

**Environmentally Benign Metal-Catalyzed
Living Radical Polymerization:
Polymerization in Water and Iron Catalysis**

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GENERAL INTRODUCTION

Background

1 Approach to Environmentally Benign System

Chemistry has definitely contributed to enriching human life, but chemical processes have often given rise to environmental issues, such as global warming, environmental pollution (air, water and land) and depletion of resources. Thus, for almost any chemical synthesis, environmentally benign production systems are now required as well as new benign reactions. Given these contexts and social trends, "Green Chemistry" has actively been studied around the world, where "green" means to minimize environmental impacts and/or to maximize sustainability in chemical reactions (Figure 1), though, however attractive it may seem, the word "green" is often controversial.¹⁻³

For example, an approach to *green* chemistry is to use environmentally benign solvents, or green solvents,⁴⁻⁶ such as water,⁷ ionic liquids^{8,9} and supercritical CO₂,^{10,11} instead of flammable, toxic, and/or corrosive organic solvents. For metal-catalyzed reactions, in addition, the use of abundant and safer metals like iron is favorable, rather than precious or potentially less benign metals, such as rhodium, palladium, copper, ruthenium, rhenium and platinum.

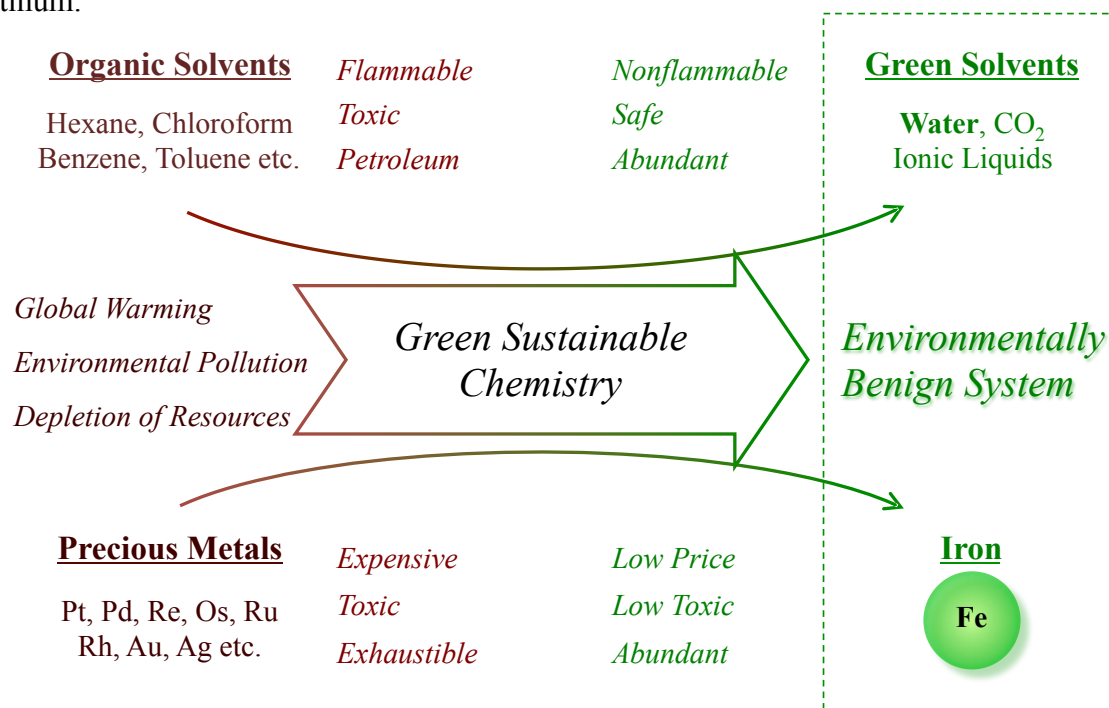


Figure 1. Approach to environmentally benign system (green sustainable chemistry)

With these considerations, the author has set the primary research objective of this thesis work with two segments:

"Environmentally Benign Precision Polymerization"

(A) Precision polymerization in water; and

(B) Precision polymerization with iron catalysis.

2 Water in Organic Reaction

Water is critically important and essential for life on earth, accounting for approximately 60 % of human body and 70 % of the earth's surface. Deceivingly simple in structure, water is nevertheless anomalous in properties: high polarity, potentially both acid and base, hydrogen bonding, high specific heat, high latent heat, high surface tension (cohesive energy), and an extremely good solvent (over 60 elements are dissolved in the sea) (Figure 2). All organisms utilize these unique properties for survival, and surprisingly efficient and selective biochemical reactions take place in water. Additionally, water is environmentally benign (or *green*): abundant, inexpensive, nonflammable, non-explosive, noncorrosive, nontoxic, no carcinogenic and no mutagenic; thus it has attracted a great attention as a green reaction medium.

However, it is not so straightforward to run organic reactions in water, because water acts not only as an ambient solvent but as a chemical, or a highly polar and potentially reactive molecule that could cause side reactions with an intermediate and/or a catalyst. It is therefore rather common for chemists to be careful for contaminating water and in turn to often use dehydrated solvents.

It is also true, however, that organic reactions "in water"^{7,12–18} or "on water"^{19,20} ("aqueous" reactions) have indeed been reported for the last several decades. Despite the potential drawbacks, additional advantages over those in organic solvents are sometimes found, typically higher reaction rate and better selectivity. For example, in 1980, Breslow and co-workers reported an over 700-fold acceleration in a Diels-Alder reaction of butanone



Water

Unique Properties

*Hydrogen Bonding, High Polarity,
High Specific Heat, High Latent Heat,
High Surface Tension*

Environmentally Benign Properties

*Low Price, Abundant,
Safe, Non-flammable*

Figure 2. Water has many unique and environmentally benign properties.

in water, which was attributed to the so-called hydrophobic effect.²¹ A similar acceleration was reported in the iodine-transfer radical cyclization of triethylborane.²² According to Kobayashi *et al.*, water-tolerant Lewis acids allow enantioselective ring-opening reactions of aromatic *meso* epoxides in water, with selectivity higher than in dichloromethane.²³

Water as solvent has been used far more widely in polymerization, most typically dispersion, suspension, and emulsion polymerizations, via the free-radical mechanism. These heterogeneous processes are all well established and industrially very important, producing commodity polymers in a multi-million metric ton per year scale, including polystyrene poly(vinyl chloride), poly(vinyl acetate), polybutadiene, and many others. In these examples, the use of water primarily stems from its excellent heat dissipation (temperature control by high heat capacity) and relatively high boiling point. Emulsion and dispersion "living" polymerizations, either radical or ionic, are another hot topic of interest these years (see below).

More recently, the homogeneous polymerization in water has also attracted attention. Grubbs *et al.*, for instance, developed the ring-opening metathesis polymerization of water-soluble cyclo-olefins (norbornenes) in aqueous media, with water-soluble ruthenium complexes carrying an *N*-heterocyclic carbene (NHC) ligand decorated with a polyethylene glycol (PEG).²⁴ Another example is the living cationic polymerization of *p*-hydroxystyrene (vinyl phenol) with water-tolerant Lewis acids (BF₃OEt₂) reported by Satoh *et al.*, in a sense challenging the common sense that water disturbs ionic reactions.²⁵ Bulky zincates are also reported to work in water as initiators for anionic polymerization of *N*-isopropyl acrylamide.²⁶

3 Iron: Properties and Catalysis

Iron is the most abundant heavy element (approx. 30 wt%) in the Earth, the second abundant metal after aluminum in the Earth's crust,²⁷ and ubiquitous and indispensable in natural life including humans. Relative to precious metals, iron is thus favored in chemistry and in industry, environmentally benign, safer, and less toxic, as well as cheaper and abundant (Figure 3). Iron is a typical transition metal that takes a wide range of oxidation states from -2 to +5 (and sometimes but rarely +6) and affords a potential of single or two-electron transfer processes. Iron-containing complexes and proteins, such as hemoglobin, catalase and cytochrome, play active roles in living organisms as biocatalysts or enzymes.

Quite naturally, and particularly in the current environment- and sustainability-conscious

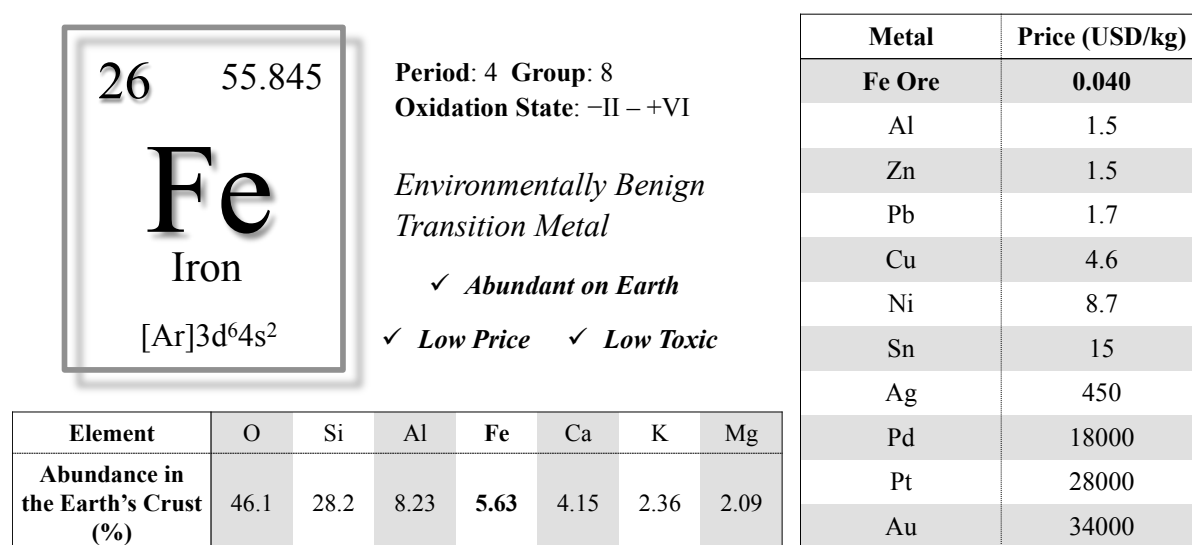


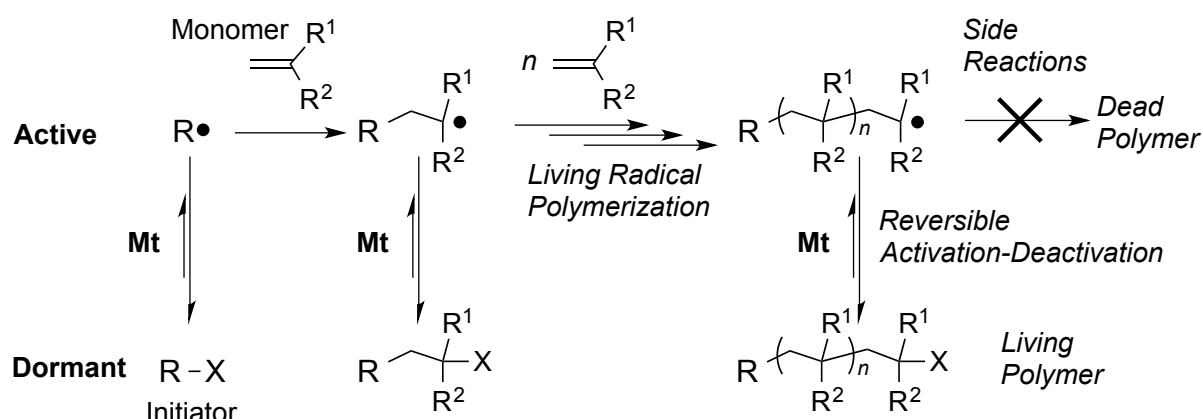
Figure 3. Properties of iron, which is the most environmentally benign transition metal

society, these advantageous features of element iron encourage chemists to apply iron compounds as catalysts for organic and polymer syntheses.

Historically, following to the invention of the Haber–Bosch process and Friedel-Crafts reactions with iron catalysts, Reppe employed a carbon monoxide-ligated iron(0) complex $[\text{Fe}(\text{CO})_5]$ for the synthesis of alcohols from olefins, carbon monoxide and water.²⁸ Since then, various iron-catalyzed organic reactions have been developed,^{29–32} *e.g.*, cross-coupling,^{33–36} C–H activation,^{37,38} oxidation,^{39–41} reduction,^{42,43} and polymerization [coordination,^{44–47} ring opening,^{48,49} cationic,^{50–53} and radical (see Section 4.2)]. Iron catalysts are still evolving toward activity equal to or higher than precious metal-based catalysts, and they should be continuously developed for environmentally benign chemical synthesis.

4 Metal-Catalyzed Living Radical Polymerization (Mt-LRP)

Free radical polymerization has been widely utilized for industrial syntheses of polymer materials, such as thermoplastic resin, rubber and fiber, due to high monomer versatility and easy handling. Therefore, control of polymer structure and molecular weight has been strongly required in radical polymerization, but the precision control is far more difficult than in ionic counterparts, because of seemingly unavoidable built-in side reactions, bimolecular termination via radical recombination (coupling) and disproportionation. In the recent few decades, however, a variety of controlled radical polymerization methodologies have been developed; *e.g.*, metal-catalyzed (Mt-LRP,^{54–57} also known as ATRP^{58–60}), reversible addition-fragmentation chain-transfer (RAFT),^{61,62} nitroxide mediated (NMP),^{63,64} tellurium



Scheme 1. Polymerization Mechanism of Mt-LRP

mediated (TERP)⁶⁵ and organometallic mediated (OMRP) polymerizations.⁶⁶ Among them, Mt-LRP has been among the most widely utilized and actively developed owing to high end-fidelity (polymer terminal), ready design of initiators, and above all, versatile tunability of metal catalysts in accordance to monomers and desired polymer architectures.⁶⁷

In the generally accepted mechanism, Mt-LRP may be initiated with an initiating system consisting of an alkyl halide ($R-X$; X = halogen) (initiator) and a selected metal complex (Mt) (catalyst). Mt reversibly activates the carbon-halogen bond ($-C-X$) of the initiator or the growing terminal therefrom, to generate a growth-active carbon radical ($R^\bullet$), involving the one-electron redox (reduction-oxidation) processes of the metal complex (Scheme 1). Herein, the covalent, proactive but not growth-active, and terminally halogen-capped intermediate ($R\sim\sim\sim C-X$; $\sim\sim\sim$ = polymer chain) is often called "dormant" species.

With the dormant species far more thermodynamically stable and thus more dominating than the active radical species, the reversible activation-deactivation at the chain end, or the "dynamic dormant-active equilibrium", keeps the instantaneous radical concentration very low, so as to prevent bimolecular termination and undesired side-reactions. Thus, "living" polymers are obtained under these conditions. As expected to all living polymers, all the chain ends can propagate throughout the polymerization (staying "living" throughout), while the number-average molecular weight of the products is directly proportional to monomer consumption.

Therefore, Mt-LRP greatly depends on the metal catalysts, and many catalysts have so far been developed with various transition metals [*e.g.*, Ru ,^{68,69} Fe (see below), Ni ,^{70,71} and Cu ⁵⁸], ligands (*e.g.*, phosphines, amines, and pyridines), and co-catalysts or additives (*e.g.*, metal alkoxides, amines, ferrocenes, ascorbic acid, and free radical initiators).

With these considerations, the author has decided to develop environmentally benign polymerization systems, namely Mt-LRP's in water and those with iron catalysts.

4.1 Mt-LRP in Water

Radical polymerization is suitable for aqueous systems, because carbon radicals are neutral by definition and thus much more stable in water than ionic species. Additionally, given a wide range of applicable monomers, aqueous radical polymerization may offer interesting and unique tools for the synthesis of water-soluble functional polymers and for biochemical applications such as protein-polymer conjugations. Aqueous controlled radical polymerizations, both homogeneous^{72,73} and heterogeneous,^{72,74–76} have in fact been developed with various methodologies (*e.g.*, Mt-LRP,^{77–106} RAFT,^{107–109} NMP^{110–112} and TERP^{113,114}).

In Mt-LRP, for example, a Cu-catalyzed homogeneous polymerization in water was first reported in 1998 for 2-hydroxyethyl acrylate (HEA);⁸⁹ monomer conversion 86% in 12 h at 90 °C, molecular weight distribution (MWD), $M_w/M_n = 1.34$. Following to that report, aqueous Cu-catalyzed controlled polymerizations have been reported for other water-soluble functional monomers [*i.e.*, methacrylates (*e.g.*, MANa,⁷⁸ PEGMA,^{79,80} DMAEMA,^{81,82} HEMA,⁸³ MPC,^{84,85} MeDMA,⁸⁶ SEM⁸⁷ and SPMA⁸⁸), styrenes (*e.g.*, NaVBA⁹⁰ and NaSS^{91,92}), and acrylamides (*e.g.*, AAm⁹³, HEAAm,⁹⁴ AMPS⁹⁵ and ABA⁹⁶)] (Figure 4).

In these polymerizations, the irreversible deactivation of copper catalysts by water renders a large amount of catalyst (almost equivalent to the initiator) required. To decrease catalyst dose, water-stable divalent copper halides [Cu(II)X₂] have recently been employed in conjunction with reducing agents [*e.g.*, ascorbic acid,^{97,100} radical initiator⁹⁹ and zero-valent metal copper^{102,103–106}], electrode,⁹⁸ or visible light.¹⁰¹ As a result, the catalytic system with CuBr₂, TPMA, VA-044 (free radical initiator) and tetraethylammonium bromide (TEABr) led to a controlled polymerization of poly(ethylene glycol) acrylate (PEGA) even with 20 ppm catalyst.

Bio-conjugated polymers have also been obtained by copper-catalyzed aqueous living polymerization, and proteins (*e.g.*, BSA, GFP and Lysozyme) and DNAs have been conjugated with functional polymers [*e.g.*, poly(PEGMA), poly(DMAEMA) and poly(MPC)].^{115–119}

In contrast, few could be found for ruthenium-catalyzed homogeneous living radical polymerization in water so far, while the first heterogeneous (dispersion) version was reported as early as in 1999.¹²⁰ Ouchi *et al.* found that the pentamethylcyclopentadienyl (Cp*) ruthenium complex with a hydrophilic phosphine ligand [**P-PhOH**: Ph₂P(*p*C₄H₄OH)] is highly active for polymerization of PEGMA (conv. 97% in 2h; $M_w/M_n = 1.32$).¹²¹ Note that the Cp*Ru/**P-PhOH** catalyst enables such a high activity and a low catalyst loading without any co-catalyst, whereas the Cu-catalyzed systems (see above) need reducing agents in the same catalyst loading. Though effective enough, the Cp*Ru/**P-PhOH** system is not very active and still needs improvement: The system is not sufficiently soluble in pure water, and the homogeneous polymerization proceeds with PEGMA as a co-solvent as well as the monomer. The phenolic hydroxyl group of **P-PhOH** was also found to coordinate the ruthenium center of Cp*Ru, and the resulting unsuitable coordination may cause the low activity and the low water-solubility.

Since these developments, however, few further studies have been conducted, despite the potential of ruthenium complexes, less oxo-philic, functionality tolerant, and ligand-directed tunability, to offer more active catalysis in water.

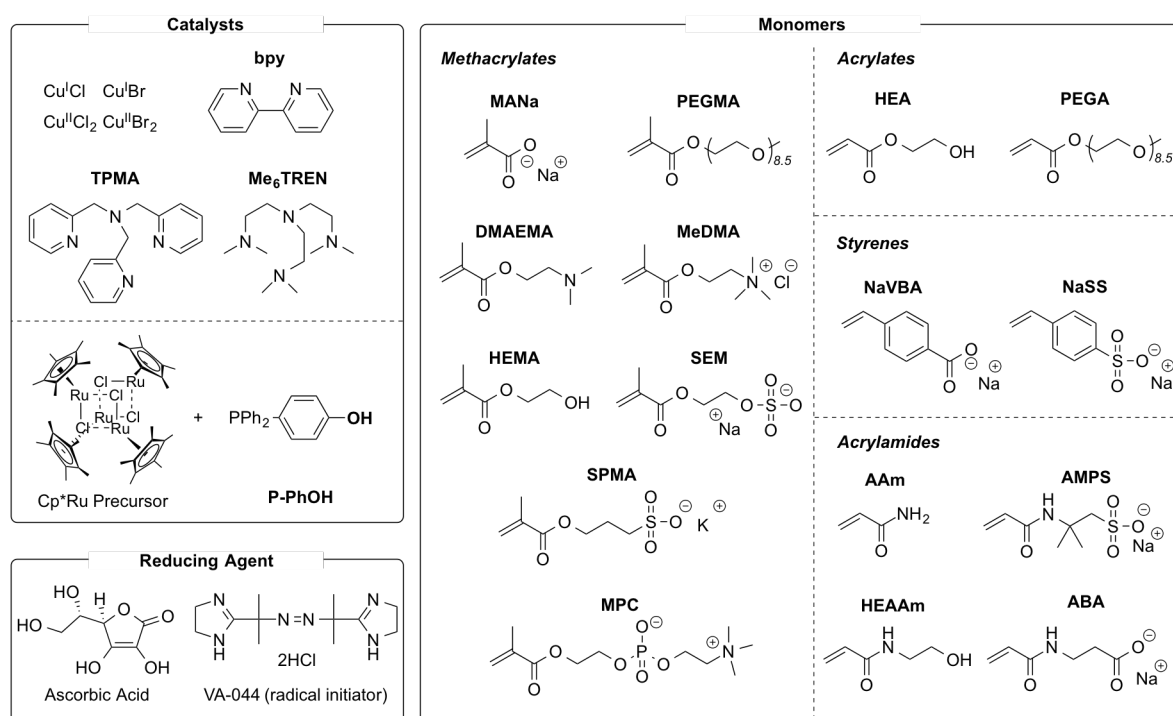


Figure 4. Catalysts, monomers and reducing agents for aqueous Mt-LRP

4.2 Iron-Catalyzed Living Radical Polymerization

In 1997, the early age of Mt-LRP, Sawamoto and co-workers reported that $\text{FeCl}_2(\text{PPh}_3)_2$ allowed living radical polymerization of methyl methacrylate (MMA) in conjunction with bromine or chlorine based initiator ($M_w/M_n \sim 1.20$).¹²² Since then, iron-catalyzed living radical polymerization has been actively developed worldwide (Figure 5).^{123–125}

In fact, a large variety of iron complexes have already been employed for catalysts, *e.g.*, iron halides, half metallocenes, iron oxides, bio-inspired complexes and enzymes. Among them, divalent and trivalent iron halides [FeX_2 and FeX_3 ($X = \text{Cl}$ or Br)] with selected ligands have been the most popular catalysts in iron-catalyzed living radical polymerization. So far, isolated complexes have extensively been investigated, *e.g.*, $\text{FeBr}_2(\text{P}n\text{Bu}_3)_2$,¹²⁶ $\text{FeCl}_2(\text{diim})$,¹²⁷ $\text{FeBr}_2(\text{DMDPE})$,¹²⁸ $\text{FeBr}_2[(\text{Cyclopentane})_3\text{TACN}]$ ¹²⁹ and $\text{FeX}_2(i\text{PrNHC})_2$,¹³⁰ (Figure 5; see there for ligand abbreviation). Many *in-situ* generated complexes from iron halides and ligands have also been reported. For example, the ligands include phosphines [*e.g.*, PPh_3 ,¹³¹ $\text{P}(n\text{Bu})_3$,^{131,132} DMDPE ¹²⁸ and DPPP ¹³³], amines [*e.g.*, $\text{N}(n\text{Bu})_3$,^{131,132,134} and TDA ^{135,136}], carboxylic acids ($i\text{PA}$ ¹³⁷), PEG,¹³⁸ crown ether,¹³⁹ polar solvents (*e.g.*, acetonitrile^{140,141} and NMP ¹⁴⁰), and halide salts (*e.g.*, TBA-Br ^{142,143} and PZN-X ¹⁴⁴).

Though extensively explored, most iron catalysts reported thus far are still inferior to the Ru or Cu counterparts in some aspects: less active, less stable, and often insufficiently tolerant of polar functional groups such as hydroxyl, amino, pyridyl and carboxyl. In fact, only a few have been reported for the iron-catalyzed LRP of functional monomers, definitely implying that this is an issue to be examined in further depth.

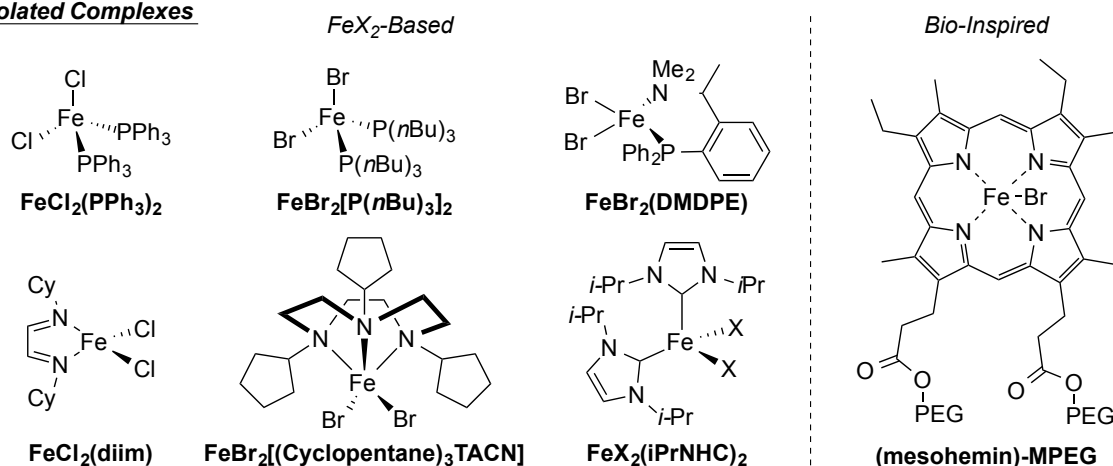
The few examples of iron-mediated LRP include the following. Iron complexes *in-situ* formed from FeBr_2 and a highly delocalized bulky phosphazanium salt (PZN-Br) enabled a controlled polymerization of PEGMA ($M_n \sim 90000$; $M_w/M_n < 1.2$).¹⁴⁴ More recently, decamethylferrocene (FeCp^*) turned out an effective cocatalyst for the $\text{FeBr}_2/\text{TBA-Br}$ system, and the tri-component system allowed not only MMA polymerization but also (co)polymerization of functional monomers (*i.e.*, PEGMA, HEMA, and MAA) that are often poisonous to organometallic complexes.¹⁴³ Gibson *et al.* reported that the diimine coordinated iron catalyst [$\text{FeCl}_2(\text{diim})$] allowed controlled polymerization of hydroxylpropyl methacrylate (HPMA) in methanol.¹²⁷

Some iron catalyzed aqueous polymerizations were also reported. For example, iron catalyzed LRP of PEGMA with the $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/\text{TDA}/\text{ascorbic acid}$ was reported to occur in water as well as in bulk.¹²⁸ Matyjaszewski and his co-workers developed a bio-inspired iron

complex [(mosohemin)-MPEG] for aqueous LRP, which was synthesized by PEG-introduction and hydrogenation of hemin.¹⁴⁵ The [(mosohemin)-MPEG] enabled controlled polymerization of PEGMA in water in the presence of KBr and ascorbic acid ($M_w/M_n \sim 1.2$). Other bio-inspired iron complexes^{146,147} and enzymes^{148–151} also employed for Mt-LRP of functional monomers in aqueous media.

Despite these rather sporadic developments, further investigation is still required toward more versatile and useful iron catalyzed systems.

Isolated Complexes



Ligands for Iron Halides

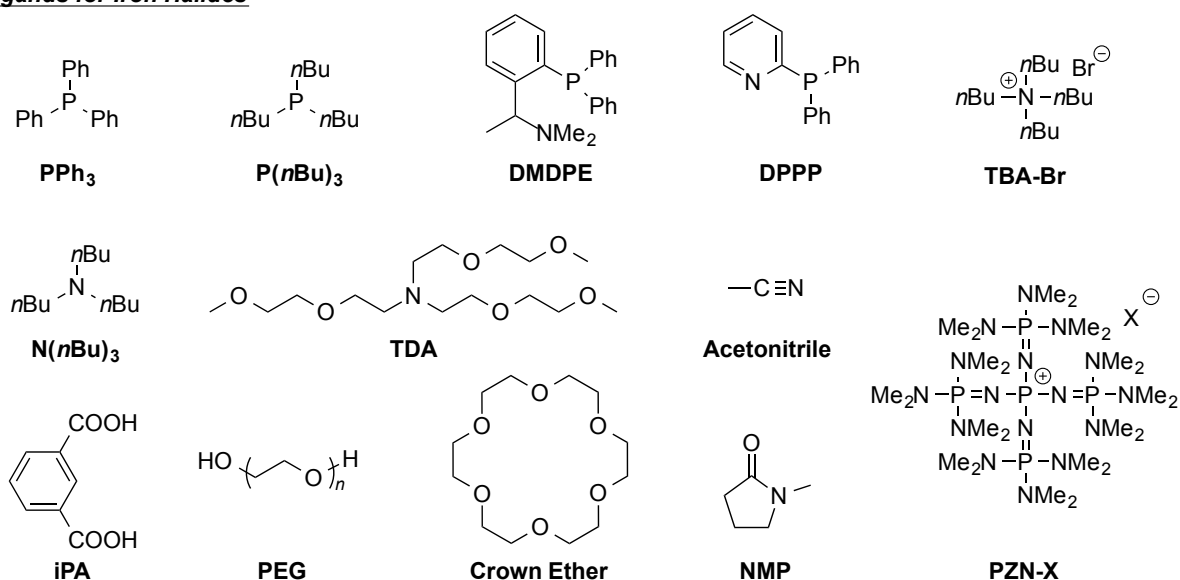


Figure 5. Iron complexes and ligands for iron-catalyzed living radical polymerization

Objectives

Given the above backgrounds, the author decided to address environmental benign metal-catalyzed living radical polymerization via catalyst design in this thesis, in particular:

- 1 *Highly Active Ruthenium Catalysis in Water*
- 2 *Robust Iron Catalysis in Living Radical Polymerizations of Functional Monomers*

1 *Highly Active Ruthenium Catalysis in Water*

As briefly reviewed above, most aqueous LRPs have been reported with copper catalysts, and ruthenium catalyzed aqueous polymerization has not been sufficiently investigated.^{120,121,152} The author believes that ruthenium complexes are suitable for aqueous LRPs, because they are less ionic, less oxo-philic, and more stable towards water than the copper counterparts. Ruthenium-catalyzed organic reactions, such as hydrogenation^{153,154} and metathesis,^{155–158} are abundantly known, where a rich family of ruthenium complexes and ligands have been examined and available. Additionally, as found by the author in part, a large variety of ruthenium complexes, particularly the Cp*Ru family, may readily be obtained *in situ* from a caged oligomeric precursor $\{[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$ or $(\text{Cp}^*\text{RuCl}_2)_n\}$ and ligands, and these *in situ* catalysts can be employed without further purification (Figure 6). Therefore, the author introduced newly designed hydrophilic ligands to Cp*Ru catalysts to improve solubility, catalytic activity and monomer versatility in water.

Additionally, water is a promising solvent to protect the catalyst from poisonous functional groups by hydration. Acidic monomers, such as methacrylic acid (MAA), are

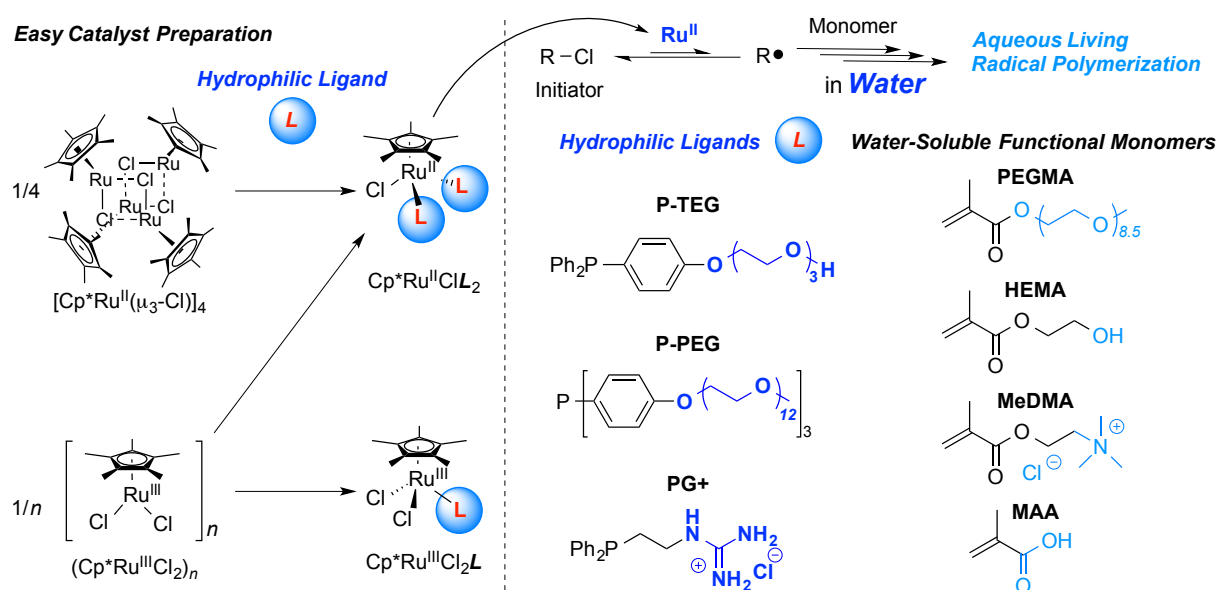


Figure 6. Ru-catalyzed aqueous living radical polymerization with hydrophilic ligand

very poisonous for metal catalyst and much difficult to control. Therefore, the author decided to investigate direct controlled polymerizations of MAA in water with water-soluble ruthenium catalysts.

2 Robust Iron Catalysis in Living Radical Polymerizations of Functional Monomers

To develop robust iron catalyst for Mt-LRPs of functional monomers, the author designed the following two phosphines as ligands for iron bromide (Figure 7).

P-PEG, which was a good ligand for ruthenium-catalyzed aqueous polymerization, was also employed for iron-catalyzed polymerization. **P-PEG** has PEG chains on the three *para* positions of triphenylphosphine. The PEG chains bring high electron density and steric hindrance to the iron catalyst, and the PEG also act as a ligand for iron catalyst.¹³⁸ For these characteristics of PEG groups, the iron catalyst with **P-PEG** was promising to enable active and tolerant iron catalysis in LRPs of functional monomers such as PEGMA and HEMA.

