AQUEOUS Cu(0) MEDIATED REVERSIBLE DEACTIVATION RADICAL

POLYMERIZATION OF 2-HYDROXYETHYL ACRYLATE

by

Mingmin Zhang

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Abstract

Reversible deactivation radical polymerization (RDRP) of 2-hydroxyethyl acrylate in D_2O was studied using Cu(0) wire and Me_6TREN, with different target chain lengths (TCL), amount of initial $Cu(II)Br_2$, and the addition sequence of ligand. Gel formation occurred under most conditions, with the amount of gel formation reduced with short target chain lengths, increased concentration of initial $Cu(II)Br_2$, and when ligand was added with the $Cu(II)Br_2$. This result was explained by the reduced concentration of adsorbed active polymer species on the Cu(0) wire surface through increased desorption rate and deactivation rate on the Cu(0) wire surface, respectively.

Gel formation was eliminated using a two-step Cu(0) *in situ* mediation process, with experiments focusing on the effects of chain length, initial Cu(I)Br, excess NaBr, temperature and residual O_2 (brought by syringe for monomer and initiator transferring) on the kinetics and molecular weight (MW) control of the system. There is no visible gel formation with the TCL range from 20 to 800 using this procedure, a result mainly attributed to the lowered number of adsorbed active species per Cu(0) particle, which are highly dispersed, greatly reducing the probability of crosslinking. The concentration of adsorbed active species on Cu(0) particle surface is the key factor controlling polymerization control and the formation of a high molecular weight (MW) shoulder seen under many conditions. Thus, physical processes such as adsorption and desorption combine with kinetic processes such as activation, propagation and deactivation on the Cu(0) surface and in the solution to influence the ability to control chain growth. Shorter target chain lengths, low activator concentration, high deactivator concentration and higher temperature (22 ℃ rather than 0 ℃) all reduce the concentration of adsorbed active species on the Cu(0) surface during the polymerization, and thus improve control. The study indicates that lower concentration of adsorbed active species is the requirement for synthesizing well defined P(HEA) in the aqueous solution, with low Đ and without high MW shoulder and insoluble gel.

Based on this insight, well defined P(HEA) with low Đ (~1.2) and no high MW shoulder was synthesized when DP_n was less than 160 in pure aqueous solvent (D_2O and H_2O). Higher MW P(HEA) (TCL=400, 87% conversion) with Đ value of 1.16 was synthesized within 75 min using *ca.* 250 ppm copper in D_2O at 22 ℃, however with a high MW shoulder observed, the first time that high MW P(HEA) with low Đ has been synthesized using such low copper levels in the purely aqueous environment.

Co-Authorship

The bulk of research was completed independently by the author, under the supervision of Dr. Michael Cunningham and Dr. Robin Hutchinson, both of whom reviewed this thesis. The material presented in Chapter 3 and Chapter 4 has been reorganized and accepted by *Polymer Chemistry*, a peer-reviewed scientific journal published by the Royal Society of Chemistry.

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ARGET	Activators regenerated by electron transfer
AIBN	Azobisisobutyronitrile
BPY	2-2'-Bipyridine
CTA	Chain transfer agent
CSTR	Continuous stirring tank reactor
DMF	Dimethylformamide
DMAc	N, N-dimethylacetamide
DBTTC	Dibenzyltrithiocarbonate
DMSO	Dimethyl sulfoxide
DP_n	Number-average degree of polymerization
DMA	N, N-dimethylacrylamide
DEA	N, N-diethylacrylamide
EGDA	Ethylene glycol diacrylate
FID	Flame ionization detector
HEA	2-Hydroxyethyl acrylate
HEBiB	2-Hydroxyethyl 2-bromoisobutyrate
HEAA	2-hydroxyethyl acrylamide
ISET	Inner-sphere electron-transfer
ICAR	Initiators for continuous activator regeneration
LCST	Low critical solution temperature behavior
MW	Molecular weight
MMD	Molecular weight distribution
MEA	2-Methoxyethyl acrylate
Me_6TREN	Tris[2-(dimethylamino)ethyl]amine
MA	Methyl acrylate
MBP	Methyl 2-bromopropionate
NMP	Nitroxide mediated polymerization
NIPAM	N-isopropylacrylamide
OSET	Outer-sphere electron-transfer
OEOMA	Oligo(ethylene oxide) methyl ether acrylate
OEOMMA	Oligo(ethylene oxide) methyl ether methacrylate

PMDETA	N,-N,-N',-N'',-N''-pentamethyldiethylenetriamine
PRE	Persistent radical effect
PEO	Polyethylene glycol
PTFE	Polytetrafluoroethylene
RDRP	Reversible deactivation radical polymerization
RAFT	Reversible addition-fragmentation chain transfer polymerization
RT	Room temperature
SARA-ATRP	Supplemental agent and reducing agent atom transfer radical polymerization
SET-LRP	Singer electron transfer living radical polymerization
TCL	Target chain length
THF	Tetrahydrofuran
TREN	Tris(2-aminoethyl)amine
TPMA	Tris(2-pyridylmethyl)amine

Chapter 1

Introduction

1.1 Background information

Reversible deactivation radical polymerization (RDRP), as a robust method to synthesize advanced polymeric materials with precisely controlled molecular weight and molecular architecture in terms of chain topology (star, combs, brushes networks) and chain composition (block, graft, gradient copolymers) with more tolerance to functional groups and impurities compared to living polymerization,[1] has attracted considerable interest for its potential to produce new polymeric materials. Of the three major families of RDRP – atom transfer radical polymerization (ATRP), nitroxide mediated polymerization (NMP) and reversible addition-fragmentation chain transfer polymerization (RAFT) – ATRP has attracted significant interest, with the highest number of publications recorded from 1995 to 2011[2] of the three kinds of RDRP. The high interest stems from the versatility of ATRP, usually run in the presence of a mixture of Cu(0), Cu(I), and/or Cu(II) species, to control chain growth of most monomer types in both aqueous and non-aqueous solution.

Cu(0) mediated RDRP has recently emerged as a variation of ATRP that provides excellent control over polymerization using low catalyst levels and mild reaction conditions. The mechanism of control is a matter of strong debate in the literature, with the two main proposals termed supplemental activator and reducing agent atom transfer radical polymerization (SARA-ATRP)[3] and single-electron transfer living radical polymerization (SET-LRP).[4] However, Cu(0) mediated RDRP of water soluble monomers, such as 2-hydroxyethyl acrylate, in aqueous solution using low catalyst level is still a significant challenge due to dissociation of deactivator Cu

complexes and other unclear side reactions. This part will be discussed in more detail in Chapter 2.

Until now, there is no published paper describing the successful synthesis of poly(2-hydroxyethyl acrylate) [P(HEA)] in aqueous solution using low copper levels (below 500 ppm) or the synthesis of higher degrees of polymerization ($DP_n \geq 200$) P(HEA) with low dispersity ($Đ \leq 1.35$) in aqueous solution. Thus, there is need to further investigate aqueous Cu(0) mediated RDRP of HEA in order to synthesize well defined P(HEA) with low Đ and without the formation of a high molecular weight shoulder using low copper levels in aqueous solution.

1.2 Thesis objectives

The thesis investigates Cu(0) wire mediated and two-step Cu(0) in situ mediated RDRP of HEA in aqueous solution with the following two objectives:

1. Improve the mechanistic understanding of gel formation and the cause of the high molecular weight shoulder observed in the molecular weight distribution (MMD) of P(HEA) produced.

2. To successfully synthesize well defined P(HEA), especially higher molecular weight P(HEA),without a shoulder and with low Đ using low copper levels in aqueous solution.

1.3 Thesis outline

The literature review of Chapter 2 presents relevant technical background for the research conducted. RDRP techniques and the two mechanisms under debate (SARA-ATRP and SET-LRP) are discussed in detail. The review is focused on the mechanism of aqueous Cu(0) mediated RDRP, with a brief overview about the use of RDRP techniques to synthesize P(HEA) and its copolymers in other solvent systems.

Chapter 3 outlines the experimental techniques developed and the results obtained for the synthesis of P(HEA) in D_2O using Cu(0) wire mediation, exploring the influence of target chain length, initial Cu(II)Br$_2$ level, and the ligand addition sequence used at the start of the reaction. Chapter 4 extends the study to the synthesis of P(HEA) using low copper level using a two-step Cu(0) *in situ* mediation process. Variables studied include target chain length, amount of initial Cu(I)Br, methods of monomer and initiator addition, and temperature. Based on the successes obtained, a few experiments were conducted to explore the polymerization in H_2O (instead of D_2O) and in a mixed-solvent system, with recommendations for future work presented in Chapter 5. Many of the experimental procedures developed as part of this effort are included as appendices, including calculation of conversion from NMR, ethylene glycol diacrylate concentrations (EGDA) measured by GC, verification of complete acetylation required for MW analysis, and the recipes for two-step Cu(0) *in situ* mediated RDRP of HEA.

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Chapter 2

Literature Review

Compared to free radical polymerization, the ability of reversible deactivation radical polymerization technique to precisely synthesize polymers has attracted significant attention. Free radical polymerization of 2-hydroxyethyl acrylate, a water soluble monomer with hydroxyl group, has been commercialized for a long time, while RDRP of HEA with main three techniques (ATRP, NMP and RAFT) is still under investigation.

2.1 Reversible deactivation radical polymerization of HEA

RAFT polymerization is controlled through the degenerative chain transfer of a chain transfer agent (CTA, normally thiocarbonylthio compound), while ATRP and NMP polymerizations are controlled through reversible deactivation of a propagating radical; these methods are shown as Scheme 2-1.[1]
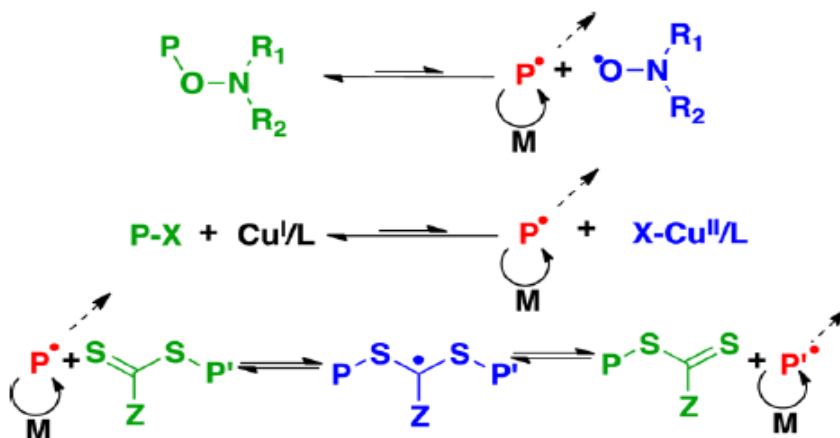
Scheme 2-1 Typical RDRP Methods: NMP (top), ATRP (middle) and RAFT (bottom).[1] Reproduced with permission from (D. Konkolewicz, P. Krys and K. Matyjaszewski, *Acc. Chem. Res.,* 2014, **47**, 3028−3036). Copyright (2014) American Chemical Society

The RAFT polymerization of HEA uses trithiocarbonate as the CTA[2] and a normal thermal initiator such as azobisisobutyronitrile (AIBN) as the initiator. Low molecular weight P(HEA) (M_n=2560) with Đ of 1.1 was synthesized in tert-butyl alcohol at 80 ℃ by Lai *et al*.,[2] and later Zhang *et al*.[3] synthesized P(HEA) macro-raft agent with Đ of 1.35 using trithiocarbonate for the production of P(HEA)-b-P(BA) in N,N-dimethylacetamide (DMAc) at 60 ℃. Using commercialized dibenzyltrithiocarbonate (DBTTC) as the CTA, Steinhauer *et al*.[4,5] successfully synthesized well defined random copolymer of HEA with 2-methoxyethyl acrylate (MEA, almost the same reactivity as HEA), P(HEA) and P(HEA)-block-P(MEA) in DMF above 70 ℃. There is no publication describing the RAFT polymerization of HEA in water.

NMP polymerization uses an alkoxyamine as the thermally-activated source of both the initial radicals and the nitroxide controlling agent, with free nitroxide sometimes added to improve the control of polymerization. Bian *et al*.[6] first reported using SG1 free nitroxide and SG1-based alkoxyamine to synthesize P(HEA) (55% conversion, Đ= 1.45 or 27% conversion, Đ=1.24) in water at 110 ℃. Recently, Hoogenboom *et al*.[7] used BlocBuilder® initiator (alkoxyamine) and SG1 free nitroxide to copolymerize HEA with 2-hydroxypropyl acrylate (HPA) in DMF at 110 ℃ to produce polymers with low Đ when the conversion is below 55%. The main difficulty with NMP of HEA in aqueous solution is that with increasing conversion the polymerization becomes less controlled, a result attributed to chain transfer to polymer at the high reaction temperatures required for the synthesis. As with copper residue in ATRP, the low conversion of P(HEA) in NMP is similarly unfavorable[8] for industrial production because removing a high amount of monomer from polymer is costly, hampering the development of an effective and industrially feasible polymerization process.

Compared to NMR and RAFT techniques, ATRP as a route to synthesize P(HEA) and its copolymers with low dispersity in protic, dipolar aprotic and even aqueous solvents has attracted more attention. Solvent choice can influence the Cu mediation reaction pathways:[1] while this is the basis for the disagreements between the SET-LRP and SARA-ATRP mechanisms (details discussed later in this chapter), it has also allowed the manipulation of reaction conditions to produce controlled P(HEA) in some studies. Coca *et al.*[9] first used the Cu(I)Br/2-2'-bipyridine (bpy) system to mediate HEA polymerization in bulk and in aqueous solution with 10,000 ppm catalyst (molar ratio of copper to monomer); 87% conversion was achieved after 12 h at 90 °C, with a polymer dispersity (Đ) of 1.34 achieved. Later ATRP efforts used the ligands N,-N,-N',-N'',-N''-pentamethyldiethylenetriamine (PMDETA) at 80 °C in both bulk[10] and at 50 °C in toluene solvent,[11] tris[2-(dimethylamino)ethyl]amine (Me$_6$TREN) in bulk[12] at room temperature to produce P(HEA) and its block copolymer with n-butyl acrylate;[10] in these studies catalyst concentration remained high, between 5,000 and 33,000 ppm. One of the goals of the current effort is to reduce the amount of catalyst for P(HEA) production.

Cu(0) mediated RDRP has attracted significant attention since the first publication reported by Percec *et al.*[13] as a method to synthesize polymers with narrow molar mass distribution and high chain-end functionality at high rate at room temperature or below. Two mechanisms, SET-LRP[14] and supplemental activator and reducing agent (SARA)-ATRP[15] were proposed to explain the Cu(0) mediated RDRP mechanism, with the debate in the literature ongoing (as described in more detail below). This method has also been used to synthesize P(HEA) with mixed success, depending on the solvent and Cu(0) source utilized, as summarized in the next two chapters.

Based on this review, we find that Cu(0) mediated RDRP of HEA has already partially satisfied our research goals: fast rate of polymerization in aqueous solution at low

temperatures to produce polymer with high conversion and low Đ. The obvious deficit is that all of the previous studies use very high copper levels, and that there is little data published about the production of higher molecular weight P(HEA). Thus, this investigation aims to reduce the copper dosage using Cu(0) wire or two-step Cu(0) *in situ* mediation, as well as to adapt the technique to effectively synthesize high molecular weight P(HEA) in aqueous solution.

2.2 Proposed aqueous SET-LRP mechanism

Prior to the 2006 publication by Percec *et al.*[13] that presented the SET-LRP mechanism for Cu(0) mediated RDRP in protic solvents (MeOH, EtOH, ethylene glycol), dipolar aprotic solvents (DMSO, DMF) and water in the presence of N-ligands (TREN and Me_6TREN), other research groups did not pay specific attention to Cu(0) mediated RDRP, although some work had been done. Matyjaszewski *et al.*[16] first investigated Cu(0) mediated RDRP in bulk for MA (90 ℃), MMA (70 ℃) and styrene (110 ℃) in 1997, and concluded that the system followed the normal ATRP mechanism, with Cu(0) mainly working as a reducing agent; it was also mentioned that the Cu(0) could directly react with the alkyl halide initiator and polymer halide dormant species to form a radical and Cu(I)X, but the reverse reaction was not considered as a possibility. According to the SET-LRP mechanism proposed by Percec, the Cu(0) acts as activator and Cu(I)X is just a transient intermediate species that forms the activator "nascent" Cu(0) and deactivator $Cu(II)X_2/L$ *via* disproportionation. During the activation and deactivation process, alkyl halide radical anion intermediates are produced *via* a low activation energy outer-sphere single-electron-transfer rather than a high activation energy inner-sphere electron-transfer as in the ATRP mechanism.
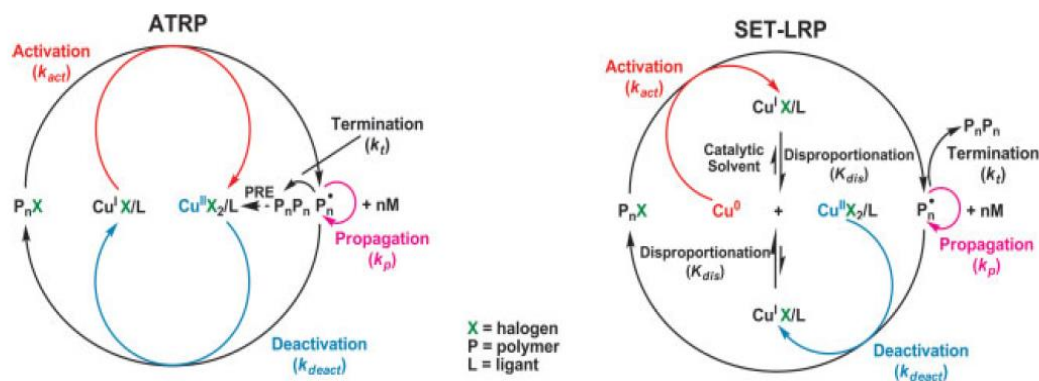
Scheme 2-2 Mechanisms of ATRP (on the left) and SET-LRP (on the right); X=Cl, Br, I; L=nitrogen-based ligand.[17] Reproduced from (M. J. Monterio, T. Guliashvili, V and V. Percec, *Polym. Sci., Part A: Polym. Chem.,* 2007, **45**, 1835–1847) with permission of John Wiley and Sons
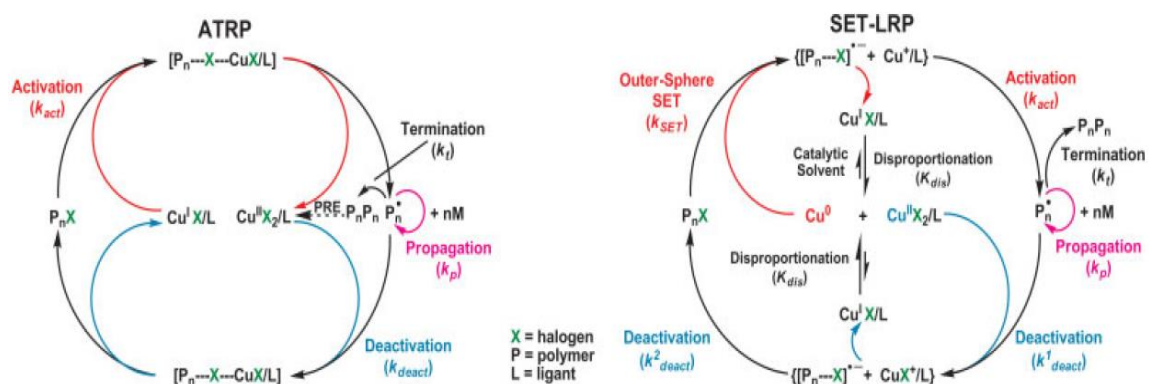
Scheme 2-3 Catalytic cycles in ATRP (on the left) and SET-LRP (on the right); X=Cl, Br, I; L=nitrogen-based ligand.[17] Reproduced from (M. J. Monterio, T. Guliashvili, V and V. Percec, *Polym. Sci., Part A: Polym. Chem.,* 2007, **45**, 1835–1847) with permission of John Wiley and Sons

The mechanisms that differentiate the SET-LRP mechanism from the normal ATRP mechanism and catalytic cycles are presented as Scheme 2-2 and 2-3.

