methyl phenylacetate dithiocarbamate
MW	Molecular weights
MWD	Molecular weight distribution
Nap-PTZ	10-(1-naphthalenyl)-phenothiazine
NMP	Nitroxide mediated polymerization
NMR	Nuclear magnetic resonance
NVP	N-vinylpyrrolidone
<i>o</i> ATRP	Metal-free or organo-catalyzed atom transfer radical
	polymerization
OEOMA	Oligoethyleneoxide methacrylate
OMRP	Organometallic mediated radical polymerizatioin
OMRP-DT	Organometallic mediated radical polymerizatioin operating via a
	degenerative transfer mechanism

OMRP-RT	Organometallic mediated radical polymerizatioin operating via a
	reversible termination mechanism
OSET	Outer sphere electron transfer
OTf	Triflate: trifluoromethyanesulfonate
PC	Photocatalyst
PDI	Polydispersity index
PEO	Poly(ethyleneoxide)
Ph-PTZ	10-phenylphenothiazine
PhICAR	Photochemical Initiators for continuous activator regeneration
	atom transfer radical polymerization
<i>photo</i> ATRP	Photochemically mediated atom transfer radical polymerization
PMDETA	N,N,N',N",N" – pentamethyldiethylenetriamine
ppm	Parts per million
PRE	Persistent radical effect
PS	Polystyrene
PxDPMA	N-(2-hydroxybenzyl)-N,N-bis(2-pyridylmethyl)amine
R _{a0}	Rate of alkyl halide activation by Cu^0 ; $k_{a0}[RX]S/V$
Rg	Rate of radical generation
Rt	Rate of radical termination
R-TEMPO	Alkyl-TEMPO adduct
RA	Reducing agent
RAFT	Reversible addition fragmentation chain-transfer
RDE	Rotating disk electrode
RDS	Rate-determining step
RDRP	Reversible deactivation radical polymerization
ROMP	Ring-opening metathesis polymerization
RP	Conventional radical polymerization
RX	Alkyl halide
S/V	Surface area to volume of solution ratio
SARA ATRP	Supplemental activator and reducing agent atom transfer radical
	polymerization
SCE	Saturated Calomel Electrode
SDS	Sodium dodecyl sulfate
seATRP	Simplified electrochemically mediated atom transfer radical
	polymerization
SEC	Size exclusion chromatography
SEM	Scanning electron microscopy
SET-LRP	Single electron transfer living radical polymerization
Sn(EH)₂	Tin(II) ethyl hexanoate
SP-PLP-EPR	Single-pulse pulsed-laser-polymerization electron paramagnetic
	resonance
SR&NI ATRP	Simultaneous reverse and normal initiation atom transfer radical
	polymerization
St	Styrene

Tetrabutyl ammonium bromide
Triethylamine
2,2,6,6-tetramethylpiperidine 1-oxyl
Tellurium mediated radical polymerization
Thermogravimetric analysis
Tetrahydrofuran
tetramethylethylenediamine
N,N,N',N'-tetrakis(2-pyridylmethyl)ethylenediamine
Tris(2-pyridylmethyl)amine
1-(4-methoxy-3,5-dimethylpyridin-2-yl)- <i>N</i> -((4-methoxy-3,5-
tris(// methons 2.5 dimethologidin 2.4)methologine
tis((4-methoxy-3,3-umethypynum-2-yi)methyi)amme
Tris(aminoethyl)amine
Trithiocarbonate
Ultraviolet
Ultraviolet Visible Near infrared Spectroscopy
Vinyl acetate
Zinc Oxide

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