PGBoc is a phosphine ligand containing *tert*-butoxycarbonyl (Boc) protected guanidine, and this ligand is expected to form a stable PN-chelate iron complex. Other PN- or

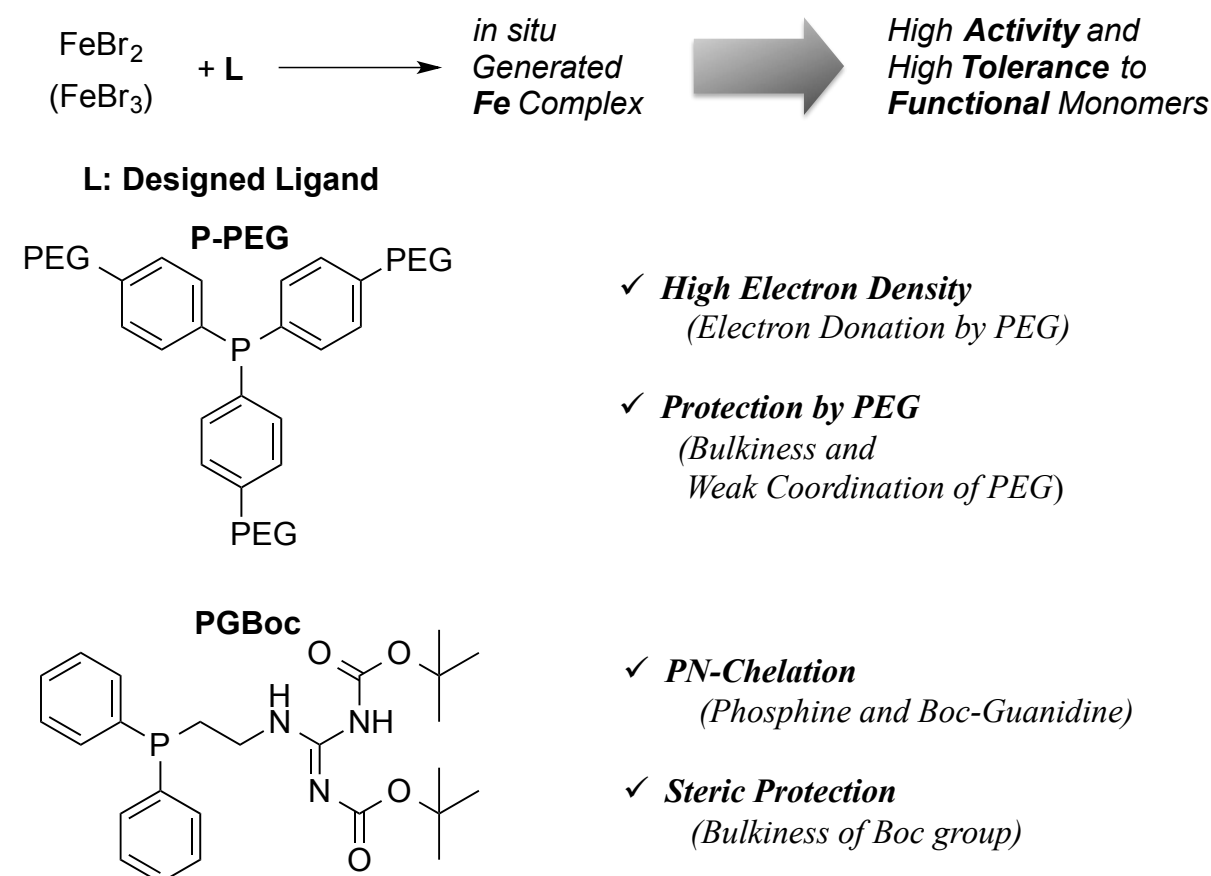


Figure 7. Ligand design toward robust iron catalysis for LRPs of functional monomers

PO-chelating ligands were reported to improve catalytic activity in iron catalyzed LRP.^{128,133,159} Additionally, **PGBoc** are promising ligand for steric protection of iron catalyst from functional groups by the bulkiness of Boc groups. For these reason, **PGBoc** was also employed for iron catalyzed LRPs to enhance catalytic activity and tolerance to functional monomers.

Outline of This Study

The present thesis consists of two parts including six chapters, all directed towards "green" catalysis for living radical polymerization: **Part I** (Chapter 1–4) focused on ruthenium-catalyzed aqueous living radical polymerization with newly designed hydrophilic ligands (Figure 8). **Part II** (Chapter 5, 6) deals with iron-catalyzed living radical polymerization of functional monomers with phosphine ligands designed to improve stability and activity of iron catalysts.

Chapter 1 focuses on the ruthenium-catalyzed living radical polymerization with a novel hydrophilic ligand (**P-TEG**) synthesized by introducing triethylene glycol (TEG) to the *para* position of triphenylphosphine. **P-TEG** was combined with a tetrameric Cp*Ru precursor $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$ to form a hydrophilic ruthenium complex, and the resultant complex enabled homogeneous controlled polymerization of PEGMA in water (conversion over 90% in 20 min; $M_w/M_n < 1.16$). This Cp*Ru/**P-TEG** catalyst showed high activity to allow decreasing catalyst dose ($[\text{Ru catalyst}]_0/[\text{Initiator}]_0 = 1/100$) and controlled polymerization of HEMA at 0 °C. The catalyst also enabled aqueous syntheses of block copolymers (i.e., PEG-*block*-PHEMA and PEG-*block*-PMeDMA).

Chapter 2 deals with a PEG-containing phosphine (**P-PEG**) as a highly water-soluble ligand for ruthenium catalyst toward aqueous living radical polymerization. **P-PEG** was mixed and heated with $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$ to obtain a ruthenium complex *in situ*, and the obtained complex showed higher water-solubility than a **P-TEG** ruthenium complex. The Cp*Ru/**P-PEG** catalyst allowed aqueous controlled polymerization of PEGMA: the conversion reached over 90% in 1 hour, and the molecular weight distributions (MWDs) of the obtained polymer were very narrow ($M_w/M_n = 1.14\text{--}1.16$). A trivalent ruthenium precursor $[(\text{Cp}^*\text{RuCl}_2)_n]$ was also employed with **P-PEG** for aqueous polymerization to

improve controllability, and this $(\text{Cp}^*\text{RuCl}_2)_n/\text{P-PEG}$ catalyst enabled controlled aqueous polymerization of PEGMA and HEMA, though HEMA polymerization was not controlled with $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$ precursor. Furthermore, the catalyst showed sufficiently high activity to allow reducing catalyst dose ($[\text{Ru cat}]_0/[\text{Init}]_0 = 1/100$).

Chapter 3 presents the high controllability and high monomer versatility of a ruthenium catalyst coordinated by a guanidine-embedded phosphine ligand (**PG+**). The catalyst, in situ obtained from $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$ and **PG+**, is highly soluble in water and allowed controlled polymerization of PEGMA and HEMA in water or ethanol, as well as of hydrophilic monomers (MMA, MA, St) in toluene/ethanol (85/15, v/v). Another catalyst prepared from $(\text{Cp}^*\text{RuCl}_2)_n$ with **PG+** enabled aqueous controlled polymerization of PEGMA, HEMA and MeDMA: the monomer conversions reached almost 90%, and the M_w/M_n values of the obtained polymers were 1.09–1.13 (PEGMA), 1.13–1.21 (HEMA) and 1.13–1.20 (MeDMA), and high end-functionality was indicated by ^1H NMR analysis of the obtained poly(HEMA) ($F_n \sim 0.96$). The catalytic activity was sufficiently high to reduce catalyst dose in aqueous PEGMA polymerization: the obtained polymer was still controlled ($M_w/M_n \sim 1.36$) even at 1/200 amount of catalyst for the polymer chain.

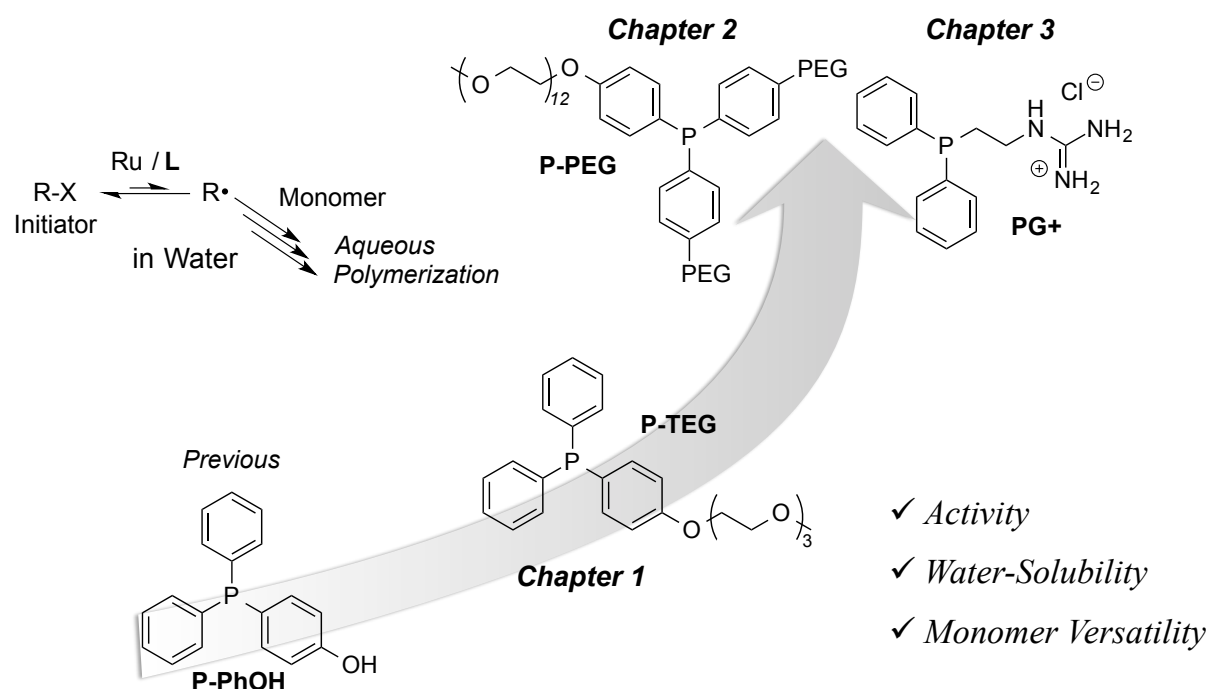


Figure 8. Ligand designs for aqueous living radical polymerization.

Chapter 4: Direct (Co)Polymerization of MAA in Water

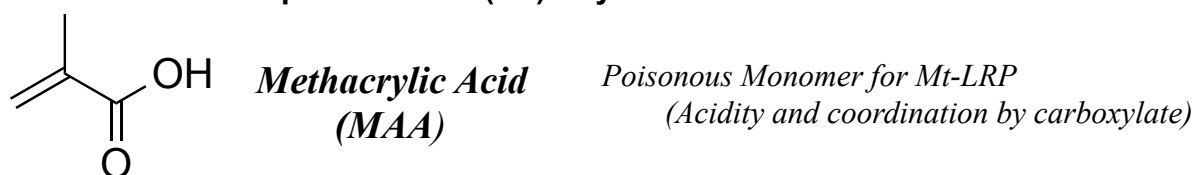


Figure 9. Methacrylic acid (MAA)

Chapter 4 focused on aqueous living radical polymerization of methacrylic acid (MAA). MAA is a typical acidic monomer and extremely difficult to control by metal-catalyzed living polymerization because metal complexes are poisoned by MAA (Figure 9). However, the ruthenium catalysts coordinated by the above-mentioned ligands (**P-TEG**, **P-PEG** and **PG+**) enabled controlled random copolymerization of MAA and PEGMA (50/50, mol%) in water. In particular, the $(\text{Cp}^*\text{RuCl}_2)_n/\text{P-PEG}$ catalyst was suitable for MAA polymerization and allowed MAA homopolymerization and synthesis of PEG-*block*-PMAA in water.

In **Chapter 5**, various phosphine ligands (PR_3) were employed with FeBr_2 to improve the catalytic activity and stability of the resultant iron complexes $[\text{FeBr}_2(\text{PR}_3)_2]$. The ligands that contained electron-donating groups on *para* position of PPh_3 $\{[\text{P}(\text{MeOPh})_3]$ or $[\text{Ph}_2\text{P}(\text{Me}_2\text{NPh})]\}$ allowed controlled polymerization of PEGMA, smoothly proceeding to high conversion ($\sim 90\%$, $M_w/M_n < 1.2$). Furthermore, **P-PEG** led to tolerance for hydroxyl group (-OH) (Figure 10). Accordingly, the $\text{FeBr}_2/\text{P-PEG}$ catalyst enabled controlled random copolymerization of HEMA, PEGMA, MMA, and benzyl methacrylate.

Chapter 6 deals with iron complex prepared from iron bromide and a Boc-guanidine pendent phosphine (**PGBoc**) for living radical polymerization of functional monomers. **PGBoc** is a promising ligand for active and robust iron catalyst due to PN chelation and bulkiness of Boc-guanidine. The $\text{FeBr}_2/\text{PGBoc}$ allowed highly active living polymerization of PEGMA: the monomer smoothly and almost completely consumed ($> 95\%$ in 24 h), and the molecular weights of obtained polymer were fairly controlled ($M_w/M_n = 1.22\text{--}1.25$). Furthermore, the catalyst prepared from **PGBoc** and iron bromide (FeBr_2 or FeBr_3) enabled controlled (co)polymerization of HEMA. By using $\text{FeBr}_2/\text{PGBoc}$ catalyst, copolymerization of PEGMA and HEMA (1/1) proceeded smoothly, and the obtained polymers were controlled ($M_w/M_n = 1.27\text{--}1.35$). Moreover, FeBr_3 enhanced controllability and allowed controlled homopolymerization of HEMA ($M_w/M_n = 1.21$), though the polymerization became slower than with FeBr_2 .

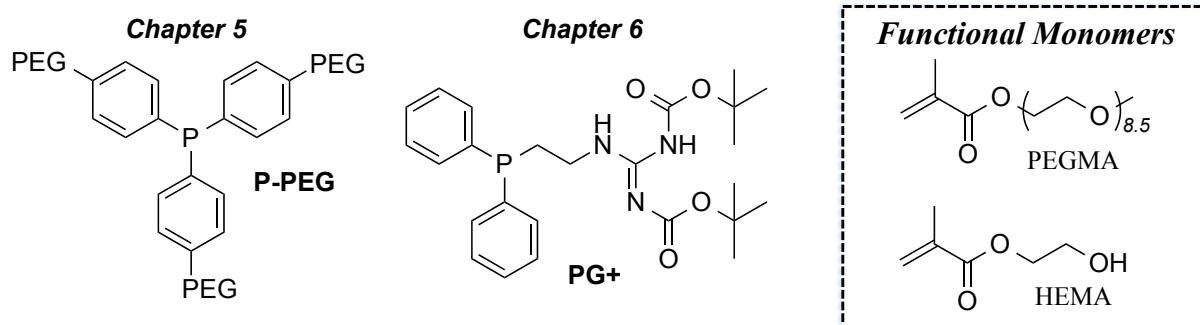


Figure 10. Ligands for iron catalyzed living polymerization of functional monomers

In conclusion, this thesis presents environmentally benign metal-catalyzed living radical polymerization: ruthenium catalyzed aqueous polymerization and robust iron catalyzed polymerization of functional monomers. Customized ligands and precursors improved water-solubility, catalytic activity, stability, and versatility toward the environmental benign systems. The author believes that the researches in this thesis contribute to further developments of environmentally benign and green sustainable chemistry as well as polymer chemistry.

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PART I

Highly Active Living Radical Polymerization in Water with Water-Soluble Ruthenium Catalyst

Chapter 1

Design of a Hydrophilic Ruthenium Catalyst for Metal-Catalyzed Living Radical Polymerization: Highly Active Catalysis in Water

Abstract

A novel hydrophilic phosphine ligand for ruthenium catalyst was synthesized toward useful living radical polymerization in water. Triethylene glycol (TEG) was introduced at *para* position of triphenylphosphine and the resultant TEG-decorated ligand was combined with Cp*-based ruthenium precursor ($[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$) to prepare hydrophilic ruthenium complex. The obtained ruthenium complex induced homogeneous controlled polymerization of poly(ethylene glycol) methacrylate (PEGMA) in water: the monomer conversion reached over 90% in 20 min., and the obtained polymers showed narrow MWD ($M_w/M_n < 1.16$). The ruthenium catalyst was active enough to allow decrease in catalyst amount ($[\text{Ru}]_0/[\text{Initiator}]_0 = 1/100$) or polymerization at low temperature, 0 °C [for 2-hydroxyethyl methacrylate (HEMA)]. The catalyst also induced aqueous block copolymerization for the combination of water-soluble monomers: PEGMA/HEMA and PEGMA/methyl chloride-quaternized 2-(dimethylamino)ethyl methacrylate (MeDMA).

Introduction

Water is an ideal solvent for polymerizations in terms of sustainability because it is not only eco-friendly but also much cheaper than organic counterparts. In addition, water solvent is essential when polymer chain is connected with biomolecule via bio-conjugation through controlled polymerization: the inherent functions of biomolecules could be diminished unless water is used as the solvent.

So far, some controlled radical polymerizations have been developed using various methodologies, such as metal-catalyzed (ATRP),¹⁻⁹ nitroxide-mediated (NMP),^{10,11} reversible addition fragmentation chain transfer (RAFT),^{12,13} tellurium-mediated (TERP),¹⁴ and cobalt-mediated (CMRP).¹⁵ Above all, metal-catalyzed living radical polymerization is user-friendly due to the simple procedure and versatile design of the initiator/catalyst. However, use of metal sometimes incurs limitation of the utility, because the catalyst could suffer from poisoning by polar solvents including water, leading to loss of catalytic activity. Especially, for ruthenium (Ru)¹⁶ and iron (Fe)¹⁷⁻¹⁹ catalysis, an active and useful system in water is still limited, in contrast to copper (Cu)-based.²⁰⁻³⁸ Since required compatibility of the central metal of catalyst depends on bioapplications, active catalysis in water is important for each central metal.

Recently, Sawamoto and co-worker found that coordination of phenolic phosphine ligand (**P-PhOH**) on Cp*-based (Cp* = pentamethyl-cyclopentadienyl) ruthenium catalyst allowed living radical polymerization of water-soluble methacrylate monomers in water¹⁶ (Figure 1). The catalytic activity was high enough to induce fast controlled radical polymerization even at lower temperature (40 °C). However, the hydrophilicity of the phenol-based ligand was insufficient for the resultant complex to be perfectly soluble in water. The polymerization seems to proceed nearly homogeneously, but indeed the catalyst is just dispersed thanks to liquid monomers of amphiphilic features. Furthermore, the reactive phenoxy anion could

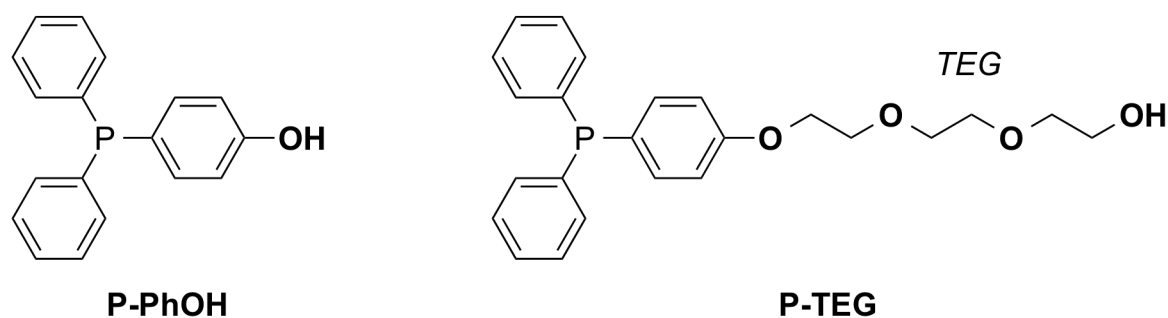


Figure 1. Hydrophilic phosphine ligands for ruthenium catalyzed aqueous polymerization.

coordinate on ruthenium center to deactivate the catalyst, which is described later.

In this chapter, the author introduced triethylene glycol (TEG) as hydrophilic group from the phenol site of **P-PhOH** via substituent reaction to prepare the TEG-decorated phosphine ligand (**P-TEG**). The hydroxy group of TEG would not affect the ligation of phosphorus (P) or polymerization control, since radical polymerization can be controlled in alcohol solvents using similar phosphine-based ruthenium catalyst. Consequently, coordination of **P-TEG** on ruthenium catalyst allowed very active living radical polymerization in water.

Experimental

Materials

PEGMA [$\text{CH}_2\text{C}(\text{CH}_3)\text{COO}(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_3$; $n = 8.5$ (number-average)] (Aldrich) and HEMA (Aldrich; > 99%) were purified by passing through an inhibitor-removal column (Aldrich) and were subsequently degassed by three-time vacuum-argon bubbling cycles before use. The ruthenium tetramer precursor $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$ ^{39,40} and $\text{H}-(\text{MMA})_2\text{-Cl}$ ⁴¹ initiator [$\text{H}(\text{CH}_2\text{CMeCO}_2\text{Me})_2\text{Cl}$]; an MMA dimer chloride] were prepared according to the literature. (4-Hydroxyphenyl)diphenylphosphine and materials for preparation of $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$, listed below, were used as received without further purification and handled in a glovebox (MBraun Labmaster 130, M. Braun Inertgas-Systeme GmbH, Garching, Germany) under a moisture- and oxygen-free argon atmosphere ($\text{H}_2\text{O} < 1$ ppm; $\text{O}_2 < 1$ ppm): ruthenium(III) chloride hydrate (Wako; > 99.9%); 1,2,3,4,5-pentamethylcyclopentadiene (TCI; > 93%); and lithium triethylhydridoborate (Aldrich, 1.0 M solution in THF). Toluene (Kishida Kagaku; purity 99.5%) was dried and purified by passing through purification columns (Solvent Dispensing System, SG Water USA, Nashua, NH; Glass Contour) and bubbled with dry nitrogen for more than 15 min immediately before use. Water (Wako; distilled), buffer solutions (TCI) and ethanol (Wako; super dehydrated) were bubbled with dry nitrogen for more than 15 min immediately before use. 1,2,3,4-tetrahydronaphthalene (tetralin; internal standard for ^1H NMR) was dried over calcium chloride and distilled from calcium hydride. MeDMA (methyl chloride-quaternized 2-(dimethylamino)ethyl methacrylate) (Wako; >97.0%), 2-[2-(2-Chloroethoxy)ethoxy]-ethanol (TCI; >96%), K_2CO_3 (Wako; > 99.5%), NaCl (Wako; > 99.5%), DMF (Wako; super dehydrated), diethyl ether (Wako; > 99.5%), hexane (Wako; > 96.0%), ethyl acetate (Wako; > 99.5%), silica gel (Wako; Wakogel® C-200) are used as received.

Ligand Synthesis (P-TEG)

A suspension of (4-hydroxyphenyl)diphenylphosphine (913 mg, 3.28 mmol), 2-[2-(2-chloroethoxy)ethoxy]ethanol (580 mg, 3.44 mmol) and K_2CO_3 (544 mg, 3.94 mmol) in DMF (15 mL) was stirred at 90 °C for 40 h under argon. After evaporation of DMF at 50 °C, diethyl ether (80 mL) was added to the residue. The organic layer was washed with water (1 × 60 mL) and brine (1 × 60 mL), and then the aqueous layer was extracted by diethyl ether (2 × 60 mL). The combined organic layer was dried over anhydrous Na_2SO_4 . After filtration, the filtrate was evaporated under vacuum. **P-TEG** was isolated by silica gel column chromatography using hexane/ethyl acetate (50/50) as an eluent in 70% yield (947 mg). 1H NMR (500 MHz, $DMSO-d_6$): δ 7.44–7.33 (m, 6H), 7.26–7.15 (m, 6H), 7.00 (d, J = 7.7 Hz, 2H), 4.56 (t, J = 5.4 Hz, 1H), 4.10 (t, J = 4.6 Hz, 2H), 3.74 (m, J = 4.6 Hz, 2H), 3.61–3.56 (m, 2H), 3.56–3.51 (m, 2H), 3.48 (dt, J = 5.4, 5.2 Hz, 2H), 3.41 (t, J = 5.2 Hz, 2H). ^{13}C NMR (125 MHz, methanol- d_4): δ 161.2, 139.3, 139.2, 136.7, 136.5, 134.5, 134.3, 129.6, 129.5, 129.4, 129.2, 129.1, 116.0, 115.9, 73.7, 71.8, 71.4, 70.8, 68.5, 62.2. ^{31}P NMR (202 MHz, toluene- d_8): δ -6.1. ESI-MS: m/z 433.23 ($[M+Na]^+$; calcd. 433.15).

Polymerization Procedures

Polymerization was carried out by the syringe technique under dry argon in baked glass tubes equipped with a three-way stopcock or in sealed glass vials. An example for PEGMA polymerization with the $H-MMA_2-Cl/[Cp^*Ru(\mu_3-Cl)]_4/P-TEG$ in water is given below. $[Cp^*Ru(\mu_3-Cl)]_4$ (2.2 mg, 0.0020 mmol), 100 mM **P-TEG** in toluene (0.16 mL, 0.016 mmol), and toluene (1.0 mL) was placed in a Schlenk tube. The solution was heated to 60 °C for 2 h to prepare ruthenium complex. After cooling the mixture to room temperature and removal of toluene under vacuum, PEGMA (0.88 mL, 2.0 mmol), buffer solution (TCI B0178; pH 8.0) (3.02 mL) and 200 mM $H-MMA_2-Cl$ in ethanol (0.10 mL, 0.020 mmol) were added; the total volume was 4.0 mL. Immediately after mixing, aliquots (0.50–1.0 mL each) of the solution were injected into baked glass tubes, which were then sealed (except when a stopcock was used) and placed in an oil bath kept at 40 °C. In predetermined intervals, the polymerization was terminated by adding methanol containing air to the reaction mixture and cooling it to -78 °C in dry ice-methanol. Monomer conversion was determined by 1H NMR from the integrated peak area of the olefinic protons of the monomer with ethanol as an internal standard. Obtained polymer solutions were evaporated under vacuum and dissolved in DMF

(1.0 wt%). After filtration of the solutions, the filtrates were analysed with SEC.

Another example for HEMA polymerization with the H-MMA₂-Cl/[Cp*Ru(μ₃-Cl)]₄/**P-TEG** in water-ethanol mixed solvent (1/1 v/v%) is also given below. [Cp*Ru(μ₃-Cl)]₄ (2.2 mg, 0.0020 mmol), 100 mM **P-TEG** in toluene (0.16 mL, 0.016 mmol), and toluene (1.0 mL) was placed in a Schlenk tube. The solution was heated to 60 °C for 2 h to prepare ruthenium complex. After cooling the mixture to room temperature and removal of toluene under vacuum, HEMA (0.97 mL, 8.0 mmol), ethanol (1.36 mL), water (1.52 mL) and 500 mM H-MMA₂-Cl in ethanol (0.16 mL, 0.080 mmol) were added; the total volume was 4.0 mL. Immediately after mixing, aliquots (0.50–1.0 mL each) of the solution were injected into baked glass tubes, which were then sealed (except when a stopcock was used) and placed in an oil bath kept at polymerization temperature (40 °C or 0 °C). In predetermined intervals, the polymerization was terminated, and the monomer conversion was determined, followed by SEC analysis in the same way as mentioned above.

For synthesis of PEG-*block*-PHMEA with [Cp*Ru(μ₃-Cl)]₄/**P-TEG** in water is given below. [Cp*Ru(μ₃-Cl)]₄ (5.4 mg, 0.0050 mmol), 100 mM **P-TEG** in toluene (0.40 mL, 0.040 mmol), and toluene (1.0 mL) was placed in a Schlenk tube. The solution was heated to 60 °C for 2 h to prepare ruthenium complex. After cooling the mixture to room temperature and removal of toluene under vacuum, 0.75 mL of ethanol was added, leading to 27 mM solution in ethanol. PEG-Cl (*M_n* ~ 4500) (0.36 g, 0.080 mmol), HEMA (0.97 mL, 8.0 mmol) and water (2.73 mL) were placed in another Schlenk tube and the 27 mM catalyst solution in ethanol (0.30 mL, 0.0080 mmol) was added (total volume: 4.0 mL). Immediately after mixing, aliquots (0.50–1.0 mL each) of the solution were injected into baked glass tubes, which were then sealed (except when a stopcock was used) and placed in an oil bath kept at 40 °C. In predetermined intervals, the polymerization was terminated, and the monomer conversion was determined, followed by SEC analysis.

For synthesis of PEG-*block*-PMeDMA with [Cp*Ru(μ₃-Cl)]₄/**P-TEG** in water is given below. Ruthenium catalyst solution (27 mM in ethanol) was prepared in the same way as for PEG-*block*-PHEMA synthesis. PEG-Cl (*M_n* ~ 4500) (0.36 g, 0.080 mmol), MeDMA (0.83 g, 4.0 mmol), water (3.60 mL), ethanol (0.10 mL) and 27 mM ruthenium catalyst solution in ethanol (0.30 mL) were placed in a Schlenk tube; the total volume was 4.0 mL. The polymerization was performed in the same way as for PEG-*block*-PHEMA synthesis. Obtained polymer solutions were evaporated under vacuum and dissolved in water (0.1 wt%). After filtration of the solutions, the filtrates were analysed with aqueous GPC equipped with

columns specific to cationic water-soluble polymers.

Measurements

For neutral (co)polymers of PEGMA or HEMA, M_n and M_w/M_n were measured by size exclusion chromatography at 40 °C in DMF containing 10 mM LiBr as an eluent on three polystyrene-gel columns (Shodex KF-805L; exclusion limit = 4×10^6 ; particle size = 10 μm ; pore size = 5000 Å; 0.8 cm i.d. $\times$ 30 cm; flow rate, 1.0 mL min⁻¹) connected to a PU-2080 pump and a RI-1530 refractive-index detector, and a UV-1570 ultraviolet detector (all from Jasco). The columns were calibrated against 13 standard poly(MMA) samples (Polymer Laboratories; M_n = 630–1 200 000; M_w/M_n = 1.02–1.30). For PEG-*block*-PMeDMA, M_n and M_w/M_n were measured by size exclusion chromatography at 40 °C in H₂O containing 100 mM NaNO₃ as an eluent on a polymethacrylate-gel column (TOSOH TSK-GEL® G3000PW_{XL}-CP; exclusion limit = 1×10^5 ; particle size = 7 μm ; 7.8 mm I.D. $\times$ 30 cm; flow rate, 1.0 mL min⁻¹) connected to a PU-1580 pump, a RI-930 refractive-index detector, and a UV-970 ultraviolet detector (all from Jasco), similarly calibrated against standard PEO samples. ¹H NMR and ³¹P NMR spectra were measured at room temperature on a JEOL JNM-ECA500 spectrometer operating at 500.16 and 202.47 MHz, respectively. For the ³¹P NMR analyses, a capillary of diethyl phosphite solution (50 mM in toluene-*d*₈) was used as an internal chemical shift standard (7.08 ppm for the phosphite).

Results and Discussion

1 Ligation of P-TEG on Cp*-Based Ruthenium Complex

The TEG-decorated phosphine, **P-TEG**, was mixed with a tetrameric precursor of pentamethyl-cyclopentadienyl (Cp*) ruthenium complexes ([Cp*Ru(μ₃-Cl)]₄) in toluene at 60 °C to prepare corresponding phosphine complex [Cp*RuCl(**P-TEG**)_n] (Figure 2). Here, to study the coordination number of the phosphine ligand, they were mixed on three different ratios, [Ru]₀/[**P-TEG**]₀ = 1/1, 1/2 and 1/3 molar ratios, and ³¹P NMR was directly measured for the resultant solutions. In the case of the ratio of 1/1 or 1/2, no peak derived from “free” or non-coordinated phosphine was observed at around -6 ppm, and instead a new peak appeared at 40 ppm, likely derived from coordinated phosphine. In sharp contrast, when more than two equivalents of phosphine was used ([Ru]₀/[**P-TEG**]₀ = 1/3), both peaks from free and coordinated phosphine ligands were observed. These results indicated that two

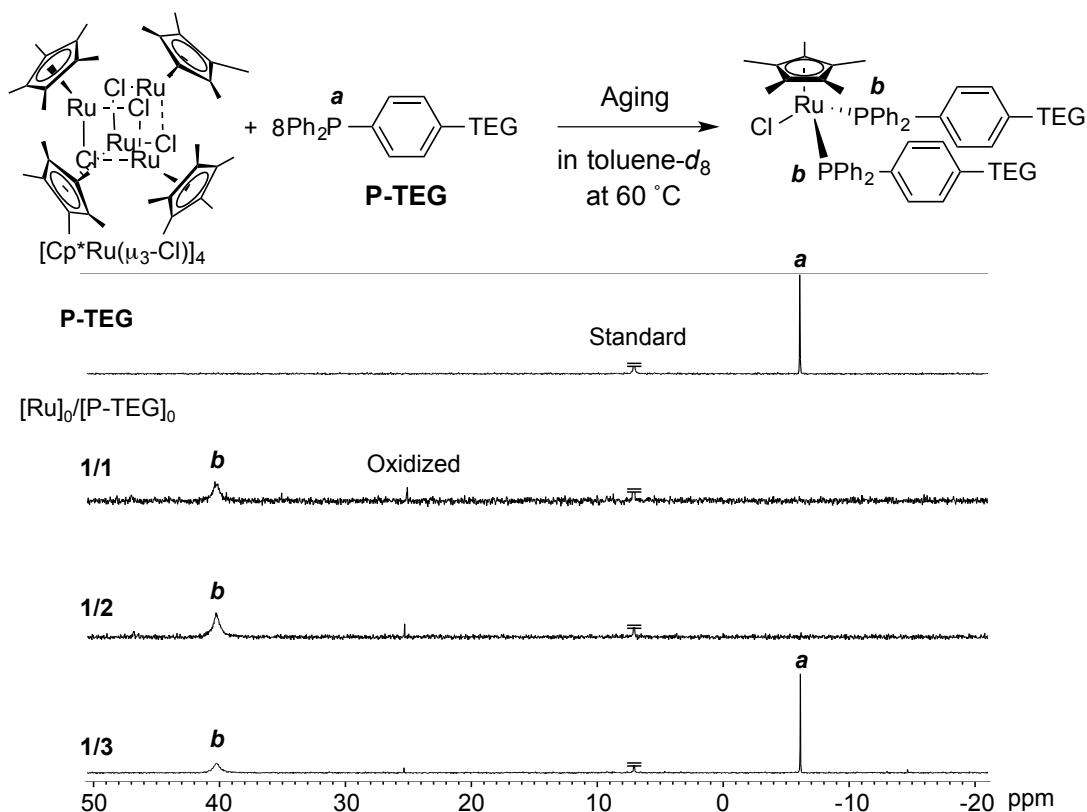


Figure 2. Ligation scheme of **P-TEG** on Cp^* -based ruthenium complex and ^{31}P NMR spectra of **P-TEG** and complexes prepared with 1:1, 1:2 or 1:3 ratio ($[\text{Ru}]_0/[\text{ligand}]_0$) in $\text{toluene-}d_8$ at r.t.: $[\text{P-TEG}]_0 = 8.0\text{ mM}$; $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]_0 = 1.0\text{ mM}$, $[\text{P-TEG}]_0 = 4.0\text{ mM}$; $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]_0 = 1.0\text{ mM}$, $[\text{P-TEG}]_0 = 8.0\text{ mM}$; $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]_0 = 1.0\text{ mM}$, $[\text{P-TEG}]_0 = 12.0\text{ mM}$.

phosphine ligands were coordinated on ruthenium center to give $[\text{Cp}^*\text{RuCl}(\text{P-TEG})_2]$ via the aging process.

When the ratio was 1/2, only one peak was observed likely from coordinating phosphine (*b*) in the ^{31}P NMR spectrum, though a minor one was from the oxidized phosphine. On the other hand, when the phenolic ligand (**P-PhOH**) was employed, another peak was clearly observed in addition to the peak from coordinating phosphine (Figure 3). This peak is probably derived from phosphine ligand whose phenoxy group is ligating on ruthenium. Therefore, **P-TEG** would be more suitable than **P-PhOH** as the ligand selectively giving the two phosphine-coordinating complex $[\text{Cp}^*\text{RuCl}(\text{phosphine})_2]$. In the following polymerizations, the author heated the solution of $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$ and 2 equivalents of **P-TEG** before polymerization and the resultant complex was used as the catalyst without purification.