Table 2-1 Mechanism comparison of normal ATRP vs. SET-LRP vs. SARA-ATRP

normal ATRP	Activator	Cu(I)X/L
	Deactivator	Cu(II)X$_2$/L which is produced *via* persistent radical effect
	Electron Transfer	Homolytic atom transfer of the halogen *via* inner-sphere electron-transfer (high energy barrier)
SET-LRP	Activator	Cu(0)
	Deactivator	Cu(II)X$_2$/L which is produced *via* Cu(I)X/L instantaneous disproportionation in disproportionation favored solvent
	Electron Transfer	Heterolytic atom transfer of the halogen *via* outer-sphere electron-transfer (low energy barrier)
SARA-ATRP	Activator	Cu(I)X/L works as main activator which is produced *via* comproportionation between Cu(0) and Cu(II)X$_2$/L; Cu(0) works as the supplemental activator and participates in the reversible reaction
	Reducing Agent	Cu(0) functions as the reducing agent
	Deactivator	Cu(II)X$_2$/L which is mainly produced *via* persistent radical effect rather than disproportionation
	Electron Transfer	Homolytic atom transfer of the halogen *via* inner-sphere electron-transfer (high energy barrier)

According to the ATRP mechanism shown in Scheme 2-3, the radical R$^{\bullet}$ and the deactivator Cu(II)X$_2$/L species are formed through the homolytic atom transfer of the halogen radical atom from the RX dormant species to the activator Cu(I)X/L *via* an inner-sphere electron-transfer (ISET). The SET-LRP mechanisms proposes that the radical R$^{\bullet}$ and intermediate Cu(I)X/L species are formed through heterolytic atom transfer of the halogen radical atom from the RX dormant species to the activator Cu(0) *via* an outer-sphere electron-transfer (OSET) and the intermediate Cu(I)X/L instantaneously disproportionates to "nascent" Cu(0) and deactivator Cu(II)X$_2$/L; thus Cu(II) is produced *via* disproportionation rather than activation and its accumulation is not *via* the persistent radical effect,[18] as proposed in the ATRP mechanism. For better understanding of this point, Table 2-1 summarizes the differences between the two mechanisms. It is important to note that for SET-LRP, the Cu(0) mediated RDRP is a heterogeneous polymerization that exhibits surface-dependent kinetics.[14(b),19]

2.2.1 Supporting evidence

Percec *et al.* systematically investigated two representative systems to support their mechanistic claims: vinyl chloride (VC)[20-22] and methyl acrylate (MA).[17,19]

The best result for the synthesis of PVC by RDRP was a Đ of 1.53 with a conversion of 19% after 19 h in bulk, using the mediating system of ICH$_2$PhCH$_2$I/Cu(0)/bpy (2,2'-bipyridine) at 130 ℃; the low conversion was explained by the hypothesis that Cu(II)Br$_2$/bpy would not be accessible by a conventional PRE mechanism since the radical polymerization of VC was dominated by chain transfer to monomer rather than by bimolecular termination. In a system of VC initiated with CHI$_3$ and catalyzed by Cu(0)/TREN at 25 ℃ in H$_2$O/THF, the conversion was close to 70% with Đ ≈ 1.5 after 10 h, and even in aqueous polymerization with sodium dodecyl sulfate (SDS) as a surfactant, the conversion reached 80% after 40 h with the Đ from 1.5 to 1.6. Based on the above experimental observations, Percec *et al.*[13] proposed that this polymerization involved

activation mediated by Cu(0) *via* single electron transfer (SET) both in the initiation and propagation steps, inactive Cu(I)X/L species disproportionated into "nascent" Cu(0) activator and Cu(II)X$_2$/L deactivator species, and that degenerative chain transfer (DCT) occurred in the "living" radical polymerization (LRP).

In the later study of the Cu(0)-mediated "living" radical polymerization of MA initiated with methyl 2-bromopropionate (MBP) at 25 °C in DMSO using Me$_6$TREN as a ligand, Percec's research group[17] proposed the SET-LRP mechanism based on the evidence that the rate of polymerization was extremely fast at 25 °C or lower, consistent with the hypothesis that the activation of the initiator and of the propagating dormant species by Cu(0) *via* heterolytic outer-sphere electron-transfer was faster and needed less energy than that required for the homolytic inner-sphere electron-transfer process responsible for ATRP. In addition, the molecular weight distribution was narrower than for ATRP, indicating less bimolecular termination and favoring the hypothesis that the creation of deactivator was *via* disproportionation rather than the PRE.

In addition, it was shown that when decreasing the Cu(0) particle size[14(b)] or the copper wire surface (surface area),[19] the calculated apparent rate constant of propagation (k_p^{app}) decreased remarkably: using uniform copper wire (commercial copper wire for scientific experiment), the k_p^{app} had a positive linear relationship with (SA)$^{0.44}$ (SA=copper wire surface area). This finding supports the hypothesis that the Cu(0) mediated RDRP is a heterogeneous polymerization with surface-dependent kinetics. Furthermore, Lligadas *et al.*[14(b)] observed that the solvent and ligand choices greatly affected the experimental results for Cu(0) mediated RDRP, another differentiating feature for SET-LRP compared to ATRP in the presence of Cu(0).

Table 2-2[14(c)] Approximate ligand-dependent $K_{dis.equili}$ of Cu(I)Br determined *via* UV–VIS spectroscopy

Solvent	$K_{dis.equili}$ at 1 equivalent of Me$_6$TREN	$K_{dis.equili}$ at various equivalents of Me$_6$TREN
Acetone	1.89×10^2	$4.12 \times 10^2/0.50$
Acetone/10% H$_2$O	4.38×10^2	$8.66 \times 10^2/0.67$
DMAC	5.5×10^1	$4.99 \times 10^2/0.33$
DMF	6.7×10^1	$9.75 \times 10^2/0.50$
DMF/10% H$_2$O	2.74×10^2	$9.18 \times 10^2/0.50$
DMSO	3.6×10^1	$1.05 \times 10^2/0.50$
DMSO/10% H$_2$O	8.5×10^1	$2.14 \times 10^4/0.50$
EC	3.7×10^1	$6.3 \times 10^1/0.70$
EtOH	1.85×10^2	$2.09 \times 10^2/0.67$
H$_2$O	1.40×10^3	n.d./2.00^a
MeOH	7.48×10^2	$2.63 \times 10^3/0.90$
MeOH/10% H$_2$O	4.84×10^2	$5.9 \times 10^2/0.90$
NMP	8.5×10^1	$4.75 \times 10^2/0.33$
PC	5.1×10^1	$7.3 \times 10^2/2.00$

^{a} n.d. not determined, absorbance indicates greater than 100% disproportionation

The combination of solvent and ligand favors disproportionation of Cu(I)X/L as the key step in the SET-LRP mechanism. In a typical SET-LRP system with the Cu(0)/Me$_6$TREN catalyzed polymerization of methyl acrylate (MA) initiated by methyl 2-bromopropionate (MBP) in DMSO at 25 °C, a continuous increase of CuBr$_2$ absorbance was observed, as measured by an online

UV−VIS spectrophotometer,[14(d)] during the entire polymerization process. In addition, almost 100% chain-end functionality of the polymer was maintained from 10% to 95% monomer conversion, as determined using quantitative ¹H-NMR spectroscopy and MALDI-TOF spectrometry performed before and after thio−bromo "click" chemistry and chain extension in the presence of an internal standard. The above observation indicates Cu(0) does not reduce $CuBr_2$ and that $CuBr_2$ is not produced *via* the ATRP persistent radical effect in the DMSO-based system. As water is more polar than DMSO, SET-LRP advocates believe that aqueous-based Cu(0) mediated RDRP is more likely to follow the SET-LRP mechanism, which is supported by the larger equilibrium constant of disproportionation listed in Table 2-2.

2.2.2 Key equilibrium constants

In SET-LRP mechanism, there are two very important equilibrium constants, $K_{equili,set}$ and $K_{dis,equili,}$ with especially the latter a means to differentiate the SET-LRP mechanism from SARA-ATRP. $K_{equili,set}$, defined by $\frac{k_{act,Cu(0)-PX}}{k_{act,Cu(II)X_2/L}}$, is the equilibrium constant of SET-LRP obtained from a set of experiments with a constant concentration of initiator and amount of Cu(0) and varying concentrations of $Cu(II)X_2$. $K_{dis,equili}$, defined by $\frac{k_{dis}}{k_{com}}$ [15(d)], (k_{dis} is the rate constant of disproportionation and k_{com} is the rate constant of comproportionation) is the equilibrium constant of disproportionation described by following chemical equilibrium (equation 1).[14(c)]

$$Cu(I)X/L + Cu(I)X/L \underset{k_{com}}{\overset{k_{dis}}{\rightleftharpoons}} Cu(0) + Cu(II)X_2/L + L \text{ (eq 1)}$$
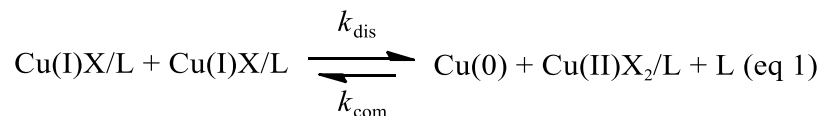
Therefore, the expression is as below:

$$K_{dis,equili} = \frac{k_{dis}}{k_{com}} = \frac{[Cu(II)X_2/L][L]}{[Cu(I)X/L]^2} \quad \text{(expression 1)}$$

2.3 Proposed aqueous SARA-ATRP mechanism

After the SET-LRP mechanism was proposed in 2007, Matyjaszewski *et al.*[15(a)] immediately pointed out that the proposed mechanism violated the principle of microscopic reversibility, because if $K_{dis,equili}$ was larger than 1 and Cu(II)X_2/L works as a deactivator ($k_{deact,Cu(II)X_2/L}$ $> k_{deact,Cu(I)X/L}$), the main activator should be Cu(I)X ($k_{act,Cu(I)X} > k_{act,Cu(0)}$) rather than "nascent" Cu(0) ($k_{act,Cu(I)X} < k_{act,Cu(0)}$) according to expression 2 shown as below.

$$\frac{k_{act,Cu(0)}}{k_{act,Cu(I)X}} = \frac{k_{deact,Cu(I)X/L}}{k_{deact,Cu(II)X_2/L}}\ 1/(K_{dis,equili}) \quad \text{(expression 2)}$$
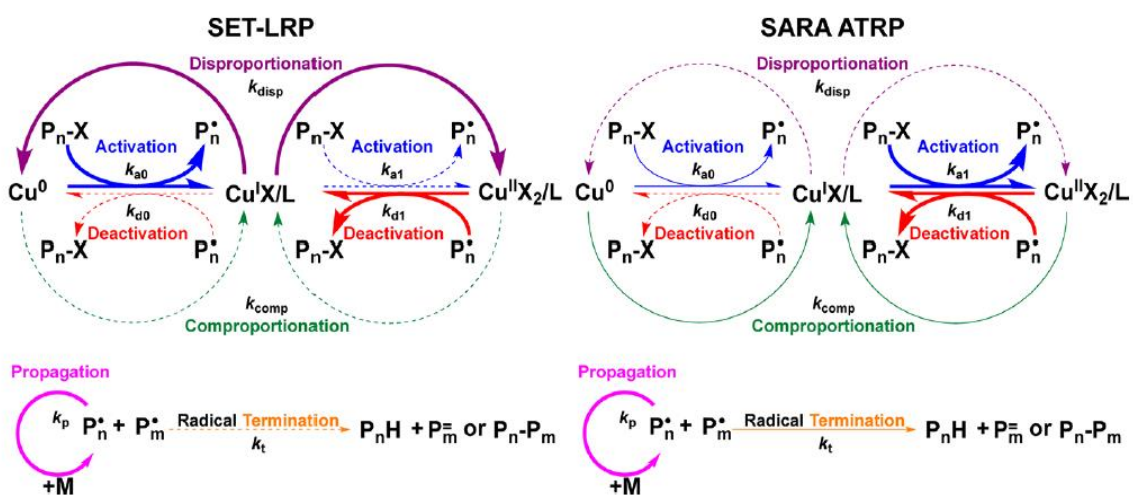
Scheme 2-4[15(c)] SET-LRP mechanism and SARA-ATRP mechanism comparison.[a] Reproduced from (C. Peng, M. Zhong, Y. Wang, Y. Kwak, Y. Zhang, W. Zhu, M. Tonge, J. Buback, S. Park, P. Krys, D. Konkolewicz, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2013, **46,** 3803−3815). Copyright(2013) American Chemical Society

[a] Bold arrows illustrate major (dominating) reactions, regular solid lines represent contributing reactions and dashed lines represent minor reactions that can be neglected

After several years of research, Matyjaszwski's research group proposed an alternative mechanism, SARA-ATRP, for Cu(0) mediated RDRP both in polar[15(c)] and non-polar solvents[23] as well as aqueous solvent.[24] The SARA-ATRP mechanism emphasizes the role of Cu(0) as a

supplemental activator (SA), with Cu(I)X remaining the main activator ($k_{act,Cu(I)X} > k_{act,Cu(0)}$)

in the system. At the same time Cu(0) works as a reducing agent (RA) to produce Cu(I)X through

reaction with Cu(II)X$_2$/L by the so-called comproportionation process. During the activation and

deactivation process, alkyl halide radical anion intermediates are produced *via* inner-sphere

electron transfer, as illustrated in Scheme 2-4.[15(c)] The differences between the two schemes are

also outlined in Table 2-1. It must be noted that in both the SET-LRP and SARA-ATRP

mechanisms, the Cu(0) mediated RDRP is considered as a heterogeneous polymerization with

surface-dependent reaction rate.[14(b),15(b),19]

2.3.1 Supporting evidence

Wang *et al.*[17] investigated the Cu complexes of Me$_6$TREN to quantify the disproportionation of

Cu(I)Br/Me$_6$TREN in DMSO, DMF, and MeCN. The calculated K$_{dis,equili}$ was 10^{-2}-10^{-1} in DMF

and DMSO and was 10^{-4} in MeCN using expression 1, which conflicted with the result reported

by Rosen *et al.*[14(c)] that K$_{dis,equili}$ was 10^{1}-10^{2} in DMF and DMSO. What was more, they studied

the relative activation rates of alkyl halides by Cu(0) and Cu(I) with Me$_6$TREN and found

reactions catalyzed by Cu(I)/Me$_6$TREN were significantly faster than those employing Cu(0).[15(a)]

Using spectrophotometric measurement and mass balance calculations, the same paper[15(a)]

reported that the concentration of Cu(II) initially increased and then decreased to a certain

equilibrium value while Cu(I) was constantly accumulated, even after the alkyl halide was

consumed, a finding consistent with the conclusion that the slow comproportionation process

dominates in the system of Cu(0)/Me$_6$TREN/ PhCH$_2$Cl in MeCN. The above observation supports

the notion that in the Cu(0) mediated RDRP system with Me$_6$TREN in DMSO/DMF/MeCN,

Cu(0) acts both as a reducing agent (regenerating Cu(I) activator by reacting with accumulated

Cu(II) in the system) and as a supplemental activator, which activates alkyl halides slowly

compared to Cu(I)Br.

In a further kinetic study,[15(b)] Cu(0) mediated RDRP of MA in the presence of solvent DMSO with the ligands TPMA and Me$_6$TREN, the Matyjaszewski group found that TPMA-based complexes did not undergo significant disproportionation in DMSO, while the Me$_6$TREN complexes could disproportionate to some extent. Despite this fact, the TPMA-based complexes gave good control over the molecular weight and the molecular weight distribution (M$_w$/M$_n$=1.1−1.3) for the polymerization of MA, indicating that the polymerization is well controlled without instantaneous disproportionation of Cu(I)Br, in support of the SARA-ATRP mechanism. For Cu(0) wire mediated RDRP of MA in DMSO with TPMA, they observed the apparent propagation rate constant increased with the Cu(0) wire surface area according to a power law order of 0.47,[15(b)] which is very similar to the reported value of 0.44 by Nguyen *et al.*[19] for the Me$_6$TREN-based system. Thus, both groups are in agreement that the Cu(0) mediated RDRP is a heterogeneous polymerization with surface-dependent kinetics.

In polar non-aqueous solvents, Matyjaszewski's research group measured both the rate constants of activation and the equilibrium constant of disproportionation to support the SARA-ATRP mechanism. The activation rate constants for MBP and Br-capped poly(methyl acrylate) by Cu(0) wire and Cu(I)Br in the DMSO with excess amount of Me$_6$TREN at 25 ℃ were reported to be $k_{act,Cu(0)-RX}$=1.8 × 10^{-4} cm s^{-1}, $k_{act,Cu(0)-PX}$=1.0 × 10^{-4} cm s^{-1} and $k_{act,Cu(I)X}$=3.2 × 10^2 M^{-1} s^{-1};[15(c)] thus, the activation rate of MBP by 1 mM Cu(I)Br/Me$_6$TREN is similar to the activation rate by 2 km Cu(0) wire with diameter of 0.25 mm in 7 mL of DMSO. In the same system with MBP and excess amount of Me$_6$TREN in the DMSO at 25℃, the calculated rate constants are k_{com}=9.0 × 10^{-4} cm s^{-1} and k_{dis}=2.0 × 10^{-5} cm s^{-1} (K$_{dis,equili}$=2.2×10^{-2}) in DMSO, as well as 3.5 × 10^{-3} cm s^{-1} and 3.1 × 10^{-6} cm s^{-1} (K$_{dis,equili}$=8.9×10^{-4}) in binary solvent [MA/DMSO=2/1 (v/v)], respectively.[15(d)] The above experiment data supports the proposed SARA-ATRP mechanism: since the activation of alkyl halides by Cu(I) species is significantly faster than by Cu(0), the

activation step involves inner-sphere electron transfer rather than an outer-sphere electron transfer, in DMSO comproportionation is slow but occurs faster than disproportionation, and the activation by Cu(I)X species is much faster than disproportionation. Thus, the role of Cu(0) in this system is to slowly and continuously supply Cu(I) activating species and radicals, by supplemental activation and comproportionation, to compensate for Cu(I)X lost due to the unavoidable radical termination reactions.

In a recent paper, Matyjaszewski's research group even reported using water as the solvent. Although disproportionation was thermodynamically favored, the SARA-ATRP mechanism worked in such a system because alkyl halides were much more rapidly activated by Cu(I) than by Cu(0).[24]

2.3.2 Key equilibrium constants

In the SARA-ATRP mechanism, there is one key equilibrium constant, the equilibrium constant of disproportionation measured $K_{dis,equili}$ by expression 1 with a value lower than 1. There is another very important equilibrium based on the principle of microscopic reversibility, expressed by expression 2. The $k_{deact,Cu(I)X/L}$ is normally calculated through expression 2 with three known rate constants ($k_{act,Cu(0)}$, $k_{act,Cu(I)X}$ and $k_{deact,Cu(II)X2/L}$) and the calculated $K_{dis,equili.}$

2.4 Effect of water in Cu(0) mediated RDRP of HEA

Using water as the solvent instead of organic solvents such as DMF or DMSO has obvious environmental advantages and is also advantageous in terms of heat removal and promoting the rate of polymerization. In addition, water as a polar solvent has special effects on the Cu(0) mediated RDRP of HEA. As discussed previously, solvent polarity and ligand type can influence the key rate constants of disproportionation and comproportionation, which are at the heart of the

disagreement between the SET-LRP and SARA-ATRP mechanisms. What is more, water could influence the polymerization rate *via* varying activation rate and deactivation rate, possibly due to the combined effects of reduced energy required to break the C-Br bond and competitive coordination of solvent and ligand with the Cu(I) and Cu(II) species.[25] It was concluded that the large ATRP equilibrium constant in aqueous media generated high radical concentrations and consequently an increased rate of termination.[26] However, another factor that complicates the system of ATRP in water is the partial dissociation of the halide ion from deactivator complex, leading to inefficient deactivation of the propagating radicals.[27] Smolne *et al*. studied the second factor and proposed the dissociation mechanism shown as Scheme 2-5.[28] Although written for the Cu(I)/Cu(II) SARA-ATRP mechanism, loss of Cu(II) would also upset the balance of activation and deactivation according to SET-LRP.
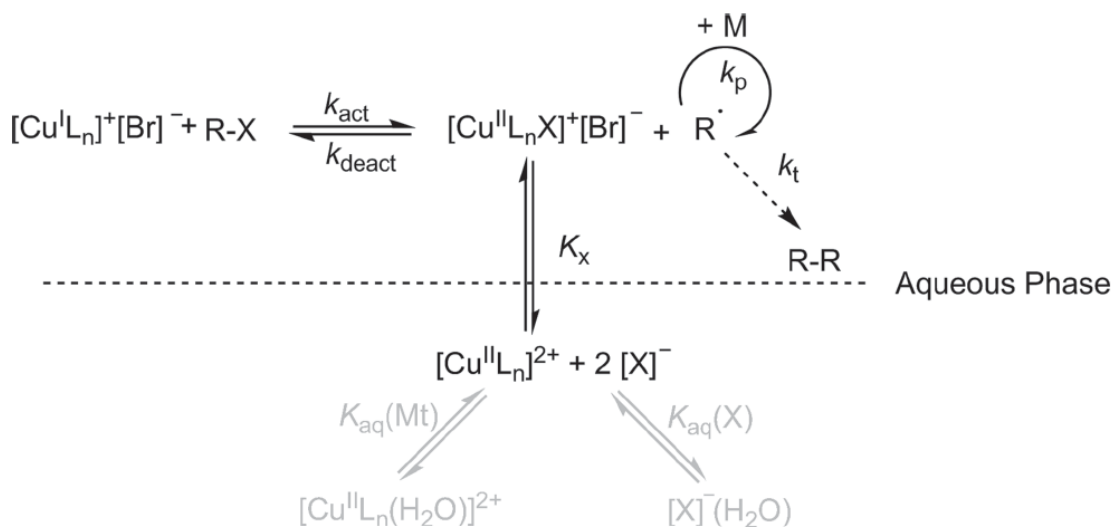
Scheme 2-5 Suggested mechanism of Cu-mediated ATRP in aqueous solution; L_n ligand with n complexing sites, R–X initiator, M monomer, R$^\bullet$ propagating radical, k_p propagation rate constant, k_t termination rate constant, K_x halide dissociation equilibrium constant, K_{aq} (Mt) equilibrium constant of water complexation, K_{aq} (X) equilibrium constant for hydration of the halide ion.[28] Reproduced from (S. Smolne and M. Buback, *Macromol. Chem. Phys.*, 2015, **216**, 894−902) with permission of John Wiley and Sons

It was proposed that addition of NaX could shift the constant K_x (the equilibrium constant for the halide dissociation) to the side of $[Cu(II)L_nX]^+[Br]^-$ to reduce this dissociation; this addition lower polymerization rates but improves control and reduces dispersity, while the activation rate constant and deactivation rate constant will not be affected according to recent research.[28] This strategy is employed in the aqueous Cu(0) mediated RDRP of HEA studied here.

2.5 Conclusion

SARA-ATRP and SET-LRP mechanisms both are both able to explain Cu(0)-mediated polymerizations, as the two mechanisms are not totally incompatible.[29] The balance of activation supplied by Cu(0) and Cu(I) species may be quite dependent on the specific system, with the relative rates of disproportionation and comproportionation sensitive to solvent choice.

A major source of controversy for Cu(0)-mediated RDRP in polar solvents (DMSO, DMF) is the actual concentration of $Cu(II)Br_2$ and the difference between calculated equilibrium constant of disproportionation by Matyjaszewski's group[15(d)] with excess amount of $Me_6TREN(K_{dis,equili}=10^{-2}-10^{-4})$ and by Percec's group[14(c)] $(K_{dis,equili}=10^1-10^4)$ with MBP/Me_6TREN ratio of 1:1 or 1:0.5, although the two research groups use the same expression (equation 1) and similar experimental methods.

In water, a recent report describes that, although the equilibrium constant of disproportionation is larger than 1, the rate of activation by Cu(I) is not only faster than by Cu(0) but also faster than disproportionation of Cu(I), a finding which favors the SARA-ATRP mechanism.[24] This study will not resolve this difference, but instead extends the application of Cu(0)-mediated RDRP to the production of higher-MW P(HEA) with narrow dispersity in aqueous solution.

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Chapter 3

Cu(0) Wire Mediated RDRP of 2-Hydroxyethyl Acrylate

Abstract

Cu(0) wire mediated RDRP of 2-hydroxyethyl acrylate was investigated for production of varying target polymer chain lengths, also examining the effect of initial $Cu(II)Br_2$ and the sequence of Me_6TREN addition on the MW control. The extent of gel formation decreases with decreasing polymer chain length and increasing amount of initial $Cu(II)Br_2$. Interestingly, changing the reagent addition sequence from HEA (monomer), Me_6TREN (ligand), $Cu(II)Br_2$ and HEBiB (initiator) to the addition sequence HEA, $Cu(II)Br_2/Me_6TREN$ and HEBiB decreases the extent of gel formation significantly and lowers polymer dispersity (Đ).

3.1 Introduction

Cu(0) wire mediated RDRP of methyl acrylate (MA) in DMSO as an example system was investigated by Percec's research group[1,2] and Matyjaszewski's research group.[3] Although there are significant mechanistic debates, well defined P(MA) with high chain end functionality was successful synthesized using low levels of soluble copper species (soluble copper species contributed only by Cu(0) wire). Later Chan *et al.* investigated Cu(0) mediated RDRP of MA in continuous processes for industrial application, first using copper tube as both the tubular reactor and as a catalyst source,[4] then using copper tube followed by inert stainless steel tubing in which the reaction rate was maintained by using ascorbic acid as a reducing agent to initiate polymerization of MA and generate soluble copper species,[5] and also using copper wire in a continuous stirred tank reactor (CSTR).[6] As described below, Cu(0) wire mediated RDRP of HEA has been investigated in batch studies, with significant difficulties encountered compared to

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MA. Thus, as a first step to explore the continuous production of P(HEA) in aqueous solution, it is necessary to better understand the batch system.

Using Cu(0) wire, Nicol et al.[7] firstly reported P(HEA) synthesis in dimethyl sulfoxide (DMSO) with Me_6TREN and PMDETA and in water with Me_6TREN, PMDETA and tris(2-aminoethyl)amine (TREN). Target chain length (TCL) was 30, and $Cu(II)Br_2$ was added to the system such that P(HEA) with high conversion and very low Đ (1.07) was produced at 25 ℃ using a molar ratio of $[Initiator]_0:[Me_6TREN]_0:[Cu(II)Br_2]_0=1:0.11:0.05$; thus the catalyst concentration was higher than 1,600 ppm, even neglecting the contribution of copper species from the Cu(0) wire. Later, Leng et al.[8] reported using Cu(0) wire with Me_6TREN in pure water as well as in a binary mixture of methanol and water (30 vol% MeOH) to synthesize P(HEA); in contrast to the findings of Nicol et al.,[7] a significant fraction of insoluble gel was formed for TCL=200, and the best reported Đ value was 1.46. Konkolewicz et al.[9] successfully produced block copolymer of HEA with oligo(ethylene oxide) methyl ether acrylate of molecular weight 480 to form both $P(OEOMA_{480})$ homopolymer and $P(OEOMA_{480})_{50}$-b-$P(HEA)_{100}$ block copolymer with Đ of 1.24 in water with measured ca. 600 ppm soluble copper at 22 ℃ using Cu(0) wire with Me_6TREN and 200 ppm initial $Cu(II)Br_2$. Most recently, Samanta et al.[10] reported the formation of thick gel on the Cu(0) wire surface when synthesizing P(HEA) with even TCL=20 in water using Cu(0) wire with Me_6TREN; the gel formation was suppressed by addition of extra $Cu(II)Br_2$ (10,000 ppm) to the system to form P(HEA) with Đ=1.21. The authors proposed that the high concentration of propagating radicals adsorbed on the Cu(0) wire surface undergo crosslinking reactions with neighboring groups, with the reaction suppressed in the presence of added deactivator, a hypothesis that will be further explored in this work.

Before investigating the industrial continuous process of Cu(0) wire mediated RDRP of HEA in aqueous solution, it is very important to find the key variables and important difficulties for this system, Cu(0) wire mediated RDRP of HEA with batch process in aqueous solution, especially under low soluble copper catalyst conditions. The effect of polymer chain length, amount of initial Cu(II)Br$_2$ and ligand addition sequence will be investigated and discussed.

3.2 Experimental

3.2.1 Materials

2-Hydroxyethyl 2-bromoisobutyrate (95%, Sigma-Aldrich), Cu(II)Br (99%, Sigma-Aldrich), NaBr (≥99%, Sigma-Aldrich), tris[2-(dimethylamino)ethyl]amine (97%, Sigma-Aldrich), and ethylene glycol diacrylate (90%, technical grade, Sigma-Aldrich) were used as received. D$_2$O (99.9%, Cambridge Isotope Laboratories) was used as received.

Copper(0) wire (≥99.9%, diameter 1.0 mm, Sigma-Aldrich) was activated by hydrochloric acid (Fisher)[12] by immersion in hydrochloric acid for 10 min, washing with methanol and drying prior to use.

2-Hydroxyethyl acrylate (96%, Sigma-Aldrich) was purified as follows: hydroquinone (laboratory grade, Fisher Scientific, 0.05 wt.%) was added to a solution of HEA in water (25% v/v) before a series of 12 times solvent extraction with hexane (reagent, ACP Chemicals) to remove the ethylene glycol diacrylate. The aqueous layer was salted with NaCl (≥ 99%, Sigma-Aldrich, 200 g/L) and then filtered to remove undissolved NaCl. The monomer was then separated from the aqueous layer by extraction with diethyl ether (4 times) to remove acrylic acid. Hydroquinone (0.05 wt.%) was added to the diethyl ether layer before evaporation *via* rotary evaporator. The ether layer was dried by adding molecular sieves (0.5 wt.%) and then evaporated

in a rotary evaporator at 34 ℃. The purified HEA was filtered through an alumina column to remove hydroquinone and acid residue prior to use.

P(HEA) was acetylated by acetic anhydride (reagent, Fisher Scientific) in pyridine (≥99%, Sigma-Aldrich) as follows: 60 mg P(HEA) was dissolved completely in 1.5 ml pyridine in a 5 ml flask, followed by addition of 0.3 ml acetic anhydride. The solution was stirred overnight to allow for complete acetylation, air dried at room temperature, and then vacuum dried at 60 ℃ overnight.

3.2.2 Techniques

^{1}H-NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer at 23 ℃ in D_2O to determine HEA conversion and polymer $M_{n, NMR}$ and in DMSO-d_6 to verify complete acetylation; detailed spectra information and calculations are provided in Appendix 2 and 3. The gel permeation chromatograph (GPC) consisted of a Waters 2960 separation module with four Styragel packed columns HR 0.5, HR 1, HR 3 and HR 4 (Waters Division Millipore) connected to a Waters 410 refractive index (RI) detector operating at 35℃. Tetrahydrofuran (THF, reagent, ACP Chemicals) was used as eluent at a flow rate of 0.3 mL·min^{-1}. The $M_{n,GPC}$ and Đ were determined by polystyrene (PS) standards over the range of 870-875000 g·mol^{-1}.

A Varian CP-3800 GC was used to quantitatively measure EGDA in the purified HEA. The GC system consisted of a CP-8410 autosampler, CP-1177 isothermal split/splitless injector, 30M chrompack capillary column (CP-Sil 8 CB), oven and a flame ionization detector (FID). (Programmed temperature profile, calibration curve and sample analysis are in Appendix 1.)

3.2.3 Procedure for Cu(0) wire mediated RDRP of 2-hydroxyethyl acrylate

For TCL=50, activated Cu(0) wire (length=10 cm and diameter=1 mm) was bent into a carousel reaction tube (Radley, tube A) with a magnetic stir bar, and reagents were added in the following

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order HEA (2750 μL, 26.24 mmol), Me$_6$TREN (97%, 28.9 μL, 0.105 mmol), NaBr (45.9 mg, 0.446 mmol) and D$_2$O (8 mL). A PTFE reaction cap with silicon suba-seal (Radley) was fixed on the carousel reaction tube, and connected to a Schlenk line. Three cycles of freeze-pump-thaw for degassing were performed. HEBiB (95%, 82.6 μL), 100 μL of stock solution containing 1.17 mg Cu(II)Br$_2$ and D$_2$O (3.9 mL) were added into the other carousel reaction tube (tube B) with a magnetic stir bar. After three cycles of freeze-pump-thaw, the solution from tube B was transferred by syringe into tube A which was immersed in the water bath at room temperature to start the polymerization under stirring and a nitrogen blanket. Samples were taken at different time by syringe. At every time, a small amount of the sample was used for the analysis of monomer conversion and M$_{n,NMR}$ calculation. The remaining sample was filtered through an alumina column to remove catalyst and ligand prior to GPC sample preparation.

3.3 Results and discussion

3.3.1 Effect of polymer chain length

The synthesis of P(HEA) in water using activated Cu(0) wire as catalyst, Me$_6$TREN as ligand and ethyl-2-bromoisobutyrate (EBiB) as initiator at 25 ℃ has been studied recently by two groups. Interestingly, one reported successful synthesis of P(HEA) with Đ=1.07, TCL=30, and monomer conversion of 97%, achieved with the addition of *ca.* 1666 ppm Cu(II)Br$_2$,[7] while the other reported the formation of significant insoluble gel on the surface of the Cu(0) wire for TCL=200 in the absence of added Cu(II)Br$_2$ in water and in methanol/water mixtures with water content of 70 vol% or higher.[8] Subsequent work[10] using activated Cu(0) wire, Me$_6$TREN and the water soluble initiator oligo(ethylene glycol) methyl ether 2-bromoisobutyrate, found significant gel formation even at TCL=20. To further explore whether DP$_n$ is also a factor, we synthesized P(HEA) under similar conditions (Scheme 3-1) using the water soluble initiator 2-hydroxyethyl

2-bromoisobutyrate (HEBiB), with conversion and number average molecular weight (M_n) calculated from ^{1}H-NMR spectra (D_2O is used as solvent instead of water.).

As described in the experimental section, M_n and Đ were also measured by gel permeation chromatography, after acetylation of the P(HEA).
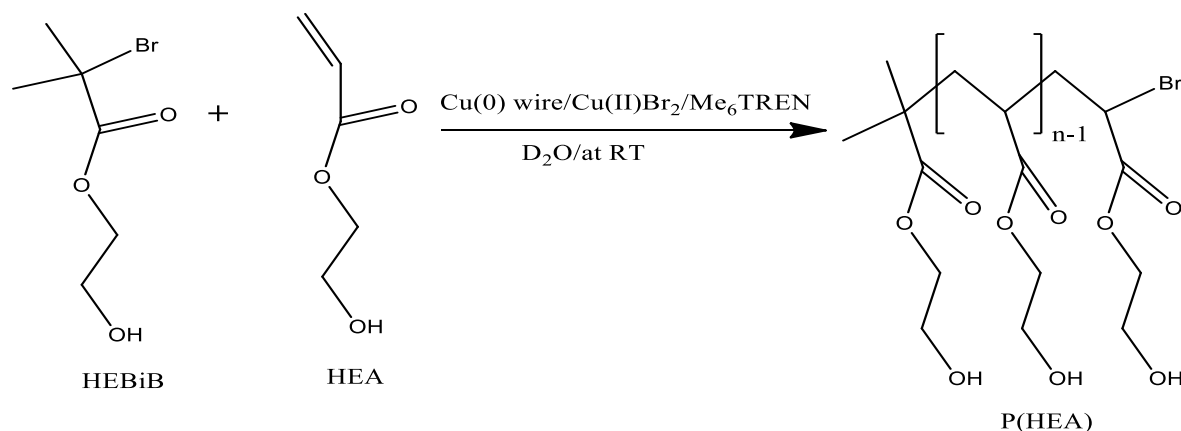
Scheme 3-1 Cu(0) wire mediated RDRP of 2-hydroxyethyl acrylate at room temperature (RT)

As seen in Figure 3-1, polymer precipitated out of solution at the Cu(0) wire surface, with about 40 wt.% of the initial HEA consumed by formation of insoluble gel during the 120 min reaction, as estimated by the mass of material.

Because of the significant amount of gel formation, the HEA conversion and $M_{n,NMR}$ calculations based on ^{1}H-NMR spectra are not reliable. Table 3-1 reports the GPC-measured M_n values of the soluble polymer fraction as a function of reaction time, with broad MMD found throughout the reaction; the resulting MMDs are bimodal in character, with a high MW shoulder observed (Figure 3-2).