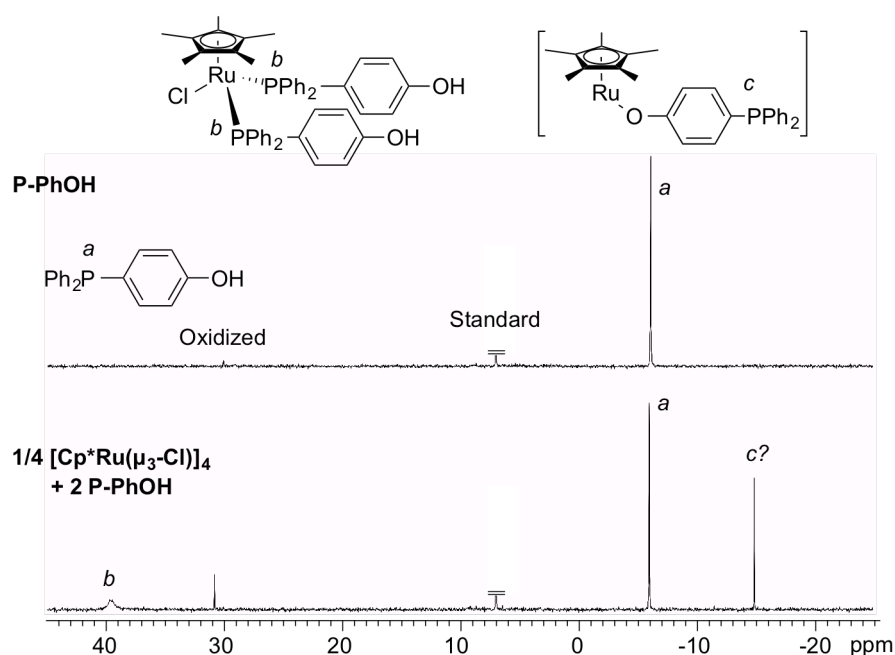


Figure 3. ^{31}P NMR spectra of P-PhOH and Cp*-based ruthenium complexes prepared with 1:2 ratio ($[\text{Ru}]_0:[\text{Ligand}]_0$) in toluene- d_8 at r.t.: $[\text{P-PhOH}]_0 = 8.0 \text{ mM}$; $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]_0 = 1.0 \text{ mM}$, $[\text{P-PhOH}]_0 = 8.0 \text{ mM}$.

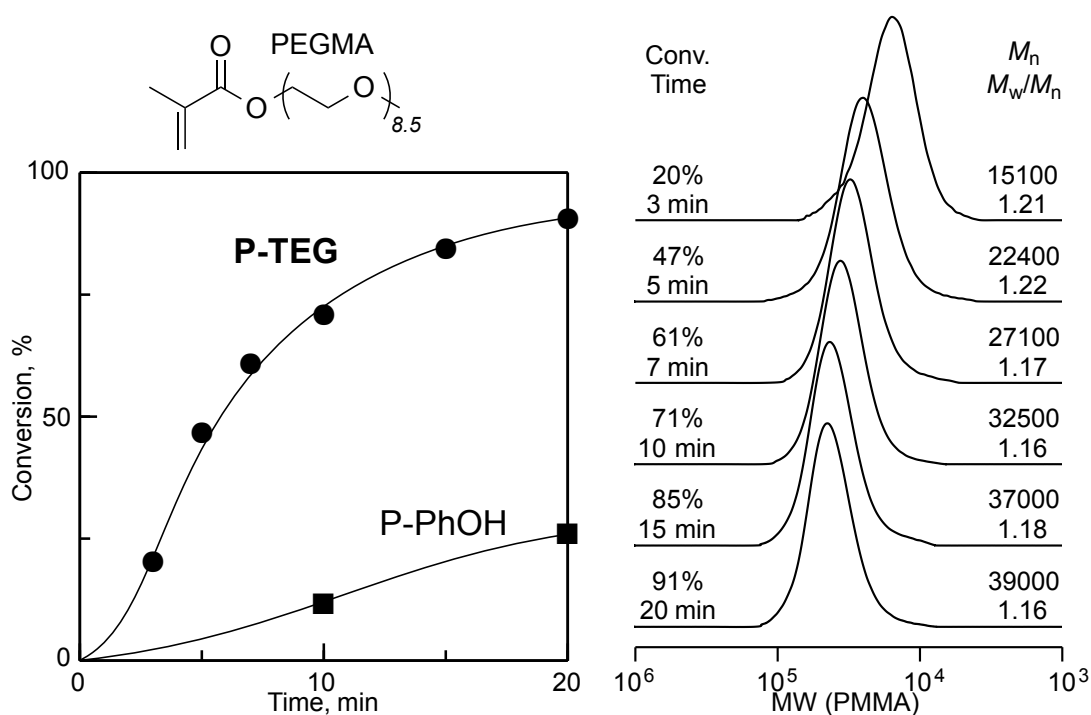


Figure 4. Effects of ligand on aqueous polymerizations of PEGMA with H-(MMA) $_2$ -Cl/ $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]/\text{ligand}$ in H_2O at 40°C : $[\text{PEGMA}]_0 = 500 \text{ mM}$; $[\text{H-(MMA)}_2\text{-Cl}]_0 = 5.0 \text{ mM}$; $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]_0 = 0.5 \text{ mM}$; $[\text{ligand}]_0 = 4.0 \text{ mM}$.

2 Aqueous Living Radical Polymerization of PEGMA

The *in situ* synthesized **P-TEG** ruthenium catalyst was used for living radical polymerization of PEGMA in water at 40°C, in conjunction with a chloride-type initiator [H-(MMA)₂-Cl] (Figure 4). Note that amine cocatalyst was not employed, although it is usually necessary for ruthenium-catalyzed system in organic solvent. Nevertheless, the monomer was smoothly consumed and the conversion reached over 90% in less than half hour (91%, 20 minutes). SEC analyses of obtained polymers showed the polymerization was fairly controlled: molecular weight was increased with conversion and molecular weight distributions (MWDs) were narrow ($M_w/M_n \sim 1.16\text{--}1.22$) through polymerization. By contrast, when **P-PhOH** was used, the polymerization was slower and MWDs of obtained polymers were broader ($M_w/M_n \sim 1.32\text{--}1.40$). Thus, faster polymerization with better control was possible through modification with TEG chain for the phenol site of **P-PhOH**.

3 Decrease in Catalyst Dose

Most of practical applications with hydrophilic polymers, little metal residue is highly required, especially for bioapplications. Use of catalyst insoluble in water might be useful in terms of removal of metal residue, but in this case controllability would be sacrificed. One simple but feasible idea is utilizing very lower amount of catalyst for homogeneous polymerization, though it may be not perfect panacea. The active catalysis with the **P-TEG** catalyst encouraged the author to decrease the amount of catalyst for the polymerization.

In above polymerization, one-tenth amount of catalyst was used for the initiator ($[\text{cat}]_0/[\text{init}]_0 = 1/10$). Lower catalyst amount of 1/50 and 1/100 were tested for the polymerization (Figure 5). Consequently, polymerizations proceeded even with such lower amount of catalyst without serious loss of polymerization rate, and polymerizations were basically controlled, though the MWDs of obtained polymers were broader. As shown in a photograph of the polymerization solution, the polymerization solution of 1/100 was almost colorless indicating very low amount of ruthenium catalyst. Unfortunately, further decrease in catalyst (i.e., 1/200) resulted in much broader MWDs of obtained polymers.

4 HEMA Polymerization at Low Temperature in Aqueous Media

HEMA is also an important water-soluble methacrylate monomer, and the polymer has been used for functional materials such as soft contact lens. High catalytic activity of **P-TEG** ligated ruthenium catalyst for aqueous polymerization of PEGMA encouraged the

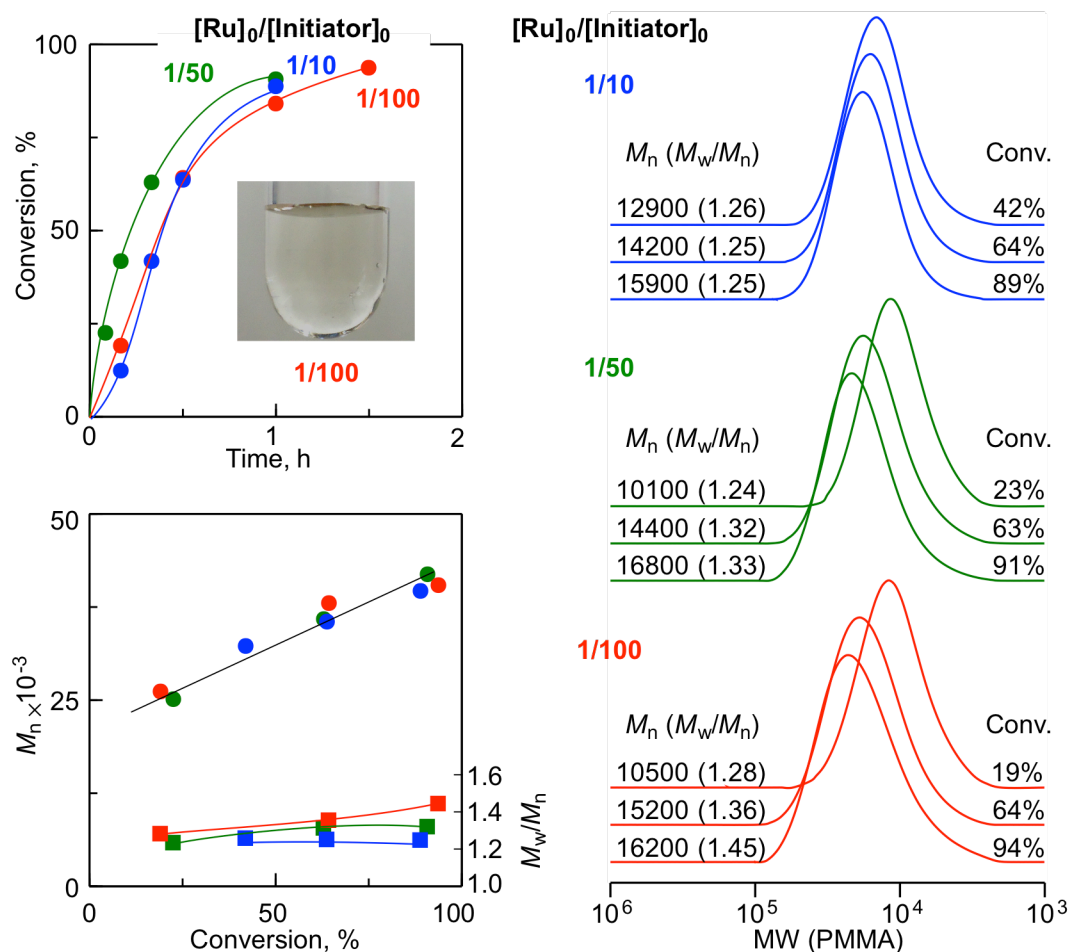


Figure 5. Decrease in catalyst dose on aqueous polymerizations of PEGMA with H-(MMA)₂-Cl/[Cp*Ru(μ₃-Cl)]₄/P-TEG in H₂O at 40 °C: [PEGMA]₀ = 500 mM; [H-(MMA)₂-Cl]₀ = 20 mM; [[Cp*Ru(μ₃-Cl)]₄]₀ = 0.5, 0.1 or 0.05 mM; [P-TEG]₀ = 4.0, 0.8 or 0.4 mM.

author to apply it for HEMA polymerization. Since it has been reported that HEMA polymerization in neat water incurs cross-linking reaction to give insoluble gel,⁴² the author used water-ethanol mixed solvent (1/1 v/v%) (Figure 6).

Consequently, HEMA was also polymerized with the P-TEG ligated ruthenium complex to reach high conversion (>80%) and SEC curves of the obtained polymers showed narrow MWDs ($M_w/M_n \sim 1.2$). The mixed solvent with ethanol allowed polymerization at 0 °C without freezing and the polymerization smoothly proceeded even at 0 °C to give higher conversion (~90%), though the polymerization got slower. Thus, catalytic activity of the P-TEG ligated ruthenium complex was sufficiently high to catalyze aqueous polymerization even at lower temperature. This would be a great advantage for bio-conjugation application using temperature-sensitive biomolecules.

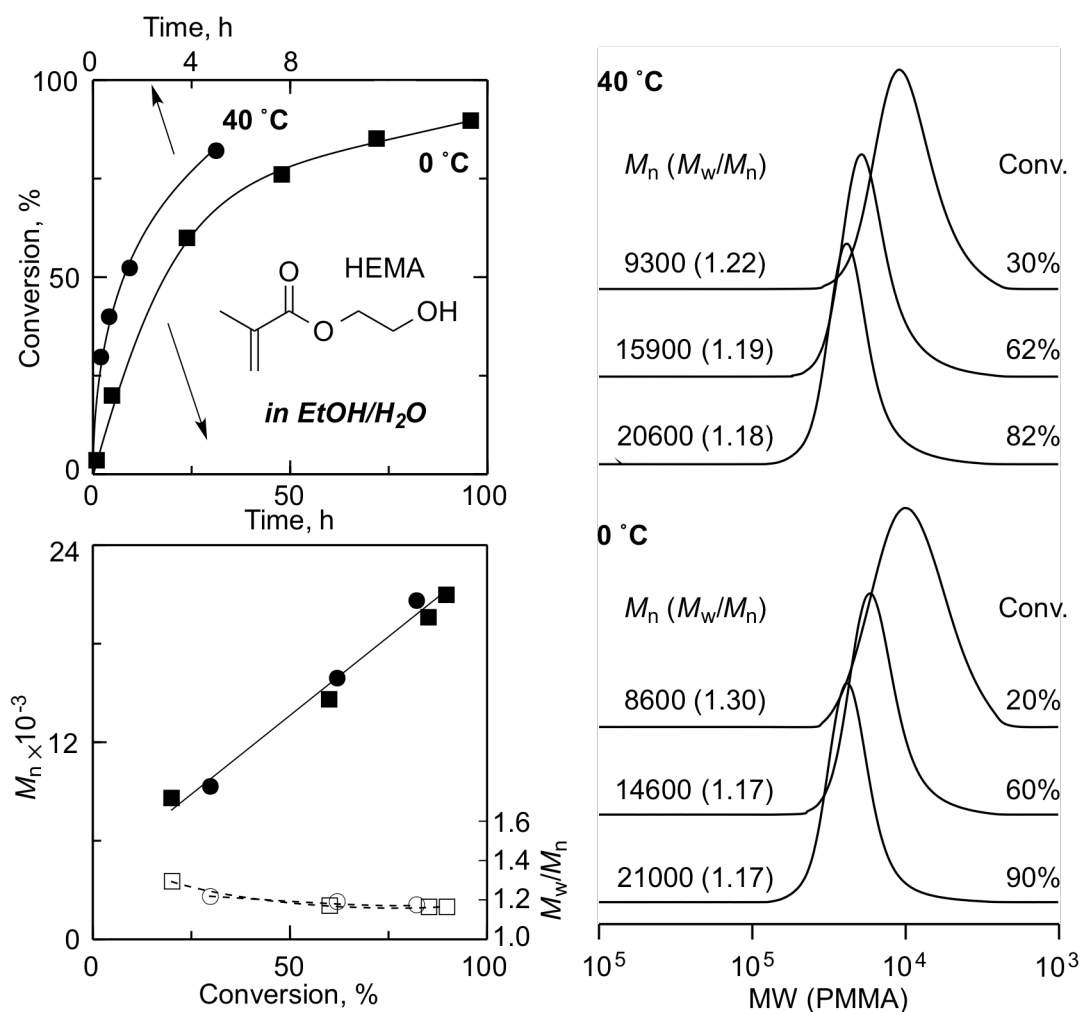


Figure 6. Effects of temperature on HEMA polymerizations with H-(MMA)₂-Cl/[Cp*Ru(μ_3 -Cl)]₄ in ethanol/water (1/1, v/v) at 40 °C or 0 °C: [HEMA]₀ = 2.0 M; [H-(MMA)₂-Cl]₀ = 20 mM; [[Cp*Ru(μ_3 -Cl)]₄]₀ = 0.5 mM; [P-TEG]₀ = 4.0 mM.

5 Aqueous Block Copolymerization with PEG

Block copolymerization is a very important application with living polymerization techniques because it would involve various possibilities. The results on controlled propagation in water with the P-TEG ligated ruthenium complex motivated the author to prepare block copolymers in water by using hydrophilic macroinitiator. Herein, polyethylene glycol (PEG)-based initiator (PEG-Cl: M_n = 4500, M_w/M_n = 1.04) was selected as the macroinitiator because PEG is one of the most important water-soluble polymers due to the high biocompatible features. Herein the author used an ammonium salt-based methacrylate carrying cationic pendant side chain (MeDMA) as well as HMEA as the monomer for the second block segment (Figure 7).

In both of the polymerizations, the monomers were smoothly consumed and finally the conversion reached around 90% in 4 hours. SEC curves of the obtained polymers clearly shifted to higher molecular weight increase in the monomer conversion almost keeping the unimodal distributions. However, in the case of polymerization of MeDMA, small shoulder peaks were clearly detected at lower molecular weight region, although the ratio to the main peak was gradually decreased as the polymerization proceeded. The molecular weight distributions curves were obtained by aqueous SEC equipped with columns suitable for analyses of cationic polymers in water, which was different from that for analyses of HEMA-based block copolymers with DMF eluent. This may affect the SEC analyses, resulting in clear bimodal molecular weight distribution curves. It may be necessary to improve the condition of aqueous SEC analyses,⁴³ but it is likely concluded that the propagations in the two block copolymerizations in water are fairly controlled.

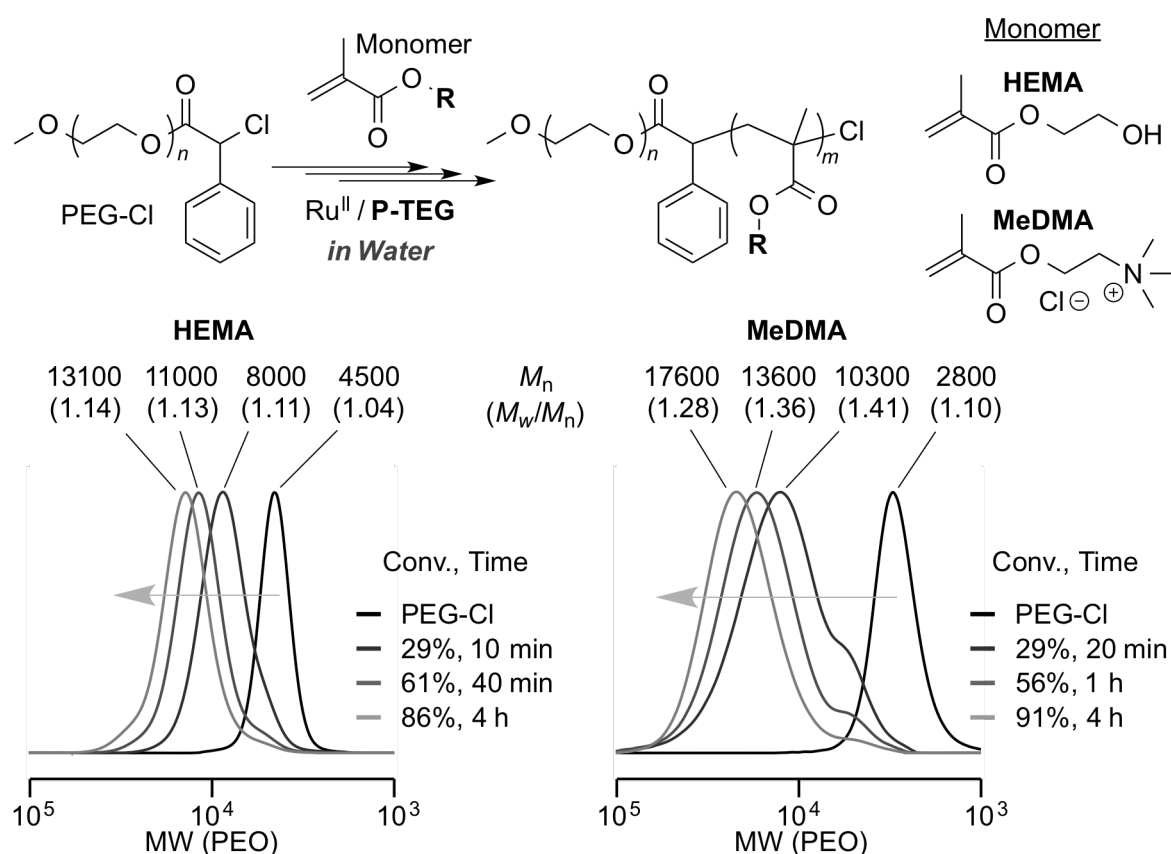


Figure 7. Aqueous block polymerizations of HEMA or MeDMA with PEG-Cl ($M_n \sim 5000$) in water/ethanol (9/1, v/v) at 40 °C: $[\text{HEMA}]_0 = 2000 \text{ mM}$, $[\text{PEG-Cl}]_0 = 20 \text{ mM}$, $[[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]_0 = 0.5 \text{ mM}$, $[\text{P-TEG}]_0 = 4.0 \text{ mM}$; $[\text{MeDMA}]_0 = 1000 \text{ mM}$, $[\text{PEG-Cl}]_0 = 20 \text{ mM}$, $[[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]_0 = 0.5 \text{ mM}$, $[\text{P-TEG}]_0 = 4.0 \text{ mM}$.

Conclusions

In this chapter, the author newly designed a TEG-decorated phosphine ligand (**P-TEG**) for ruthenium-catalyzed living radical polymerization in water. The two-phosphine ligated complex $[\text{Cp}^*\text{RuCl}(\text{P-TEG})_2]$ showed high activity for aqueous controlled radical polymerization of PEGMA in conjunction with a chlorine-based initiator without any cocatalysts. The high activity allowed reduction in catalyst dose and controlled catalysis for HEMA polymerization even at low temperature as well as aqueous block copolymerizations of hydrophilic monomers. The author believe that the catalytic system with the **P-TEG** ligated ruthenium complex is highly suitable for precise preparation of water-soluble polymers further leading to development in terms material- and bio-applications.

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- (43) Indeed, measured value of M_n for PEG-Cl ($M_n = 2800$) was much lower than ideal, although it was calculated under PEG-based calibration. In such aqueous SEC, hydrophobic moieties in hydrophilic polymers likely affect elution behaviors even though they are minor components.

Chapter 2

Water-Soluble Ruthenium Catalyst with Polyethylene Glycol (PEG) for Highly Active Aqueous Living Radical Polymerization

Abstract

A hydrophilic phosphine ligand with poly(ethylene glycol) (PEG) pendant $\text{P}[p\text{C}_4\text{H}_4\text{O}(\text{CH}_2\text{CH}_2\text{O})_{12}\text{Me}]_3$ was designed for highly active ruthenium catalysis in aqueous living radical polymerization. Two equivalents of the designed ligand was heated with Cp^* -based ruthenium precursor $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$ in 1/2 ratio of precursor/ligand, and the resultant complex was utilized as a catalyst for aqueous polymerization without purification. The catalyst showed good water-solubility and allowed controlled polymerization of PEGMA in water: the monomer conversion reached over 90% in 1 h, and molecular weight distributions of the obtained polymer were narrow ($M_w/M_n = 1.14 - 1.16$). However, aqueous polymerization of HEMA was uncontrolled with the catalyst. To improve controllability, a polymeric trivalent ruthenium precursor $[(\text{Cp}^*\text{RuCl}_2)_n]$ was employed. As a result, controlled aqueous polymerization of HEMA was enabled: SEC and ^1H NMR analyses of the obtained polymer showed narrow molecular weight distributions ($M_w/M_n = 1.16 - 1.22$) and high end-functionality ($F_n = 0.94$). Furthermore, the catalyst showed sufficiently high activity to allow reducing the amount of catalyst to 1/100 molar ratio to the initiator.

Introduction

Environmental friendly solvents (“green” solvents) such as water, supercritical CO₂ and ionic liquids have recently attracted great attentions and have been actively developed in organic syntheses instead of flammable, toxic, and/or corrosive organic solvents.^{1,2} Among them, water has unique chemical and physical properties such as high polarity, surface tension, specific heat and latent heat as well as “green” properties such as nontoxicity, nonflammable, low cost, and abundance on earth. For these features, many organic reactions have been developed in water,^{3–8} and particularly free radical polymerization has been widely utilizing in water for industrial polymer syntheses.

On the other hand, transition metal catalyzed living radical polymerization (Mt-LRP or ATRP) has been developed as powerful and useful tool for precision polymer synthesis since first reported in 1995.^{9–16} Thus, aqueous Mt-LRP is promising for syntheses of water-soluble functional polymers and bio-applications as well as environmental friendly systems. However, a large amount of catalyst was required in aqueous Mt-LRP due to decomposition or deactivation of metal catalyst by water,^{17–20} and metal residue in the resultant polymer was a serious problem for various applications. Recently, several copper-catalyzed aqueous polymerizations have been reported with relatively water-stable copper(II) halides and reducing agents to decrease the amount of catalyst.^{21–27} By contrast, ruthenium-^{28,29} or iron-^{30,31} catalyzed aqueous LRPs have still been limited, though ruthenium-catalyzed systems showed advantage as mentioned below.

The author have recently found that triethylene glycol (TEG)-substituted triphenylphosphine-based ligand [PPh₂(pC₄H₄OTEG): **P-TEG**] has great activity for ruthenium catalyzed aqueous living radical polymerization of PEGMA in conjunction with Cp*-based ruthenium precursor [Cp*Ru(μ₃-Cl)]₄.²⁹ Note that the ruthenium catalyst allowed aqueous polymerization control with a tiny amount of catalyst without any additives though a large amount of catalyst or some additives such as reducing agents were necessary in copper-based systems. However, the **P-TEG** ligand is not hydrophilic sufficient to solubilize the ruthenium catalyst in pure water, although homogeneous polymerization was achieved in water thanks to PEGMA acted as co-solvent. Therefore, in this chapter, a more water-soluble nonionic phosphine ligand with polyethylene glycol (PEG) pendant [P(pC₄H₄OPEG)₃: **P-PEG**] was designed to improve water-solubility and catalytic activity in water. The **P-PEG** was combined with Cp*Ru precursors to form catalysts, and the resultant catalyst employed for aqueous polymerization of water-soluble monomers.

Experimental

Materials

PEGMA [$\text{CH}_2\text{C}(\text{CH}_3)\text{COO}(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_3$; $n = 8.5$ (number-average)] (Aldrich) and 2-hydroxyethyl methacrylate (HEMA) (Aldrich; > 99%) were purified by passing through an inhibitor-removal column (Aldrich) and were subsequently degassed by three-time vacuum-argon bubbling cycles before use. **P-PEG**,³² **P-TEG**,²⁹ a ruthenium tetramer precursor $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$ ^{33,34} and H-(MMA)₂-Cl³⁵ initiator $[\text{H}(\text{CH}_2\text{CMeCO}_2\text{Me})_2\text{Cl}]$ were prepared according to the literature. Dichloro(pentamethylcyclopentadienyl)ruthenium(III) polymer $[(\text{Cp}^*\text{RuCl}_2)_n]$ (Aldrich) and materials for preparation of $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$, listed below were used as received without further purification and handled in a glovebox (MBraun Labmaster 130, M. Braun Inertgas-Systeme GmbH, Garching, Germany) under a moisture- and oxygen-free argon atmosphere ($\text{H}_2\text{O} < 1$ ppm; $\text{O}_2 < 1$ ppm): ruthenium(III) chloride hydrate (Wako; > 99.9%); 1,2,3,4,5-pentamethylcyclopentadiene (TCI; > 93%); and lithium triethylhydridoborate (Aldrich, 1.0 M solution in THF). Toluene (Kishida Kagaku; purity 99.5%) was dried and purified by passing through purification columns (Solvent Dispensing System, SG Water USA, Nashua, NH; Glass Contour) and bubbled with dry nitrogen for more than 15 min immediately before use. Water (Wako; distilled), ethanol (Wako; super dehydrated) and THF (Wako; super dehydrated) were bubbled with dry nitrogen for more than 15 min immediately before use. MeDMA (methyl chloride-quaternized 2-(dimethylamino)ethyl methacrylate) (Wako; >97.0%), Poly(ethylene glycol) monomethyl ether $[\text{HO}(\text{CH}_2\text{CH}_2\text{O})_n\text{Me}$; $n = 12$ on average] (Aldrich), *p*-toluenesulfonyl chloride (Aldrich; > 99%), pyridine (Wako; dehydrated), H_2O_2 (TCI; 35% in water), BBr_3 (TCI; *ca.* 1 M in CH_2Cl_2), phenylsilane (TCI; > 97%), NaOH (Wako; > 97%), HCl (Wako; 35-37% in water), Na_2SO_4 (Wako; > 99%), K_2CO_3 (Wako; > 99.5%), NaCl (Wako; > 99.5%), CH_2Cl_2 (Wako; super dehydrated), DMF (Wako; super dehydrated), acetone (Wako; super dehydrated), hexane (Wako; > 96.0%), ethyl acetate (Wako; > 99.5%), silica gel (Wako; Wakogel® C-200) are used as received.

Polymerization Procedures

Polymerization was carried out by the syringe technique under dry argon in baked glass tubes equipped with a three-way stopcock or in sealed glass vials. An example for polymerization of PEGMA with H-MMA₂-Cl/ $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$ /**P-PEG** in water is given below. $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$ (2.2 mg, 0.0020 mmol), 100 mM **P-PEG** in toluene (0.16 mL, 0.016

mmol), and toluene (1.0 mL) was placed in a Schlenk tube. The solution was heated to 60 °C for 12 h to prepare ruthenium complex. After cooling the mixture to room temperature and removal of solvent under vacuum, PEGMA (0.88 mL, 2.0 mmol), H₂O (3.02 mL) and 200 mM H-MMA₂-Cl in ethanol (0.10 mL, 0.020 mmol) were added; the total volume was 4.0 mL. Immediately after mixing, aliquots (0.50–1.0 mL each) of the solution were injected into baked glass tubes, which were then sealed (except when a stopcock was used) and placed in an oil bath kept at 40 °C. In predetermined intervals, the polymerization was terminated by cooling the reaction mixture to –78 °C in dry ice-methanol. Monomer conversion was determined by ¹H NMR from the integrated peak area of the olefinic protons of the monomer with ethanol as an internal standard is given below.

For polymerization of HEMA with (Cp*RuCl₂)_n precursor, (Cp*RuCl₂)_n (2.5 mg, 8.0/*n* μmol) and 40 mM **P-PEG** in EtOH (0.4 mL, 16 μmol) were stirred overnight in a Schlenk tube at room temperature, and then HEMA (0.97 mL, 8.0 mmol), H₂O (2.47 mL) and 500 mM H-MMA₂-Cl in ethanol (0.16 mL, 0.080 mmol) were added to the solution; the total volume was 4.0 mL. After that, the same procedures as with [Cp*Ru(μ₃-Cl)]₄ precursor were applied.

Measurements

For poly(PEGMA) or poly(HEMA), *M_n* and *M_w/M_n* were measured by size exclusion chromatography at 40 °C in DMF containing 10 mM LiBr as an eluent on three polystyrene-gel columns (Shodex KF-805 L; exclusion limit = 4 × 10⁶; particle size = 10 μm; pore size = 5000 Å; 0.8 cm i.d. × 30 cm; flow rate, 1.0 mL min^{–1}) connected to a PU-2080 pump and a RI-1530 refractive-index detector, and a UV-1570 ultraviolet detector (all from Jasco). The columns were calibrated against 13 standard poly(MMA) samples (Polymer Laboratories; *M_n* = 630–1 200 000; *M_w/M_n* = 1.02–1.30). ¹H NMR and ³¹P NMR spectra were measured at room temperature on a JEOL JNM-ECA500 spectrometer operating at 500.16 and 202.47 MHz, respectively. For the ³¹P NMR analyses, a capillary of diethyl phosphite solution (50 mM in toluene-*d*₈) was used as an internal chemical shift standard (7.08 ppm for the phosphite).

Results and Discussion

1 ^{31}P NMR Analyses for Coordination Behavior of P-PEG to $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$

The phosphine ligand with PEG chains on the three *para* position of triphenylphosphine (**P-PEG**) was combined with a tetrameric Cp^* ruthenium precursor $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$ in toluene at $60\text{ }^\circ\text{C}$ to form a **P-PEG**-coordinated ruthenium complex (Figure 1). To investigate the complex structure, they were mixed in two different ratios, 1/1 or 1/2 of $[\text{Ru}]_0$ to $[\text{P-PEG}]_0$, and the resultant solutions were analyzed by ^{31}P NMR in D_2O after evaporation of toluene. For 1/1 ratio, a peak derived from free **P-PEG** (*a*: -11 ppm) completely disappeared, and a new peak likely from a coordinating phosphine (*b*: 35 ppm) was observed. For 1/2 ratio, the peak of free **P-PEG** also disappeared, and a new peak (*c*: 37 ppm) appeared

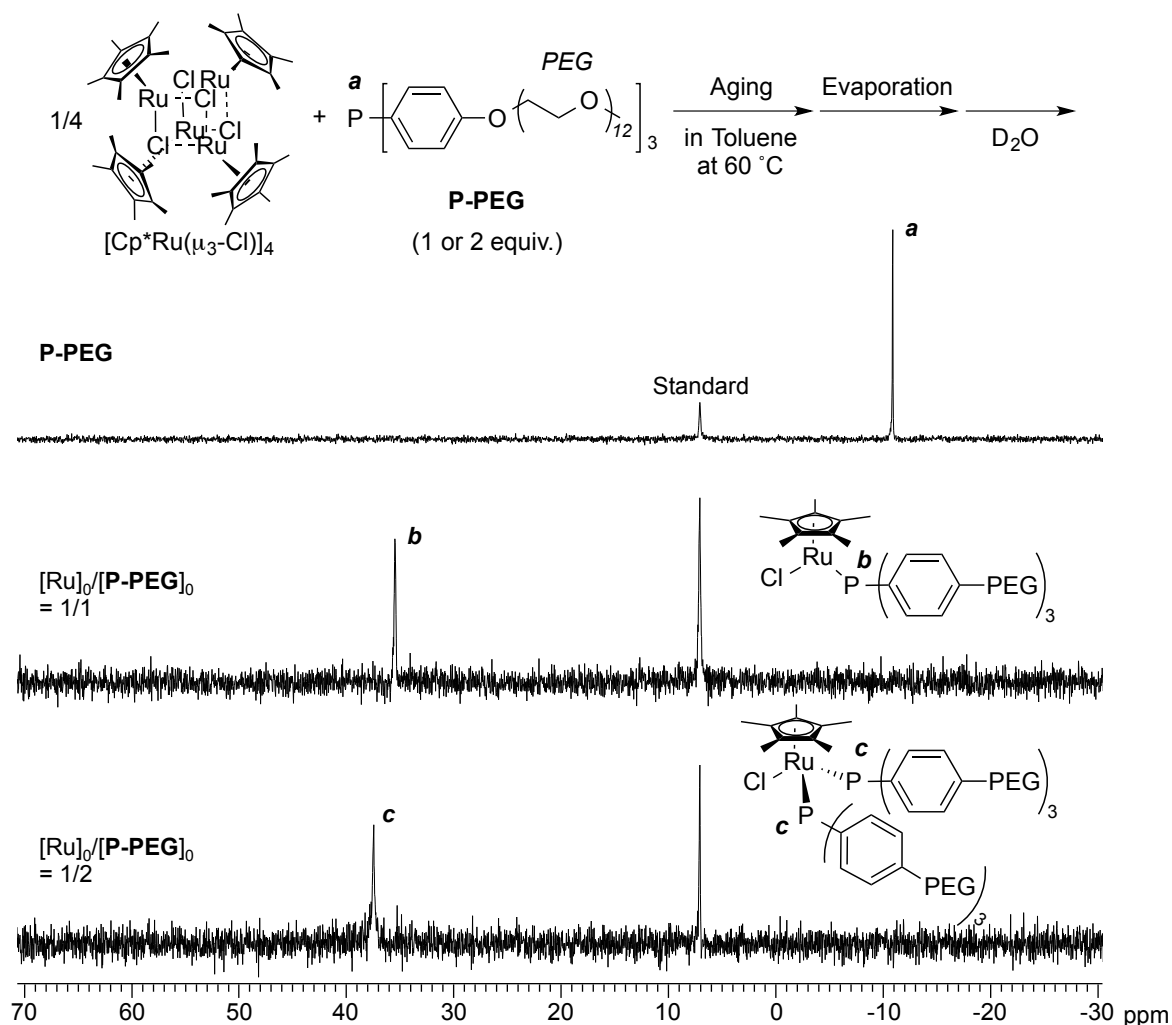


Figure 1. Coordination scheme and ^{31}P NMR spectra of **P-PEG** and complexes prepared with 1:1 or 1:2 ratio ($[\text{Ru}]_0$: $[\text{P-PEG}]_0$) in D_2O at r.t.: $[\text{P-PEG}]_0 = 8.0\text{ mM}$; $[[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]]_0 = 1.0\text{ mM}$, $[\text{P-PEG}]_0 = 4.0\text{ mM}$; $[[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]]_0 = 1.0\text{ mM}$, $[\text{P-PEG}]_0 = 8.0\text{ mM}$.

in a little lower magnetic field than **b**. These results indicated the one **P-PEG** coordinating ruthenium complex $[\text{Cp}^*\text{RuCl}(\text{P-PEG})]$ was obtained in the 1/1 mixing ratio, and the two **P-PEG** coordinating complex $[\text{Cp}^*\text{RuCl}(\text{P-PEG})_2]$ was obtained in the 1/2 ratio. In the following polymerizations, the ruthenium complex prepared in the 1/2 ratio of Ru to **P-PEG** was utilized as a catalyst without further purification.

2 Improvement of Water-Solubility by PEGylation

As mentioned above, Cp^* ruthenium bis-phosphine complexes $[\text{Cp}^*\text{RuCl}(\text{P-TEG})_2]$, $[\text{Cp}^*\text{RuCl}(\text{P-PEG})_2]$ were synthesized with $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$ and two equivalents of ligands. The resultant solutions were evaporated under vacuum to remove toluene, and then water was added to test the water-solubility of ruthenium complexes (Figure 2). As a result, $\text{Cp}^*\text{RuCl}(\text{P-TEG})_2$ was almost no soluble in water as shown in the left picture. By contrast, $\text{Cp}^*\text{RuCl}(\text{P-PEG})_2$ showed good water-solubility probably due to PEG pendants. The high water-solubility most likely contributes to effective catalysis in aqueous living radical polymerization.

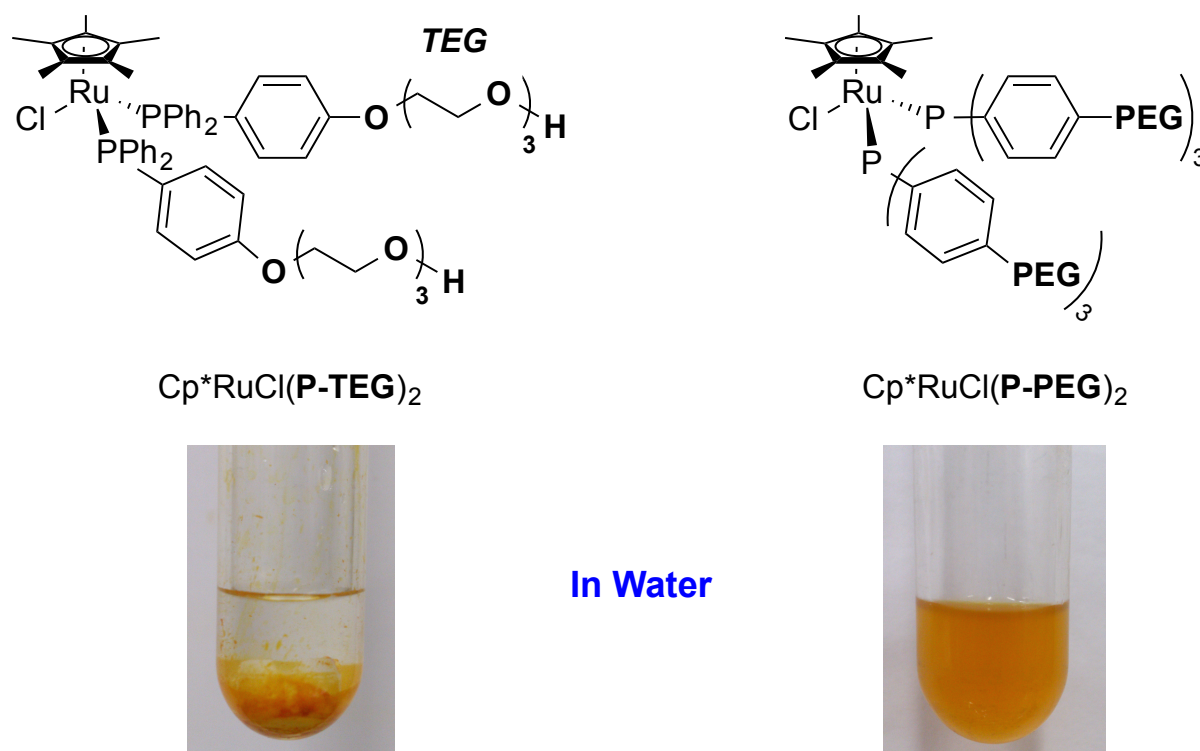


Figure 2. Water-solubility test of ruthenium complexes with **P-TEG** (left) or **P-PEG** (right): $[[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]_0 = 0.5 \text{ mM}$, $[\text{ligand}]_0 = 4.0 \text{ mM}$ in water.

3 Aqueous Living Radical Polymerization with $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$ and P-PEG

The ruthenium catalyst *in situ* synthesized from $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$ and **P-PEG** was employed for aqueous polymerization of PEGMA in water at 40 °C without any co-catalysts, in conjunction with a chlorine type initiator $[\text{H}-(\text{MMA})_2\text{-Cl}]$ (Figure 3). The polymerization was extremely fast: the monomer conversion reached over 90% in 1 hour even at such a mild condition. In spite of the fast polymerization, the obtained polymer was fairly controlled: in SEC analyses, the molecular weight increased along with the monomer conversion while keeping monomodal curve, and the molecular weight distributions (MWDs) were really narrow ($M_w/M_n = 1.14\text{--}1.16$). In contrast, aqueous polymerization of HEMA with the same catalyst obtained uncontrolled polymers ($M_w/M_n > 4.0$; bimodal peaks). As shown in SEC curves, very high molecular weight polymer ($M > 10^5$) was generated in the initial stage, and the peak top of the lower molecular weight polymer ($M \sim 10^4$) shifted along with conversion. These results indicated uncontrolled polymerization occurred only in the initial stage due to high instant concentration of active radical species.

4 Enhancement of Controllability in Aqueous Polymerization by Another Ruthenium Precursor: $(\text{Cp}^*\text{RuCl}_2)_n$

To prevent uncontrolled polymerization, another trivalent ruthenium [Ru(III)] precursor $[(\text{Cp}^*\text{RuCl}_2)_n]$ was employed for aqueous living radical polymerization. The $[(\text{Cp}^*\text{RuCl}_2)_n]$

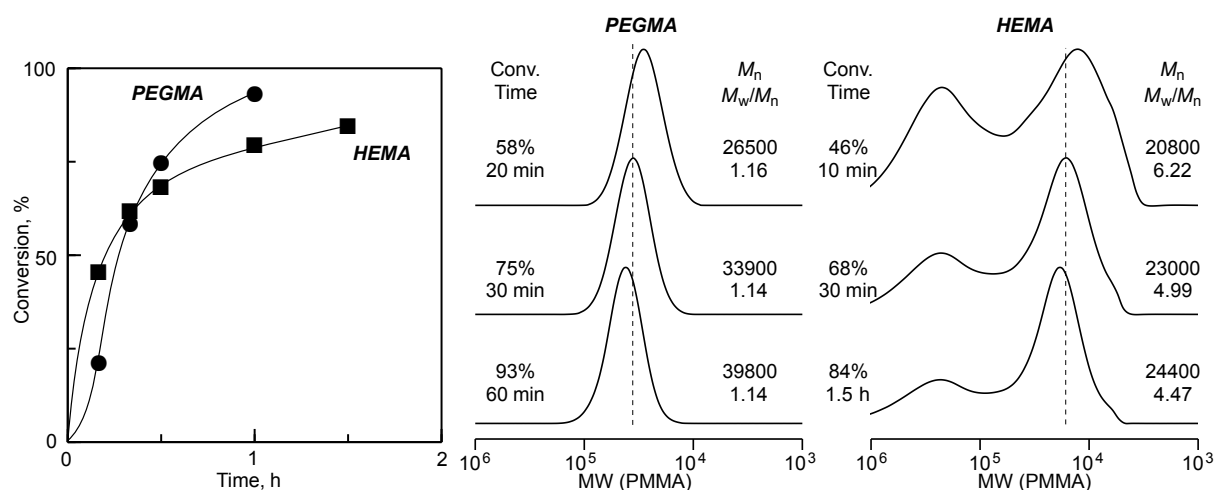


Figure 3. Aqueous polymerization of PEGMA with $\text{Ru(II)}:[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$ and **P-PEG** in H_2O at 40 °C: $[\text{PEGMA}]_0 = 500 \text{ mM}$, $[\text{H}-(\text{MMA})_2\text{-Cl}]_0 = 20 \text{ mM}$, $[[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4]_0 = 0.5 \text{ mM}$, $[\text{P-PEG}]_0 = 4.0 \text{ mM}$; $[\text{HEMA}]_0 = 2000 \text{ mM}$, $[\text{H}-(\text{MMA})_2\text{-Cl}]_0 = 20 \text{ mM}$, $[[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4]_0 = 0.5 \text{ mM}$, $[\text{P-PEG}]_0 = 4.0 \text{ mM}$.

is well known and often used as a precursor to synthesize phosphine-ligated Cp* ruthenium complexes: bis-phosphine divalent ruthenium complex $[\text{Cp}^*\text{RuCl}(\text{phosphine})_2]$ and mono-phosphine trivalent complex $[\text{Cp}^*\text{RuCl}_2(\text{phosphine})]$ can be obtained from the precursor: $[\text{Cp}^*\text{RuCl}(\text{phosphine})_2]$ is mainly obtained by mixing the precursor with 2 equivalents of phosphine in ethanol, and $[\text{Cp}^*\text{RuCl}_2(\text{phosphine})]$ is obtained by mixing with 1 equivalent of phosphine.^{36,37}

Now the Ru(III) precursor and 2 equivalents of **P-PEG** is stirred overnight in ethanol at room temperature, and the resultant solution utilized for aqueous polymerization without purification. The ruthenium/**P-PEG** solution probably contain the deactivator $[\text{Cp}^*\text{RuCl}_2(\text{P-PEG})]$ as well as the activator $[\text{Cp}^*\text{RuCl}(\text{P-PEG})_2]$. Therefore, enhancement of controllability in aqueous polymerization is expected due to lower instant concentration of radicals in the initial stage.

Thus, the catalyst prepared with $(\text{Cp}^*\text{RuCl}_2)_n$ and **P-PEG** was utilized for aqueous polymerization of HEMA in water at 40 °C with H-(MMA)₂-Cl initiator without any co-catalyst (Figure 4). The obtained polymer was much more controlled ($M_w/M_n = 1.16\text{--}1.22$) than that with Ru(II) precursor, though the polymerization became slower (Conv. 91% in 12 h). In the similar condition, aqueous polymerization of PEGMA also achieved with $(\text{Cp}^*\text{RuCl}_2)_n$ and **P-PEG** (Figure 5): the conversion reached over 97% in 3 hours, and

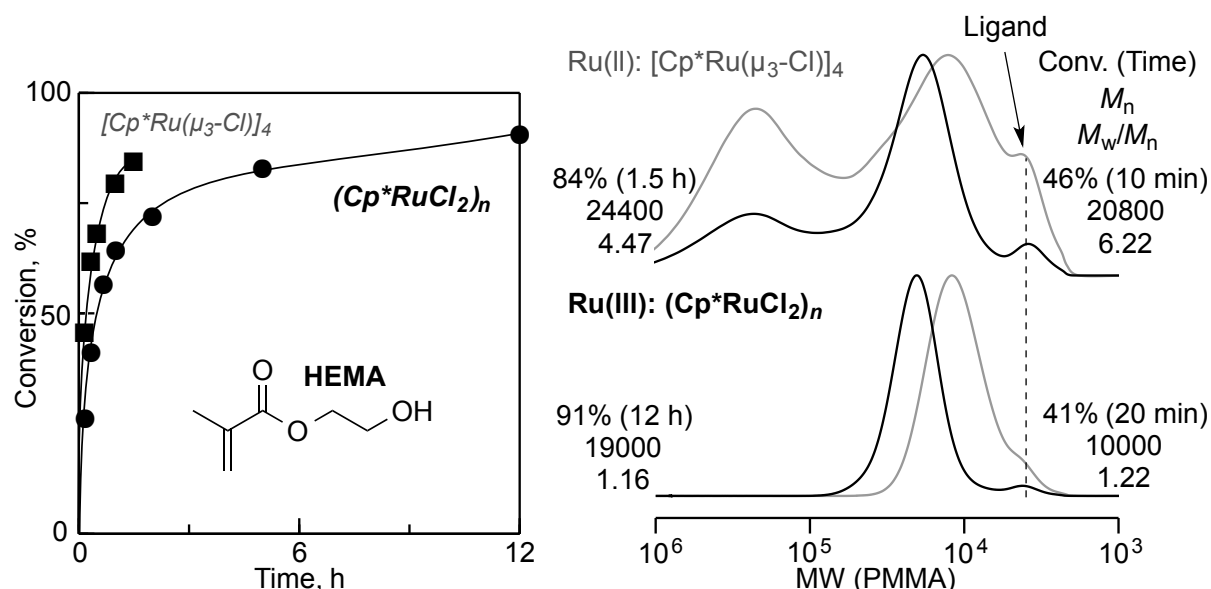


Figure 4. Effect of the precursor, Ru(II): $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$ or Ru(III): $(\text{Cp}^*\text{RuCl}_2)_n$, in aqueous polymerization of HEMA at 40 °C: $[\text{HEMA}]_0 = 2000 \text{ mM}$; $[\text{H}-(\text{MMA})_2\text{-Cl}]_0 = 20 \text{ mM}$; $[[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4]_0 = 0.5 \text{ mM}$ or $[(\text{Cp}^*\text{RuCl}_2)_n] = 2.0/n \text{ mM}$; $[\text{P-PEG}]_0 = 4.0 \text{ mM}$.

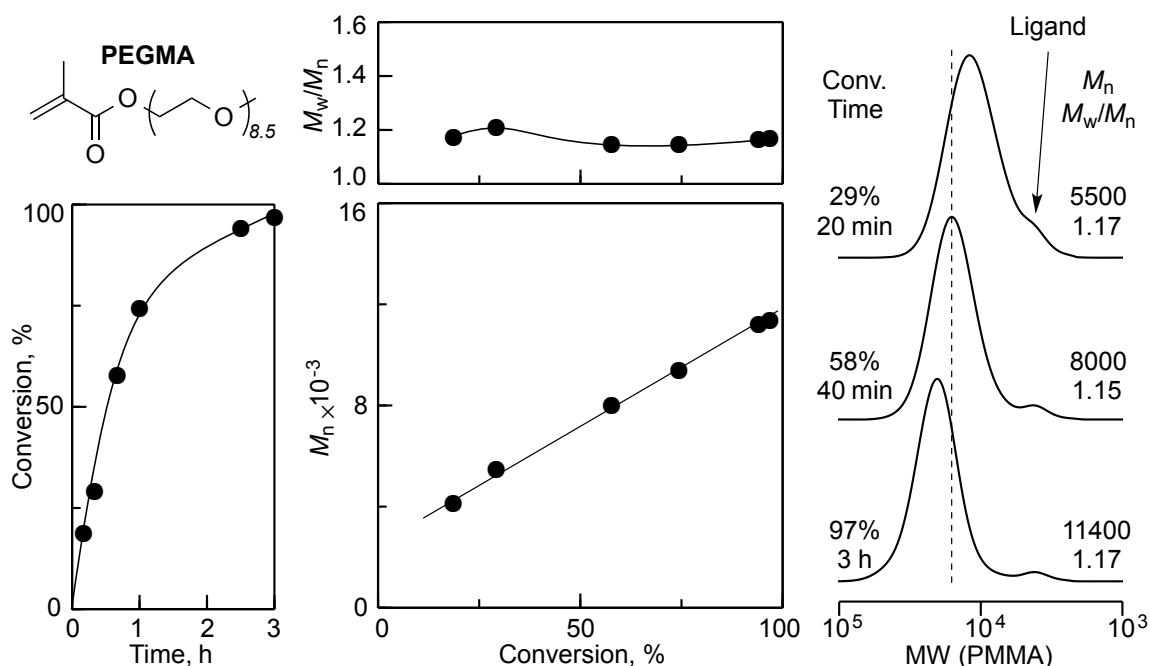


Figure 5. Polymerization of PEGMA in H₂O at 40 °C with (Cp**RuCl*₂)_{*n*}: [PEGMA]₀ = 500 mM; [H-(MMA)₂-Cl]₀ = 20 mM; [(Cp**RuCl*₂)_{*n*}] = 2.0/*n* mM; [P-PEG]₀ = 4.0 mM.

molecular weight distribution of the obtained polymer was really narrow ($M_w/M_n = 1.15-1.17$).

Note that no co-catalyst employed in this aqueous system, whereas aluminum isopropoxide was needed for polymerization in organic solvent with $(\text{Cp}^*\text{RuCl}_2)_n$ and phosphine ligand.^{38,39}

5 ¹H NMR Analysis of Poly(HEMA) Prepared with (Cp*RuCl₂)_n and P-PEG

To study the polymer structure, the author investigated ^1H NMR analysis of the obtained polymer in aqueous polymerization with $(\text{Cp}^*\text{RuCl}_2)_n$ and **P-PEG** [Conversion = 39% in 20 min., $M_n(\text{conv}) = 5300$]: $[\text{HEMA}]_0 = 2.0 \text{ M}$; $[\text{ECPA}]_0 = 20 \text{ mM}$; $[(\text{Cp}^*\text{RuCl}_2)_n]_0 = 2.0 \text{ mM}$; $[\text{P-PEG}]_0 = 4.0 \text{ mM}$ in H_2O at 40°C . As shown in the spectrum (Figure 6), small peaks corresponding to terminal structure (**a** – **c**, **f'**) were observed in addition to the main-chain peaks (**d** – **h**): **a** – **c** derived from α -end and **f'** derived from ω -end. Molecular weight of the polymer [$M_n(\text{NMR})$] was calculated from the integral ratio of the signals, and functionality of the polymer (F_n) was estimated from the ratio of $M_n(\text{conv})$ to $M_n(\text{NMR})$: $M_n(\text{conv}) = 5300$, $M_n(\text{NMR}) = 5600$, $F_n = 0.94$. This high functionality value indicated the almost all polymer chains generated from the initiator and capped by chlorine, though few unfavorable terminals were obtained by side-reactions such as disproportionation and coupling.

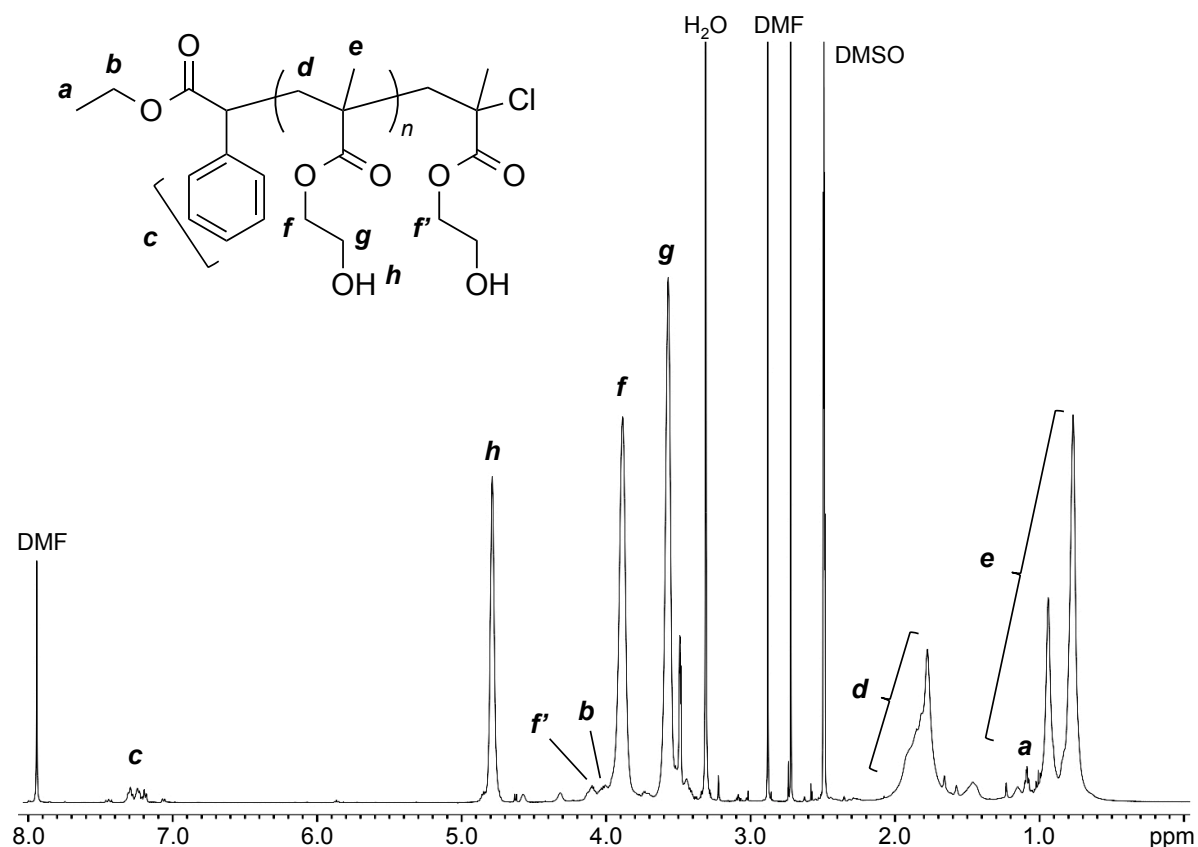


Figure 6. ¹H NMR spectrum (500 MHz) of polyHEMA obtained by aqueous living radical polymerization with Ru(III)/**P-PEG**: 2 wt% in DMSO-*d*₆ at r.t..

6 Reducing the Amount of Catalyst

Reducing the amount of catalyst is a simple but feasible approach for reducing metal residue in the resultant polymer, which is one of the most crucial problems for practical application with hydrophilic polymers. However, as mentioned above, aqueous polymerization catalyst is difficult to control with a small amount of catalyst due to deactivation of catalyst by water. The highly active catalysis of the (Cp*RuCl₂)_{*n*}/**P-PEG** encouraged the author to reduce the amount of catalyst in aqueous polymerization of PEGMA in pure water at 40 °C (Table 1). The amount of catalyst was decreased from [Ru]₀ = 2.0 mM (same condition as above polymerization) to 1.0–0.1 mM with [PEGMA]₀/[H-(MMA)₂-Cl] = 500/20 mM. For 0.2 mM, the molecular weight distributions (MWDs) were still relatively narrow (*M*_w/*M*_n ~ 1.4) even at such a small amount of catalyst. This result showed the (Cp*RuCl₂)_{*n*}/**P-PEG** system had great catalytic activity and potential for wide application. Unfortunately, in the case of 0.1 mM catalyst, the MWDs were broader (*M*_w/*M*_n > 1.8), and the molecular weight was not increased with conversion in SEC analyses.

Table 1. Reducing the Amount of Catalyst on Aqueous Polymerization with (Cp*RuCl₂)_n and P-PEG^a

Entry	[Ru] ₀ (mM)	[Ru] ₀ : [Initiator] ₀	Time (h)	Conv. (%)	<i>M</i> _n ^b	<i>M</i> _w / <i>M</i> _n ^b
1	2.0	1:10	0.33	29	5500	1.17
2			3	97	12400	1.10
3			1	26	5900	1.19
4	1.0	1:20	5	54	8200	1.19
5			2	28	6800	1.36
6			2	64	10400	1.44
7	0.4	1:50	24	72	11100	1.39
8			2	66	14800	1.84
9			24	76	14800	1.81

^a[PEGMA]₀ = 500 mM; [H-(MMA)₂-Cl]₀ = 20 mM; [Ru]₀/[P-PEG]₀ = 1/2 in water at 40 °C.^bBy size-exclusion chromatography calibrated with PMMA standards.

Conclusion

A water-soluble phosphine ligand with three PEG pendants (**P-PEG**) was employed for high water-solubility and active catalysis in aqueous living radical polymerization. Two ruthenium precursors, Ru(II): [Cp*Ru(μ₃-Cl)]₄ and Ru(III): (Cp*RuCl₂)_n, were utilized with **P-PEG** to synthesize Cp*-based ruthenium complexes, and both complexes showed good water-solubility and high catalytic activity in water. The Ru(II)/**P-PEG** catalyst allowed fast and controlled aqueous polymerization of PEGMA (Conv. 93% in 1 h, *M*_w/*M*_n = 1.14-1.16); however, polymerization of HEMA was not controlled (*M*_w/*M*_n > 4). In contrast, the Ru(III)/**P-PEG** catalyst enabled controlled aqueous polymerization of HEMA (*M*_w/*M*_n = 1.16–1.22) as well as PEGMA, due to suppression of uncontrolled reaction in the initial stage by keeping low concentration of radicals. The high catalytic activity allowed reducing the amount of catalyst to very low concentration (0.2 mM). The author strongly believe the high activity and versatility of the Ru(III)/**P-PEG** catalyst is useful for water-soluble polymer synthesis toward wide applications such as bio-conjugation.

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Chapter 3

Guanidine-Embedded Phosphine Ligands for Active Metal-Catalyzed Living Radical Polymerization in Water

Abstract

A guanidine-embedded phosphine $\text{Ph}_2\text{PCH}_2\text{CH}_2\text{NHC}(\text{NH}_2)_2\text{Cl}$ (**PG+**) was synthesized as a hydrophilic ligand for metal-catalyzed polymerization in water. The **PG+** was mixed with a pentamethylcyclopentadienyl (Cp^*) based ruthenium (II) precursor $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$ to form a water-soluble ruthenium complex, and the resultant complex showed high catalytic activity for living radical polymerization of hydrophilic monomers (e.g., PEGMA and HEMA) in water as well as for that of hydrophobic counterparts (e.g., MMA, MA, and St) in toluene/ethanol. The controllability for aqueous polymerization with the ligand was further improved by using ruthenium (III) precursor $[(\text{Cp}^*\text{RuCl}_2)_n]$ instead of $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$ to give very narrow MWDs ($M_w/M_n = 1.1\text{--}1.2$), and indeed living polymerization of an ammonium chloride pendent methacrylate monomer (MeDMA) in water was realized, though the original system resulted in poor control. The high catalytic activity allowed balance of reduction in catalyst dose with polymerization control ($M_w/M_n = 1.36$ with 1/200 amount of catalyst for the polymer chain).

Introduction

Water is most important liquid for human and shows some unique properties relative to organic counterparts, such as non-toxicity, non-flammability, high polarity, high specific heat, high latent heat, and, needless to say, low cost due to abundance on earth. Owing to these properties, water has attracted great attentions as a *green* solvent from the viewpoint of sustainable and environmentally benign chemistry.¹⁻⁴ Unfortunately, however, water molecules often disturb organic reactions because of unfavorable side-reactions or deactivations with intermediates and/or catalysts. On the other hand, radical reaction or polymerization can be done even in water because radical species is neutral and thus survive in water, and actually most of industrial processes with radical polymerization are performed with water solvent (i.e., dispersed and emulsion).

Living (controlled) radical polymerization (LRP) has attracted attentions as a polymerization tool to produce well-defined polymers and actually some practical applications has been performed by LRP.⁵ Especially, transition metal-catalyzed living radical polymerization (Mt-LRP⁶⁻⁹ or ATRP¹⁰⁻¹³) has been widely used in various fields because of high usability and ease of initiator design. However, Mt-LRP has disadvantage of condition limitation relative to other LRP systems such as RAFT,^{14,15} because metal catalyst sometimes suffer from deactivation by polar groups. Thus, polymerization control in water is not so straightforward. So far, though some examples have been reported with copper,¹⁶⁻²⁹ iron,³⁰⁻³² and ruthenium.^{33,34} The author have recently found that triphenylphosphine carrying poly(ethylene glycol) [P(*p*-C₄H₄-PEG)₃] is useful as a hydrophilic ligand for ruthenium-catalyzed LRP in water. The resultant ruthenium complex showed high catalytic activity as well as high water-solubility and allowed polymerization control with a tiny amount of ruthenium without any co-catalysts. However, use of the PEG pendent complex is unfavorable for SEC analyses of obtained polymers, because the SEC curve is sometimes overlapped with those of obtained polymers.

In this paper, we designed a new hydrophilic phosphine ligand with guanidinium salt substituent (**PG+**) to prepare hydrophilic ruthenium catalyst independent of macromolecular ligand. The guanidino group is contained in one of natural amino acids (i.e., arginine) and the residue exists as the guanidinium cation in our body. Guanidinium salt is highly soluble and stable in neutral water owing to resonance stabilization, and well known and often used as denaturant of proteins. Furthermore, the hydrophilicity of guanidinium could be switched to hydrophobicity by pH, which inspires possibility that obtained hydrophilic polymer can be

separated from metal residue. These features encouraged us to design guanidinium salt-based ligand and the catalyst for aqueous living radical polymerization.

Experimental

Materials

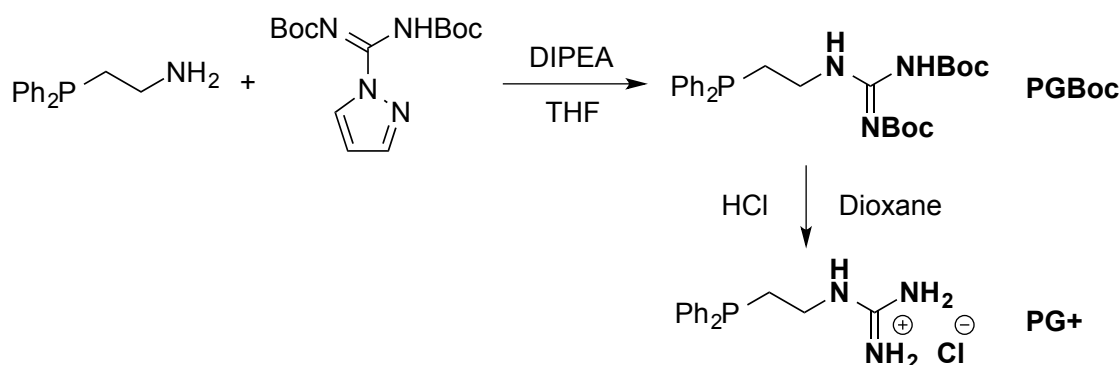
PEGMA [$\text{CH}_2\text{C}(\text{CH}_3)\text{COO}(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_3$; $n = 8.5$ (number-average)] (Aldrich) and HEMA (2-hydroxyethyl methacrylate) (Aldrich; > 99%) were purified by passing through an inhibitor-removal column (Aldrich) and were subsequently degassed by three-time vacuum-argon bubbling cycles before use. MMA (methyl methacrylate), MA (methyl acrylate) and St (styrene) [all from Tokyo Kasei (TCI); > 99%] were dried overnight over calcium chloride, and distilled from calcium hydride under reduced pressure before use. The ECPA (ethyl α -chlorophenylacetate) was purified by distillation under reduced pressure before use. The ruthenium tetramer precursor $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$ ^{35,36} and H-(MMA)₂-Cl³⁷ initiator $[\text{H}(\text{CH}_2\text{CMeCO}_2\text{Me})_2\text{Cl}]$; an MMA dimer chloride] were prepared according to the literature. Materials for preparation of $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$, listed below, and dichloro(pentamethylcyclopentadienyl)ruthenium(III) polymer $[(\text{Cp}^*\text{RuCl}_2)_n]$ (Aldrich) were used as received without further purification and handled in a glovebox (MBraun Labmaster 130, M. Braun Inertgas-Systeme GmbH, Garching, Germany) under a moisture- and oxygen-free argon atmosphere ($\text{H}_2\text{O} < 1$ ppm; $\text{O}_2 < 1$ ppm): ruthenium(III) chloride hydrate (Wako; > 99.9%); 1,2,3,4,5-pentamethylcyclopentadiene (TCI; > 93%); and lithium triethylhydridoborate (Aldrich, 1.0 M solution in THF). Toluene (Kishida Kagaku; purity 99.5%) was dried and purified by passing through purification columns (Solvent Dispensing System, SG Water USA, Nashua, NH; Glass Contour) and bubbled with dry nitrogen for more than 15 min immediately before use. Water (Wako; distilled), ethanol (Wako; super dehydrated) and THF (Wako; super dehydrated) were bubbled with dry nitrogen for more than 15 min immediately before use. 1,2,3,4-tetrahydronaphthalene (tetralin; internal standard for ¹H NMR) was dried over calcium chloride and distilled from calcium hydride. MeDMA (methyl chloride-quaternized 2-(dimethylamino)ethyl methacrylate) (Wako; >97.0%), *N,N'*-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine (TCI; >98.0%), *N*-ethyldiisopropylamine (Wako; >97.0%), 2-(diphenylphosphino)ethylamine (Aldrich; >95.0%), hydrogen chloride (*ca.* 4mol/L in 1,4-Dioxane) (TCI), hexane (Wako; > 96.0%), ethyl acetate (Wako; > 99.5%), silica gel (Wako; Wakogel® C-200) were used as received.

Ligand Synthesis (Scheme 1)*Synthesis of PGBoc*

To a solution of *N,N'*-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine (1.49 g, 4.80 mmol) and *N*-ethyldiisopropylamine (4.15 g, 32.1 mmol) in THF (100 mL), 2-(diphenylphosphino)ethylamine (1.00 g, 4.36 mmol) was added dropwise under argon. After stirring overnight at room temperature, the solvent was evaporated under vacuum. **PGBoc** was isolated by silica gel column chromatography using hexane/ethyl acetate (90/10) as an eluent in 67% yield (1.37 g). ¹H NMR (500 MHz, chloroform-*d*): δ 11.42 (s, 1H), 8.54 (br, 1H), 7.49–7.42 (m, 4H), 7.36–7.29 (m, 6H), 3.60 (br, 2H), 2.38 (t, 2H), 1.51 (s, 9H), 1.49 (s, 9H). ³¹P NMR (202 MHz, chloroform-*d*): δ -20.9.

Synthesis of PG+

PGBoc (1.37 g, 2.90 mmol) was added to a 4.0 M hydrogen chloride solution in 1,4-dioxane (24 mL). After stirring overnight at room temperature, **PG+** was isolated by evaporation under vacuum in quantitative yield. ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.46–7.34 (m, 10H), 3.25–3.14 (m, 2H), 2.33 (t, 2H). ³¹P NMR (202 MHz, methanol-*d*₄): δ -20.3.