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a)   60 min-TCL=50   b)   Replicated experiment at 120 min-TCL=50

c)   120 min-TCL=20   d)   Wire at 120 min-TCL=20

e)   Wire at 120 min-TCL=20 with 500 ppm Cu(II)Br$_2$

Figure 3-1 Gel formation in Cu(0) wire mediated RDRP of HEA at room temperature. Reaction conditions: HEA=2.75 mL (below 0.2 wt.% EGDA), D$_2$O=12 mL, 30 mM NaBr and 10 cm Cu(0) wire (diameter=1.0 mm), [HEA]$_0$/[HEBiB]$_0$/[Cu(II)Br$_2$]$_0$/[Me$_6$TREN]$_0$=50:1:0.01:0.2 (a and b); 20:1:0.004:0.08 (c and d) and 20:1:0.01:0.2 (e)

Thus we find that insoluble gel formation occurs on the Cu(0) wire surface even in the presence of added Cu(II)Br$_2$ (200 ppm) and NaBr (30 mM), in agreement with Leng *et al.*.[8]
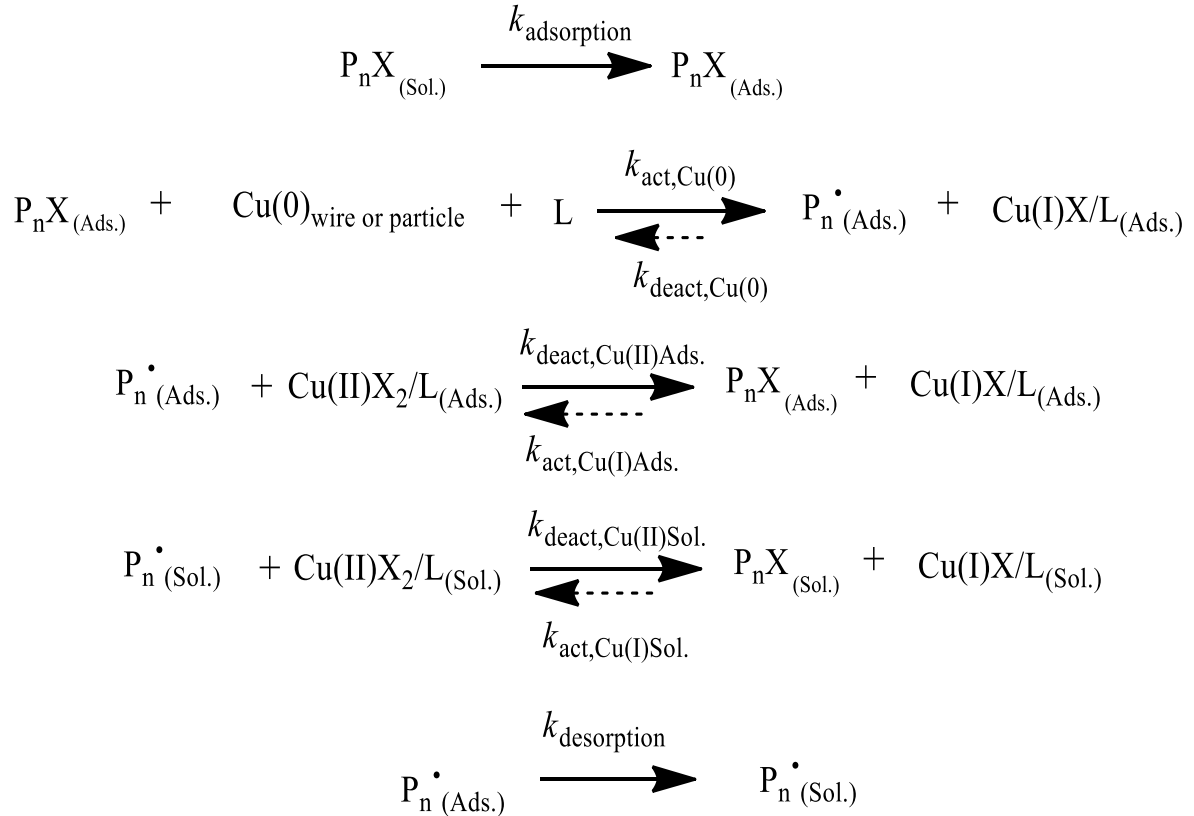
$$P_nX_{(Sol.)} \xrightarrow{k_{adsorption}} P_nX_{(Ads.)}$$

$$P_nX_{(Ads.)} \;+\; Cu(0)_{wire\ or\ particle} \;+\; L \underset{k_{deact,Cu(0)}}{\overset{k_{act,Cu(0)}}{\rightleftharpoons}} P_n^{\bullet}{}_{(Ads.)} \;+\; Cu(I)X/L_{(Ads.)}$$

$$P_n^{\bullet}{}_{(Ads.)} \;+\; Cu(II)X_2/L_{(Ads.)} \underset{k_{act,Cu(I)Ads.}}{\overset{k_{deact,Cu(II)Ads.}}{\rightleftharpoons}} P_nX_{(Ads.)} \;+\; Cu(I)X/L_{(Ads.)}$$

$$P_n^{\bullet}{}_{(Sol.)} \;+\; Cu(II)X_2/L_{(Sol.)} \underset{k_{act,Cu(I)Sol.}}{\overset{k_{deact,Cu(II)Sol.}}{\rightleftharpoons}} P_nX_{(Sol.)} \;+\; Cu(I)X/L_{(Sol.)}$$

$$P_n^{\bullet}{}_{(Ads.)} \xrightarrow{k_{desorption}} P_n^{\bullet}{}_{(Sol.)}$$

$P_n^{\bullet}{}_{(Ads.)}$ (extremely high) leads to gel formation and shoulder in MMDs

$P_n^{\bullet}{}_{(Ads.)}$ (high but not extremely high) leads to shoulder in MMDs

Scheme 3-2 Proposed mechanism of Cu(0) mediated RDRP of HEA in D$_2$O or H$_2$O, adapted from Leng *et al.*[8] and Samanta *et al.*.[10] P$_n$X($_{Sol.}$) denotes dormant species in solution; P$_n$X($_{Ads.}$) denotes dormant species adsorbed on the Cu(0) surface; P$_n^{\bullet}$($_{Sol.}$) denotes active species in solution; P$_n^{\bullet}$($_{Ads.}$) denotes active species adsorbed on the Cu(0) surface; L denotes ligand

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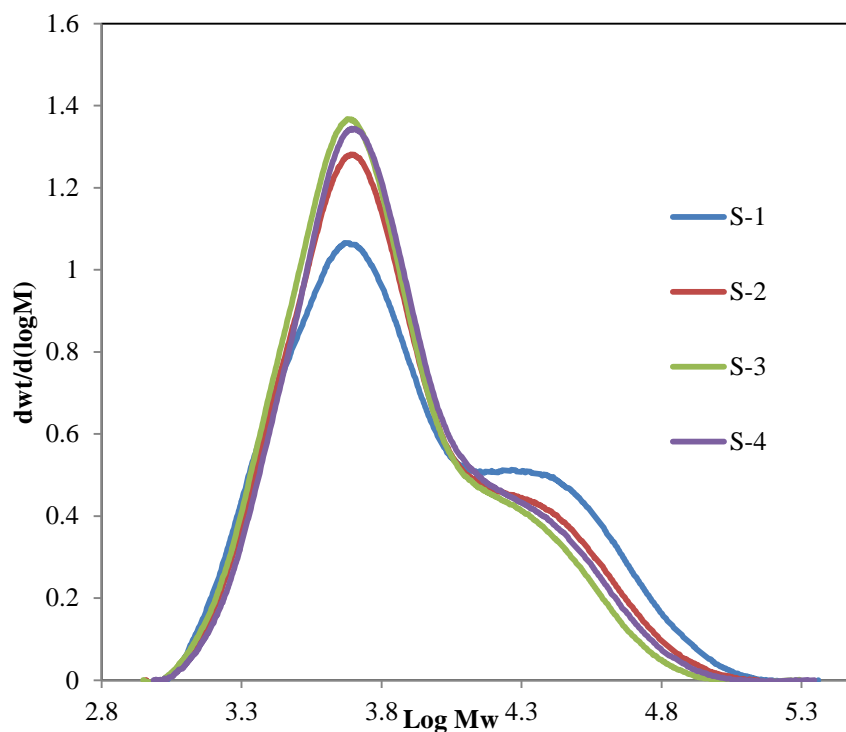
Figure 3-2 Molar mass distribution of P(AcHEA). Reaction conditions: HEA=2.75 ml, D_2O=12 ml, $[HEA]_0/[HEBiB]_0/[Cu(II)Br_2]_0/[Me_6TREN]_0$=50:1:0.01:0.2, 30 mM NaBr and 10 cm Cu(0) wire (diameter=1.0 mm). See Table 3-1 for sample information

Upon changing the TCL from 50 to 20 ($[HEA]_0/[HEBiB]_0/[Cu(II)Br_2]_0/[Me_6TREN]_0$=20:1:0.004:0.08), the gel formation is significantly reduced (Figure 3-1c and 3-1d). It should be noted that the Đ of P(HEA) produced over Cu(0) wire is larger than 1.5 with a high MW shoulder observed in all three experiments. Gel formation has been attributed[10] to the fast adsorption of P(HEA) dormant chains (with strong hydrophobic backbone) to the Cu(0) wire surface and slow desorption of P(HEA) radicals from the surface (Scheme 3-2), such that the adsorbed P(HEA) radicals beyond some high concentration form cross-linked insoluble polymer, with the specific mechanism of gel formation unclear. This

proposed explanation could explain the different results between Nicol's and Leng's studies if P(HEA) radicals with different DP_n have significantly different desorption rates from Cu(0) wire surface. The high MW shoulder seen in the MMDs could be attributed to reaction of the adsorbed P(HEA) radicals of longer length, with shorter adsorption times for the shorter chains. As the number of adsorbed P(HEA) radicals is dependent on the Cu(0) wire surface area, it is only for shorter Cu(0) wire with high water content that some slight improvement in control of P(HEA) was observed.[8] This suggests that using small sized Cu(0) particles as catalyst instead of wire could eliminate the gel formation at high DP_n ($DP_n > 30$), as Cu(0) wire increases the local concentration of polymer chains on the surface compared to highly dispersed particles.

Table 3-1 MW analysis of soluble fraction of P(HEA) formed by Cu(0) wire mediated RDRP of HEA at RT (22 – 25 °C). Reaction conditions: HEA=2.75 mL (below 0.2 wt.% EGDA), D_2O=12 mL, 30 mM NaBr and 10 cm Cu(0) wire[a] (diameter=1.0 mm), $[HEA]_0/[HEBiB]_0/[Cu(II)Br_2]_0/[Me_6TREN]_0$=50:1:0.01:0.2

Sample No.	Time (min)	$M_{n,GPC}$[b]	Đ[c]
S-1	30	3960	2.49
S-2	60	3840	2.13
S-3	90	3630	1.93
S-4	120	3890	1.99

[a] Hydrochloric acid-activated Cu(0) wire.[11] [b] $M_{n,GPC}=M_{n,P(AcHEA)} \times (116.12/158.15)$ [$M_{n,P(AcHEA)}$ is the refractive index (RI) data of acetylated P(HEA) relative to PS standard using THF as eluent]. [c] Đ is measured by RI [verification of complete acetylation in Appendix 3].

3.3.2 Effect of initial Cu(II)Br$_2$

Upon increasing the amount of initial Cu(II)Br$_2$ to 500 ppm ([HEA]$_0$/[HEBiB]$_0$/[Cu(II)Br$_2$]$_0$/[Me$_6$TREN]= 20:1:0.01:0.2), we observe less insoluble gel on the Cu(0) wire surface (Figure 3-1e), which is in agreement with the previous observation[10] that deactivation can occur on the Cu(0) surface and a high concentration of deactivator can reduce gel formation.

3.3.3 Effect of ligand addition sequence

There are two methods of ligand addition that were investigated. One method is as described in Section 3.2.3 (Procedure for Cu(0) wire mediated RDRP of 2-hydroxyethyl acrylate). The other method added the reagents in the following order: tube B containing Cu(II)Br$_2$/Me$_6$TREN complex and HEBiB was added into tube A (containing HEA, NaBr, D$_2$O and Cu(0) wire) after degassing. Between the two methods, the only difference is the ligand (Me$_6$TREN) addition, changed from being premixed with HEA in tube A, to being premixed with Cu(II)Br$_2$ and HEBiB in tube B. With a TCL=20 and after 120 min reaction, interestingly, the color of polymerization solution is quite different (Figure 3-3) and there is no visible gel formation on the copper wire surface using the second method of ligand addition. What is more, the MMD of P(HEA) using the second method is much narrower than that produced using the first method and shows no high molecular weight shoulder (Figure 3-4).

Interestingly, while both Me$_6$TREN and HEA are colorless, the solution turns brown when the two are mixed (Figure 3-5), which indicates a strong interaction or even chemical reaction. Although the exact mechanism of color change is unknown, it is possible there is Morita-Baylis-Hillman reaction[13] between acrylate esters (work both as the electrophile and as the activated alkene) under the tertiary amine (Me$_6$TREN as the catalyst).
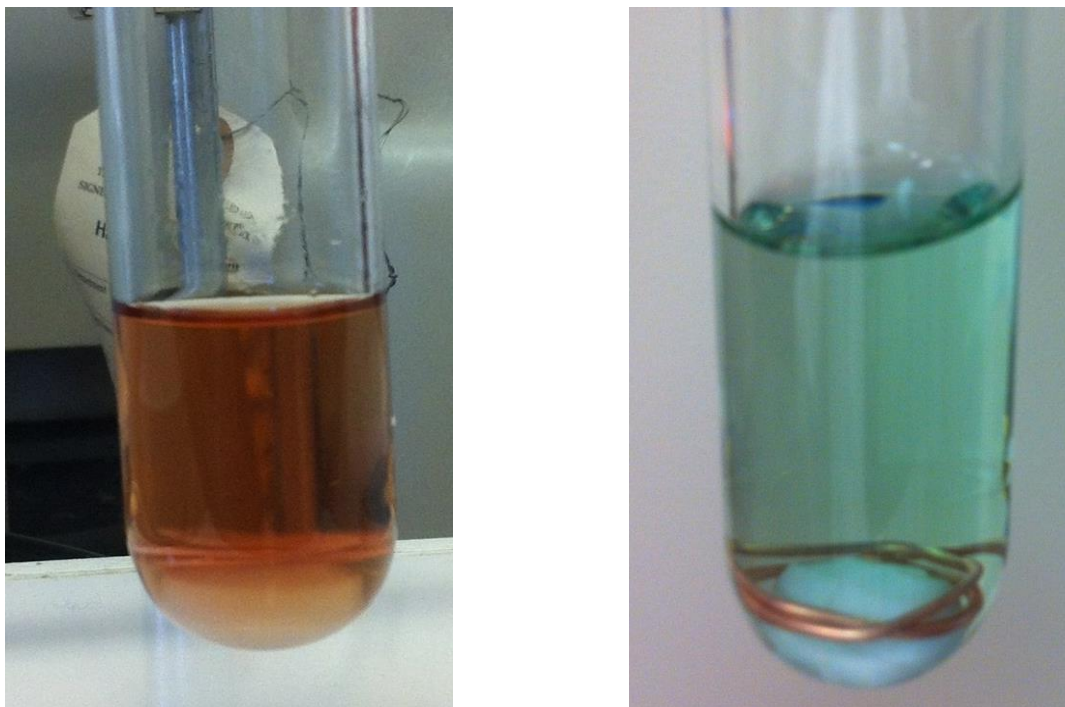
Figure 3-3 Color of polymerization systems. Reaction conditions: HEA=2.75 mL (below 0.2 wt.% EGDA), D_2O=12 mL, 30 mM NaBr and 10 cm Cu(0) wire (diameter=1.0 mm), $[HEA]_0/[HEBiB]_0/[Cu(II)Br_2]_0/[Me_6TREN]_0$=20:1:0.01:0.2; TCL=20 with first method of ligand addition (Left) TCL=20 with second method of ligand addition (Right)

The polymer solution using the second method has a blue color, possibly because with the first method of ligand addition, the ligand could not coordinate well with $Cu(II)Br_2$, leading to the reduction of effective deactivator concentration.

This result suggests that gel formation could be avoided at TCL=20 using the second method of ligand additions with 500 ppm initial $Cu(II)Br_2$. However, the overall level of Cu in the system is higher due to solubilized species from the Cu(0) wire, and the TCL is still quite low. Thus, our research focus moved to the two-step Cu(0) *in situ* mediated RDRP of HEA described in the following chapter.
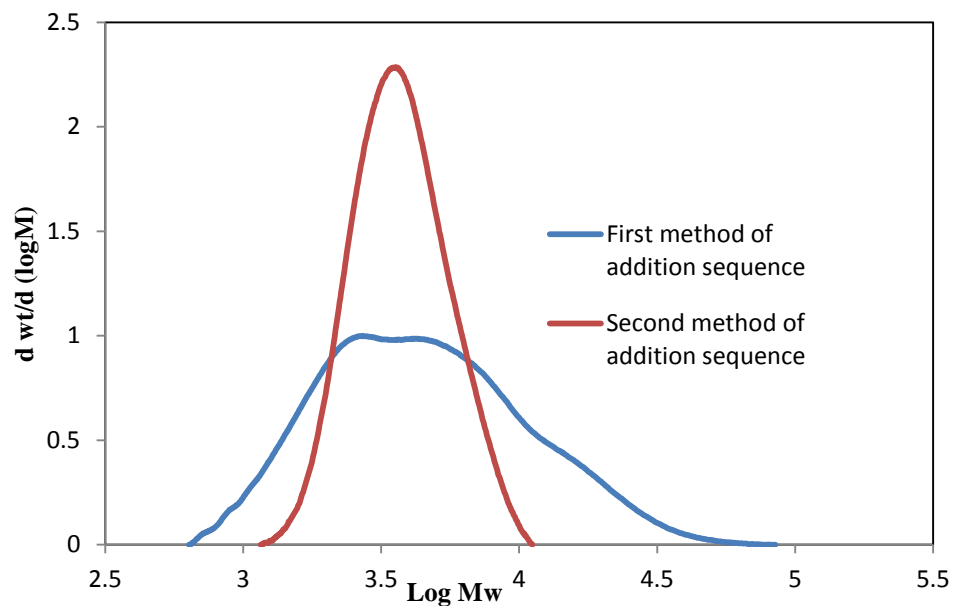
Figure 3-4 Molar mass distribution of P(AcHEA). Reaction conditions: HEA=2.75 mL (below 0.2 wt.% EGDA), D_2O=12 mL, 30 mM NaBr and 10 cm Cu(0) wire (diameter=1.0 mm), $[HEA]_0/[HEBiB]_0/[Cu(II)Br_2]_0/[Me_6TREN]_0$=20:1:0.01:0.2

Figure 3-5 Color of HEA (Left) and HEA/Me$_6$TREN with the molar ratio of 20:0.2 (Right)

3.4 Conclusion

The reversible deactivation radical polymerization (RDRP) of 2-hydroxyethyl acrylate in D_2O using Cu(0) wire with Me_6TREN at different TCL, initial amount of $Cu(II)Br_2$ and ligand addition sequence was investigated. Short chain length and high concentration of deactivator reduced gel formation. This result was explained by the reduced concentration of adsorbed active species on the Cu(0) wire surface through increased desorption rate and deactivation rate on the Cu(0) wire surface respectively. Interestingly, the ligand addition sequence could influence gel formation, possibly by significantly changing the effective deactivator concentration.

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Chapter 4

Two-Step Cu(0) *In Situ* Mediated RDRP of 2-Hydroxyethyl Acrylate

Abstract

Reversible deactivation radical polymerization (RDRP) of 2-hydroxyethyl acrylate in D_2O with two-step Cu(0) *in situ* mediation was investigated. The reasons for the presence of a high molecular weight (MW) shoulder in the molecular weight distribution (MMD) and the effects of excess NaBr, temperature and residual oxygen (brought by transferring monomer and initiator with syringe) were studied. The concentration of active species on the Cu(0) surface, which was influenced by Cu(0) type (wire or particle), polymer chain length, activator and deactivator concentrations, was the key factor in understanding the presence of insoluble gel and/or a high MW shoulder. High molecular weight P(HEA) (target chain length =400, 87% conversion) with Đ=1.16 was synthesized within 75 min using only *ca.* 250 ppm copper at room temperature. This is the first reported preparation of high MW P(HEA) with a low Đ using such a low copper catalyst concentration in a purely aqueous environment.

4.1 Introduction

Poly(2-hydroxyethyl acrylate) hydrogels synthesized by radical polymerization of 2-hydroxyethyl acrylate (HEA) have wide utility in biomedical and biomaterial applications.[1] As was previously discussed, a number of studies explore the synthesis of P(HEA) using metal-catalyzed RDRP. However, only limited success has been achieved in aqueous solution with conventional ATRP or with Cu(0) mediated systems using copper wire.

Rather than use copper wire or powder directly, Feng *et al.*[8,9] reported a procedure by which Cu(0) is generated *in situ* through disproportionation of Cu(I)Cl/Me$_6$TREN in

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dimethylformamide (DMF)/water (v/v 1/1); this novel SET-LRP implementation was used to synthesize poly(N-isopropylacrylamide-b-HEA) with Đ=1.10 at 25 ℃ using 10,000 ppm catalyst.

Zhang *et al*. further developed this approach to perform Cu(0) *in situ* mediated SET-LRP in pure water[10] and sheep serum.[11] In this procedure, which we will call two-step Cu(0) *in situ* mediation, Cu(I)Br/Me$_6$TREN is first allowed to fully disproportionate in solution to Cu(0) (visible as dispersed particles) and Cu(II)Br$_2$ at a molar ratio of 1:1, with polymerization commencing after transfer of monomer and initiator to the solution using a cannula to avoid exposure to oxygen.

A wide range of monomers were polymerized in aqueous solution using this new approach, including P(HEA) with TCL=20 and very low Đ=1.07 at room temperature in water, and P(HEA) of the same chain length with Đ=1.15 at 0 ℃ in sheep serum. In both cases, the catalyst concentration was high: 20,000 ppm (molar ratio of copper to monomer) in water and 40,000 ppm in sheep serum. In addition, although the molar mass distributions (MMD) had low dispersity, a small shoulder on the high MW side can be observed in the distributions presented as supporting information.[10]

Based on this review of the literature there is still significant work to be done to synthesize P(HEA) with low dispersity and high molar mass in water using reduced catalyst concentration (less than 500 ppm). As part of this exploration, we also address key mechanistic questions based on the heterogeneous Langmuir-Hinshelwood mechanism shown as Scheme 4-1 (the same as Scheme 3-2), proposing possible reasons why insoluble gel is formed in aqueous solution during P(HEA) synthesis using Cu(0) wire and the cause of the high MW shoulder seen in P(HEA) MMDs synthesized in aqueous Cu(0) mediation.
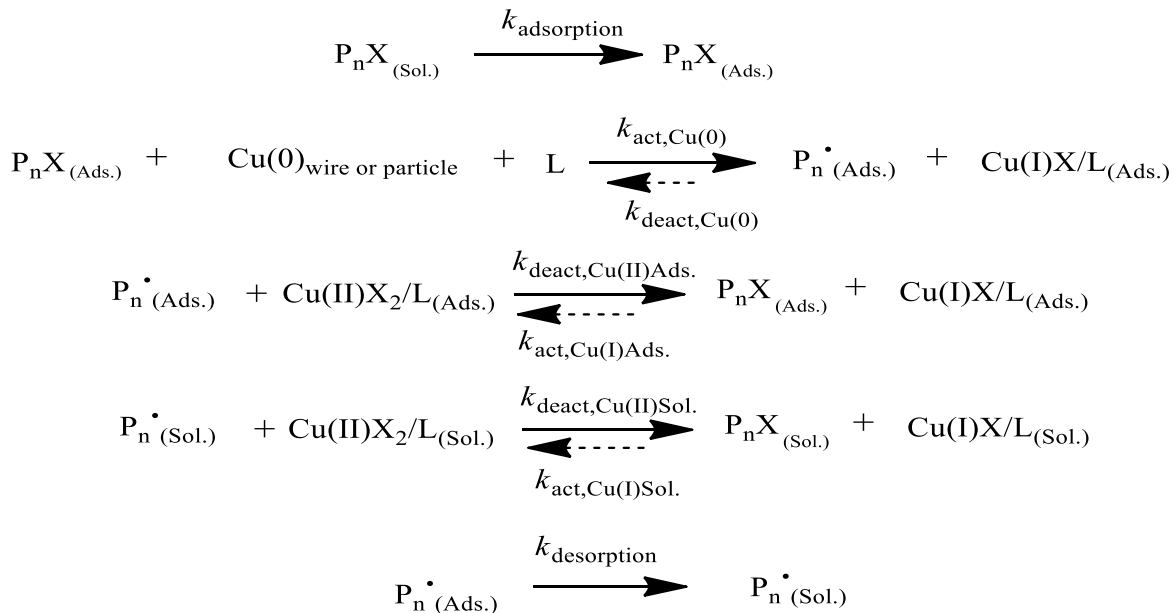
$$P_nX_{(Sol.)} \xrightarrow{k_{adsorption}} P_nX_{(Ads.)}$$

$$P_nX_{(Ads.)} \; + \quad Cu(0)_{wire\ or\ particle} \quad + \quad L \;\; \underset{k_{deact,Cu(0)}}{\overset{k_{act,Cu(0)}}{\rightleftarrows}} \;\; P_n^{\bullet}{}_{(Ads.)} \quad + \quad Cu(I)X/L_{(Ads.)}$$

$$P_n^{\bullet}{}_{(Ads.)} \;\; + \; Cu(II)X_2/L_{(Ads.)} \;\; \underset{k_{act,Cu(I)Ads.}}{\overset{k_{deact,Cu(II)Ads.}}{\rightleftarrows}} \;\; P_nX_{(Ads.)} \quad + \quad Cu(I)X/L_{(Ads.)}$$

$$P_n^{\bullet}{}_{(Sol.)} \;\; + \; Cu(II)X_2/L_{(Sol.)} \;\; \underset{k_{act,Cu(I)Sol.}}{\overset{k_{deact,Cu(II)Sol.}}{\rightleftarrows}} \;\; P_nX_{(Sol.)} \quad + \quad Cu(I)X/L_{(Sol.)}$$

$$P_n^{\bullet}{}_{(Ads.)} \xrightarrow{k_{desorption}} P_n^{\bullet}{}_{(Sol.)}$$

$P_n^{\bullet}{}_{(Ads.)}$ (extremely high) leads to gel formation and shoulder in MMDs

$P_n^{\bullet}{}_{(Ads.)}$ (high but not extremely high) leads to shoulder in MMDs

Scheme 4-1 Proposed mechanism of Cu(0) mediated RDRP of HEA in D_2O or H_2O, adapted from Leng et al.[6] and Samanta et al..[7] $P_nX_{(Sol.)}$ denotes dormant species in solution; $P_nX_{(Ads.)}$ denotes dormant species adsorbed on the Cu(0) surface; $P_n^{\bullet}{}_{(Sol.)}$ denotes active species in solution; $P_n^{\bullet}{}_{(Ads.)}$ denotes active species adsorbed on the Cu(0) surface; L denotes ligand

In addition, we explore the effects of NaBr, temperature and adventitious oxygen on the polymerization of HEA in aqueous Cu(0) mediation. We demonstrate the production of comparatively high molecular weight P(HEA) [($M_{n,GPC}$=32400 Da, Đ=1.16, 87% conversion, TCL=400), ($M_{n,GPC}$=69540 Da, Đ=1.35, 79% conversion, TCL=800)] using low catalyst concentration, *ca*. 250 ppm, at 22 ℃ in aqueous solution under not strictly oxygen-free conditions (transfer of monomer and initiator by syringe).

4.2 Experimental

4.2.1 Materials

Cu(I)Br (99%, Sigma-Aldrich) was used as received. Other materials were obtained as described in Chapter 3.

4.2.2 Techniques

Monomer purification and polymer characterizations were done as described in Chapter 3. Some polymer samples were analyzed by aqueous GPC with PEO standard (detailed in Appendix 5).

4.2.3 Procedure for two-step Cu(0) *in situ* mediated RDRP of 2-hydroxyethyl acrylate

Desired amounts of Me$_6$TREN and D$_2$O (detailed recipes are in Appendix 4) were added into a carousel reaction tube (tube A) with a magnetic stir bar. After three cycles of freeze-pump-thaw for degassing, the solution of tube A was immersed in liquid nitrogen and Cu(I)Br added to tube A through an opened silicon suba-seal in the PTFE reaction cap, followed by evacuation (1 min) and filling with nitrogen (1 min) twice. Tube A was immersed in the water bath at 22 or 0 ℃. Disproportionation took place for 30 min under a nitrogen blanket, with the start time as the point at which the frozen solution completely melted. A specific amount of HEA, HEBiB, NaBr and D$_2$O (detailed recipes are in Appendix 4) were added into the other clean carousel reaction tube (tube B) with a magnetic stir bar. After three cycles of freeze-pump-thaw, the solution of tube B was transferred by syringe or cannula into tube A to start the polymerization. At the required time, the PTFE reaction cap was opened and hydroquinone (inhibitor, 2 wt.%) was added to stop the polymerization. The sample was frozen in the NMR tube and taken immediately for ^{1}H-NMR analysis. The remaining solution was filtered through an alumina column to remove catalyst and ligand for further GPC sample preparation. MMDs of some polymer samples produced with inadequate degassing and nitrogen protection are contained in Appendix 6.

4.3 Results and discussion

Step 2

Cu(I)Br

Me$_6$TREN/D$_2$O
(Degassed)

30 min
full disproportionation

Cu(0) *in situ*
Cu(II)Br$_2$/Me$_6$TREN
D$_2$O

+

HEA   polymerization
HEBiB
D$_2$O   0°C/22°C/35°C
NaBr or not
(Degassed)

P(HEA)

Step 1
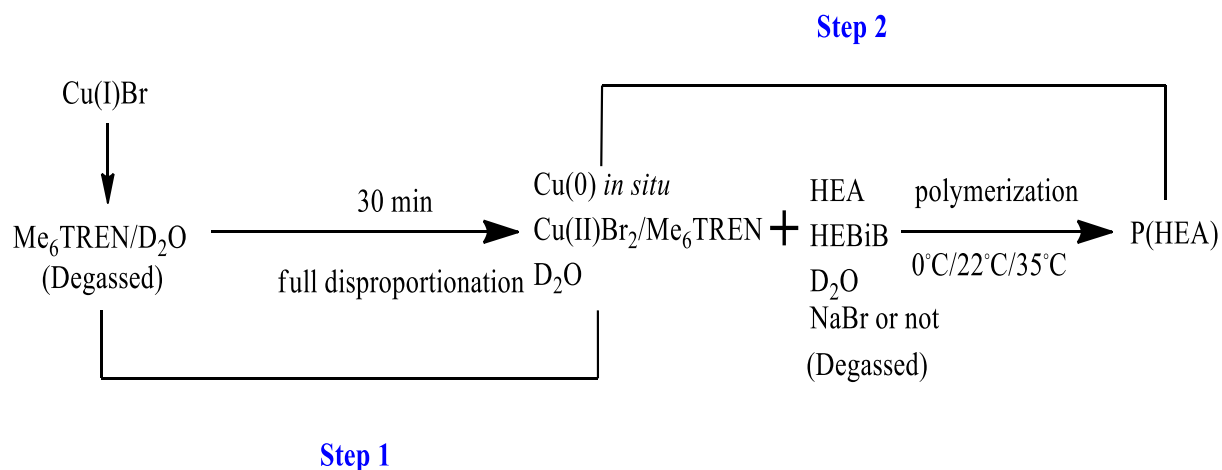
Scheme 4-2 Two-step Cu(0) *in situ* mediated RDRP of HEA

A full disproportionation of Cu(I)Br/Me$_6$TREN to form Cu(0) and Cu(II)Br$_2$ *in situ* is a practical method to prepare small sized Cu(0) particles and deactivator Cu(II)Br$_2$ complex at an equal molar ratio (Scheme 4-2), as reported by Zhang *et al*..[10]

In that work, this technique was used to synthesize low molecular weight P(HEA) (TCL=20) in water without gel formation. Herein, we successfully apply the methodology to synthesize P(HEA) over a wide TCL range, up to target chain length of 800. In addition, the influence of temperature (22 vs. 0 °C), initial Cu(I)Br levels, residual O$_2$ (affected by syringe vs cannula transfer of monomer and initiator) and added NaBr is explored. Throughout this investigation, no gel formation was observed in the presence of the Cu(0) generated *in situ* over the complete range of conditions (Figure 4-1).

As shown by Figure 4-1, solid Cu(0) particles are certainly observed in solution under varying conditions. However, the dispersed nature of the particles (compared to Cu wire) prevents gel formation, as the number of adsorbed active species per Cu(0) particle is significantly lowered.

a) TCL=800 in D$_2$O

b) TCL=50 in D$_2$O

Figure 4-1 No gel formation in the two-step Cu(0) *in situ* mediated RDRP of HEA in D$_2$O for TCL=800 (a) and TCL=50 (b). Small black specks represent Cu(0) particles, with the more intense blue color in (b) due to the higher catalyst concentration of 8,000 ppm

Note that gel formation can also be avoided with Cu(0) wire as mediating agent by increasing the hydrophilic character of the active species to some extent for the polymer chains, for example by using P(EO)[9] or P(OEOMA$_{480}$)[11] as a macro-initiator.

4.3.1 The origin of the high MW shoulder in P(HEA) MMDs

Table 4-1 summarizes the recipes and key results for a series of experiments performed with target chain lengths between 20 and 100, with monomer and initiator transferred to the reaction solution by syringe after allowing the Cu(I)Br to disproportionate to Cu(0) and Cu(II)Br$_2$.The first entry (Experiment TCL20-1) is similar to the experimental

conditions of Zhang *et al.*,[15] the only difference being choice of initiator, HEBiB in our work and 2, 3-dihydroxypropyl 2-bromo-2-methylpropanoate for Zhang *et al.*. P(HEA) with Đ=1.14 was produced, in reasonable agreement with the previous results (Đ=1.07).

Table 4-1 Two-step Cu(0) *in situ* mediated RDRP of HEA in 4 ml D_2O and transferring HEA, HEBiB and D_2O by syringe; entry 1-6 (15 vol% monomer), entry 7-11 (27 vol% monomer); entry 2 [TCL20-1, HEA (0.633 wt.% EGDA) traced by GC (detail in Appendix 1)], other entries [HEA (below 0.2 wt.%EGDA) traced by GC (detail in Appendix 1)]

Experiment	$[M]_0:[I]_0:[C]_0:[L]_0/$ $[NaBr]_0$ [a]	Cu ppm	T^b (°C)	React. time (min)	Conv.[c] (%)	$M_{n,th}$ [d]	$M_{n,NMR}$ [e]	$M_{n,GPC}$ [f]	$Đ^g$
TCL20-1	20:1:0.4:0.4	20,000	22	30	>99.9	2530	2820	2840	1.14
TCL20-2	20:1:0.4:0.4	20,000	22	30	>99.9	2530	2550	2960	1.15
TCL20-3	20:1:0.1:0.1/1.2	5,000	0	25	98.4	2500	2510	2470	1.15
TCL50-1	50:1:0.4:0.4	8,000	0	5	97.5	5870	5860	5580	1.18
TCL50-2	50:1:0.4:0.4/4.8	8,000	0	20	>99.9	6010	5880	5900	1.19
TCL50-3	50:1:0.1:0.1/1.2	2,000	0	19	89.2	5390	5360	4690	1.26
TCL100-1	100:1:0.4:0.4	4,000	0	10	98.3	11630	11790	10490	1.24
TCL100-2	100:1:0.1:0.1	1,000	0	10	89.5	10600	10570	10350	1.39
TCL100-3	100:1:0.1:0.1/1.2	1,000	0	30	97.3	11510	12350	9780	1.18
TCL100-4	100:1:0.1:0.1/1.2	1,000	0	10	16.0	2070	2190	3380	1.98
TCL100-5	100:1:0.1:0.1/1.2	1,000	22	16	93.6	11080	12540	9080	1.18

[a] $[M]_0:[I]_0:[C]_0:[L]_0/[NaBr]_0=[HEA]_0:[HEBiB]_0:[Cu(I)Br]_0:[Me_6TREN]_0/[NaBr]_0.$ [b] Disproportionation and polymerization temperatures are the same. [c] Conversion is calculated *via* ^{1}H-NMR spectrum (detail in Appendix 2). [d] $M_{n,th}=M_{HEA}\times TCL \times$ conversion $+ M_{initiator}$. [e] End-group method to calculate M_n of polymer based on ^{1}H-NMR spectrum $[M_{n,NMR}= M_{HEA}\times \bar{N}$ (calculated number average unit of monomer per initiator) $+ M_{initiator}]$ (details in Appendix 2). [f] $M_{n,GPC}=M_{n,P(AcHEA)} \times (116.12/158.15)$ $[M_{n,P(AcHEA)}$ is the refractive index (RI) data of acetylated P(HEA) relative to PS standard using THF as eluent]. [g] Đ is measured by RI (verification of complete acetylation in Appendix 3)

However, a clear high MW shoulder is seen in the MMD, a phenomenon that is observed also for higher target chain lengths, as shown in Figure 4-1. One potential explanation for this observation is the presence of ethylene glycol diacrylate (EGDA) impurity in commercial HEA, a difunctional monomer that could lead to branching and even crosslinking during polymerization. Other studies have found that this impurity disrupts control in RDRP systems.[12] For most reactions, we used purified HEA, which reduced the EGDA content from 0.63 to below 0.2 wt.%. However, it appears as if this purification is not necessary, as there is no significant difference in the polymer MMD (and dispersity) when the reaction was done using commercial HEA without purification (Experiment TCL20-2, see Figure 4-2a).
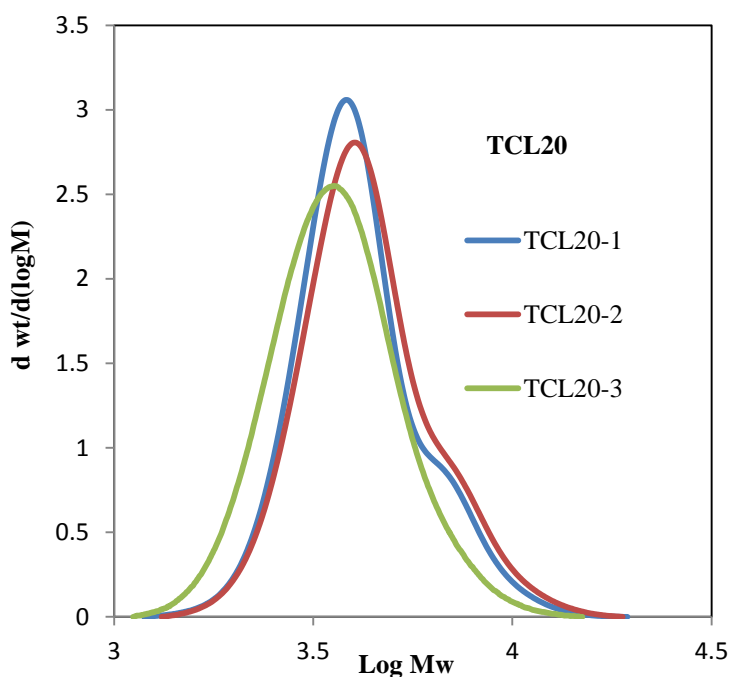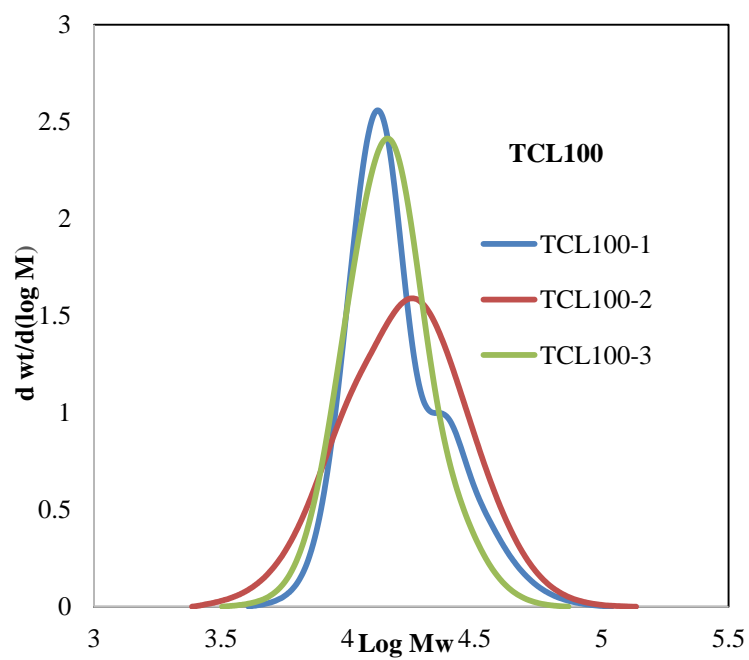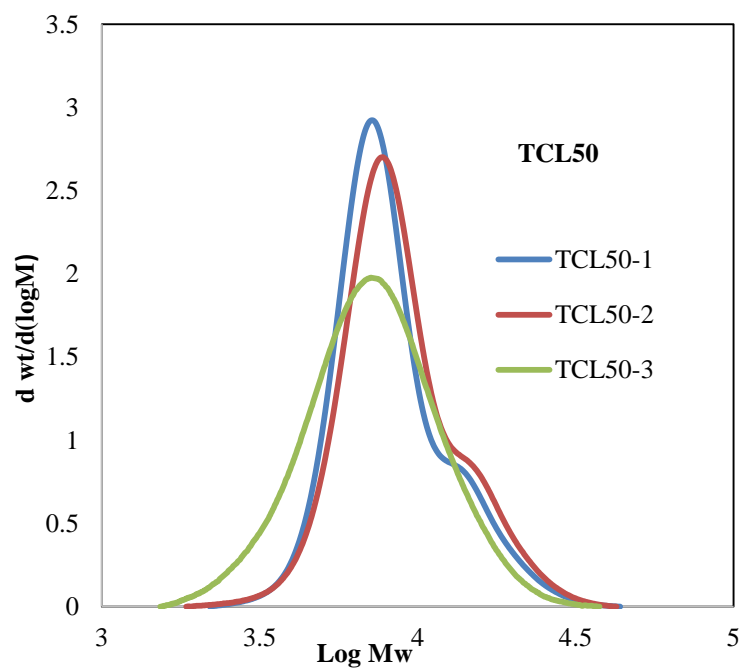
Figure 4-2 Molar mass distributions of P(AcHEA) with TCL of 20 (a), 50 (b) and 100 (c). Experimental details presented in Table 4-1

To explore the origins of this shoulder, the reaction temperature was decreased from 22 to 0 ℃ in order to slow the polymerization rate for kinetic studies. Keeping the $[HEBiB]_0:[Cu(I)Br]_0:[Me_6TREN]_0$ ratios at 1:0.4:0.4, changing the target chain length from 20 to 100 results in a decrease of Cu level from 20,000 to 4,000 ppm (with respect to monomer). However, the polymerization rate for Experiment TCL50-1 and Experiment TCL100-1 remains fast, with high conversion reached within 10 min. The P(HEA) chain lengths remain very close to the target value, but the high MW shoulder remained (Figure 4-2), and Đ increased slightly to 1.24 for TCL100-1.