Scheme 1. Synthesis Scheme of **PG+**

Polymerization Procedures

Polymerization was carried out by the syringe technique under dry argon in baked glass tubes equipped with a three-way stopcock or in sealed glass vials. An example for polymerization of PEGMA with the H-MMA₂-Cl/[Cp**Ru*(μ₃-Cl)]₄/**PG+** in water is given below. [Cp**Ru*(μ₃-Cl)]₄ (2.2 mg, 0.0020 mmol), 100 mM **PG+** in ethanol (0.16 mL, 0.016 mmol), and toluene (1.44 mL) were placed in a Schlenk tube. The solution was heated to 60 °C for 2 h to prepare ruthenium complex. After cooling the mixture to room temperature and removal of solvent under vacuum, PEGMA (0.88 mL, 2.0 mmol), H₂O (3.02 mL) and 200 mM H-MMA₂-Cl in ethanol (0.10 mL, 0.020 mmol) were added; the total volume was

4.0 mL. Immediately after mixing, aliquots (0.50–1.0 mL each) of the solution were injected into baked glass tubes, which were then sealed (except when a stopcock was used) and placed in an oil bath kept at 40 °C. In predetermined intervals, the polymerization was terminated by cooling the reaction mixture to –78 °C in dry ice/methanol. Monomer conversion was determined by ¹H NMR from the integrated peak area of the olefinic protons of the monomer with ethanol as an internal standard. For MMA, St and MA, the same procedures as described above were applied, except that monomer conversion was determined from residual monomer concentration measured by gas chromatography with *n*-octane as an internal standard. Another example for aqueous polymerization of HEMA with (Cp*RuCl₂)_n, (Cp*RuCl₂)_n (2.5 mg, 8.0/*n* μmol), **PG+** (4.9 mg, 16 μmol) and ethanol (0.4 mL, 16 μmol) were placed in a Schlenk tube. The solution was stirred overnight at room temperature, and then HEMA (0.97 mL, 8.0 mmol), H₂O (2.47 mL) and 500 mM H-MMA₂-Cl in ethanol (0.16 mL, 0.080 mmol) were added to the solution; the total volume was 4.0 mL. After that, the same procedures as with [Cp*Ru(μ₃-Cl)]₄ precursor were applied.

Measurement

For poly(MMA), poly(St) and poly(MA), M_n and M_w/M_n were measured by size exclusion chromatography at 40 °C in THF as an eluent on three polystyrene-gel columns (Shodex LF-404; exclusion limit = 2×10^6 ; particle size = 6 μm; pore size = 3000 Å; 0.46 cm i.d. $\times$ 25 cm; flow rate, 0.3 mL min⁻¹) connected to a DU-H2000 pump, a RI-74 refractive-index detector, and a UV-41 ultraviolet detector (all from Shodex). The columns were calibrated against 13 standard poly(MMA) samples (Polymer Laboratories; M_n = 630–1 200 000; M_w/M_n = 1.02–1.30) or 13 standard poly(St) samples (Polymer Laboratories; M_n = 500–3 840 000; M_w/M_n = 1.01–1.14). For poly(PEGMA) or poly(HEMA), M_n and M_w/M_n were measured by size exclusion chromatography at 40 °C in DMF containing 10 mM LiBr as an eluent on three polystyrene-gel columns (Shodex KF-805 L; exclusion limit = 4×10^6 ; particle size = 10 μm; pore size = 5000 Å; 0.8 cm i.d. $\times$ 30 cm; flow rate, 1.0 mL min⁻¹) connected to a PU-2080 pump and a RI-1530 refractive-index detector, and a UV-1570 ultraviolet detector (all from Jasco). The columns were calibrated against 13 standard poly(MMA) samples (Polymer Laboratories; M_n = 630–1 200 000; M_w/M_n = 1.02–1.30). For Poly(MeDMA), M_n and M_w/M_n were measured by size exclusion chromatography at 40 °C in H₂O containing 100 mM NaNO₃ as an eluent on a polymethacrylate-gel column (TOSOH TSK-GEL[®] G3000PW_{XL}-CP; exclusion limit = 1×10^5 ; particle size = 7 μm; 7.8

mm I.D. $\times$ 30 cm; flow rate, 1.0 mL min⁻¹) connected to a PU-1580 pump, a RI-930 refractive-index detector, and a UV-970 ultraviolet detector (all from Jasco), similarly calibrated against standard PEO samples. ¹H NMR and ³¹P NMR spectra were measured at room temperature on a JEOL JNM-ECA500 spectrometer operating at 500.16 and 202.47 MHz, respectively. For the ³¹P NMR analyses, a capillary of diethyl phosphite solution (50 mM in toluene-*d*₈) was used as an internal chemical shift standard (7.08 ppm for the phosphite).

Results and Discussion

1 ³¹P NMR Analysis for Coordination of PG+ on Ruthenium Complex

The guanidine-containing ligand (PG+) was prepared through deprotection of **PGBoc**,

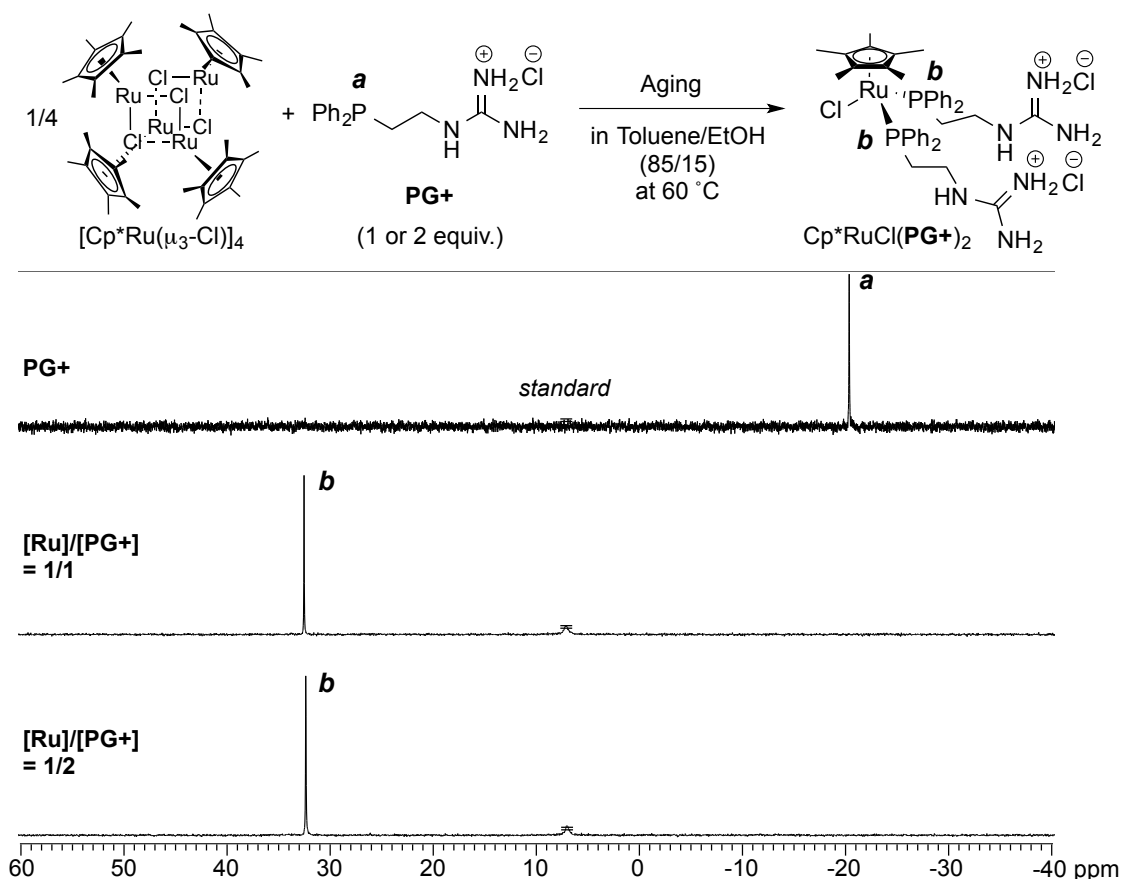


Figure 1. Coordination scheme and ³¹P NMR spectra of **PG+** and complexes prepared with 1:1 or 1:2 ratio ([Ru]₀:**PG+**₀) in toluene-*d*₈/ethanol (85/15, v/v) at r.t.: **PG+**₀ = 8.0 mM; [[Cp*Ru(μ₃-Cl)]₄]₀ = 1.0 mM, **PG+**₀ = 4.0 mM; [[Cp*Ru(μ₃-Cl)]₄]₀ = 1.0 mM, **PG+**₀ = 8.0 mM.

which was synthesized by mixing 2-(diphenylphosphino)ethylamine with a guanidinylation reagent (Scheme 1). The **PG+** was mixed with pentamethylcyclopentadienyl (Cp^*) ruthenium tetrameric precursor ($[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$) in toluene/ethanol (85/15, v/v) at 60 °C on different ratios, $[\text{Ru}]_0/[\text{PG}+]_0 = 1/1$ or $1/2$ molar ratios, and the resultant solutions were analyzed by ^{31}P NMR spectroscopy to study coordination pattern (monodentate vs bidentate: Figure 1).³⁸ If the guanidine moiety coordinates on ruthenium of bidentate fashion with the phosphine site, the two-equivalent condition would give a “free phosphine” peak in ^{31}P NMR spectrum. As a result, for the both ratios, such a free phosphine peak was not observed at around -20 ppm (*a*) and a new peak appeared at around 32 ppm (*b*) likely derived from **PG+** coordinated to ruthenium. These results were in contrast to the case with the pre-protected ligand, **PGBoc**, where some phosphine peaks were observed along with the non-coordinated peak, likely due to presence of dynamic coordination by the Boc-guanidine group (Figure 2). From these results, it is speculated that two **PG+** ligands coordinate on a ruthenium center only with the phosphine site to give $\text{Cp}^*\text{RuCl}(\text{PG}+)_2$. The **PG+** complex was indeed

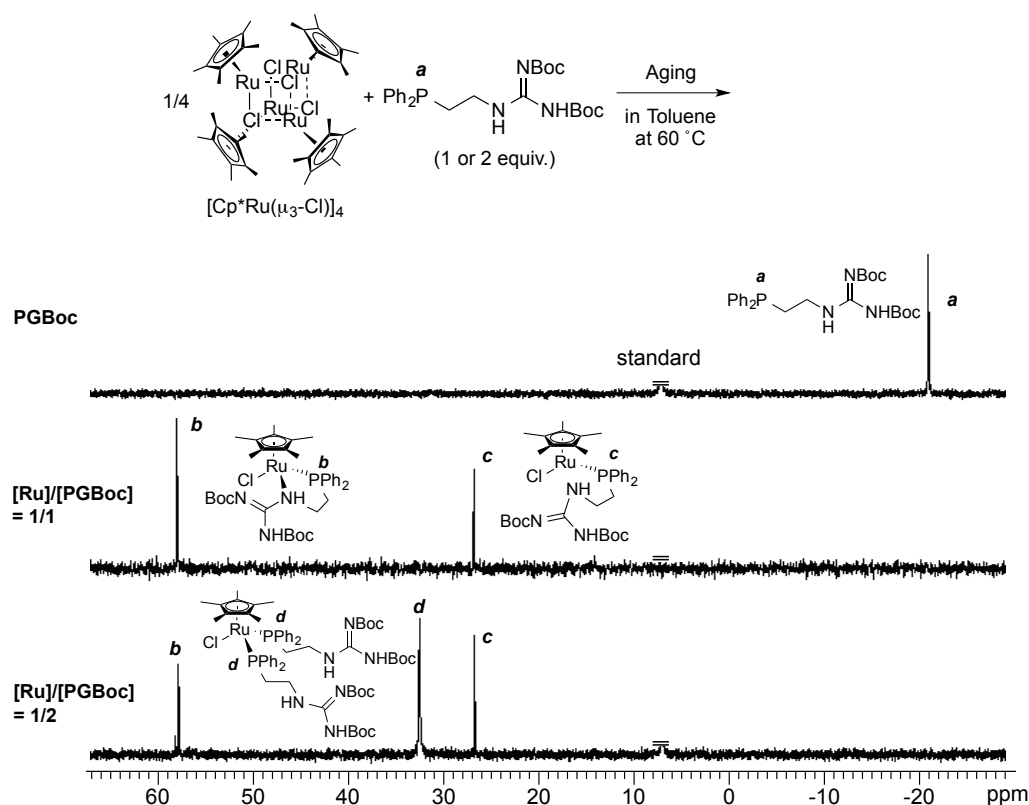


Figure 2. Coordination scheme and ^{31}P NMR spectra of **PGBoc** and complexes prepared with 1:1 or 1:2 ratio ($[\text{Ru}]_0:[\text{PGBoc}]_0$) in toluene- d_8 at r.t.: $[\text{PGBoc}]_0 = 8.0$ mM; $[[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]_0 = 1.0$ mM, $[\text{PGBoc}]_0 = 4.0$ mM; $[[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]_0 = 1.0$ mM, $[\text{PGBoc}]_0 = 8.0$ mM.

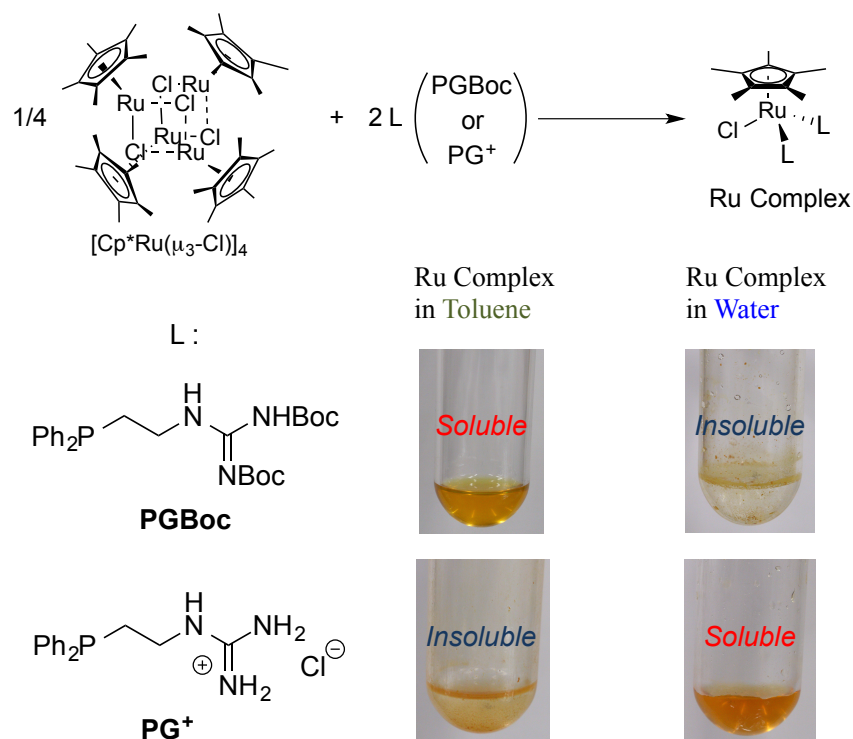


Figure 3. Solubility comparison of Ru complexes with **PGBoc** or **PG⁺**

soluble in water to give homogeneous yellow solution but apparently insoluble in toluene and the results were totally different from with **PGBoc** (Figure 3). In the following polymerizations, 2 equivalents of **PG⁺** to ruthenium was mixed and heated with the precursor $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$ before polymerization and the resultant complex was used as the catalyst without purification.

2 Aqueous Polymerizations with PG⁺ Ruthenium Catalyst

The **PG⁺**-ruthenium complex was then used as a catalyst for metal-catalyzed living radical polymerization in water in conjunction with a chlorine-based initiator $[\text{H}-(\text{MMA})_2\text{-Cl}]$. Methacrylate carrying PEG pendant (PEGMA) was first employed as a hydrophilic monomer. Consequently, the monomer was smoothly consumed to give high conversion at a moderate rate (Figure 4: 88%, 24 h). Number-averaged molecular weights (M_n s) of obtained polymers were linearly increased as the monomer conversion. The molecular weight distributions (MWDs) were narrow ($M_w/M_n < 1.2$) and the SEC curves clearly shifted to higher molecular weight keeping narrow MWDs (Table 1, Entry 1–4). Despite the mild condition (i.e., cocatalyst free and low temperature), the polymerization smoothly proceeded to give controlled polymers, similar to with previous hydrophilic ruthenium catalysts.^{33,34}

Such high catalytic activity for living radical polymerization in water was also observed in copper-catalyzed systems.^{12,26,39,40} Actually, the polymerization was carried out in ethanol instead of water under same condition as the above polymerization, resulting in slower polymerization (Table 1, Entry 5–8; Figure 5). However, MWDs of obtained polymers were narrower than those in water.

The catalytic system with the **PG**+–ruthenium complex also allowed polymerization control for HEMA, i.e., another typical hydrophilic methacrylate monomer. It was reported that free radical polymerization of HEMA in water is generally difficult due to cross-linking reactions, but the polymerization proceeded homogeneously to give controlled polymers (Entry 9–11; Figure 6). Ethanol solvent is also available for HEMA polymerization to give controlled polymers (Entry 12–14). However, when a methacrylate monomer with

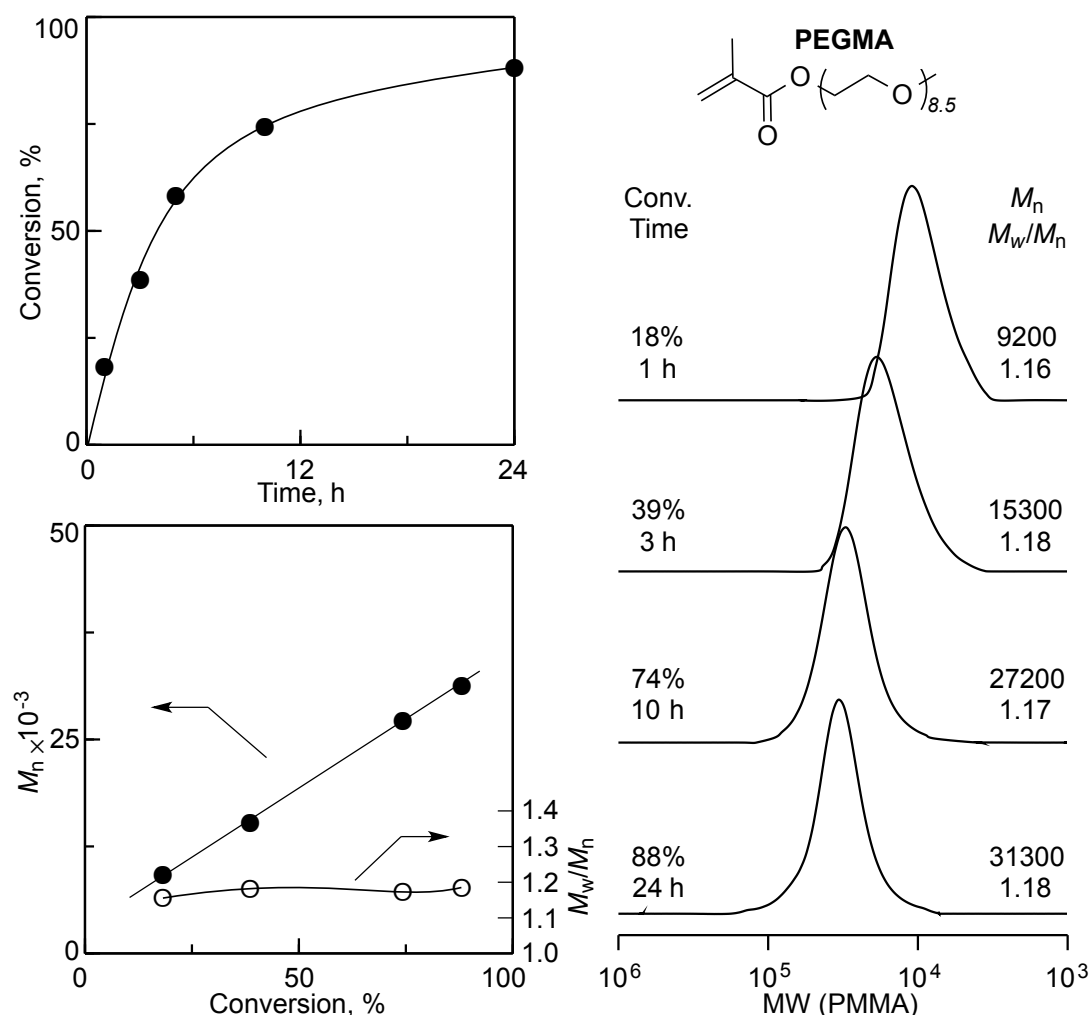
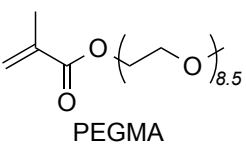
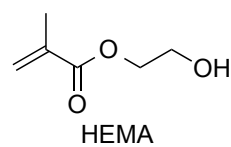
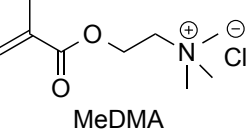
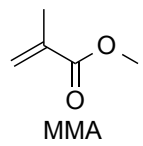
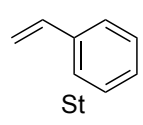
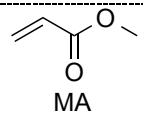


Figure 4. Aqueous living radical polymerization of PEGMA in water with **PG**+: [PEGMA]₀ = 500 mM; [H-(MMA)₂-Cl]₀ = 5.0 mM; [[Cp*Ru(μ₃-Cl)]₄]₀ = 0.5 mM; [**PG**]₀ = 4.0 mM.

ammonium chloride pendant (MeDMA) was used as the monomer for aqueous polymerization, runaway polymerization took place to give broader MWDs (Entry 15–16: $M_w/M_n > 1.8$), which is probably due to the inherent higher propagation ability.

Table 1. Polymerizations of Various Monomers with [Cp*Ru(μ_3 -Cl)]₄ and PG+

Entry	Monomer	Solvent	Time (h)	Conv. (%)	M_n^a	M_w/M_n^a
1	 PEGMA	H ₂ O	1	18	9200	1.16
2			3	39	15300	1.18
3			10	74	27200	1.17
4			24	88	31300	1.18
5			50	49	17000	1.10
6			100	58	19300	1.12
7			200	74	25100	1.11
8			300	93	32100	1.12
9	 HEMA	H ₂ O	1	36	12700	1.25
10			2	62	17200	1.24
11			4	84	21800	1.30
12			5	44	12900	1.23
13			10	72	19200	1.23
14			18	96	22300	1.24
15	 MeDMA	H ₂ O	2	74	11200 ^b	2.08 ^{b, c}
16			6	89	12900 ^b	1.84 ^{b, c}
17	 MMA	Toluene/EtOH (85/15)	3	26	2500	1.33
18			5	38	3300	1.26
19			10	54	4900	1.15
20			24	78	7300	1.09
21			35	85	8000	1.08
22	 St	Toluene/EtOH (85/15)	100	28	3000 ^d	1.10 ^d
23			300	52	5500 ^d	1.06 ^d
24			500	66	6700 ^d	1.06 ^d
25			700	82	8100 ^d	1.06 ^d
26	 MA	Toluene/EtOH (85/15)	5	42	4100	1.51
27			10	61	6300	1.35
28			24	86	8500	1.26

^aBy size-exclusion chromatography (SEC) calibrated with PMMA standards. ^bBy SEC calibrated with PEO standards. ^cMultimodal. ^dBy SEC calibrated with PSt standards. Polymerization conditions {PEGMA: [PEGMA]₀ = 500 mM; [H-(MMA)₂-Cl]₀ = 5.0 mM; [[Cp*Ru(μ_3 -Cl)]₄]₀ = 0.5 mM; [PG+]₀ = 4.0 mM at 40 °C. HEMA: [HEMA]₀ = 2000 mM; [H-(MMA)₂-Cl]₀ = 20 mM; [[Cp*Ru(μ_3 -Cl)]₄]₀ = 0.5 mM; [PG+]₀ = 4.0 mM at 40 °C. MeDMA: [MeDMA]₀ = 1000 mM; [[Cp*Ru(μ_3 -Cl)]₄]₀ = 0.5 mM; [PG+]₀ = 4.0 mM at 40 °C. MMA, St, MA: [Monomer]₀ = 4000 mM; [H-(MMA)₂-Cl]₀ = 40 mM; [[Cp*Ru(μ_3 -Cl)]₄]₀ = 1.0 mM; [PG+]₀ = 8.0 mM at 80 °C.}

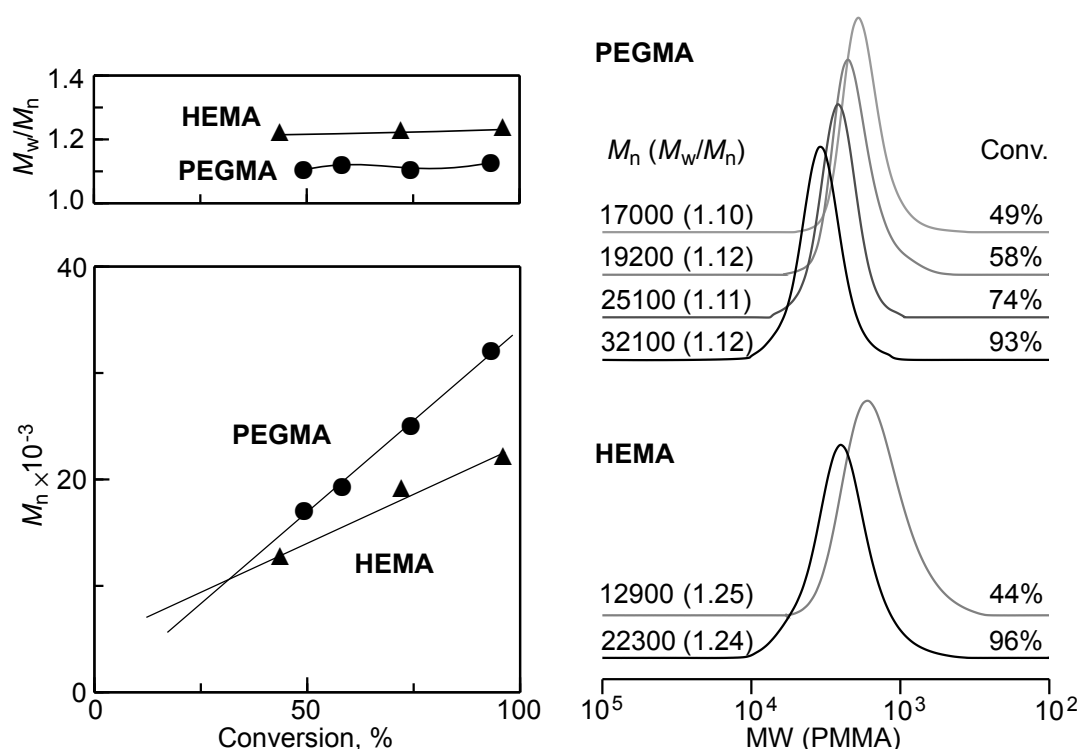


Figure 5. Living Radical Polymerization of hydrophilic monomers (PEGMA, HEMA) in ethanol at 40 °C with **PG+**: [PEGMA] = 500 mM, [H-(MMA)₂-Cl]₀ = 5.0 mM, [[Cp*Ru(μ_3 -Cl)]₄]₀ = 1.0 mM, [PG+]₀ = 8.0 mM.

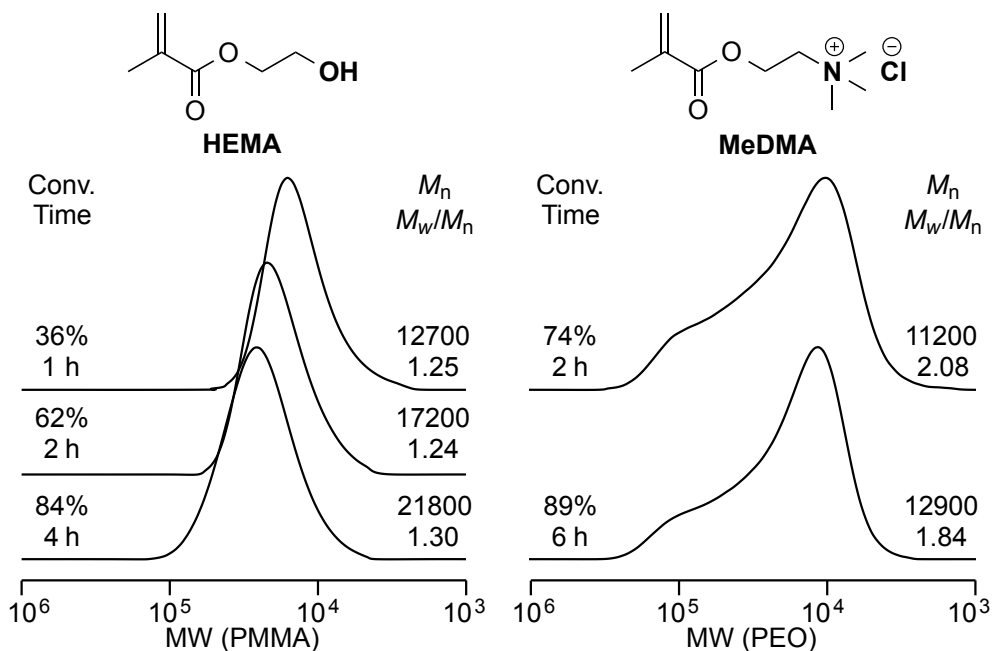


Figure 6. Aqueous living radical polymerizations of HEMA or MeDMA in water with Ru(II) precursor and **PG+**: [HEMA]₀ = 2000 mM, [H-(MMA)₂-Cl]₀ = 20 mM, [[Cp*Ru(μ_3 -Cl)]₄]₀ = 0.5 mM, [PG+]₀ = 4.0 mM; [MeDMA]₀ = 1000 mM, [H-(MMA)₂-Cl]₀ = 20 mM, [[Cp*Ru(μ_3 -Cl)]₄]₀ = 0.5 mM, [PG+]₀ = 4.0 mM.

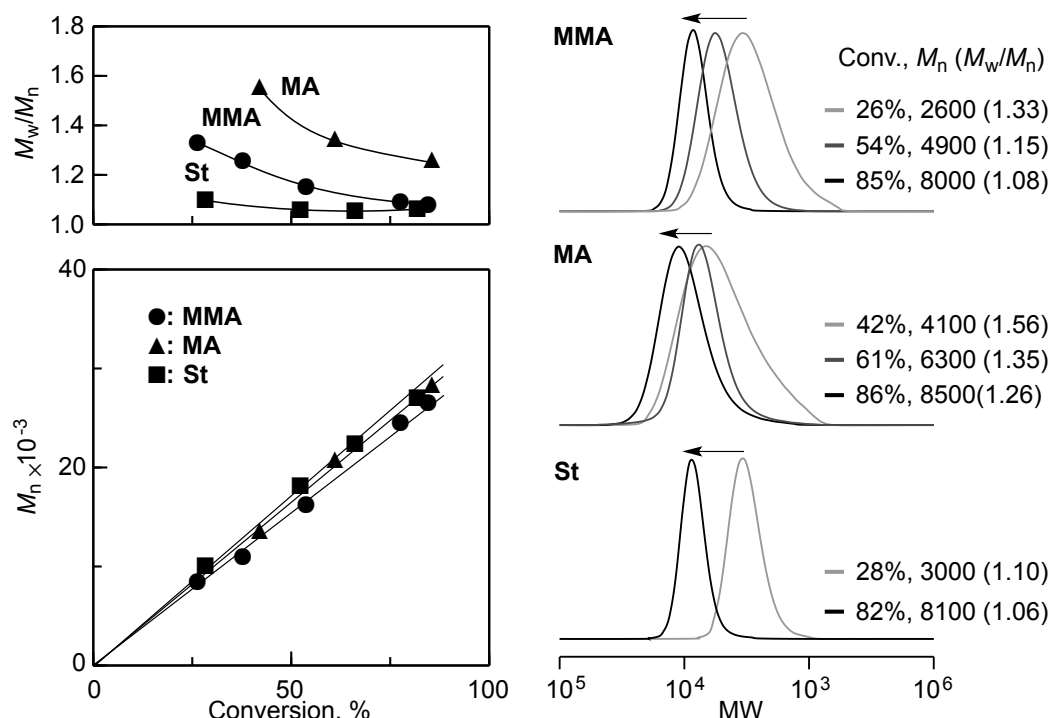


Figure 7. Living radical polymerization of hydrophobic monomers (MMA, MA, St) in toluene/ethanol (85/15, v/v) at 80 °C with **PG+**: $[\text{Monomer}]_0 = 4.0 \text{ M}$; $[\text{H-(MMA)}_2\text{-Cl}]_0 = 40 \text{ mM}$; $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]_0 = 1.0 \text{ mM}$, $[\text{PG}^+]_0 = 8.0 \text{ mM}$.

The **PG+**-ruthenium complex was also available as a catalyst for polymerization of hydrophobic monomers, such as MMA, St, and MA (Entry 17–28, Figure 7). For these polymerizations, mixture solvent of ethanol and toluene was effective to control polymerization in homogeneous fashion. Although polymerization rate depended on monomer, the SEC curves shift to higher molecular weight in these polymerizations while keeping narrow MWDs. Thus, the complex was found to be effective as a catalyst for living radical polymerization in various solvents including water.

3 Polymeric Trivalent Ruthenium Precursor $[(\text{Cp}^*\text{RuCl}_2)_n]$ with **PG+**

The **PG+**-ruthenium complex was found to be a useful catalyst for living radical polymerizations in various solvents including water. However, the polymerization of MeDMA in water was not controlled, as shown above, which is probably due to that the instant concentration of radical species was higher for halogen capping reaction (i.e., deactivation) to be controlled efficiently with higher oxidized complex [i.e., Ru(III)]. Based on this speculation, the ruthenium precursor was changed from the divalent ruthenium $[\text{Ru(II)}: [\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]]$ to the trivalent $[\text{Ru(III)}: (\text{Cp}^*\text{RuCl}_2)_n]$. When the Ru(III)-based

precursor is used instead of Ru(II)-based, the Ru(III) species can be reduced to Ru(II) by phosphine in ethanol^{41–44} but part of Ru(III) remain. It is expected that the ratio [Ru(III)]/[Ru(II)] during polymerization could be higher than with Ru(II)-based precursor and thus the situation be useful for runaway polymerizations.

Thus, the polymeric precursor, $(\text{Cp}^*\text{RuCl}_2)_n$, was mixed with 2 equivalents of **PG+** overnight at room temperature in ethanol, and the resultant solution was used as catalyst without purification. The *in situ* synthesized ruthenium complex was employed for polymerizations of water-soluble monomers (PEGMA, HEMA, MeDMA) in water at 40 °C without any co-catalysts, in conjunction with the chloride-type initiator $[\text{H}-(\text{MMA})_2-\text{Cl}]$

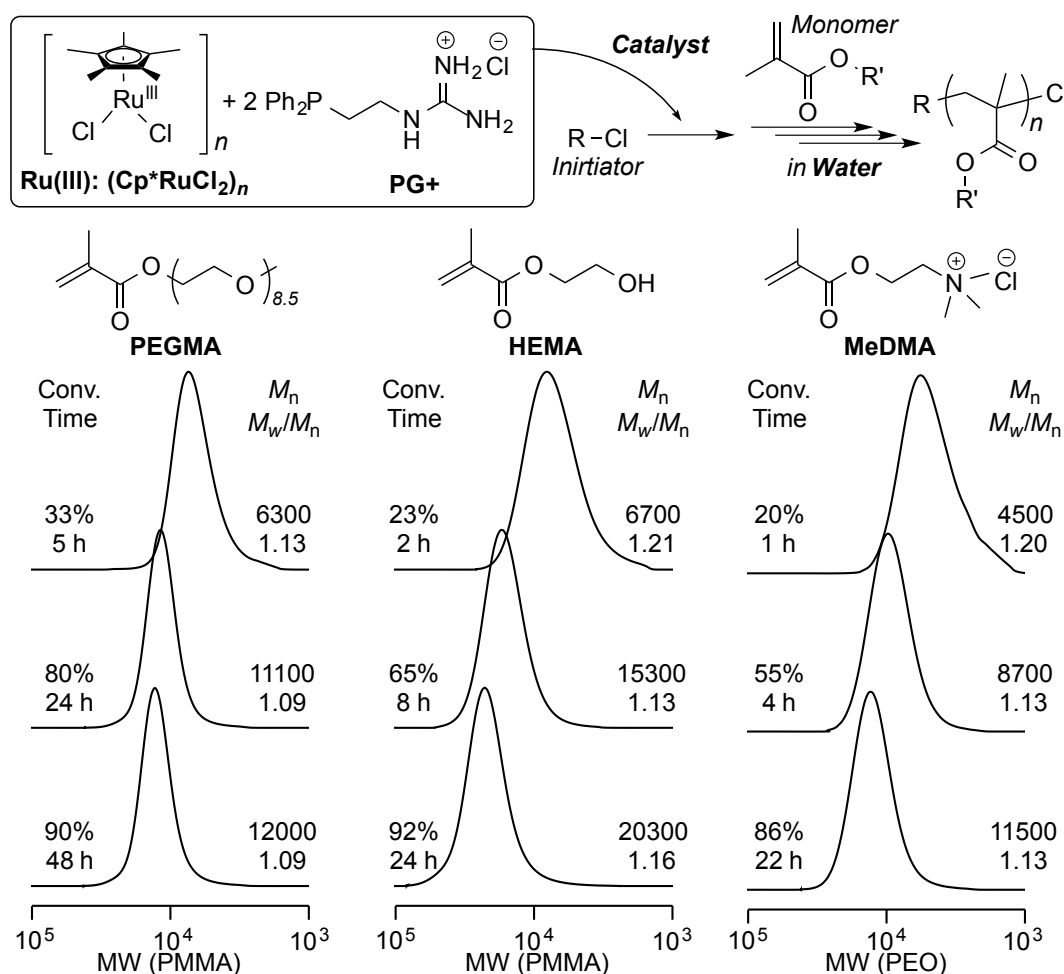


Figure 8. Ru(III) precursor $[(\text{Cp}^*\text{RuCl}_2)_n]$ was employed in Aqueous living radical polymerization of water-soluble monomers (PEGMA, HEMA, MeDMA) with **PG+** in water at 40 °C: $[\text{PEGMA}]_0 = 500 \text{ mM}$, $[\text{H}-(\text{MMA})_2-\text{Cl}]_0 = 20 \text{ mM}$, $[(\text{Cp}^*\text{RuCl}_2)_n]_0 = 2.0 \text{ mM}$, $[\text{PG}^+] = 4.0 \text{ mM}$; $[\text{HEMA}]_0 = 2.0 \text{ M}$, $[\text{H}-(\text{MMA})_2-\text{Cl}]_0 = 20 \text{ mM}$, $[(\text{Cp}^*\text{RuCl}_2)_n]_0 = 2.0 \text{ mM}$, $[\text{PG}^+] = 4.0 \text{ mM}$; $[\text{MeDMA}]_0 = 1.0 \text{ M}$, $[\text{H}-(\text{MMA})_2-\text{Cl}]_0 = 20 \text{ mM}$, $[(\text{Cp}^*\text{RuCl}_2)_n]_0 = 2.0 \text{ mM}$, $[\text{PG}^+] = 4.0 \text{ mM}$.

(Figure 8). In all the polymerization, the monomers smoothly consumed; the conversions reached almost 90%, although the rates were slower than those with $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$. From the SEC curves and M_w/M_n of obtained polymers, the molecular weight linearly increased with monomer conversion, keeping narrow MWDs in all of the polymerizations ($M_w/M_n < 1.25$), and most importantly, polymerization of MeDMA can be also controlled with this system ($M_w/M_n = 1.13\text{--}1.20$).

4 Structure Analysis of Poly(HEMA)

To confirm control degree of the polymerization with $(\text{Cp}^*\text{RuCl}_2)_n$ and **PG+** in water, we measured ^1H NMR of poly(HEMA) obtained with the aqueous catalytic system [the monomer conversion was 33%, $M_n(\text{conv}) = 4500$]. As shown in Figure 9, in addition to the major peaks from the main chain protons (**a–e**), minor peaks corresponding to terminal structure were observed: **f**, **g** and **h** derived from α -end; **c'** from ω -end. The $M_n(\text{NMR})$ was calculated from the integration ratios of these signals, and initiator moiety functionality (F_n) was estimated from the ratio of $M_n(\text{conv})$ to $M_n(\text{NMR})$: $M_n(\text{conv}) = 4500$, $M_n(\text{NMR}) = 4700$, $F_n = 0.96$. The high end-functionality indicated that the initiation and propagation were controlled even in water and polymer chains almost completely generated from initiator.

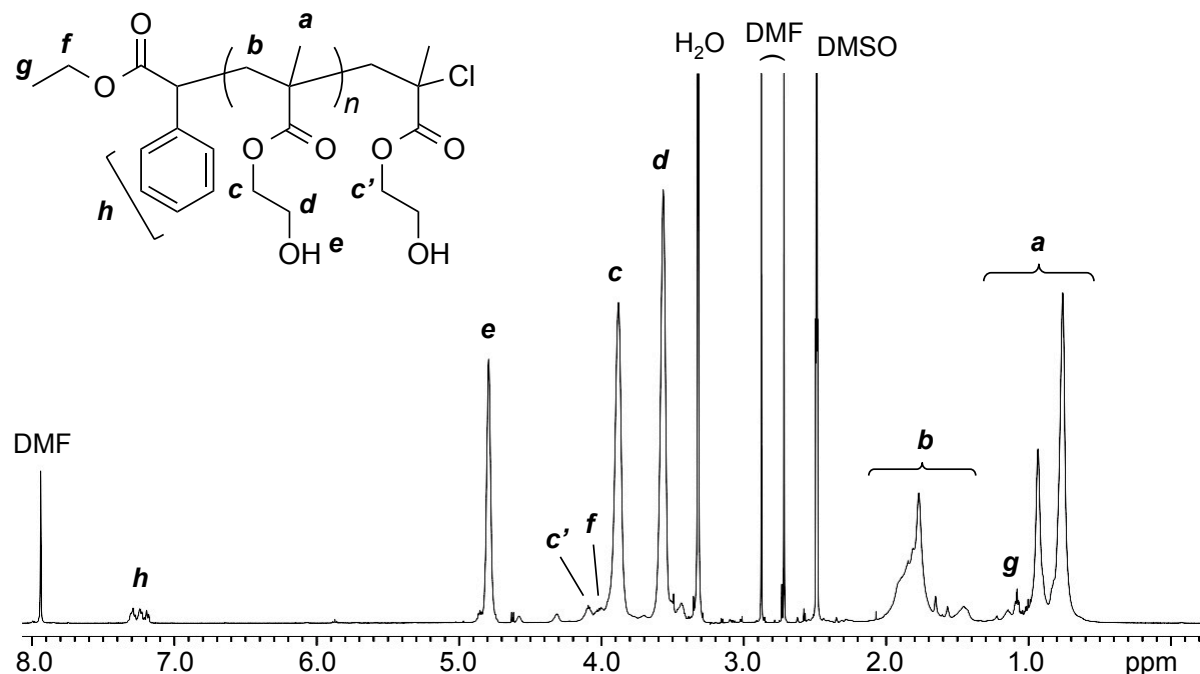


Figure 9. ^1H NMR spectrum of polyHEMA [$M_n(\text{conv}) = 4500$] obtained by aqueous living radical polymerization with $(\text{Cp}^*\text{RuCl}_2)_n$ and **PG+** in H_2O : $[\text{HEMA}]_0 = 2000$ mM, $[\text{ECPA}]_0 = 20$ mM, $[(\text{Cp}^*\text{RuCl}_2)_n]_0 = 2.0$ mM, $[\text{PG+}]_0 = 4.0$ mM.

Table 2. Reducing the Amount of Catalyst in Aqueous Polymerization of PEGMA with (Cp*RuCl₂)_n and PG+

Entry	[Ru] ₀ (mM)	[Ru] ₀ :[Initiator] ₀	Time (h)	Conv. (%)	<i>M</i> _n ^b	<i>M</i> _w / <i>M</i> _n ^b
1	1.0	1:20	8	63	9600	1.10
2	0.4	1:50	8	47	8300	1.16
3	0.2	1:100	8	34	7700	1.24
4	0.1	1:200	8	21	10400	1.36

^a[PEGMA]₀ = 500 mM; [H-(MMA)₂-Cl]₀ = 20 mM; [(Cp*RuCl₂)_n]/[PG+]₀ = 1/2 in water at 40 °C. ^bBy size-exclusion chromatography calibrated with PMMA standards.

Minor peaks that were probably from chlorine terminal were also observed (4.20 – 4.70 ppm), but accurate integration of the peaks and estimation of the functionality were difficult. However the rough estimation was reasonable assuming that chlorine is quantitatively incorporated at the terminal.

5 Decrease in the Amount of Catalyst

The active catalysis with PG+ ligand for polymerization in water encouraged the author to realize the polymerization control using lower amount of catalyst. Small amount of metal catalyst is required to obtain polymers containing less amount of the metal residue, especially for practical applications of water-soluble polymers toward bio-applications such as protein-polymer conjugation, as well as to make the production process cheaper.

Thus, polymerization of PEGMA in water was performed with lower concentration of ruthenium catalyst than 2.0 mM in conjunction with 20 mM of initiator ([PEGMA]₀ = 500 mM): [Ru]₀ = 1.0, 0.40, 0.20 and 0.10 mM (Table 2). Colors of the polymerization solutions

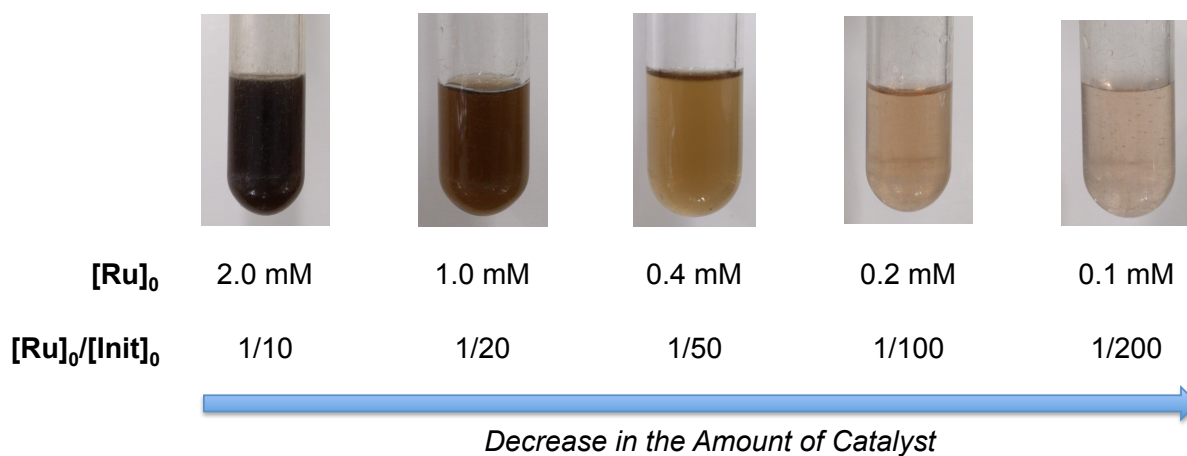


Figure 10. Photographs of reaction solutions in the aqueous polymerization of PEGMA with (Cp*RuCl₂)_n and PG+.

derived from ruthenium complex gradually faded, as catalyst concentrations got lower (Figure 10). The molecular weights and MWDs of obtained polymers were fairly controlled under all the condition to give unimodal SEC curves ($M_w/M_n < 1.4$), however the polymerization rate became lower and the MWD was a little broader according to the catalyst concentration ($M_w/M_n \sim 1.36$ at $[\text{Ru}]_0 = 0.1 \text{ mM}$).

Conclusion

In this chapter, a guanidinium cation-embedded phosphine compound (**PG+**) was employed as a ligand for ruthenium-catalyzed living radical polymerization in water. The ruthenium complex prepared with $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$ and **PG+** showed high catalytic activity without relying on cocatalyst for controlled polymerizations of hydrophilic monomers (PEGMA and HEMA) in water as well as those of hydrophobic counterparts (MMA, MA and St) in toluene/ethanol (85/15, v/v). The control ability was further improved by using $(\text{Cp}^*\text{RuCl}_2)_n$ as the precursor complex in place of $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$: control of the polymerization of more reactive monomer (i.e., MeDMA) became possible. The high catalytic activity of the **PG+** ruthenium catalyst allowed polymerization control in water with small amount of ruthenium catalyst. These results may open the door to precise syntheses of functional polymers in water especially toward bio-applications.

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Chapter 4

Ruthenium-Catalyzed Living Radical Polymerization of Methacrylic Acid in Water: Direct Controlled Polymerization of Acidic Monomer

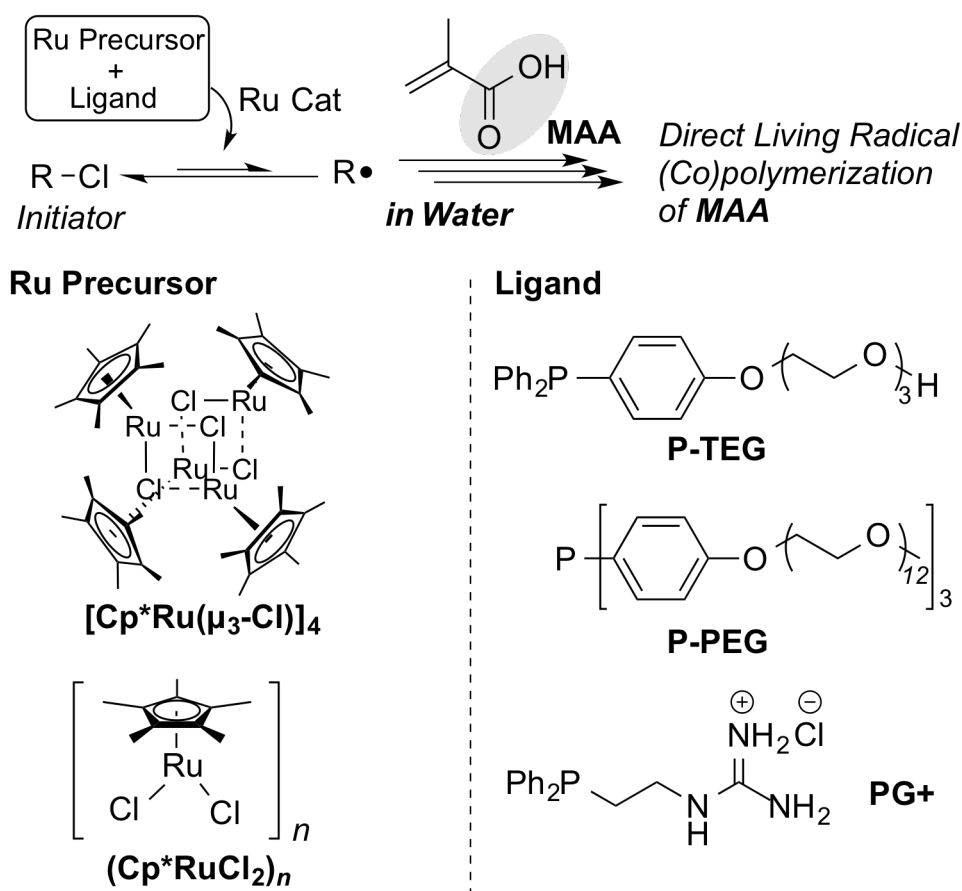
Abstract

Controlled radical polymerization of methacrylic acid (MAA) without protection has been one of the unresolved subjects in metal-catalyzed living radical polymerization, because most of conventional catalysts undergo deactivation during the polymerization through unfavorable interaction or ligand exchange with the carboxyl acid moiety. In this chapter, the author realized controlled radical (co)polymerization of MAA with highly active ruthenium catalysis in water without relying on the protection. For example, a ruthenium catalyst that is prepared from a Ru(III)-based precursor $[(\text{Cp}^*\text{RuCl}_2)_n]$ and a polyethylene glycol (PEG) pendent phosphine-based ligand induced copolymerization of MAA with PEG-pendant methacrylate (PEGMA) in water in conjunction with a halogen initiator. The conversions of both monomers smoothly reached higher values ($\sim 70\%$) and obtained polymers expressed relatively narrow molecular weight distributions ($M_w/M_n \sim 1.4$). Control of the homopolymerization of MAA, which is more challenging, was also realized with the aqueous system, although the achieving conversion was lower. By using the PEG-based initiator, PEG-PMAA block copolymers were precisely synthesized in water.

Introduction

Metal-catalyzed living radical polymerization (LRP) or atom transfer radical polymerization (ATRP) has been widely used for construction of well-defined polymeric architectures as well as hybrid of polymer with other molecules. The advantage of metal-catalyzed system over other LRP systems is ease in designing initiators carrying carbon–halogen bond and handling the procedure. On the other hand, available monomers are sometimes limited depending on catalyst because the polar side chain could affect the catalysis through interaction with metal center, and thus robustness and wide usability have been required for the catalyst of LRP as well as high activity.

Among vinyl monomers, acidic monomers such as methacrylic acid (MAA) or acrylic acid (AA) are categorized as the most difficult monomer for metal-catalyzed LRP.^{1–3} Despite of the difficulty in controlled polymerization of the acidic monomers, the (co)polymers of MAA or AA are important as functional polymers for various applications, such as polyelectrolytes, pH sensitive materials, coating materials, dispersant, and drug delivery carriers.⁴ The block copolymers containing the acidic segment have also attracted attentions,



Scheme 1. Ruthenium Catalyzed Living Radical (Co)polymerization of MAA

and for example, block copolymers with PEG are useful for dual sensitive material to pH and temperature,^{5,6} morphology control of calcium carbonate^{7,8} and encapsulation of lysozyme.⁹ Some efforts have been directed to controlled radical polymerization of the acidic monomer,^{10–16} but to the author's knowledge, there are little examples to demonstrate controlled polymerization up to higher conversion. Some examples on controlled random copolymerizations of acidic monomer with other comonomers were reported, but in most cases, the feed ratio of acidic monomer was much lower than that of comonomer to realize polymerization control. One approach to realize controlled homopolymerization of the carboxyl monomer is that polymerization is performed in water under higher pH condition to weaken the effect of acid side chain on catalysis by converting the $-\text{COOH}$ into $-\text{COO}^-\text{Na}^+$.¹³ However, this could cause limitation of the application as well as necessity in additional treatment of neutralization for use as acidic polymer.

From the above background, the author's effort in this chapter is directed to metal-catalyzed LRP of MAA "without deprotection" and "in neutral water". He has recently developed very active ruthenium catalysts available for living radical polymerizations of water-soluble monomers in water (see in the Chapter 1–3).¹⁷ To help the water solubility, phosphine ligands having hydrophilic substituents, such as triethylene glycol (**P-TEG**), poly(ethylene glycol) (**P-PEG**), and guanidinium chloride (**P-PG+**) were incorporated in ruthenium catalysts via aging process with ruthenium precursors ($[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$ and $[(\text{Cp}^*\text{RuCl}_2)_n]$) before polymerization. The expected effects on controlled polymerization of MAA are the high catalytic activities in water as well as the protection from the unfavorable interaction of MAA with ruthenium by the hydrophilic ligand (Scheme 1).

Experimental

Materials

PEGMA $[\text{CH}_2\text{C}(\text{CH}_3)\text{COO}(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_3; n = 8.5 \text{ (number-average)}]$ (Aldrich) was purified by passing through an inhibitor-removal column (Aldrich) and were subsequently degassed by three-time vacuum-argon bubbling cycles before use. Methacrylic acid (MAA) (TCI; > 99%) was distilled under reduced pressure before use. **P-TEG**,¹⁷ **P-PEG**,¹⁸ **PG+**,²⁶ a ruthenium tetramer precursor $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$,^{27,28} $\text{H}-(\text{MMA})_2\text{-Cl}$ ²⁹ initiator $[\text{H}(\text{CH}_2\text{CMeCO}_2\text{Me})_2\text{Cl}]$ and PEG-Cl $\{[\text{Me}(\text{OCH}_2\text{CH}_2)_n\text{OCOCH}(\text{Ph})\text{Cl}]\}$; a chlorine capped

polyethylene glycol methyl ether initiator: $M_n = 4300$, $M_w/M_n = 1.26$ by SEC in water with PEO calibrations.³⁰ were prepared according to the literature. Dichloro(pentamethylcyclopentadienyl)ruthenium(III) polymer $[(Cp^*RuCl_2)_n]$ (Aldrich) and materials for preparation of $[Cp^*Ru(\mu_3-Cl)]_4$, listed below, were used as received without further purification and handled in a glovebox (MBraun Labmaster 130, M. Braun Inertgas-Systeme GmbH, Garching, Germany) under a moisture- and oxygen-free argon atmosphere ($H_2O < 1$ ppm; $O_2 < 1$ ppm): ruthenium(III) chloride hydrate (Wako; $> 99.9\%$); 1,2,3,4,5-pentamethylcyclopentadiene (TCI; $> 93\%$); and lithium triethylhydridoborate (Aldrich, 1.0 M solution in THF). Toluene (Kishida Kagaku; purity 99.5%) was dried and purified by passing through purification columns (Solvent Dispensing System, SG Water USA, Nashua, NH; Glass Contour) and bubbled with dry nitrogen for more than 15 min immediately before use. Water (Wako; distilled) and ethanol (Wako; super dehydrated) were bubbled with dry nitrogen for more than 15 min immediately before use. Acetic acid (Wako; $> 99.7\%$), acetonitrile (Wako; $> 99.5\%$) and THF (Wako; $> 97.0\%$) were used as received.

Polymerization Procedure

Polymerization was carried out by the syringe technique under dry argon in baked glass tubes equipped with a three-way stopcock or in sealed glass vials. An example for copolymerization of MAA and PEGMA with $H-MMA_2-Cl/(Cp^*RuCl_2)_n/P-PEG$ in water is given below. $(Cp^*RuCl_2)_n$ (2.5 mg, $8.0/n$ μ mol) and 40 mM **P-PEG** in ethanol (0.4 mL, 16 μ mol) were stirred overnight in a Schlenk tube at room temperature, and then PEGMA (0.88 mL, 2.0 mmol), MAA (0.17 mL, 2.0 mmol), H_2O (2.79 mL) and 500 mM $H-MMA_2-Cl$ in ethanol (0.16 mL, 0.080 mmol) were added to the solution; the total volume was 4.0 mL. Immediately after mixing, aliquots (0.50–1.0 mL each) of the solution were injected into baked glass tubes, which were then sealed (except when a stopcock was used) and placed in an oil bath kept at 40 °C. In predetermined intervals, the polymerization was terminated by cooling the reaction mixture to -78 °C in dry ice-methanol. Monomer conversions were determined by 1H NMR from the integrated peak area of the olefinic protons of the monomer with ethanol as an internal standard.

Measurements

For PMAA, P(PEGMA)-*ran*-PMAA or PEG-*block*-PMAA, M_n and M_w/M_n were

Table 1. Aqueous Copolymerization of Methacrylic Acid (MAA) and PEGMA (50/50)^a

Entry	Catalyst	Time (h)	Conversion (%) (MAA/PEGMA)	M_n^b	M_w/M_n^b
1	Ru(II) ^c / P-TEG	0.33	40/37	5500	1.60
2		2	62/62	7100	1.52
3	Ru(II) ^c / P-PEG	0.33	58/55	6800	2.06
4		2	84/82	8000	1.93
5	Ru(II) ^c / PG+	1	26/24	4400	1.32
6		6	53/51	6300	1.51
7	Ru(III) ^d / P-TEG	0.33	29/30	4300	1.31
8		3	63/61	6900	1.39
9	Ru(III) ^d / P-PEG	0.33	40/42	5000	1.36
10		2	66/66	7000	1.39
11	Ru(III) ^d / PG+	10	18/18	3200	1.36

^a[MAA]₀ = 500 mM; [PEGMA]₀ = 500 mM; [H-(MMA)₂-Cl]₀ = 20 mM; [Ru]₀ = 2.0 mM; [ligand]₀ = 4.0 mM in water at 40 °C. ^bBy size-exclusion chromatography calibrated with PEO standards. ^cRu(II) = [Cp*Ru(μ₃-Cl)]₄. ^dRu(III) = (Cp*RuCl₂)_n

copolymerization of MMA / PEGMA (1/1) was investigated. Though the polymerization became slower than PEGMA homopolymerization, the two monomers were consumed in parallel and the conversions reached 70% in 7 h. SEC analyses of the obtained polymers showed the copolymerization was controlled: the molecular weights increased with the monomer conversion, and the molecular weight distributions (MWDs) were relatively narrow (M_w/M_n = 1.36–1.42).

2 Effects of Catalyst Structures

The author previously developed various water-soluble ruthenium catalysts that were prepared from the combinations of a precursor [Ru(II) or Ru(III)] and a ligand (**P-TEG**, **P-PEG** or **PG+**). These catalysts were employed for aqueous copolymerization of MAA and PEGMA in the same condition as above (Figure 2, Table 1). In all polymerizations, the two monomers were converted in parallel and the molecular weights increased along with the conversion in SEC analyses. For all ligands, Ru(III) precursor [(Cp*RuCl₂)_n] led to slower polymerization and narrower molecular weight distributions of the obtained copolymers than Ru(II) precursor [Cp*Ru(μ₃-Cl)]₄. In the case of Ru(III) precursor, **P-PEG** brought the fastest polymerization and the highest monomer conversion among the ligands (Entry 7–11), though the MWDs were almost same for all ligands (M_w/M_n < 1.4). These results showed Ru(III)/**P-PEG** catalyst was the most suitable for aqueous polymerization of MAA, and therefore this catalyst was employed in the following polymerization.

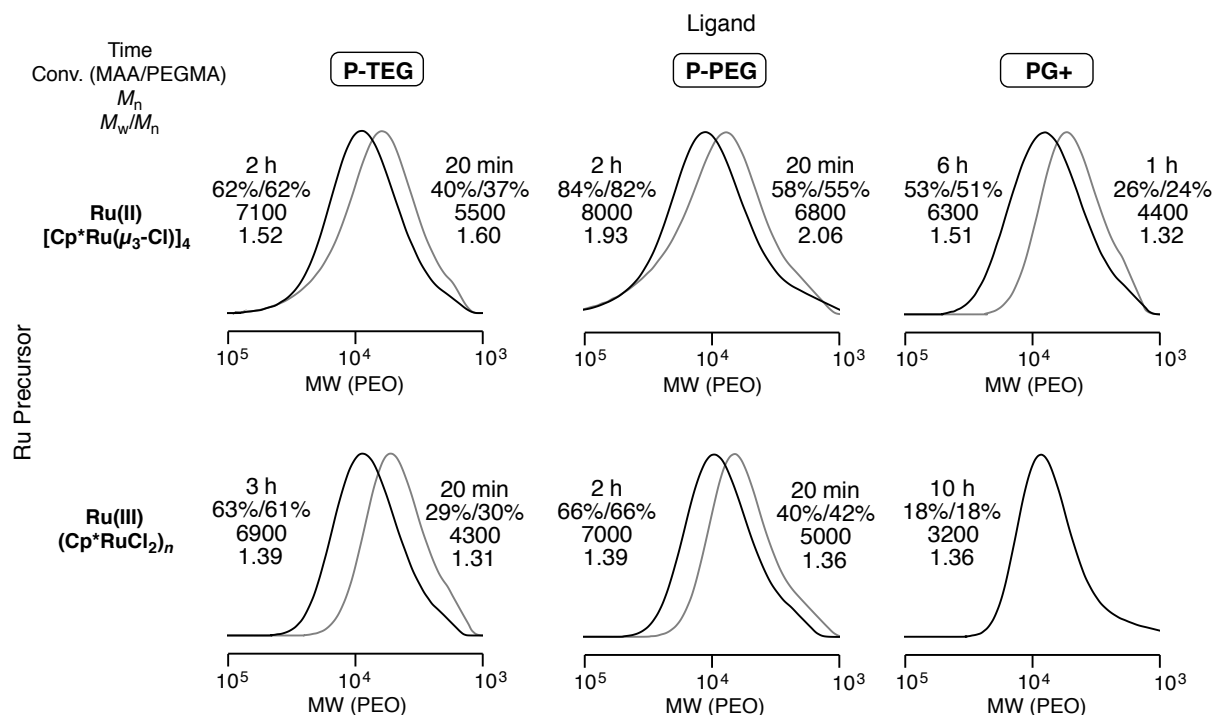


Figure 2. GPC traces of aqueous copolymerization of MAA and PEGMA: $[\text{MAA}]_0 = 500 \text{ mM}$; $[\text{PEGMA}]_0 = 500 \text{ mM}$; $[\text{H-(MMA)}_2\text{-Cl}]_0 = 20 \text{ mM}$; $[\text{Ru}]_0 = 2.0 \text{ mM}$; $[\text{ligand}]_0 = 4.0 \text{ mM}$ in water at 40°C .

3 Aqueous Homopolymerization of MAA

The Ru(III)/P-PEG catalyst applied for aqueous homopolymerization of MAA at 40°C , in conjunction with H-(MMA)₂-Cl (Figure 3A). In the SEC analyses of the obtained polymers, the molecular weight increased with the conversion and MWDs were not very broad ($M_w/M_n = 1.56$), though the polymerization was slower than the copolymerization (Conv. 36% in 2 h).

Additionally, a chlorine type PEG initiator (PEG-Cl: $M_n = 4300$, $M_w/M_n = 1.26$ in aqueous SEC) was also employed for MAA homopolymerization on similar condition to H-(MMA)₂-Cl system (Figure 3B). The fast polymerization proceeded (Conv. 46% in 2h) and the SEC curves of the obtained polymers clearly shifted from PEG-Cl initiator to higher molecular weight keeping relatively narrow MWDs ($M_w/M_n < 1.4$). This result indicated PEG-*block*-PMAA was successfully synthesized by the aqueous ruthenium catalyzed polymerization.

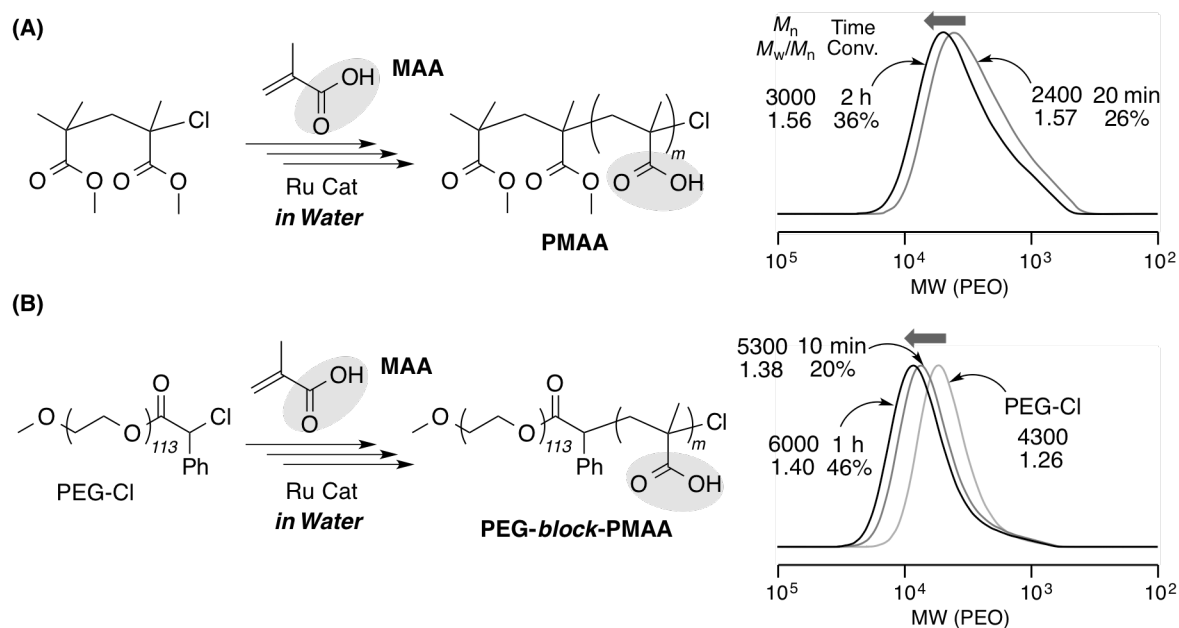


Figure 3. Ruthenium-catalyzed aqueous homopolymerization of MMA with H-(MMA)₂-Cl (A) or PEG-Cl (B): [MAA]₀ = 1000 mM; [Initiator]₀ = 20 mM; [(Cp**RuCl*₂)_{*n*}]₀ = 2.0/*n* mM; [**P**-PEG]₀ = 4.0 mM in water at 40 °C.

Conclusion

Living radical (co)polymerizations of MAA were achieved with very active hydrophilic ruthenium catalysts. The polymerizations were performed in neutral water at 40°C, where the MAA conversion reached up to higher conversion than with conventional catalytic systems. Crucial is that the catalytic system is very active and well-controlled in water, and presumably the acidic side chain in MAA and the polymer could favor hydration or solvation with water rather than interaction with ruthenium center. The author believed the aqueous ruthenium catalyzed systems opened the door for precise syntheses of various hydrophilic (co)polymers including acidic functionality.

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PART II

Robust Iron Catalysis for Living Radical Polymerization of Functional Monomers

Chapter 5

Phosphine-Ligand Decoration toward Active and Robust Iron Catalysts in LRP

Abstract

Phosphine ligands were designed to enhance the catalytic activity of iron(II) complexes $[\text{FeBr}_2(\text{PR}_3)_2]$ for metal-catalyzed living radical polymerization (LRP), and special efforts were directed to the improvement in catalytic activity and robustness against functional monomers. Introduction of an electron donating group {methoxy $[\text{P}(\text{MeOPh})_3]$ or N,N' -dimethylamino $[\text{Ph}_2\text{P}(\text{Me}_2\text{NPh})] \}$ onto the *para* position of triphenyl phosphine (PPh_3) allowed active and robust Fe(II) complexes that catalyzed LRP of poly(ethylene glycol) methacrylate (PEGMA) smoothly proceeding to high conversion ($\sim 90\%$), to form polymers of controlled molecular weights and its distributions ($M_w/M_n < 1.2$). In contrast, such an enhancement was absent with the parent ligand PPh_3 and those with electron-withdrawing substituents. Furthermore, the replacement of the three methoxy groups in $\text{P}(\text{MeOPh})_3$ with PEG chains led to a more robust catalyst, especially tolerant of the hydroxyl group in 2-hydroxyethyl methacrylate (HEMA). Accordingly, this catalyst enabled a four-component random living copolymerization of HEMA, PEGMA, and two alkyl methacrylates, where all the monomers randomly copolymerized into statistical copolymers of controlled molecular weights.