A further decrease in Cu level to 1000 ppm with TCL=100 (TCL100-2) led to much broader MMD (Đ=1.39), without a clear high MW shoulder (Figure 4-2c). It may be that the lower Cu(0) level decreases the amount of adsorbed polymer and thus prevents shoulder formation, with the corresponding decrease in $Cu(II)Br_2$ leading to some loss of control. Other work has suggested that at low Cu levels, addition of NaBr is needed to suppress the dissociation of the $Cu(II)Br_2$ deactivator complex and improve control.[15-17] As shown by Experiment TCL100-3, utilization of NaBr decreases Đ back to below 1.2, and also suppresses the formation of the high MW shoulder (Figure 4-2c).

While adding excess NaBr suppresses the dissociation of $CuBr_2/Me_6TREN$ (deactivator), it also significantly increases the deactivation rate and thus decreases the rate of polymerization. For a reaction time of 10 min, only 16% conversion is reached in the presence of NaBr (Experiment TCL100-4) compared to full conversion in its absence (Experiment TCL100-2), with 30 min required to achieve full conversion with NaBr (Experiment TCL100-3). In addition, a significant decrease in dispersity is observed with conversion (Đ=1.18 at full conversion of Experiment TCL100-3 compared to Đ=1.98 at 16% conversion of Experiment TCL100-4).

Finally Experiment TCL100-5 indicates that lowering the reaction temperature from 22 to 0 ℃ is not required to achieve good control. The same general results are found for target chain lengths of 20 (Experiment TCL20-3) and 50 (Experiment TCL50-3). Although copper levels were reduced by a factor of 4 compared to the base case, dispersity remains low, and no high MW shoulder can be seen (Figure 4-2).

The dispersity is slightly higher for Experiment TCL50-3 (Đ=1.26), which might be a result of the reduced conversion (89%) compared to the other cases. Interestingly, it was found that the high MW shoulder was still observed when copper level was kept at the higher level (Experiment TCL50-2, Figure 4-2b).

We conclude that although NaBr is required to reduce the dissociation of deactivator when experiments are perform at low Cu levels in aqueous solution, it is actually the lowering of the Cu amount that suppresses the formation of the high P(HEA) shoulder. This observation is consistent with the hypothesis that the shoulder is related to adsorbed P(HEA) chains on the Cu(0) particle surface, with a reduced Cu content leading to lower rates of polymer chain adsorption and thus reduced concentration of adsorbed active chains.

4.3.2 Kinetic studies

As discussed above, adding NaBr to the system slows down the rate of polymerization. Although still a very fast reaction (complete conversion at 0 °C in < 30 min), this rate reduction allows the possibility of conducting kinetic studies. One of the questions we wanted to address is whether the monomer/initiator transfer method used in the two-step Cu(0) *in situ* mediated RDRP process affected rate and/or MW control, as it is well known that the normal ATRP system operated at low Cu levels can lose activity in the presence of

oxygen due to loss of activator Cu(I)Br by oxidation to Cu(II)Br$_2$. In the two-step Cu(0) *in situ* mediation process, our transfer process by syringe introduces a small amount of adventitious oxygen into the reaction system, compared to the cannula transfer used by Zhang *et al.*.[11] Here we study the effect of the transfer procedure at 0 °C for production of P(HEA) of TCL=100 at low (1,000 ppm) Cu levels with excess NaBr. The data were collected by stopping parallel reactions at various time points rather than sampling the reaction mixture, due to the heterogeneous nature of the reaction (visible Cu(0) particles). Figure 4-3 plots the monomer conversion as a function of time, as well as the evolution of M_n and Đ as a function of conversion. First order kinetics is observed in both cases, with transfer by syringe leading to an observable induction period (~10 min) compared to transfer by cannula. The polymerization rates for the syringe-transfer experiments are comparable once the reaction commences, with high conversion reached after a total time of 20 min. Most importantly, this induction period did not affect the final M_n (very close to target) or final dispersity (~1.2).

Interestingly, a high MW shoulder is seen on the MMD of P(HEA) produced by the transfer by cannula, but is not seen when transfer is done by syringe (Figure 4-4). For both cases (and as seen with Experiment TCL100-4 in Table 4-1), the Đ of P(HEA) is significantly higher early in the reaction, with the distribution narrowing rapidly with increasing conversion.

To verify and further explore this behaviour, a similar set of experiments were conducted at 22 °C for a TCL=200; with the $[HEBiB]_0/[Cu(I)Br]_0/[Me_6TREN]_0$ kept constant at 1.0:0.1:0.1, the copper level was thus lowered to 500 ppm.
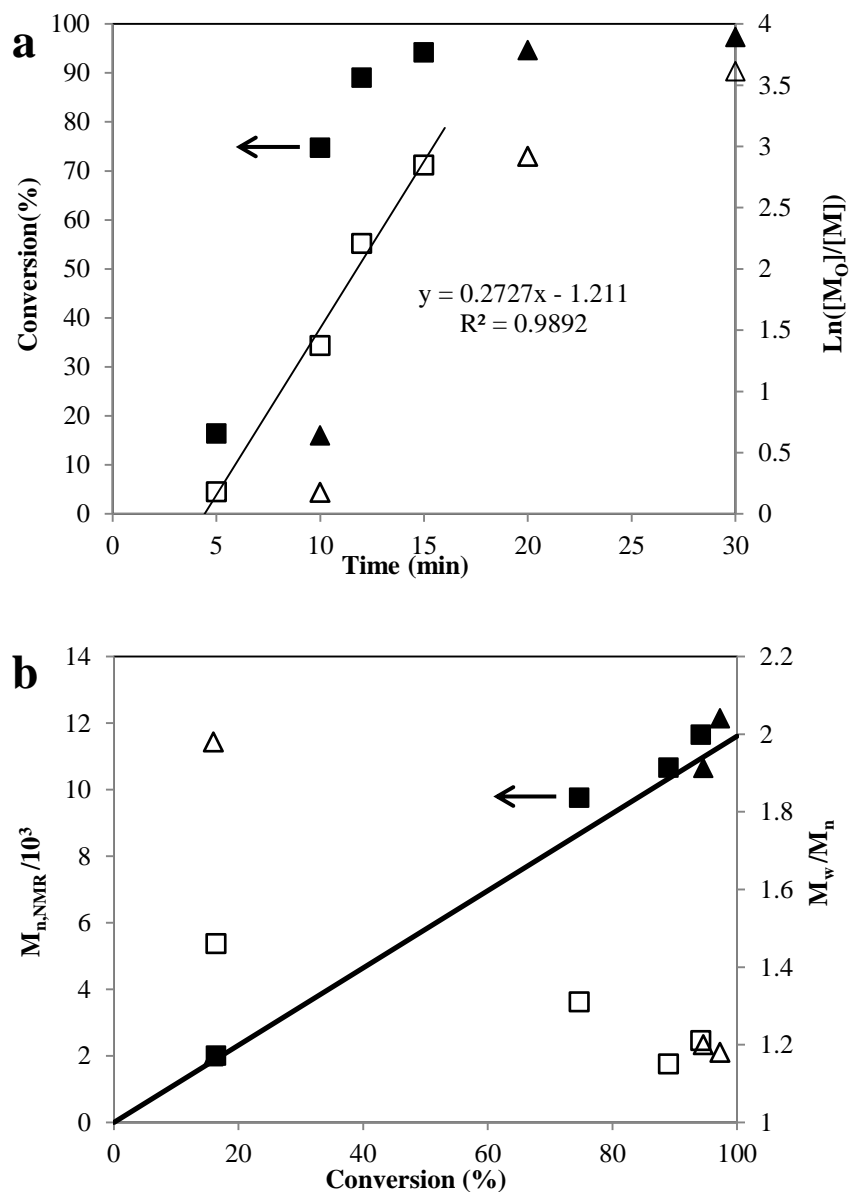
Figure 4-3 Comparing the effect of monomer/initiator transfer by cannula (squares) and syringe (triangles) for two-step Cu(0) *in situ* RDRP of HEA: monomer conversion (filled symbols) and $\ln([M]_0/[M])$ (open symbols) versus time (a); polymer $M_{n,NMR}$ (filled symbols) and dispersity (open symbols) versus conversion, with line indicating $M_{n,th}$ (b). Reaction conditions: HEA=1477 μL (below 0.2 wt.% EGDA), D_2O=4 mL, $[HEA]_0/[HEBiB]_0/[Cu(I)Br]_0/[Me_6TREN]_0/[NaBr]_0$=100:1:0.1:0.1:1.2 at 0 ℃

The results are quite consistent with the observations found for TCL=100: as shown in Figure 4-5, an induction period is still observed when transfer is completed by syringe, but the M_n of the final polymer is not affected. Indeed, with TCL=200, the dispersity is lowered to 1.10 for transfer by syringe compared to the value of 1.15 for transfer by cannula. While a high MW shoulder is seen for both cases, it is clearly reduced for the P(HEA) produced using syringe transfer.

Figure 4-4 Molar mass distribution of P(AcHEA) produced with a TCL of 100. Legend denotes transfer method (S denotes syringe, C denotes cannula), conversion, dispersity and temperature (L denotes 0 ℃ and H denotes 22 ℃)

The comparison of cannula vs. syringe transfer was done at 0 °C for TCL=100 and at 22 °C for TCL=200. To complete the study, P(HEA) was also produced using transfer by syringe for TCL=100 at 22 °C. Shorter time experiments were not conducted but, as shown in Figure 4-4, the polymer MMD produced at the higher temperature was almost identical with a slightly lower Đ. A few kinetic data points were collected at 0 ℃ for TCL=200; as shown in Figure 4-5, the induction period related to syringe transfer is greater than at 22 °C, and the time to reach full

conversion is longer (30-40 min) compared to the TCL=100 experiments (20-30 min in Figure 4-3).

Although the amount of kinetic data obtained is limited, it supports the expectations that polymerization rate increases with a decreased target chain length and with increased temperature. Surprisingly, the polymer dispersity is lower at the higher temperature and when monomer transfer is done by syringe compared to cannula, a result more clearly seen for TCL=200 (Figure 4-6) than for TCL=100 (Figure 4-4). It is possible that the higher temperature increases the desorption rate of adsorbed active species from Cu(0) surfaces, thus increasing the control.

Furthermore, while monomer and initiator transferred by syringe leads to a short induction period not seen with transfer by cannula, the procedure also slightly lower polymer dispersity, most likely due to increased control by oxidization of Cu(0) into Cu(I)Br or Cu(II)Br$_2$.
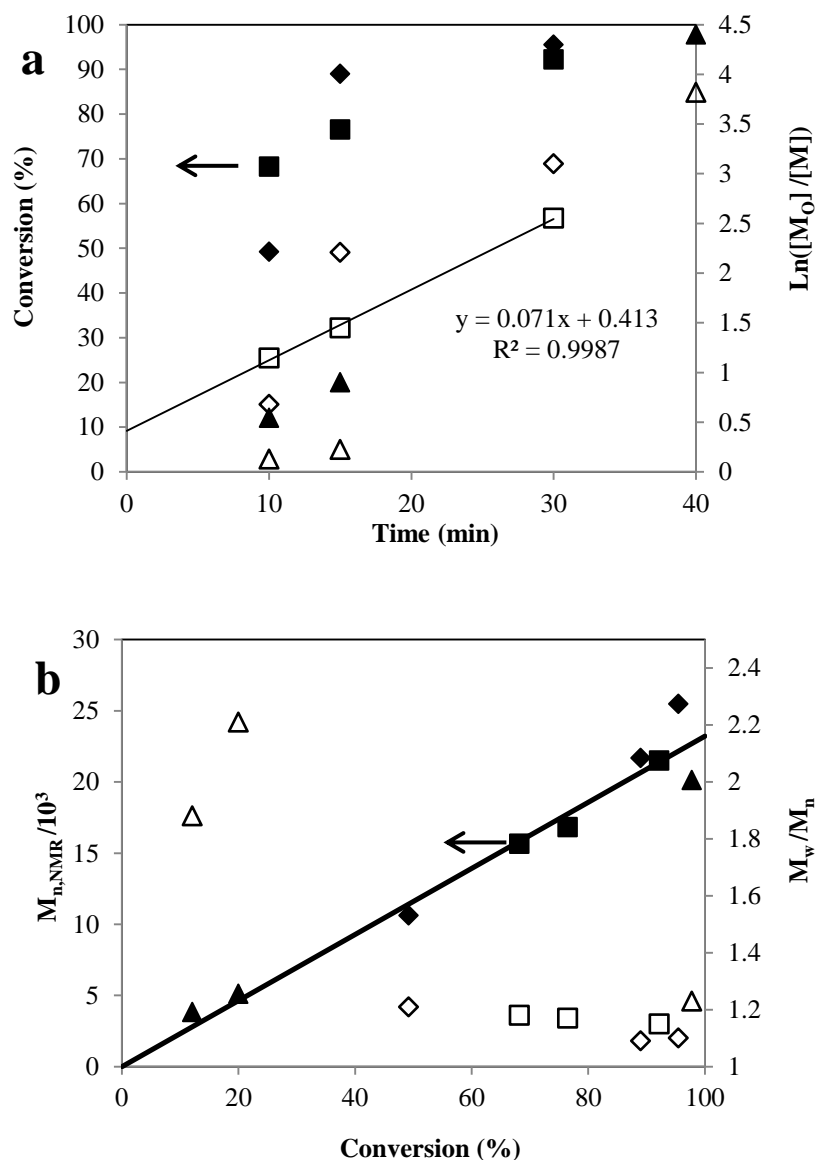
Figure 4-5 Comparing the effect of monomer/initiator transfer by cannula (squares) and syringe (triangles at 0 ℃ and diamond at 22 ℃) for two-step Cu(0) *in situ* RDRP of HEA: monomer conversion (filled symbols) and $\ln([M]_0/[M])$ (open symbols) versus time (a); polymer $M_{n,NMR}$ (filled symbols) and dispersity (open symbols) versus conversion, with line indicating $M_{n,th}$ (b); Reaction conditions: $[HEA]_0/[HEBiB]_0/[Cu(I)Br]_0/[Me_6TREN]_0/[NaBr]_0=200:1:0.1:0.1:2.4$ at 0 ℃ and at 22 ℃, HEA=2111 μL (below 0.2 wt.% EGDA), $D_2O=5.7$ ml
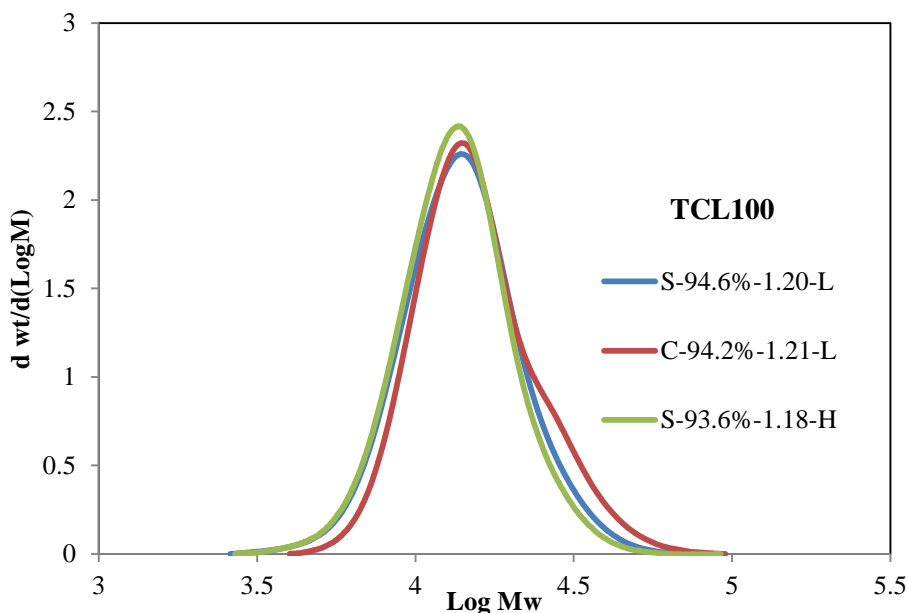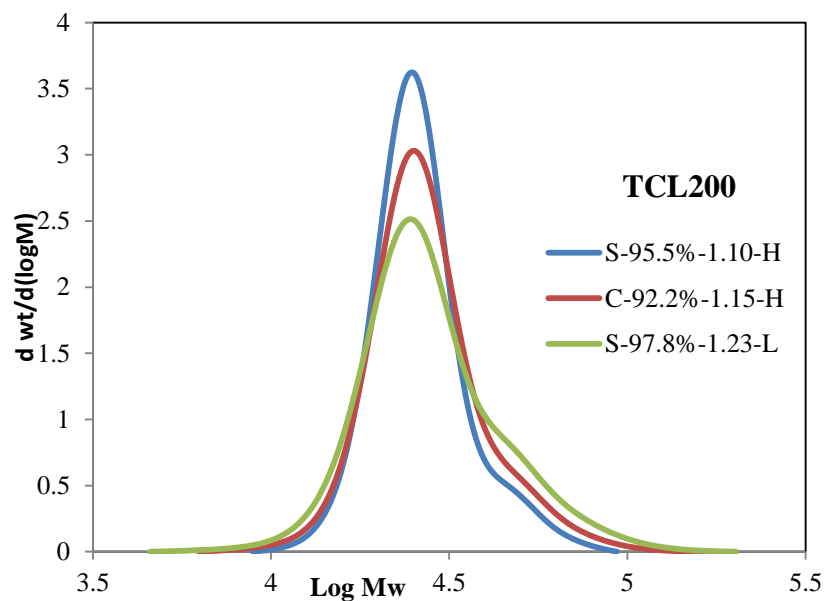
Figure 4-6 Molar mass distribution of P(AcHEA) produced with a TCL of 200. Legend denotes transfer method (S denotes syringe, C denotes cannula), conversion, dispersity and temperature (L denotes 0 ℃ and H denotes 22 ℃)

4.3.3 Synthesis of higher MW P(HEA) at low catalyst concentration

According to the above investigation, the more favorable conditions for synthesis of well defined high MW P(HEA) at lower catalyst levels with the two-step Cu(0) *in situ* mediation procedure are to use syringe transfer, conduct the reaction at 22 ℃ rather than at 0 ℃, and employ excess NaBr to suppress deactivator dissociation in the aqueous medium. Table 4-2 summarizes the synthesis conditions and properties of P(HEA) synthesized with TCL=400 and 800, using 250 ppm copper catalyst. Longer reaction times (75-120 min) are required to achieve high conversion, due to the combination of low initiator and low Cu levels compared with TCL=200.

In addition, the increase in solution viscosity becomes a factor at these higher chain lengths, with the magnetic stir bar unable to maintain agitation to full conversion.

Table 4-2 Two-step Cu(0) *in situ* mediated RDRP of HEA in D_2O, 250 ppm copper catalyst, HEA=3378 mL (below 0.2 wt.% EGDA, 27 vol% monomer)

Experiment	$[M]_0:[I]_0:[C]_0:[L]_0/[NaBr]_0$ [a]	$T^{[b]}$ (°C)	React. time (min)	Conv.[c] (%)	$M_{n,th}^{[d]}$	$M_{n,GPC}^{[e]}$	$Đ^{[f]}$
TCL400-1	400:1:0.1:0.1/3.6	0	90	88.9	41490	34280	1.22
TCL400-2	400:1:0.1:0.1/3.6	22	75	86.7	40500	32400	1.16
TCL400-3	400:1:0.1:0.1/3.6	35	75	84.2	39310	31180	1.13
TCL800-1	800:1:0.2:0.2/4.8	22	120	79.0	73430	69540	1.35

[a] $[M]_0:[I]_0:[C]_0:[L]_0/[NaBr]_0=[HEA]_0:[HEBiB]_0:[Cu(I)Br]_0:[Me_6TREN]_0/[NaBr]_0$. [b] Disproportionation and polymerization temperatures are the same. [c] Conversion is calculated via ^{1}H-NMR spectrum (detail in Appendix 2). [d] $M_{n,th}=M_{HEA}\times$ TCL $\times$ conversion $+ M_{initiator}$. [e] $M_{n,GPC}=M_{n,P(AcHEA)} \times (116.12/158.15)$ [$M_{n,P(AcHEA)}$ is the refractive index (RI) data of acetylated P(HEA) relative to PS standard using THF as eluent]. [f] $Đ$ is measured by RI (verification of complete acetylation in Appendix 3).

As discussed previously, we hypothesize the desorption and adsorption rates of P(HEA) chains are affected by the number average degree of polymerization (DP_n), making it more difficult to synthesize high MW polymer without gel formation or the occurrence of a high MW shoulder.

However, reasonable control can be achieved using low Cu levels (see Table 4-2 and Figure 4-7) in the presence of added NaBr for these higher chain lengths. Interestingly, the dispersity is lowered and the high MW shoulder is less pronounced as reaction temperature is increased with TCL=400, perhaps due to an increased desorption rate of chains from the Cu(0) surface. It may be that even lower dispersity values would be achieved at full conversions, as experiments were stopped below 90% conversion due to high viscosity. While the high MW shoulder is more pronounced for the TCL of 800, a dispersity of 1.35 was achieved.
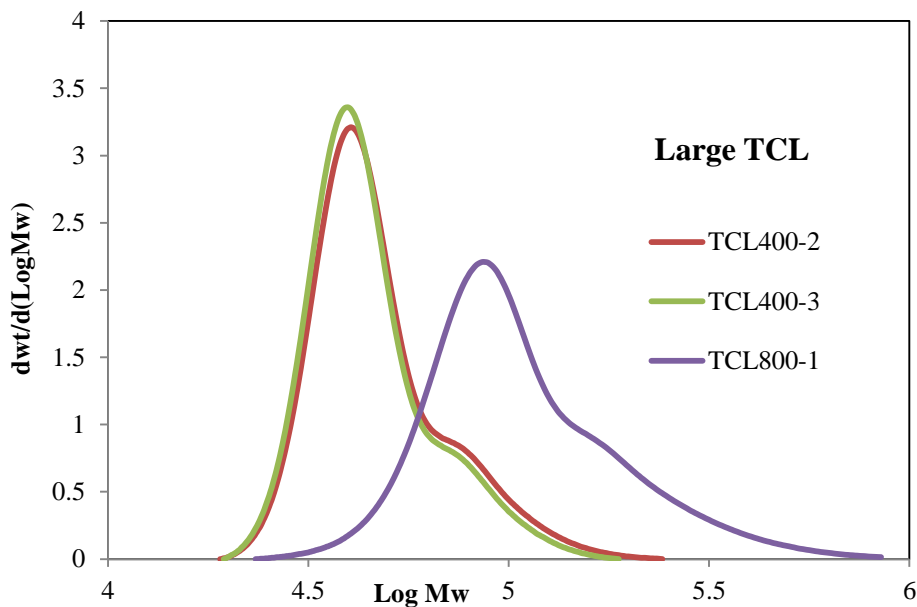
Figure 4-7 Molar mass distributions of P(AcHEA) with high TCL. Experimental details presented in Table 4-2

4.4 Conclusion

The reversible deactivation radical polymerization (RDRP) of 2-hydroxyethyl acrylate in D_2O using Cu(0) wire with Me_6TREN at different TCL and initial added Cu(II)Br_2 was investigated in the previous chapter. Short chain length and high concentration of deactivator reduced gel formation. This result was explained by the reduced concentration of adsorbed active species on the Cu(0) wire surface through increased desorption rate and deactivation rate on the Cu(0) wire surface respectively. Employing the two-step Cu(0) *in situ* mediation procedure circumvents this problem, with a set of experiments focusing on the effects of P(HEA) chain length, initial Cu(I)Br, excess NaBr, temperature and residual O_2. The concentration of adsorbed active species on the Cu(0) particle surface is believed to be the key factor for the high MW shoulder and polymerization control, which is determined by the combined effects of physical processes such as adsorption and desorption with reaction processes such as activation, propagation and deactivation on the

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Cu(0) surface, and activation, deactivation, propagation and termination in solution. Short chain length, low activator, high deactivator and high temperature (22 rather than 0 ℃) help to maintain a low concentration of adsorbed active species on the Cu(0) surface during the polymerization, the requirement for synthesizing well defined P(HEA) of low Đ without a high MW shoulder or gel in aqueous solution.

Based on these insights, well defined P(HEA) with low Đ (~1.2) and without a significant high MW shoulder was obtained when DP_n is less than 200 in aqueous solution. Higher molecular weight P(HEA) was also synthesized, albeit with the high MW shoulder observed; for a TCL=400, 87% conversion with low Đ (1.16) was synthesized within 75 min using *ca*. 250 ppm copper in D_2O at 22 ℃.

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Chapter 5

Conclusions and Recommendations for Future Work

5.1 Supplemental investigations

The main results of the investigation are presented in the previous chapter. However, a few additional experiments were conducted to explore future research directions.

5.1.1 Water

D_2O was used as the solvent for the Cu(0) wire mediated RDRP of HEA (Chapter 3) and two-step Cu(0) *in situ* mediated RDRP of HEA (Chapter 4), and high MW P(HEA) with low Đ was successfully synthesized. To facilitate industrial process development, several experiments using H_2O as the solvent were also done (Table 5-1) using the two-step Cu(0) *in situ* mediated RDRP. The polymerization procedure, conversion calculation and polymer characterization are the same as described previously.

As summarized in Table 5-1, although the control of the P(HEA) synthesized in H_2O is similar (also see Figure 5-1), the conversion achieved in the same time was significantly lower, with the experiment repeated to verify this finding. We do not know the exact reason why the conversion using H_2O is much lower than in D_2O. But we find the measured pH value of water (type 1 reagent grade, Millipore Corp.) is stabilized at 5.5-5.6, while the measured pH value of D_2O is stabilized at 6.5-6.8. The lower pH of H_2O, which may be due to absorption of CO_2 from the air during the water preparation, could affect the coordination of the ligand with the copper cation and slow down the polymerization, as it has previously been reported that acid (acrylic acid) may inhibit ATRP polymerization.[1]

Table 5-1 Two-step Cu(0) *in situ* mediated RDRP of HEA in D_2O and H_2O at 22 ℃, 250 ppm copper catalyst, HEA=3378 mL (below 0.2 wt.% EGDA, 27 vol% monomer)

Experiment	$[M]_0:[I]_0:[C]_0:[L]_0/[NaBr]_0$[a]	T^b (℃)	Solvent	React. time (min)	Conv.[c] (%)	$M_{n,th}$[d]	$M_{n,GPC}$[e]	$Đ^f$
TCL400-1	400:1:0.1:0.1/3.6	22	D_2O	75	86.7	40500	32400	1.16
TCL400-2	400:1:0.1:0.1/3.6	22	H_2O	80	41.2	19360	13760	1.23
TCL400-3	400:1:0.1:0.1/3.6	22	H_2O	90	41.0	19300	12680	1.28

[a] $[M]_0:[I]_0:[C]_0:[L]_0/[NaBr]_0=[HEA]_0:[HEBiB]_0:[Cu(I)Br]_0:[Me_6TREN]_0/[NaBr]_0$. [b] Disproportionation and polymerization temperatures are the same. [c] Conversion is calculated *via* ^{1}H-NMR spectrum (detail in Appendix 2). [d] $M_{n,th}=M_{HEA} \times TCL \times conversion + M_{initiator}$. [e] $M_{n,GPC}=M_{n,P(AcHEA)} \times \frac{116.12}{158.15}$ [$M_{n,P(AcHEA)}$ is the refractive index (RI) data of acetylated P(HEA) relative to PS standard using THF as eluent]. [f] Đ is measured by RI (verification of complete acetylation in Appendix 3).
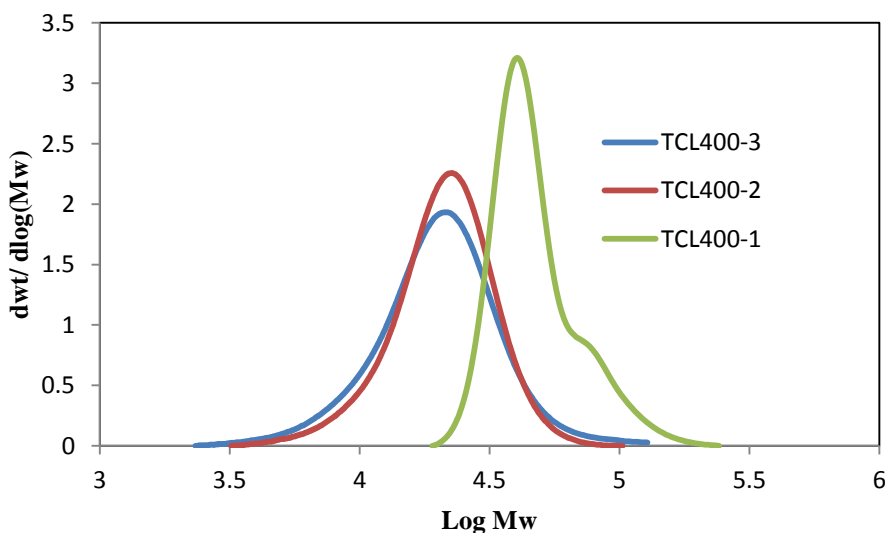

Figure 5-1 Molar mass distributions of P(AcHEA) with TCL of 400. Experimental details presented in Table 5-1

Another possible reason is that the isotope effects on hydrogen bonding make some difference.[14] Further investigation is required to find the true reason and problem solution, as any process development should continue in H_2O rather than the D_2O used here for kinetic studies.

5.1.2 Binary solvent

The results in Chapter 4 indicate that increasing the hydrophobicity of P(HEA) by increasing polymer chain length makes it more difficult to produce polymer without a significant high molecular weight shoulder in the MMD distribution, a result consistent with the explanation that P(HEA) tends to adsorbed on the Cu(0) surface rather than desorb to the aqueous solution. A possible solution to this issue is to make the solvent more hydrophobic, in order to increase the desorption rate of the adsorbed active species. One paper reported the successful synthesis of P(HEA) (TCL=200) at lower polymerization rate using Cu(0) wire mediation in a binary solvent (MeOH + 40 vol% H_2O)[2] without the formation of a high molecular weight shoulder, a finding that encouraged us to do preliminary experimentation with the two-step Cu(0) *in situ* mediation using the binary solvent system MeOH/D_2O.

As summarized in Table 5-2, the binary solvent system with MeOH contents of 40 and 50 vol% was used. However, the polymerization rate is significantly slower (Experiment TCL400-5) than compared to that in D_2O (Experiment TCL400-1) at the low Cu levels (250 ppm). When the Cu level was increased by a factor of 4 (Experiment TCL400-6) and the Cu(I) disproportionation was done in D_2O rather than the binary mixture (MeOH added with the monomer), the reaction rate increased significantly but at the expense of MW control. Thus, while the binary solvent may improve the hydrophobicity of the system, it also has a large effect on the Cu(I) disproportionation and/or activation reactions (see Chapter 2).

Table 5-2 Two-step Cu(0) *in situ* mediated RDRP of HEA in Methanol/D$_2$O at 22 ℃, HEA=3378 mL (commercial HEA with above 0.8 wt.% EGDA)

Experiment	[M]$_0$:[I]$_0$:[C]$_0$:[L]$_0$/[NaBr]$_0$[a]	Solvent (Methanol/D$_2$O,V/V)	React. time (min)	Conv.[d] (%)	M$_{n,GPC}$[e]	Đ[f]
TCL400-4[b]	400:1:0.1:0.1/3.6	40/60	300	7.5	810	1.64
TCL400-5[b]	400:1:0.1:0.1/3.6	40/60	360	8.9	840	1.45
TCL400-6[c]	400:1:0.4:0.4/4.8	50/50	20	99.9	49070	3.60

[a] [M]$_0$:[I]$_0$:[C]$_0$:[L]$_0$/[NaBr]$_0$=[HEA]$_0$:[HEBiB]$_0$:[Cu(I)Br]$_0$:[Me6TREN]$_0$/[NaBr]$_0$. [b] Disproportionation is in binary solvent (methanol/D$_2$O, 40/60). [C] Disproportionation is in D$_2$O and methanol/monomer/initiator is transferred by syringe and the solution is through nitrogen purge for 30 min not freeze-pump-thaw. [d] Conversion is calculated *via* ^{1}H-NMR spectrum (detail in Appendix 2). [e] M$_{n,GPC}$=M$_{n,P(AcHEA)}$ × 116.12/158.15 [M$_{n,P(AcHEA)}$ is the refractive index (RI) data of acetylated P(HEA) relative to PS standard using THF as eluent]. [f] Đ is measured by RI (verification of complete acetylation in Appendix 3).

It is possible that in the binary solvent, after 30 min, there is still Cu(I)Br present whose reactivity is lower than that of Cu(0) particles generated by disproportionation according to the SET-LRP mechanism. Considerable work must be done by varying methanol content and decreasing catalyst and ligand to explore whether the synthesis of high molecular weight P(HEA) without a shoulder is possible in the binary solvent mixture, or if the resulting rate of reaction is too slow compared to the aqueous system.

5.2 Summary of contributions

This work verified the previously proposed mechanism that Cu(0) mediated RDRP of HEA is greatly influenced by chain adsorption to the Cu(0) surface in water, extending the understanding by demonstrating that the formation of both a high molecular weight shoulder and insoluble

polymer was controlled by the combined effects of physical processes (adsorption and desorption) with the relative rates of reaction processes on the Cu(0) surface and in solution.

This knowledge was used to produce, for the first time, well defined P(HEA) with low Đ (~1.2) and without a significant high MW shoulder, at low copper levels in aqueous solution. While the shoulder became observable for target DP_n values greater than 200, higher molecular weight P(HEA) with a TCL=400 was synthesized to 87% conversion with low Đ (1.16) within 75 min using only ca. 250 ppm copper in D_2O at 22 ℃.

5.3 Recommendations for future work

5.3.1 Other water soluble monomers

HEA was selected as the monomer for this study due to its industrial significance, and since its radical polymerization kinetics are reasonably well understood. However, it was found that the hydrophobicity of the polymer limits the achievable MW while still remaining controlled. Other water soluble monomers such as oligo(ethylene oxide) methyl ether acrylate (OEOMA)[3-6] oligo(ethylene oxide) methyl ether methacrylate (OEOMMA)[7-10], acrylamide[11,12] and its derivatives[13] have been studied in various solvents using copper mediated RDRP. However, the target MWs were kept low and copper levels are relative high in these previous works. These potential monomers and their polymers show greater affinity to water and thus could be used to replace HEA as monomer to further investigate using the two-step Cu(0) mediated RDRP, following the methodologies established in this work. P(OEOMA), P(OEOMMA) and their block copolymers are thermo-responsive *via* low critical solution temperature behavior (LCST) with potential application in drug release control. High molecular weight poly(acrylamide) *via* free radical polymerization is widely used as a flocculating agent in wastewater treatment and oil recovery, but the synthesis of well defined high molecular weight poly(acrylamide) through

copper mediated RDRP is still challengeable and very limited.[11,12] As summarized in ref 12, to date it has not been possible to obtain Đ< 1.5 and M_n > 10,000 Da with ATRP of acrylamide, even in mixed solvents, partially due to deactivator complex coordination with acrylamide and poly(acrylamide). Wever *et al.*[12] produced poly(acrylamide) of high M_n up to 100,000 Da with Đ increasing from 1.5 to 2.5 with increasing target chain length. What is more, the reliable molecular weight measurement of poly(acrylamide) is still challenging.[11] But derivatives of acrylamide such as N-isopropylacrylamide (NIPAM), 2-hydroxyethyl acrylamide (HEAA), N, N-dimethyl acrylamide (DMA) and N,N-diethylacrylamide (DEA) were polymerized well through two-step Cu(0) *in situ* mediated system with Me_6TREN-based catalyst complex.[13]

Thus expanding this investigation of low copper catalyst solution for the RDRP of HEA to these other water soluble monomers should be a fruitful area for further research.

5.3.2 Semi-batch process and continuous process

Almost all of the studies of metal mediated RDRP of water soluble monomers have been performed in batch, with very limited investigations about semi-batch and continuous processes that are more suitable for industrial production due to advantages of heat removal and increased throughput. To the best of our knowledge, only a very few papers[6,9] investigated semi-batch operation to improve the control and reduce the Cu catalyst amount. The ATRP variant known as "initiator for continuous activator regeneration atom transfer radical polymerization" (ICAR ATRP) with ppm amount of Cu catalyst was successfully adapted to semi-batch operation to synthesize well defined P(OEOMA) and P(OEOMMA)-b-P(OEOMA) in water,[6] and "activators regenerated by electron transfer atom transfer radical polymerization" (ARGET ATRP) was implemented successfully in aqueous media to synthesize well controlled P(OEOMA)[9] using 300 ppm copper catalyst and tris(2-pyridylmethyl)amine (TPMA) ligand in the presence of an excess of NaBr.

There is no published investigation on the semi-batch process with two-step Cu(0) *in situ* mediation in water, or on the continuous production of polymer in a tubular system with copper mediated RDRP in water.

Thus semi-batch and continuous process investigations in aqueous copper mediated RDRP of water soluble monomers is of both academic interest to improve fundamental understanding and is advantageous if commercialization and scale-up of this highly exothermic polymerization system is to be achieved.