Introduction

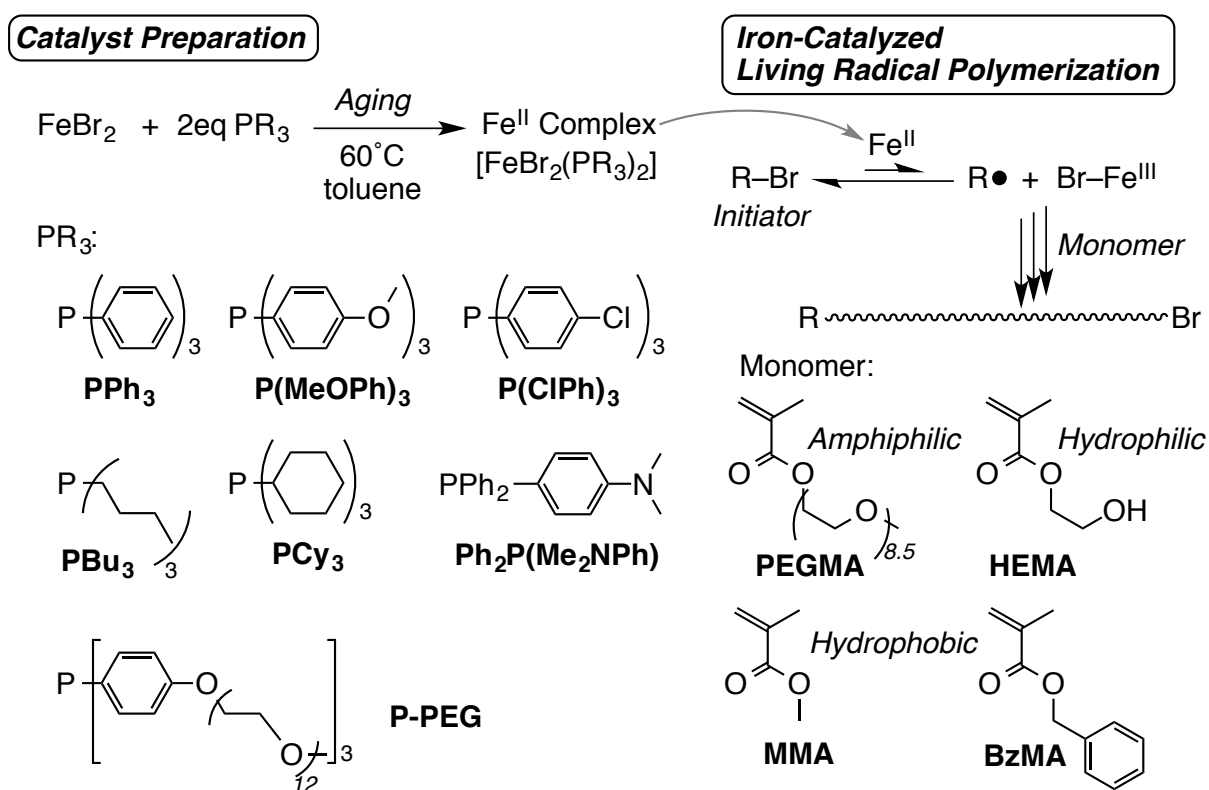
Metal-catalyzed living radical polymerization (LRP),^{1,2} or atom transfer radical polymerization,^{3,4} has been developed to provide easy-to-use synthetic tools for well-defined polymers, block copolymers, and polymer conjugates, among others. Therein a metal complex (Mt^n) is in charge of the one-electron redox catalysis ($Mt^n \leftrightarrow XMt^{n+1}$) that reversibly activates the carbon–halogen (C–X) bond of an initiator (R–X) or the growing terminal (“dormant” species) into a carbon radical, along with the regeneration of the dormant end. The reversibility allows reduction of the instant concentration of “active” radical species and thus suppresses bimolecular termination and other unfavorable side-reactions inherent in the conventional free radical polymerization. In addition, the designability of initiating systems (initiators plus catalysts), coupled with their high initiation efficiency, has now positioned the metal-catalyzed LRP as a user-friendly, reproducible, and extensively applicable versatile synthetic strategy in various fields requiring well-defined polymeric architectures, often beyond polymer chemistry toward biochemistry, medicine, materials science, and other fields. However, the use of metal complex catalysts causes some disadvantages particularly in practical applications: metal contamination in products, expensiveness of metal, and low sustainability (rare and/or toxic metals).

Iron (Fe) belongs to the group 8 transition metal and mainly assumes the +2 and +3 oxidation states, thus qualified to the catalyst of the LRP requiring one-electron redox property. As an element, iron should be more attractive for LRP catalysts than often-used transition metals such as ruthenium (Ru)⁵ and copper (Cu),⁶ because “ferrum” is abundant on Earth, inexpensive, sustainable, and possibly safer. Indeed, industries are ardently requiring active and useful iron catalysts that may lead to practical application of LRP. Additionally, the important roles of iron-mediated redox systems ubiquitously found in biology and biological systems indicate the high biocompatibility and possible bioapplications of iron catalysts.

Some research groups have in fact already developed Fe catalysts for LRPs,^{7–39} but they still seem inferior in activity and functionality-robustness to Ru- and Cu-based counterparts. A disadvantage on iron catalysts is a low tolerance to polar groups: For example, most of the hitherto developed iron LRP catalysts cannot survive in the presence of polar functionality in monomer or in solvent, often transformed into undesirable, much less active or inactive forms via ligand dissociation or ligand exchange. To the author’s knowledge, the reported iron-catalyzed LRP systems, including those by the author, have in fact been still poorly

versatile in terms of applicable monomers and reaction conditions, often accessible to only “common” monomers such as alkyl (meth)acrylates and styrene derivatives without polar and functional pendent groups. Although some Fe-catalyzed LRPs have recently been reported for functional monomers, the controllability, i.e., livingness of growing end or efficiency in block copolymerization, is still unsatisfactory.^{14,16,23,39} Given redox catalysis of some biological iron complexes in polar and aqueous environments, the previous efforts in ligand design have obviously been so insufficient that they could not educe the potential ability of iron catalysts for LRP of functional monomers yet.

These backgrounds have encouraged the author to design new phosphine ligands for iron complexes toward really “applicable” iron catalysis of LRP for functional monomers and in polar or aqueous media. In this work, various phosphine ligands were designed and selected, and simple procedures were applied where they were mixed and aged with FeBr₂ in an organic solvent. The *in situ* formed phosphine-ligated Fe(II) complexes were directly employed as catalysts for LRP of functional monomers, such as HEMA and PEGMA [CH₂=C(CH₃)–COO(CH₂CH₂O)_nCH₃; *n* = 8.5 (number-average)], along with MMA and other nonpolar alkyl methacrylates (Scheme 1). Focus was directed to the electronic effects of the



Scheme 1. Preparation of Iron Complexes with Various Phosphine Ligands and Iron-Catalyzed LRP

phosphine ligands on catalysis and to the steric effects that may protect the “central” iron from polar groups.

This paper is to report that the catalytic activity of iron complex can be enhanced by the introduction of electron donating and sometimes amphiphilic or hydrophilic groups onto triphenylphosphine and that the ligand decoration with polar and bulky PEG chain improves tolerance to highly polar groups, leading to controlled polymerization of functional monomers.

Experimental

Materials

MMA (methyl methacrylate) (Tokyo Kasei; > 99%) was dried overnight over calcium chloride, and distilled from calcium hydride under reduced pressure before use. HEMA (Aldrich; > 99%) was distilled under reduced pressure before use. BzMA (benzyl methacrylate) (TCI; > 98%) and PEGMA [$\text{CH}_2=\text{C}(\text{CH}_3)\text{COO}(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_3$; $n = 8.5$ (number-average)] (Aldrich) were purified by passing through an inhibitor-removal column (Aldrich) and were subsequently degassed by three-time vacuum-argon bubbling cycles before use. The $\text{H}(\text{MMA})_2\text{Br}$ initiator [$\text{H}(\text{CH}_2\text{CMeCO}_2\text{Me})_2\text{Br}$; an MMA dimer bromide] was prepared according to the literature.⁴⁰ FeBr_2 (Aldrich; 98%) and ligands [PPh_3 (Aldrich; 99%), $\text{P}(\text{MeOPh})_3$ (Wako; > 98%), $\text{P}(\text{ClPh})_3$ (Aldrich; 95%), PBu_3 (Strem; 99%), PCy_3 (Aldrich), and $\text{Ph}_2\text{P}(\text{Me}_2\text{NPh})$ (Aldrich; 95%)] were used as received and handled in a glove box under a moisture- and oxygen-free argon atmosphere ($\text{H}_2\text{O} < 1$ ppm, $\text{O}_2 < 1$ ppm). Toluene (Kishida Kagaku; purity 99.5%) was dried and purified by passing through purification columns (Solvent Dispensing System, SG Water USA, Nashua, NH; Glass Contour) and bubbled with dry nitrogen for more than 15 min immediately before use. *n*-Octane (internal standard for gas chromatography) and 1,2,3,4-tetrahydronaphthalene (tetralin; internal standard for ^1H NMR) were dried over calcium chloride and distilled twice from calcium hydride. Poly(ethylene glycol) monomethyl ether [$\text{HO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{Me}$; $n = 12$ on average] (Aldrich), *p*-toluenesulfonyl chloride (Aldrich; > 99%), pyridine (Wako; dehydrated), H_2O_2 (TCI; 35% in water), BBr_3 (TCI; ca. 1 M in CH_2Cl_2), phenylsilane (TCI; > 97%), NaOH (Wako; > 97%), HCl (Wako; 35–37% in water), Na_2SO_4 (Wako; > 99%), K_2CO_3 (Wako; > 99.5%), NaCl (Wako; > 99.5%), distilled water (Wako), CH_2Cl_2 (Wako;

super dehydrated), DMF (Wako; super dehydrated), acetone (Wako; super dehydrated), and ethyl acetate (Wako; > 99.5%) were used as received.

Synthesis of P-PEG⁴¹

Synthesis of Tris(4-hydroxyphenyl)phosphine Oxide [O=P(MeOPh)₃]

To a solution of P(MeOPh)₃ (5.00 g, 14.2 mmol) in acetone (50 mL), water (3.33 mL) and H₂O₂ (35% in water, 1.67 mL; 15 mmol) were slowly added. After stirring at room temperature for 1 h, the acetone was evaporated and CH₂Cl₂ (80 mL) was added. The organic layer was washed with brine (3 × 35 mL), the aqueous solution was extracted with CH₂Cl₂ (2 × 25 mL), and the combined organic solutions were dried over anhydrous Na₂SO₄. After filtration, the filtrate was evaporated under vacuum to give white solid (86% yield).

Synthesis of Tris(4-hydroxyphenyl)phosphine Oxide [O=P(HOPh)₃]

A solution of BBr₃ (1 M in CH₂Cl₂; 50 mL, 50 mmol) was slowly added at −78 °C to a solution of O=P(MeOPh)₃ (3.68 g, 10 mmol) in CH₂Cl₂ (35 mL) under argon. After being stirred at room temperature for 24 h, the solution was slowly poured into cold water (130 mL).

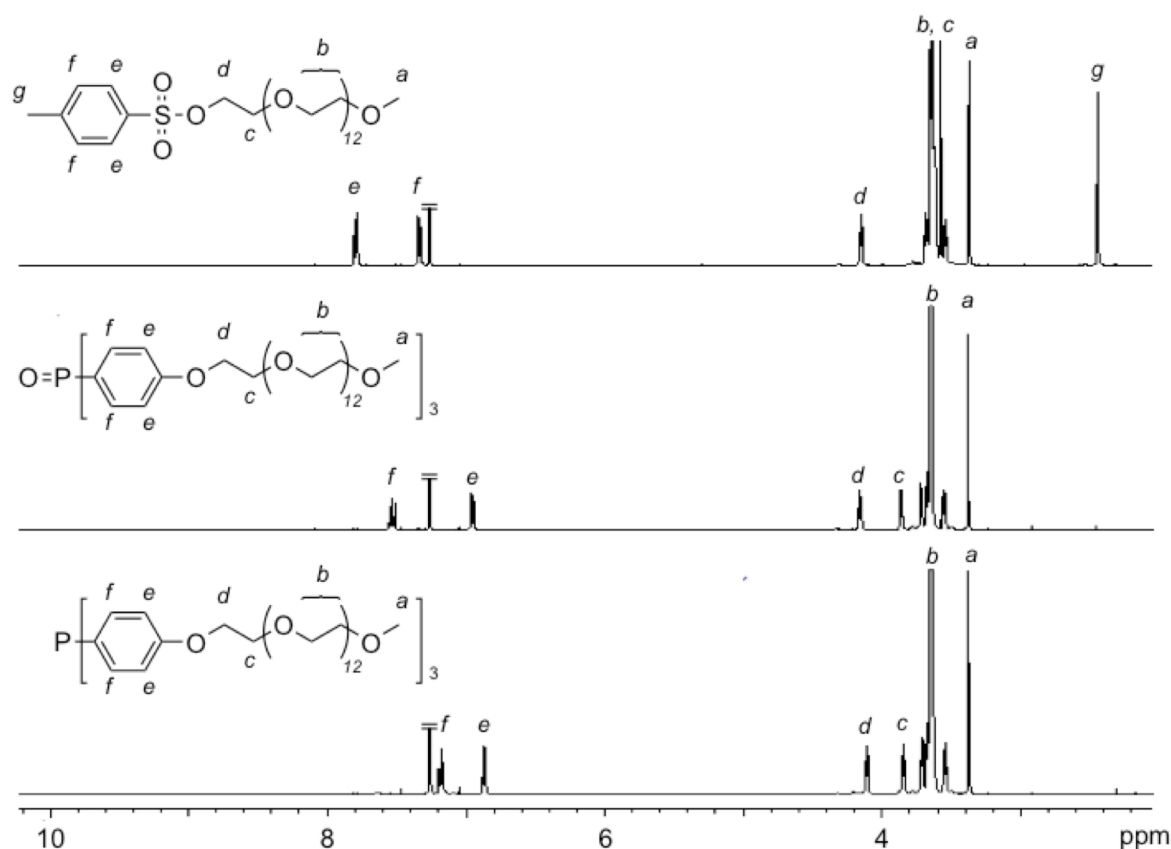


Figure 1. ¹H NMR spectra (500 MHz) of TsO-PEG, O=P-PEG or P-PEG in CDCl₃ at r.t.

After evaporation of CH_2Cl_2 , the aqueous phase was filtered and extracted with ethyl acetate (3×100 mL). The combined organic phases were washed with brine (2×10 mL). After evaporation of the solvent, recrystallization from ethyl acetate gave white solid (81% yield).

Synthesis of Poly(ethylene glycol) Methyl Ether Tosylate [TsO-PEG]

To a solution of poly(ethylene glycol) monomethyl ether (HO-PEG) (12.5 g, 22.7 mmol) and *p*-toluenesulfonyl chloride (8.66 g, 45.4 mmol) in CH_2Cl_2 (40 mL) was slowly added pyridine (3.66 mL, 45.4 mmol). The resulting solution was stirred at room temperature for 15 h. After water (10 mL) was added, NaOH was carefully added until the aqueous layer became neutral. The organic layer was washed with 1 N HCl aq and brine, successively. The organic layer was dried over anhydrous Na_2SO_4 . After filtration, the filtrate was evaporated under vacuum to give pale yellow oil (77% yield).

Synthesis of O=P-PEG

A suspension of TsO-PEG (2.13 g, 3.05 mmol), $\text{O}=\text{P}(\text{HOPh})_3$ (1.00 g, 3.05 mmol) and K_2CO_3 (4.21 g, 30.5 mmol) in DMF (70 mL) was stirred at 70 °C for 24 h under Ar. After removal of volatiles under vacuum, the residue was dissolved in CH_2Cl_2 . The organic layer was washed with 1 N HCl aq and brine, successively. The organic layer was dried over anhydrous Na_2SO_4 . After filtration, the filtrate was evaporated under vacuum (77% yield). ^{31}P NMR (202 MHz, CDCl_3): δ 29.0.

Synthesis of P-PEG

A solution of O=P-PEG (2.88 g, 1.50 mmol) and phenylsilane (3.41 mL, 30.0 mmol) in toluene (10 mL) was refluxed under argon for 24 h. After the reaction mixture was evaporated under vacuum, the residue was extracted with CH_2Cl_2 and washed with hexane. The removal of all the volatiles gave P-PEG (64% yield). Finally, the structure was characterized ^1H NMR (500 MHz, CDCl_3 : Figure 1) and ^{31}P NMR (202 Hz, CDCl_3 : δ -9.4).

Polymerization Procedures

Polymerization was carried out by the syringe technique under dry argon in baked glass tubes equipped with a three-way stopcock or in sealed glass vials. A typical example for PEGMA polymerization with the $\text{H}(\text{MMA})_2\text{Br}/\text{FeBr}_2/\text{P}(\text{MeOPh})_3$ is given below. In a round-bottom flask (50 mL) was placed FeBr_2 (4.3 mg, 0.020 mmol), $\text{P}(\text{MeOPh})_3$ (14.1 mg, 0.040 mmol), and toluene (2.91 mL) under argon gas. The solution was heated to 60 °C for 12 h to prepare bisphosphine iron complexes.⁴² After cooling the mixture to room temperature, tetralin (0.06 mL), PEGMA (0.88 mL, 2.0 mmol), and a solution of $\text{H}(\text{MMA})_2\text{Br}$ (0.15 mL,

133.7 mM in toluene) were added; the total volume was 4.00 mL. Immediately after mixing, aliquots (0.50–1.0 mL each) of the solution were injected into baked glass tubes, which were then sealed (except when a stopcock was used) and placed in an oil bath kept at 60 °C. In predetermined intervals, the polymerization was terminated by cooling the reaction mixture to –78 °C in dry ice–methanol. Monomer conversion was determined by ^1H NMR from the integrated peak area of the olefinic protons of the monomer with tetralin as an internal standard. For MMA, the same procedures as described above were applied, except that monomer conversion was determined from residual monomer concentration measured by gas chromatography with *n*-octane as an internal standard.

Measurements

For polar (co)polymers of PEGMA or HEMA, M_n and M_w/M_n were measured by size exclusion chromatography at 40 °C in DMF containing 10 mM LiBr as an eluent on three polystyrene-gel columns (Shodex KF-805 L; exclusion limit = 4×10^6 ; particle size = 10 μm ; pore size = 5000 Å; 0.8 cm i.d. $\times$ 30 cm; flow rate, 1.0 mL min $^{-1}$) connected to a PU-2080 pump and a RI-1530 refractive-index detector, and a UV-1570 ultraviolet detector (all from Jasco). The columns were calibrated against 13 standard poly(MMA) samples (Polymer Laboratories; M_n = 630–1 200 000; M_w/M_n = 1.02–1.30). For poly(MMA), M_n and M_w/M_n were measured by size exclusion chromatography at 40 °C in THF as an eluent on three polystyrene-gel columns (Shodex LF-404; exclusion limit = 2×10^6 ; particle size = 6 μm ; pore size = 3000 Å; 0.46 cm i.d. $\times$ 25 cm; flow rate, 0.3 mL min $^{-1}$) connected to a DU-H2000 pump, a RI-74 refractive-index detector, and a UV-41 ultraviolet detector (all from Shodex), similarly calibrated against standard poly(MMA) samples. ^1H NMR and ^{31}P NMR spectra were measured at room temperature on a JEOL JNM-ECA500 spectrometer operating at 500.16 and 202.47 MHz, respectively. For the ^{31}P NMR analyses, a capillary of $(\text{C}_2\text{H}_5\text{O})_2\text{POH}$ solution (50 mM in toluene- d_8) was used as an internal chemical shift standard (7.08 ppm for the phosphite).

Results and Discussion

1 Effects of the Electronic Properties with *Para*-Substituted Triphenylphosphines in PEGMA Polymerization

As shown in Scheme 1, 2 equivalents of various phosphines (PR_3) were mixed with anhydrous iron dibromide (FeBr_2) in toluene, and the solutions were kept (aged) at 60 °C for

12 h hours, to *in situ* generate the corresponding bisphosphine iron complexes $[\text{FeBr}_2(\text{PR}_3)_2]$. The resultant iron complexes were directly employed as a catalyst for polymerization of PEGMA with a bromine initiator $[\text{H}(\text{MMA})_2\text{Br}]$ in toluene.

$\text{FeBr}_2(\text{PPh}_3)_2$, an iron catalyst with the most standard phosphine ligand, triphenylphosphine (PPh_3), induced a slow polymerization, and monomer conversion was limited to below 30% (Figure 2). A ligand carrying an electron withdrawing substituent $[\text{P}(\text{ClPh})_3]$ was further less effective, virtually without monomer consumption. In contrast,

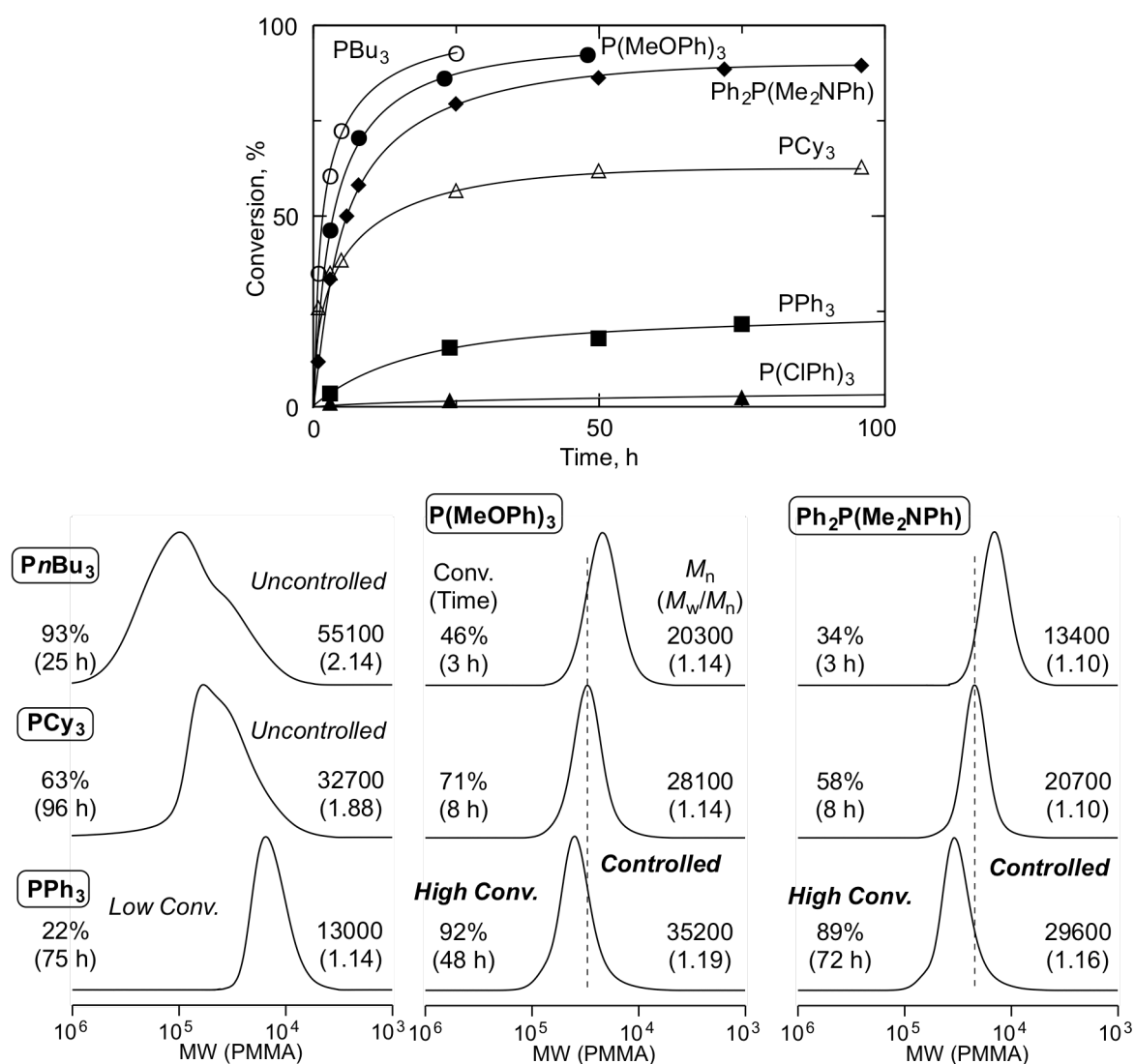


Figure 2. Effects of phosphine ligand on polymerization rate of iron-catalyzed polymerizations of PEGMA in toluene at 60 °C: $[\text{PEGMA}]_0/[\text{H}(\text{MMA})_2\text{Br}]_0/[\text{Fe-complex}]_0 = 500/5/5$ mM. The Fe-complex was prepared in prior to polymerization via aging process of FeBr_2 and 2 equivalent of phosphine ligand in toluene at 60 °C in 12 h and directly employed without purification.

when phosphines with electron donating substituents [$\text{P}(\text{Bu})_3$, PCy_3 , $\text{P}(\text{MeOPh})_3$, and $\text{Ph}_2\text{P}(\text{Me}_2\text{NPh})$] were employed, the polymerizations smoothly proceeded to give higher conversions.

Molecular weights and molecular weight distributions (MWDs) of the poly(PEGMA) obtained with these phosphine-ligated catalysts were characterized by SEC. For electron-donating alkyl phosphines ($\text{P}(\text{Bu})_3$ and PCy_3), the SEC curves were broad and sometimes bimodal ($M_w/M_n \sim 2$), indicating uncontrolled polymerizations. However, with triphenylphosphines carrying strongly electron-donating groups, such as $\text{P}(\text{MeOPh})_3$ and $\text{Ph}_2\text{P}(\text{Me}_2\text{NPh})$, the polymerizations were fairly controlled: SEC curves shifted to higher molecular weight as conversion increased, while keeping narrow molecular weight distributions ($M_w/M_n < 1.2$). Thus, enhancement of the electron density on the iron center through triphenylphosphine ligands was important in the iron-catalyzed LRP of PEGMA. Please note that there are little examples of such active catalysts to achieve higher conversions (conv. $\sim 90\%$) and narrow molecular weight distributions ($M_w/M_n < 1.20$).

2 Iron-Catalyzed Block Copolymerization of MMA with PEGMA with $\text{P}(\text{MeOPh})_3$

Ligation of $\text{P}(\text{MeOPh})_3$ on FeBr_2 was also effective for the LRP of alkyl methacrylates (MMA etc.) to give controlled polymers (Figure 3). This result encouraged the author to apply the methoxyphenyl complex for block copolymerization of MMA with PEGMA (Figure 4). To synthesize AB-type block copolymers, MMA was first polymerized. The

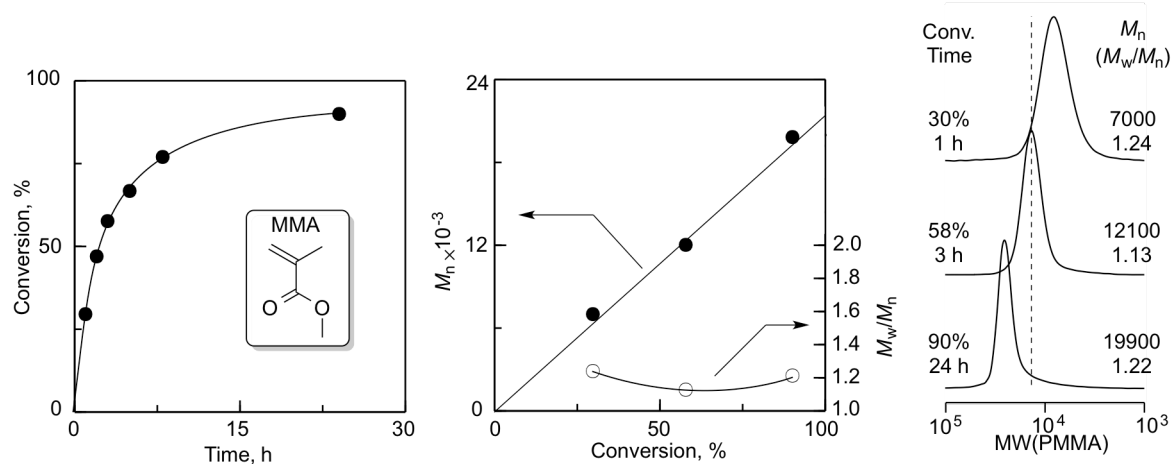


Figure 3. Iron-catalyzed polymerization of MMA with $\text{FeBr}_2\text{-P}(\text{MeOPh})_3$ complex in toluene at 60°C : $[\text{MMA}]_0/[\text{H}(\text{MMA})_2\text{Br}]_0/[\text{Fe-complex}]_0 = 4000/20/10$ mM. Fe-complex was prepared in prior to polymerization via aging process of FeBr_2 and 2 equivalent of $\text{P}(\text{MeOPh})_3$ in toluene at 60°C for 12 hours and directly employed without purification.

resulting PMMA (with a halogen-capped dormant terminal) was separated and employed as a macroinitiator for the second-stage polymerization of PEGMA.

Thus, the author first carried out MMA polymerization with $\text{FeBr}_2/\text{P}(\text{MeOPh})_3$ and the bromide initiator in toluene at 60 °C: $[\text{MMA}]_0 = 4.0 \text{ M}$; $[\text{H}(\text{MMA})_2\text{Br}]_0 = 20 \text{ mM}$; $[\text{FeBr}_2]_0 = 10 \text{ mM}$; $[\text{P}(\text{MeOPh})_3]_0 = 20 \text{ mM}$. When conversion reached about 60% in 2.5 h, the polymerization was quenched, and reprecipitation into methanol gave a colorless sample of PMMABr ($M_n = 14700$; $M_w/M_n = 1.12$; terminal Br functionality >90% by ^1H NMR) (Figure

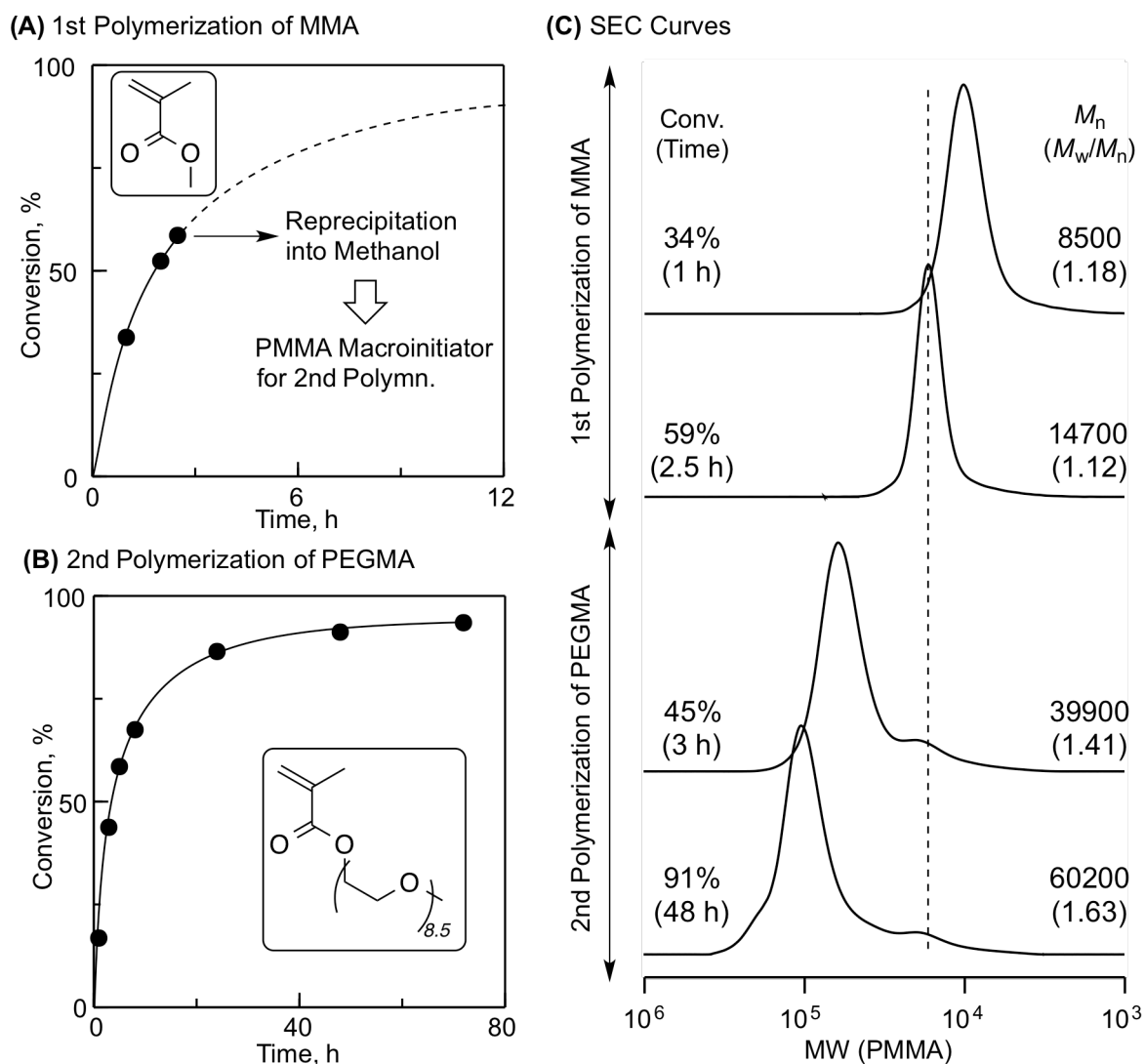


Figure 4. Iron-catalyzed block copolymerization of MMA and PEGMA with $\text{FeBr}_2/\text{P}(\text{MeOPh})_3$ complex. (A) Polymerization for synthesis of PMMA-macroinitiator: $[\text{MMA}]_0/[\text{H}(\text{MMA})_2\text{Br}]_0/[\text{Fe-complex}]_0 = 4000/20/10 \text{ mM}$ in toluene at 60 °C. (B) Polymerization for PMMA-*block*-PPEGMA: $[\text{PEGMA}]_0/[\text{PMMABr}]_0/[\text{Fe-complex}]_0 = 500/5/5 \text{ mM}$ in toluene at 60 °C.

4A). The Br-capped polymer was employed to initiate PEGMA polymerization with a freshly aged catalyst [FeBr_2 and 2eq $\text{P}(\text{MeOPh})_3$].

PEGMA conversion smoothly reached 91% in 48 h, as with the corresponding homopolymerization with $\text{H}(\text{MMA})_2\text{Br}$ (Figure 4B). Thus, the catalytic activity was well retained in the two-stage consecutive block copolymerization. In the SEC curves of the final products, a very small peak was detected, indicative of some “dead” PMMA from the first-stage polymerization, but the main peak clearly shifted to higher molecular weight keeping narrow MWD.

3 Decoration with Polar Electron-Donating Substituents toward Robust Iron Catalyst

As shown above, the introduction of electron-donating phosphines was effective to enhance the catalytic activity of iron catalysts. However, these systems were confined to the use in toluene and related nonpolar media and seem not robust enough against polar groups such as hydroxyl. For example, a polymerization solution of PEGMA with $\text{FeBr}_2/\text{P}(\text{MeOPh})_3$ immediately faded from original yellow into colorless upon addition of a few drops of methanol, suggesting dissociation of the ligands to form an unidentified phosphine-free iron complex or compound.

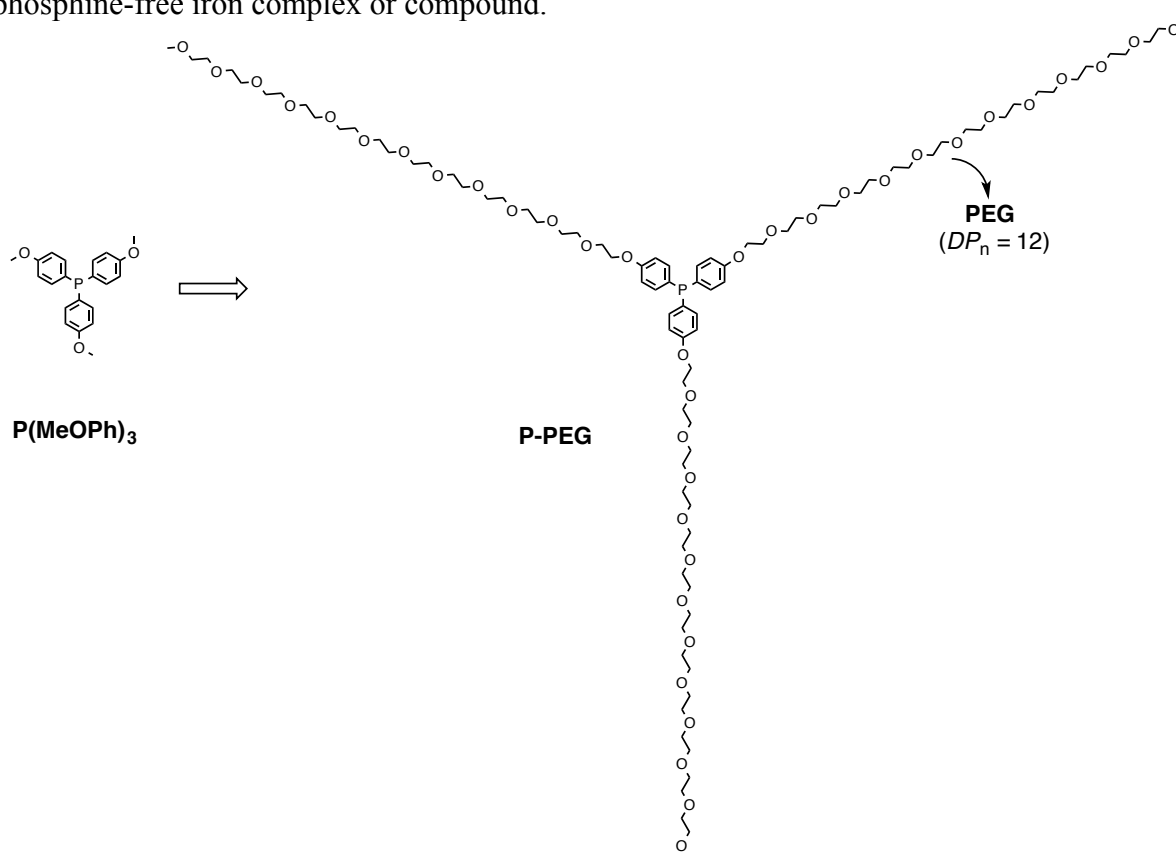


Figure 5. Decoration of *para*-substitution of triphenylphosphine with PEG chain.