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Appendices

Appendix 1.   Trace EGDA residue by GC

Table A-1 GC programming profile for EGDA residue measurement

Temperature(℃)	Rate (℃/min)	Hold (min)	Total (min)
50	-	2.15	2.15
110	15	1.00	7.15
113	0.5	1.00	14.15
250	15	2.00	25.28

Calibration curve of standard EGDA samples:

Using acetone as the solvent, different concentrations of ethylene glycol diacrylate (90%, technical grade, Sigma-Aldrich) were added to prepare standard EGDA samples as shown below in Table A-2.

Table A-2 GC standard EGDA samples

Standard Sample No.	EGDA Concentration(weight ppm)	Integral Area
Blank	0	0
1	80.82	1467
2	224.55	5616
3	486	14382
4	973.98	37610

(EGDA has a retention time of 16.6-16.7 min; HEA has a retention time of 9.4 min; Acetone has a retention time of 2.5-2.6 min.)

JMP software was used to do linear regression (details shown below).

Appendix 1. $Y = aX + b + \varepsilon$ (Regression model; Y denotes area and X denotes
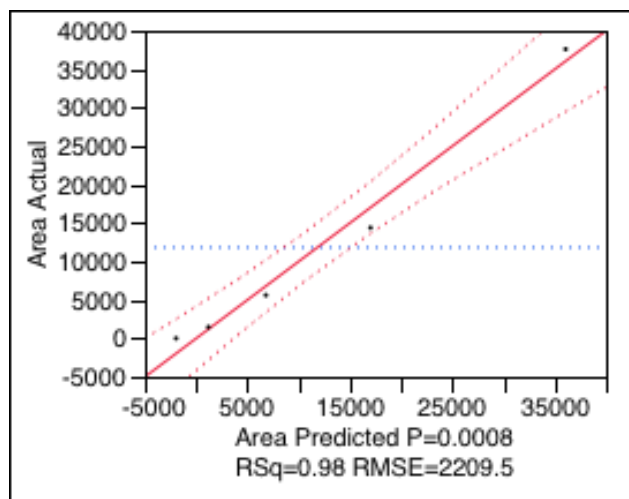
concentration.)

Figure A-1 Actual versus predicted value plot

Analysis of variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	942428215	942428215	193.0384
Error	3	14646229	4882076.2	Prob > F
C. Total	4	957074444		0.0008*

Parameter estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	-1967.141	1400.144	-1.40	0.2547
Concentration	39.035152	2.809532	13.89	0.0008*

The regression expression is Y =39.035152 X – 1967.141 (Expression 1).

Measurement of EGDA residue in the HEA:

Table A-3 EGDA in the HEA used in experiments

Sample	Integral Area	Total Amount Sample (mg)	HEA (mg, containing EGDA)	Calculated x	Calculated (wt.%)
Batch 1	10954	4351.2	868.5	331.01	0.166
Commercial HEA	39204	4526.5	754.4	1054.72	0.633
Batch 2	3184	4340.0	1047.7	131.96	0.055
Batch 3	8798	4553.4	1125.1	275.78	0.112

x denotes EGDA concentration (ppm) in the sample

Appendix 2. Conversion and end-group method to calculate $M_{n,NMR}$ *via* ^{1}H-NMR spectra

Using Experiment TCL50-3 (Chapter 4) as an example, the conversion and $M_{n,NMR}$ calculations are shown as below.
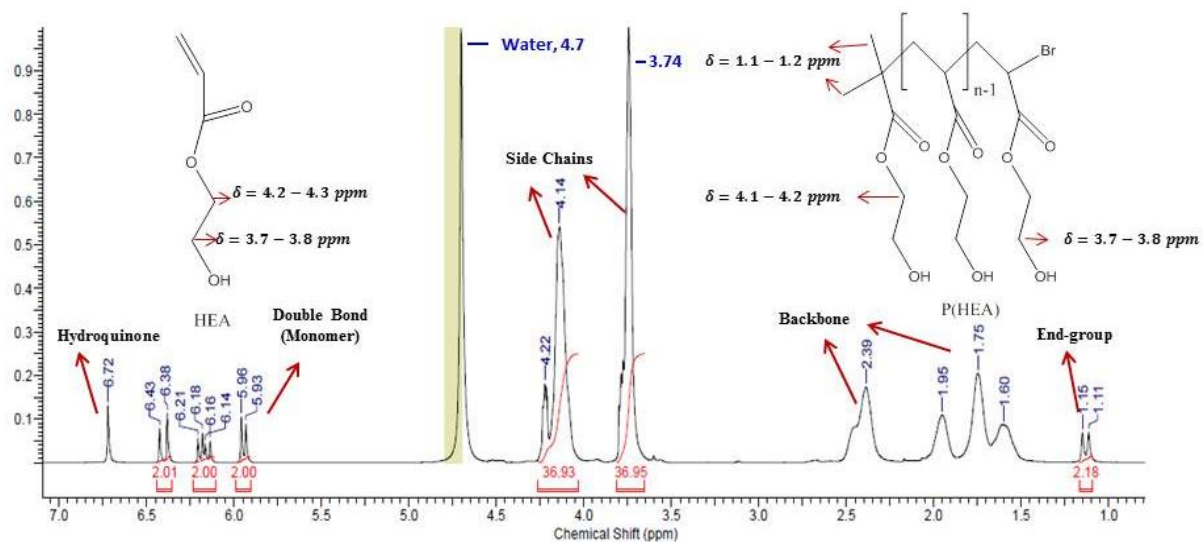

Figure A-2 ^{1}H-NMR Spectrum of Sample (Experiment TCL50-3, Chapter 4) using D_2O solvent

HEA and P(HEA): δ (ppm): 1.11, 1.15 [6H, 2(CH_3)C]; 5.93-6.43 (3H, CH_2=CH); 3.74, 4.14-4.22 [4H, COO(CH_2CH_2)OH]

Conversion=1- (molar of monomer residue)/(molar of monomers participated in the polymers)

$$=1-[(2.01+2.00+2.00)/3]/[(36.93+36.95)/4]=89.2\%$$

$$\bar{N}=[(36.93+36.95)/4-(2.01+2.00+2.00)/3-2.18/6]/(2.18/6)=16.10333$$

$$M_{n,NMR}=M_{HEA}\times\bar{N}+M_{initiator}=116.12*16.10333+211=5358$$

Appendix 3. Verification of complete acetylation of P(HEA) *via* ^{1}H-NMR spectra
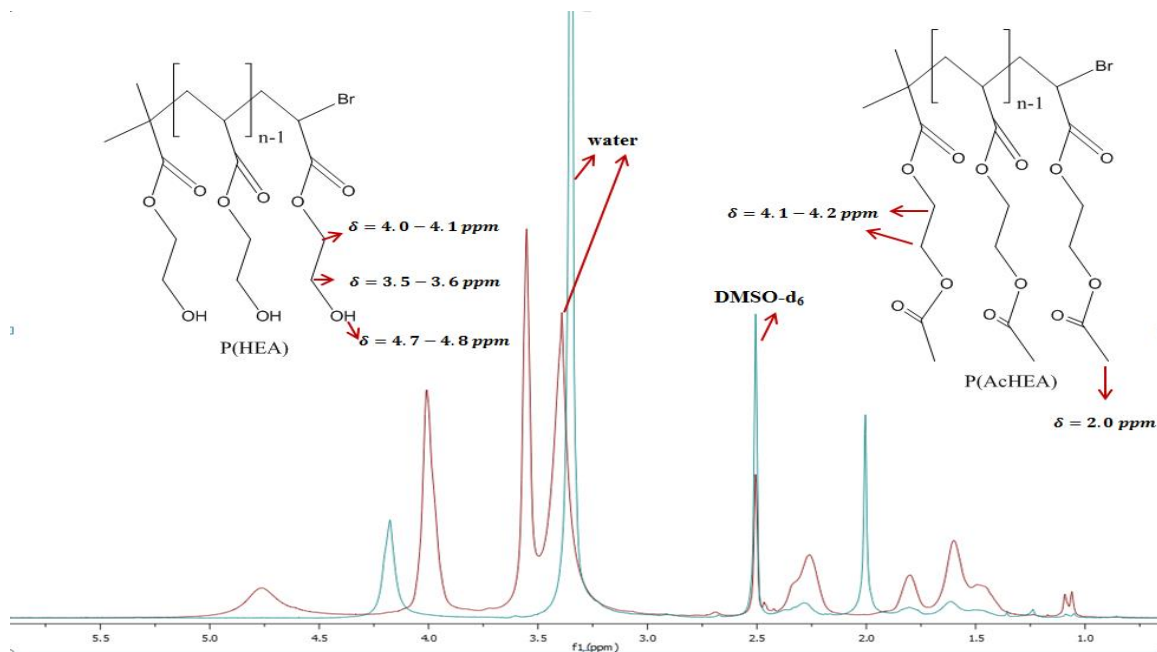

Figure A-3 Comparison ^{1}H-NMR Spectra of P(HEA) in red and P(AcHEA) in cyan with DMSO-d$_6$ solvent

P(HEA): δ (ppm): 4.76 (1H, OH), 3.55,4.01 [4H, COO(CH$_2$CH$_2$)OH]

P(AcHEA): δ (ppm): 2.00 (3H, COCH$_3$), 4.18 [4H, COO(CH$_2$CH$_2$)OOC]

Appendix 4. Recipes for TCL with two-step Cu(0) *in situ* mediated RDRP

Table A-4 Details of recipes for different target chain length with two-step Cu(0) *in situ* mediated RDRP

TCL ($[M]_0:[I]_0:[C]_0:[L]_o/[NaBr]_0$)	Components in tube A (m mole)	Components in tube B (m mole)
20 (20:1:0.4:0.4)	Me$_6$TREN: 0.14 D$_2$O: 2.0 mL CuBr: 0.14 -	HEA: 7 HEBiB: 0.35 - D$_2$O: 2 mL
20 (20:1:0.1:0.1/1.2)	Me$_6$TREN: 0.035 D$_2$O: 2.0 mL CuBr: 0.035 -	HEA: 7 HEBiB: 0.35 NaBr:0.42 D$_2$O: 2.0 mL
50 (50:1:0.4:0.4)	Me$_6$TREN: 0.056 D$_2$O: 2.0 mL CuBr: 0.056 -	HEA: 7 HEBiB: 0.14 - D$_2$O: 2.0 mL
50 (50:1:0.4:0.4/4.8)	Me$_6$TREN: 0.56 D$_2$O: 2.0 mL CuBr: 0.56 -	HEA: 7 HEBiB: 0.14 NaBr: 0.672 D$_2$O: 2.0 mL
50 (50:1:0.1:0.1/1.2)	Me$_6$TREN: 0.014 D$_2$O: 2.0 mL CuBr: 0.014 -	HEA: 7 HEBiB: 0.14 NaBr: 0.168 D$_2$O: 2.0 mL

100	Me$_6$TREN: 0.056	HEA: 14
(100:1:0.4:0.4)	D$_2$O: 2.0 mL	HEBiB: 0.14
	CuBr: 0.056	-
	-	D$_2$O: 2.0 mL
100	Me$_6$TREN: 0.014	HEA: 14
(100:1:0.1:0.1)	D$_2$O: 2.0 mL	HEBiB: 0.14
	CuBr: 0.014	-
	-	D$_2$O: 2.0 mL
100	Me$_6$TREN: 0.014	HEA: 14
(100:1:0.1:0.1/1.2)	D$_2$O: 2.0 mL	HEBiB: 0.14
	CuBr: 0.014	NaBr: 0.168
	-	D$_2$O: 2.0 mL
200	Me$_6$TREN: 0.01	HEA: 20
(200:1:0.1:0.1/2.4)	D$_2$O: 3.0 mL	HEBiB: 0.1
	CuBr: 0.01	NaBr: 0.24
	-	D$_2$O: 2.7 mL
400	Me$_6$TREN: 0.008	HEA: 32
(400:1:0.1:0.1/3.6)	D$_2$O(H$_2$O): 4.5 mL	HEBiB: 0.08
	CuBr: 0.008	NaBr: 0.288
	-	D$_2$O(H$_2$O): 4.6 mL
800	Me$_6$TREN: 0.008	HEA: 32
(800:1:0.2:0.2/4.8)	D$_2$O: 4.5 mL	HEBiB: 0.04
	CuBr: 0.008	NaBr: 0.192
	-	D$_2$O: 4.6 mL

Appendix 5. Aqueous GPC results of P(HEA) with PEO standard

The molecular weight of P(HEA) was determined with a Viscotek GPCmax 2001 + Viscotek TDA (RI+VISC+RALS); mobile phase: 0.05 M sodium nitrate (minimize ionic interferences) with 0.02% sodium azide (prevents biological growth) in water, calibrated with polyethylene oxide standards.
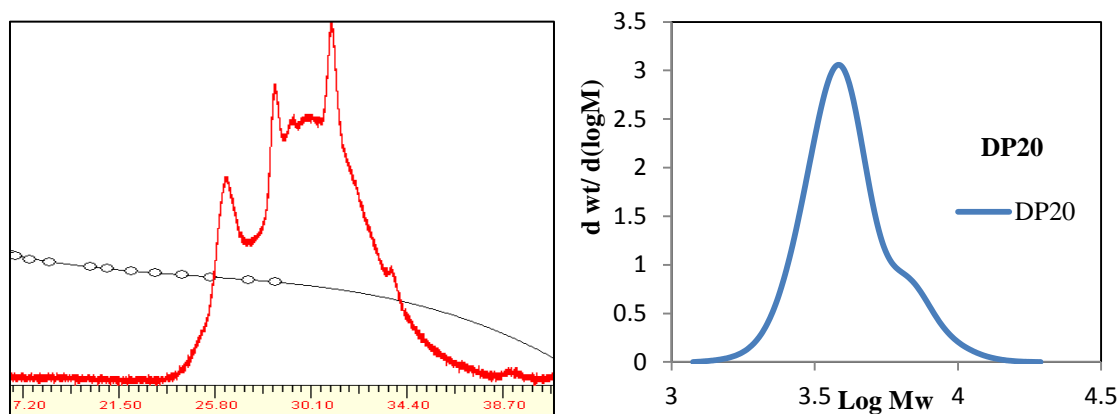

Figure A-4a Experiment TCL20 (99.9% conversion, Đ=1.14), MMD of P(HEA) in GPC using water as eluent (Left) and MMD of P(AcHEA) in GPC using THF as eluent (Right)
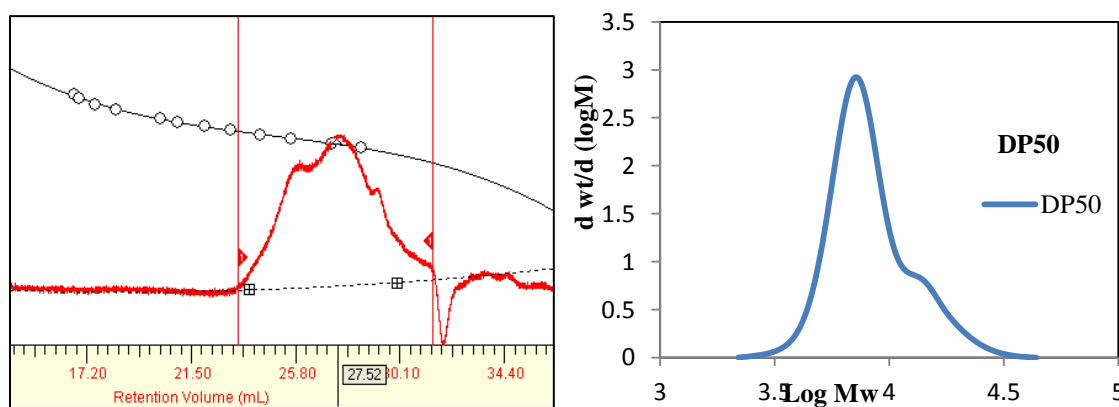

Figure A-4b Experiment TCL50 (97.5% conversion, Đ=1.18), MMD of P(HEA) in GPC using water as eluent (Left) and MMD of P(AcHEA) in GPC using THF as eluent (Right)
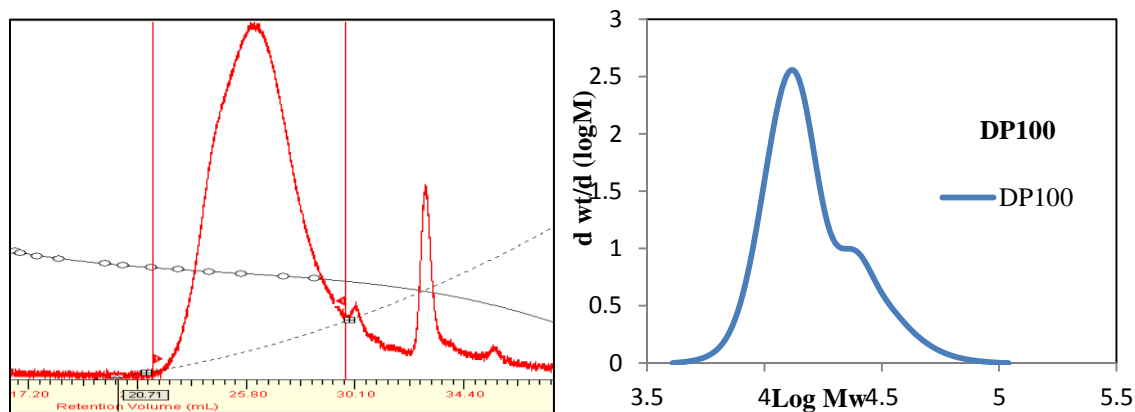
Figure A-4c Experiment TCL100 (98.3% conversion, Đ=1.24), MMD of P(HEA) in GPC using water as eluent (Left) and MMD of P(AcHEA) in GPC using THF as eluent (Right)

According to above three examples, we conclude the results of aqueous GPC using PEO standard are not reliable.

Appendix 6. Bimodal distribution

Molecular weight distribution of P(AcHEA) shows significant bimodal distribution because of not enough nitrogen protection during the reaction or incomplete degassing for the solution.
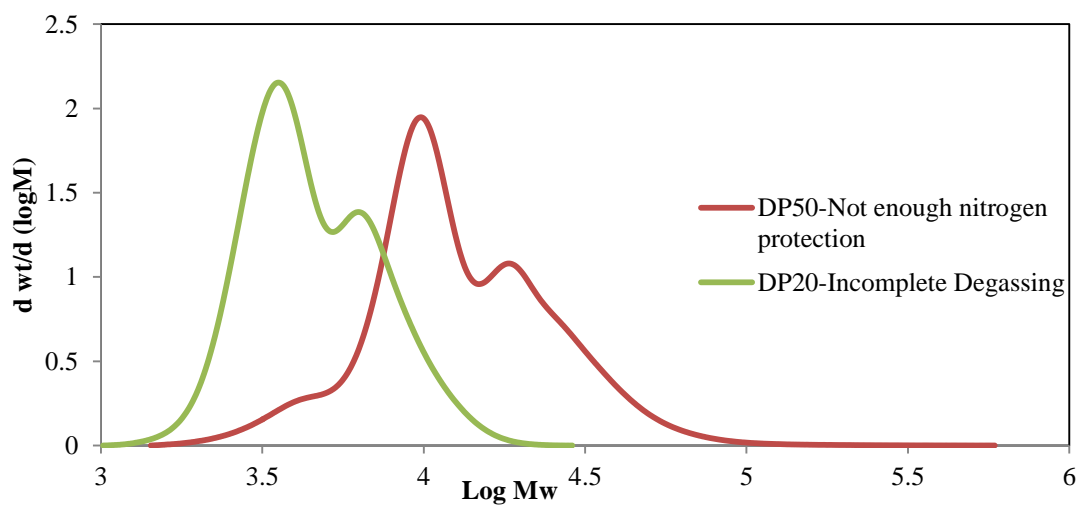

Figure A-5 MMD of P(AcHEA) with TCL20 (incomplete degassing), TCL50 (not enough nitrogen protection)