The author thus embarked on an additional design of ligand to more effectively “protect” the iron center from potentially poisonous polar groups. His focus was then directed to the replacement of the three methoxy groups ($-\text{OCH}_3$) in $\text{P}(\text{MeOPh})_3$ with poly(ethylene glycol) chains [PEG: $-\text{O}(\text{CH}_2\text{CH}_2\text{O})_{12}\text{CH}_3$] into a tris(PEGylated phenyl)phosphine **P-PEG** (Figure 5). This decoration was based on the following aspects: (i) despite its polar and polyether character, PEG would not be so poisonous to iron complexes, as suggested by the successful PEGMA polymerization discussed above; (ii) the bulkiness and higher polarity of PEG would contribute to the protection of the central iron from polar groups, sterically, electronically, or both.

4 Catalytic Activity of Iron Complex with P-PEG on PEGMA Polymerization

To examine the catalytic activity of the $\text{FeBr}_2/\text{P-PEG}$ system, the author first performed PEGMA polymerization in toluene at 60°C , under the same conditions as with $\text{P}(\text{MeOPh})_3$ (Figure 6). The aging with FeBr_2 gave a yellow homogeneous solution similar to that with the methoxy derivative, indicating a similar diphosphine ligation. The polymerization was also comparable in terms of reaction rate (catalytic activity) as well as molecular weight and MWD control: M_n was linearly increased with conversion, and M_w/M_n was kept below 1.12. Namely, the three PEG chains on the *para* positions effectively enhance catalytic activity by electron-donation and perhaps protect the iron center, without entailing adverse effects.

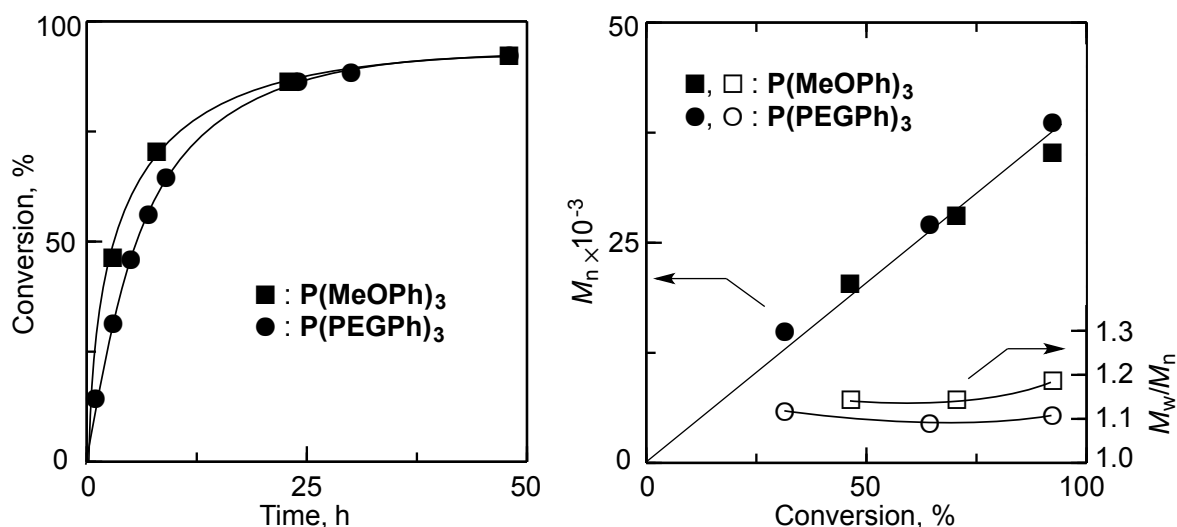


Figure 6. Conversion vs M_n and M_w/M_n plots for iron-catalyzed LRPs of PEGMA with **P-PEG** or $\text{P}(\text{MeOPh})_3$ as a ligand in toluene at 60°C : $[\text{PEGMA}]_0/[\text{H}(\text{MMA})_2\text{Br}]_0/[\text{Fe-complex}]_0 = 500/5/5$ mM. Fe-complex was prepared in prior to polymerization via aging process of FeBr_2 and 2 equivalent of phosphine ligand in toluene at 60°C in 12 h and directly employed without purification.

5 Tolerance to Hydroxyl Group of Iron Catalysts: UV-vis Analysis

When a small portion of ethanol was added to a toluene solution of the **P-PEG**-iron complex, the yellow color remained unchanged, in contrast to the fast discoloration of the $\text{P}(\text{MeOPh})_3$ system (see above). The apparent robustness of the **P-PEG**-complex was

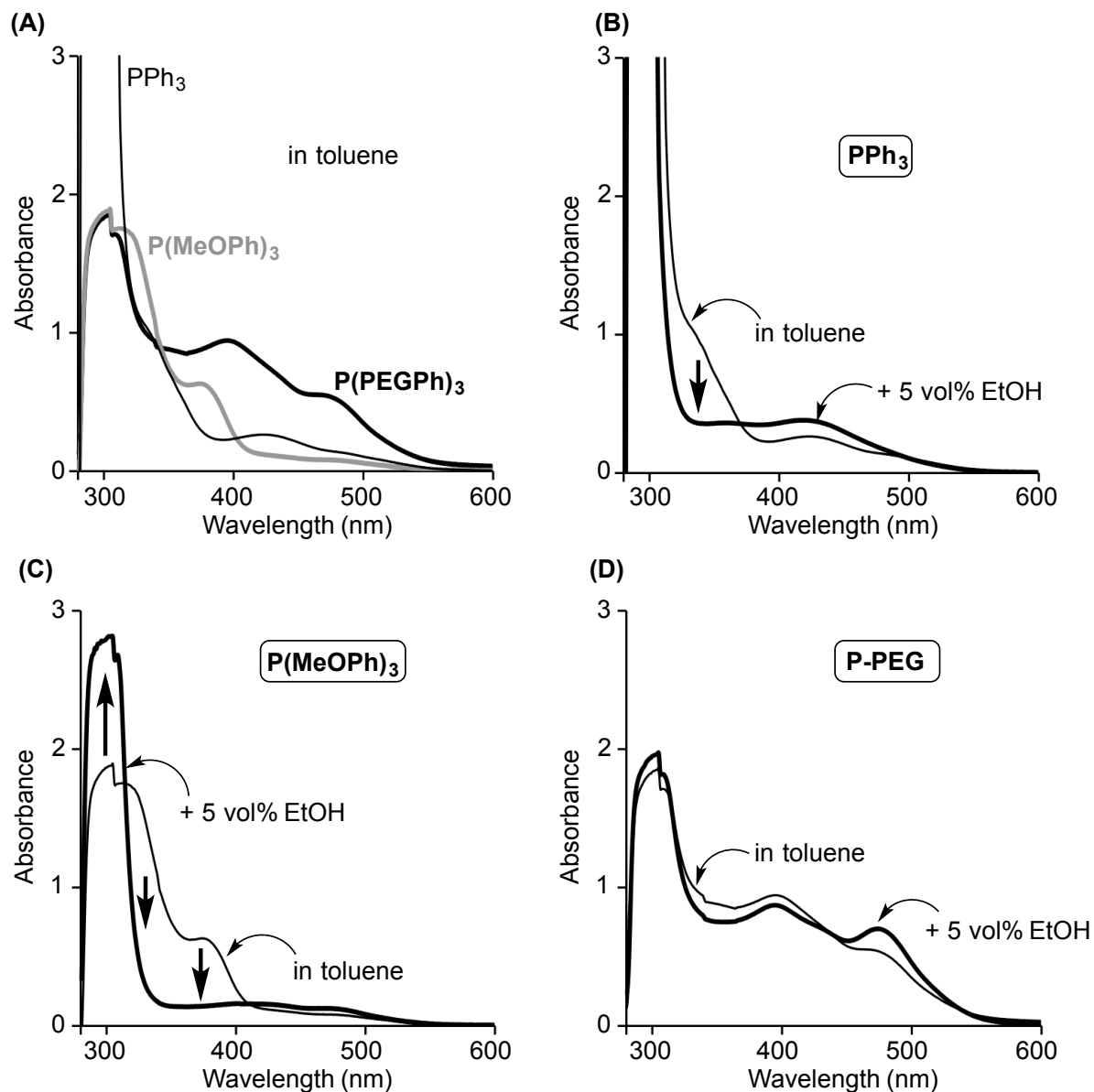


Figure 7. UV-vis spectra (280–600 nm) of FeBr_2 complexes with PPh_3 , $\text{P}(\text{MeOPh})_3$, and **P-PEG** in toluene or 5 vol% ethanol-contained toluene at room temperature: (A) comparison among the three complexes in toluene; (B–D) effects of ethanol addition on complexation [(B) PPh_3 , (C) $\text{P}(\text{MeOPh})_3$, (D) **P-PEG**]. The Fe-complex was prepared via aging process of FeBr_2 and 2 equivalent of phosphine ligand in toluene at 60 °C in 12 h ($[\text{FeBr}_2]_0 = 5.0 \text{ mM}$, $[\text{ligand}]_0 = 10.0 \text{ mM}$). The aged solutions were diluted with toluene to make 1.0 mM concentration, followed by filtration for the measurement.

further evaluated by UV–vis spectroscopy.

Figure 7 shows UV–vis spectra (280–600 nm) of FeBr_2 complexes with three phosphine ligands [PPh_3 , $\text{P}(\text{MeOPh})_3$, and **P-PEG**], either in the presence and the absence of ethanol. All the complexes were prepared by mixing and aging FeBr_2 and 2 equivalents of each phosphine in toluene at 60 °C for 12 h, and the solutions, all yellow independent of the ligands, were subject to spectroscopic analysis without further purification and treatment. The spectra generally consisted two characteristic peaks, one at 320–400 nm most likely from charge-transfer or d–d transition and the other at ~ 300 nm, indicative of a free phosphine (or ligand dissociation).

In the alcohol-free solutions (Figure 7A), the free ligand signal was very strong and off-scale with $\text{FeBr}_2(\text{PPh}_3)_2$, showing dominant ligand dissociation even in the nonpolar medium and thus the lower stability of the catalyst, as already pointed in the literature. On the other hand, free phosphine was much less detectable with $\text{P}(\text{MeOPh})_3$ or **P-PEG**, and the coordination of these *para*-substituted electron-donating ligands was relatively tight and effectively enriches electron density of the iron center.

Upon addition of ethanol (5 vol%), the yellow solutions with PPh_3 and $\text{P}(\text{MeOPh})_3$ immediately faded into colorless, while the free ligand signal enhanced and the red-shifted transition signals weakened [Figure 7 (B) and (C)]. All these indicate facile decomposition, or lesser stability, of the two complexes. Rather antithetically, the **P-PEG**-complex is apparently much more resistant to alcohol; the solution remained yellow and the whole spectrum was hardly changed (Figure 7D), unless the added ethanol was in excess over 5 vol%. These analyses supported that PEGylated phosphine-iron complex is relatively robust and tolerant of alcohol or hydroxyl group.

6 Random Copolymerization of PEGMA with HEMA

The above results with UV–vis analyses encouraged the author to employ $\text{FeBr}_2/\text{P-PEG}$ for polymerizations of functional polar monomers and specifically for quaternary random copolymerization of methacrylates [HEMA, PEGMA, MMA, and benzyl methacrylate (BzMA): Scheme 2]. Control of such a multicomponent random copolymerization of functionalized monomers is important for industrial applications, particularly with an iron catalyst.

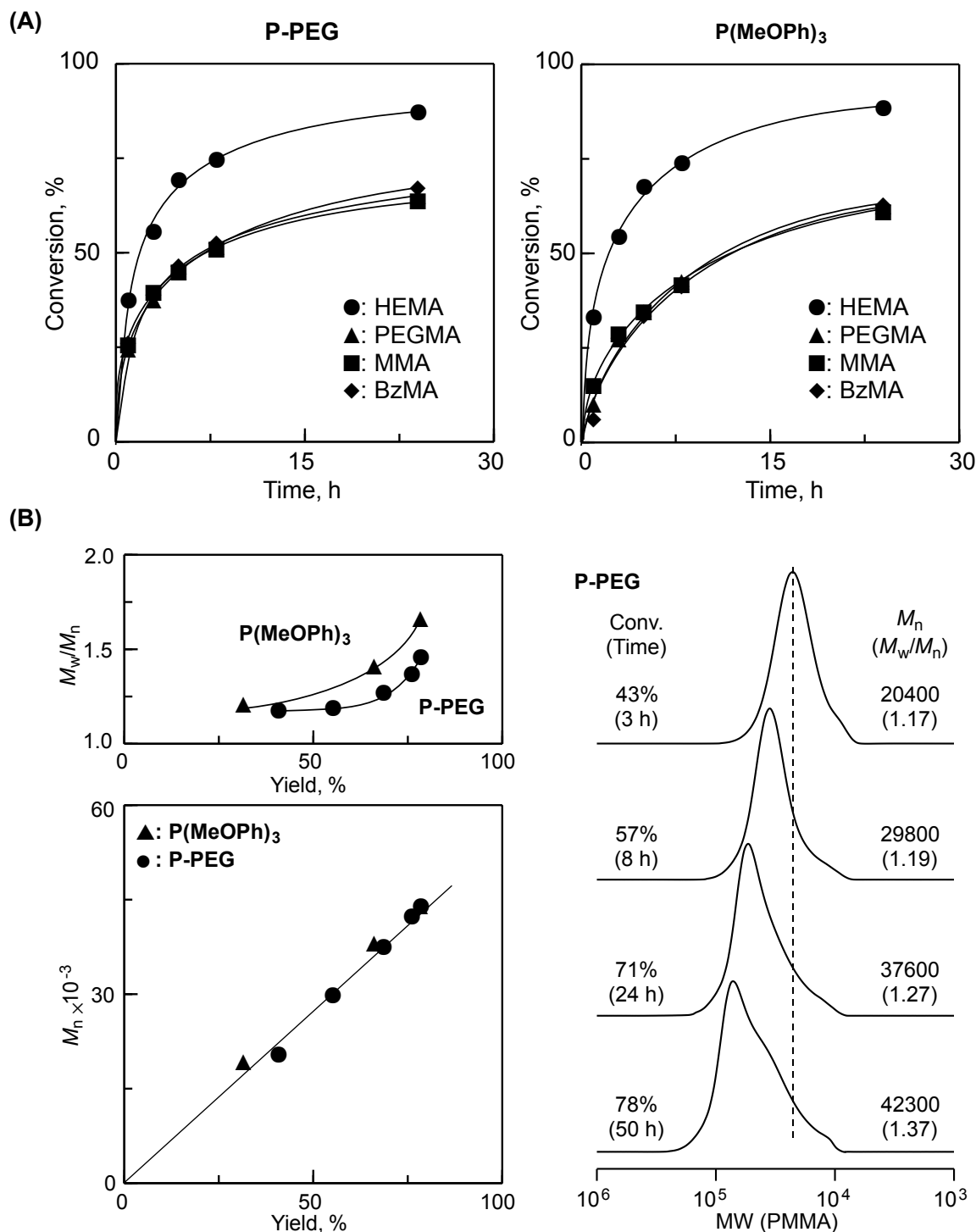
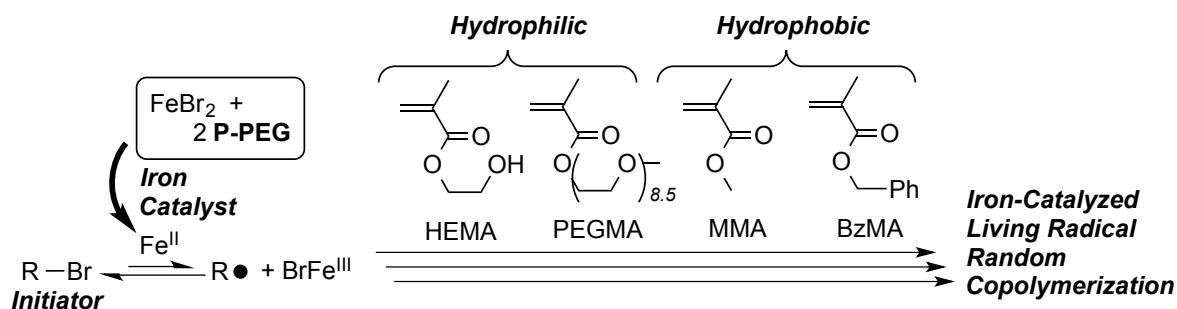


Figure 8. Iron-catalyzed living radical random copolymerization of HEMA, PEGMA, MMA and BzMA with FeBr_2 -**P-PEG** complex in toluene at 60 °C: $[\text{HEMA}]_0/[\text{PEGMA}]_0/[\text{MMA}]_0/[\text{BzMA}]_0/[\text{H}(\text{MMA})_2\text{Br}]_0/[\text{Fe-complex}]_0 = 250/250/250/250/5/5$ mM. The Fe-complex was prepared in prior to polymerization via aging process of FeBr_2 and 2 equiv of **P-PEG** in toluene at 60 °C in 12 h and directly employed without purification.



Scheme 2. Iron-Catalyzed Living Radical Random Copolymerization of HEMA, PEGMA, MMA, and BzMA with $FeBr_2$ -**P-PEG** Complex

The four monomers were smoothly consumed at similar rates, although HEMA conversion was a little higher (Figure 8A), and conversion reached over 70% in 24 h for each component [87% (HEMA); 65% (PEGMA); 64% (MMA); 67% (BzMA)]. As shown in Figure 8B, M_n s of obtained copolymers were linearly increased with copolymer yield (calculated from conversion). At the initial stages, narrow MWDs were observed ($M_w/M_n < 1.20$), but the SEC curves broadened as the polymerization proceeded, and minor peaks of apparently dead polymers chains were detected. However, the M_w/M_n values were lower than with $P(\text{MeOPh})_3$, likely due to higher tolerance to the hydroxyl group.

Conclusion

In this chapter, the author has approached robust iron-catalyzed LRPs via modification of phosphine ligand. An introduction of electron donating substitute (i.e., methoxy- or dimethylamino-) of the bis(phosphine)iron complex $[FeBr_2(PR_3)_2]$ dramatically increased polymerization rate up to higher conversion for PEGMA; nevertheless, the polymerization was well controlled to give narrow molecular weight distributions ($M_w/M_n < 1.2$). The high catalytic activity allowed iron-catalyzed block copolymerization of MMA with PEGMA. In addition, polar macromolecular (i.e., PEG) substituents on ligand were particularly effective for an enhancement of catalytic activity of polymerization of HEMA as well as PEGMA due to protection effect of iron center from polar groups. However, it was still difficult to control polymerizations of more polar monomers, such as dimethylaminoethyl methacrylate, methacrylic acid, even with the iron catalyst of the PEG-decollated ligand. Thus, the author's next efforts would be directed to other iron precursors instead of $FeBr_2$ to be combined with the related designer phosphine ligands toward more robust and applicable iron catalysts.

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Chapter 6

Guanidine-Based P-N Chelate Ligand for Iron-Catalyzed Living Radical Polymerization

Abstract

A guanidine-based P-N chelate ligand (**PGBoc**) was designed as for iron-catalyzed living radical polymerization. Due to P-N chelation and bulkiness, **PGBoc** was a promising ligand for active and robust iron-catalysis in polymerization of functional monomers. The $\text{FeBr}_2/\text{PGBoc}$ catalyst allowed highly active and controlled polymerization of poly(ethylene glycol) methacrylate (PEGMA): the monomer almost quantitatively consumed ($> 95\%$ in 24 h) and the molecular weight distributions of obtained polymers were fairly narrow ($M_w/M_n = 1.22\text{--}1.25$). In contrast, the catalyst with combination of PMePh_2 and $\text{Boc}_3\text{-guanidine}$ caused less activity for polymerization of PEGMA, and this result indicated effective P-N chelation of **PGBoc**. Furthermore, the catalyst prepared from **PGBoc** and iron bromide (FeBr_2 or FeBr_3) enabled living (co)polymerization of (2-hydroxyethyl) methacrylate (HEMA), which is a functional monomer with hydroxyl pendant: for $\text{FeBr}_2/\text{PGBoc}$, controlled copolymerization of PEGMA/HEMA (1/1) proceeded smoothly ($M_w/M_n = 1.27\text{--}1.35$). Additionally, FeBr_3 enhanced controllability and allowed controlled homopolymerization of HEMA ($M_w/M_n = 1.21$), though the polymerization became slower than FeBr_2 .

Introduction

Radical polymerization has been widely utilized for industrial synthesis of polymeric materials due to versatile and user-friendly process: a range of applicable monomers is remarkably wide and stringent conditions, such as dehydration and strict purification of reagents, are not required. The properties of polymeric materials greatly depend on the polymer structure, and thus precision polymer syntheses in radical process have been strongly desired.

Transition metal-catalyzed living radical polymerization (Mt-LRP,¹⁻³ also known as ATRP⁴⁻⁷) was first reported in 1995,¹ and have been developed as a convenient tool for precision polymer synthesis. Mt-LRP has high end-functionality, high initiation efficiency and easy initiator designability; therefore it have been widely utilized and applied in industry⁸ and biochemistry⁹ as well as polymer chemistry.¹⁰ In Mt-LRP, metal complex (M^n) reversibly activates carbon-halogen bond (R-X: “dormant” species) of initiator or growing terminal into carbon radical (R•: “active” species) along with the one electron redox of the metal complex ($M^n \leftrightarrow M^{n+1}X$). The reversible activation controls the instant radical concentration to prevent bimolecular termination and undesired side-reactions, and living radical polymerization proceeds. Thus, metal complexes play an important role in Mt-LRP and have been studied about several central metals (e.g., Ru,¹ Fe,¹¹ Ni^{12,13} and Cu⁴) with various ligands. Among them, iron (Fe)-based complexes are attractive for applications in the environmental and sustainable point of view.

Iron has been attracted attention due to low price, low toxicity, and abundance on earth. Additionally, iron has wide oxidation state from -2 to +6 (mainly +2 and +3), and many iron-containing metalloproteins (e.g., hemoglobin, catalase and cytochrome) show great activity in the biological system. Therefore, various organic reactions have been developed with iron^{14,15} and iron-catalyzed living radical polymerization has also been actively investigated.¹⁶⁻¹⁸ Unfortunately, however, most iron catalysts showed lower activity and stability compared to Ru and Cu counterparts, and especially polymerization of functional monomers have been very difficult with ordinary iron catalysts.

So far, several iron complexes have been developed for functional monomers,¹⁹⁻²⁵ however, monomer versatility and controllability are still insufficient. Therefore, more robust iron catalyst is desired for more useful and versatile system. The author have previously found that a PEG-decorated phosphine was a effective ligand to enhance tolerance of iron complex against functional groups (i.e., PEG and hydroxyl group):²⁶ the iron complex

prepared from the ligand and FeBr₂ allowed controlled copolymerization of PEGMA, HEMA, and other two alkyl methacrylates as well as homopolymerization of PEGMA and block copolymerization of PEGMA with MMA. However, the copolymerization was retarded and the molecular weight distributions became broader at high conversion ($M_w/M_n \sim 1.4$).

In this chapter, a phosphine ligand with *tert*-butoxy carbonyl (Boc)-protected guanidine [**PGBoc**: Ph₂PCH₂CH₂NHC(NBoc)NHBoc] was designed for more active and tolerant iron complex to functional monomers. **PGBoc** was a hetero P-N chelate ligand, namely both of the phosphine and Boc-protected guanidine could coordinate to iron center as other guanidine-ligated iron complexes were reported.^{27–29} The hetero P-N or P-O chelated iron complexes were reported higher activity in Mt-LRP compared to the catalyst with monodentate ligands or homo P-P or N-N chelate ligands.^{30–32} Furthermore, bulkiness of Boc-groups was expected to protect iron center from poisonous functional groups. For these reason, the author employed **PGBoc** with iron bromides toward robust iron catalysis in Mt-LRP.

Experimental

Materials

PEGMA [CH₂C(CH₃)COO(CH₂CH₂O)_nCH₃; $n = 8.5$ (number-average)] (Aldrich) and HEMA (Aldrich; > 99%) was purified by passing through an inhibitor-removal column (Aldrich) and were subsequently degassed by three-time vacuum-argon bubbling cycles before use. **PGBoc** (Chapter 3) and H-(MMA)₂-Br³³ initiator [H(CH₂CMeCO₂Me)₂Br] were prepared according to the literature. FeBr₂ (Aldrich; 98%), FeBr₃ (Aldrich; 98%) and ligands [PPh₃ (Aldrich; 99%), PMePh₂ (Aldrich; 99%), P(MeOPh)₃ (Wako; > 98%) and PNH₂ (Aldrich; > 95.0%)] were used as received without further purification and handled in a glovebox (MBraun Labmaster 130, M. Braun Inertgas-Systeme GmbH, Garching, Germany) under a moisture- and oxygen-free argon atmosphere (H₂O < 1 ppm; O₂ < 1 ppm). Toluene (Kishida Kagaku; purity 99.5%) was dried and purified by passing through purification columns (Solvent Dispensing System, SG Water USA, Nashua, NH; Glass Contour) and bubbled with dry nitrogen for more than 15 min immediately before use. THF (Wako; super dehydrated) was bubbled with dry nitrogen for more than 15 min immediately before use. 1,2,3,4-tetrahydronaphthalene (tetralin; internal standard for ¹H NMR) was dried over calcium chloride and distilled from calcium hydride. *N,N'*-bis(*tert*-butoxycarbonyl)-

1*H*-pyrazole-1-carboxamidine (TCI; > 98.0%), *N*-ethyl-diisopropylamine (Wako; > 97.0%), ethyl acetate (Wako; > 99.5%) and silica gel (Wako; Wakogel® C-200) were used as received.

Polymerization Procedure

Polymerization was carried out by the syringe technique under dry argon in baked glass tubes equipped with a three-way stopcock or in sealed glass vials. An example for PEGMA polymerization with H-MMA₂-Br/FeBr₂/**PGBoc** in toluene at 60 °C is given below. FeBr₂ (4.3 mg, 0.020 mmol), 100 mM **PGBoc** in toluene (0.4 mL, 0.040 mmol) and toluene (2.54 mL) was placed in a Schlenk tube. The solution was heated to 60 °C for 12 h to prepare iron complex. After cooling the mixture to room temperature, tetralin (0.08 mL), PEGMA (0.88 mL, 2.0 mmol) and 200 mM H-MMA₂-Br in toluene (0.10 mL, 0.020 mmol) were added; the total volume was 4.0 mL. Immediately after mixing, aliquots (0.50–1.0 mL each) of the solution were injected into baked glass tubes, which were then sealed (except when a stopcock was used) and placed in an oil bath kept at 60 °C. In predetermined intervals, the polymerization was terminated by cooling the reaction mixture to –78 °C in dry ice–methanol. Monomer conversion was determined by ¹H NMR from the integrated peak area of the olefinic protons of the monomer with tetralin as an internal standard.

Measurements

For poly(PEGMA) and poly(HEMA), M_n and M_w/M_n were measured by size exclusion chromatography at 40 °C in DMF containing 10 mM LiBr as an eluent on three polystyrene-gel columns (Shodex KF-805 L; exclusion limit = 4×10^6 ; particle size = 10 μm; pore size = 5000 Å; 0.8 cm i.d. × 30 cm; flow rate, 1.0 mL min^{–1}) connected to a PU-2080 pump and a RI-1530 refractive-index detector, and a UV-1570 ultraviolet detector (all from Jasco). The columns were calibrated against 13 standard poly(MMA) samples (Polymer Laboratories; M_n = 630–1 200 000; M_w/M_n = 1.02–1.30). For poly(MMA), M_n and M_w/M_n were measured by size exclusion chromatography at 40 °C in THF as an eluent on three polystyrene-gel columns (Shodex LF-404; exclusion limit = 2×10^6 ; particle size = 6 μm; pore size = 3000 Å; 0.46 cm i.d. × 25 cm; flow rate, 0.3 mL min^{–1}) connected to a DU-H2000 pump, a RI-74 refractive-index detector, and a UV-41 ultraviolet detector (all from Shodex). The columns were calibrated against 13 standard poly(MMA) samples (Polymer Laboratories; M_n = 630–1 200 000; M_w/M_n = 1.02–1.30). ¹H NMR and ³¹P NMR spectra

were measured at room temperature on a JEOL JNM-ECA500 spectrometer operating at 500.16 and 202.47 MHz, respectively. For the ^{31}P NMR analyses, a capillary of diethyl phosphite solution (50 mM in toluene- d_8) was used as an internal chemical shift standard (7.08 ppm for the phosphite).

Results and Discussion

1 Active Catalysis of PGBoc-Coordinated Iron Complex for PEGMA Polymerization

Phosphine ligands [PPh_3 , PGBoc , $\text{P}(\text{MeOPh})_3$ and PNH_2] were mixed with iron(II) bromide in toluene at 60 °C overnight to form iron complexes, and the resultant solutions directly employed for iron-catalyzed living radical polymerization of PEG-containing methacrylate monomer (PEGMA) in toluene at 60 °C, in conjunction with dimeric bromine

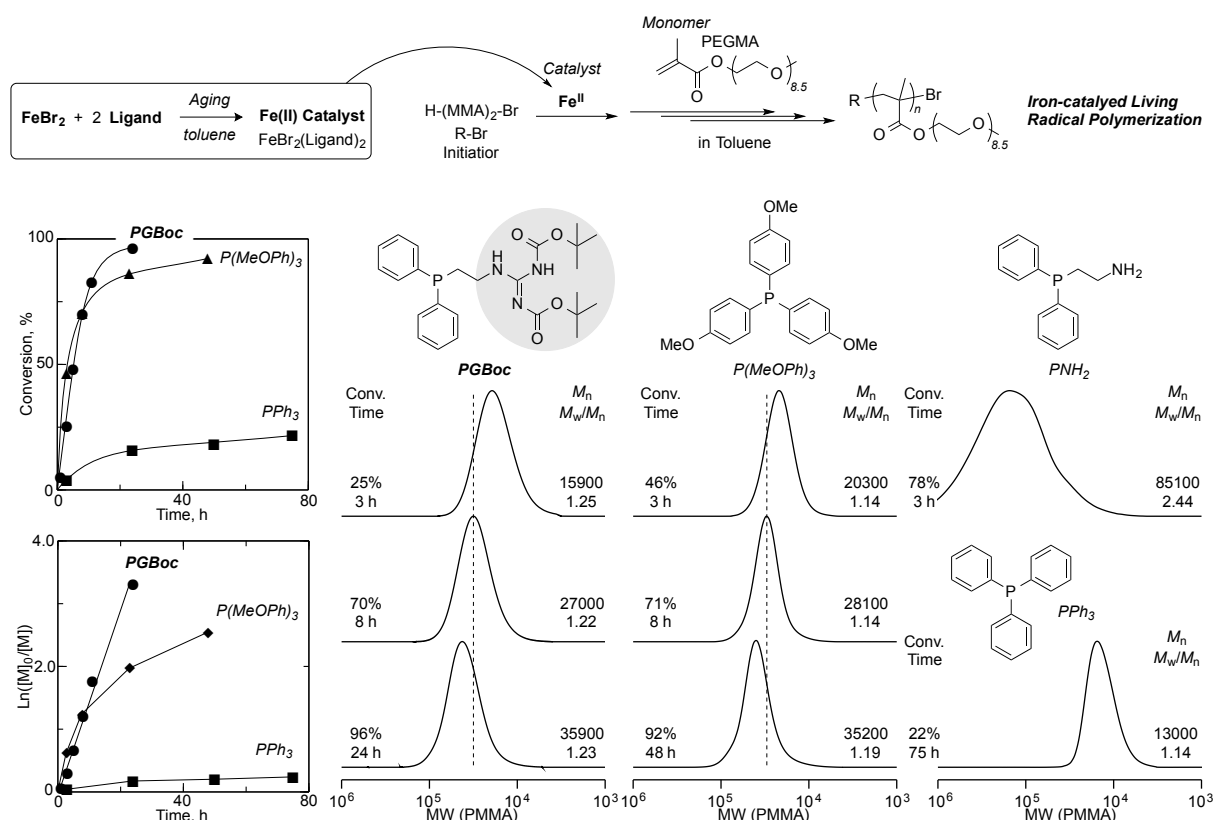


Figure 1. Effects of ligands on iron catalyzed living radical polymerization of PEGMA in toluene at 60 °C with FeBr_2 : $[\text{PEGMA}]_0 = 500 \text{ mM}$; $[\text{H-(MMA)}_2\text{-Br}]_0 = 5.0 \text{ mM}$; $[\text{FeBr}_2]_0 = 5.0 \text{ mM}$; $[\text{ligand}]_0 = 10 \text{ mM}$.

type initiator [H-(MMA)₂-Br] (Figure 1). PEGMA is a typical functional monomer and has been widely utilized for functional polymer materials such as self-assembled polymers and PEGylated biomolecules. A conventional iron catalyst obtained from FeBr₂ and PPh₃ was less active for PEGMA probably because iron catalyst was poisoned by PEG group: the monomer conversion was below 25% in 75 h. In contrast, FeBr₂/**PGBoc** catalyst increased the polymerization rate up to higher monomer conversion (> 95% in 24 hours), and the obtained polymer was fairly controlled: the molecular weights were increased as monomer conversion, and the molecular weight distributions were narrow ($M_w/M_n = 1.22\text{--}1.25$). Another P-N chelate ligand **PNH₂** allowed very fast polymerization (conversion reached at 78% in 3 h); however, the obtained polymer was not controlled ($M_w/M_n > 2.4$). On the other hand, an electron-rich triarylphosphine [P(MeOPh)₃] also showed high activity for iron-catalyzed PEGMA polymerization as the author's recent report (Conv. 92 % in 48 h, $M_w/M_n < 1.2$),²⁶ however, the first-order kinetic plot [$\ln([M]_0/[M])$ versus time] was not linear, whereas the plot with **PGBoc** was almost linear. This nonlinear plot indicated radical species were decreasing during the polymerization due to inactivation of iron catalyst.

These results suggested that iron catalyst prepared from FeBr₂ and **PGBoc** was more stable and suitable for functional polymer synthesis than those from **PPh₃**, **PNH₂** and **P(MeOPh)₃**.

2 Chelation Effect of PGBoc in Iron-Catalyzed PEGMA Polymerization

To study P-N chelation effect of **PGBoc**, either or both of Boc₃Gua and PMePh₂ were employed with FeBr₂ for polymerization of PEGMA in the same condition as mentioned above (Figure 2). For either Boc₃Gua or PMePh₂, the PEGMA conversion reached over 85% and the obtained polymers were fairly controlled ($M_w/M_n \sim 1.2$), though the polymerizations were slower than **PGBoc** and were retarded below 90% conversion. However, for the combination of Boc₃Gua and PMePh₂, the polymerization became slower and stopped around 60% conversion, and the obtained polymer was less controlled ($M_w/M_n > 1.3$). These results indicated P-N chelation of **PGBoc** was effective for iron catalyzed polymerization of PEGMA.

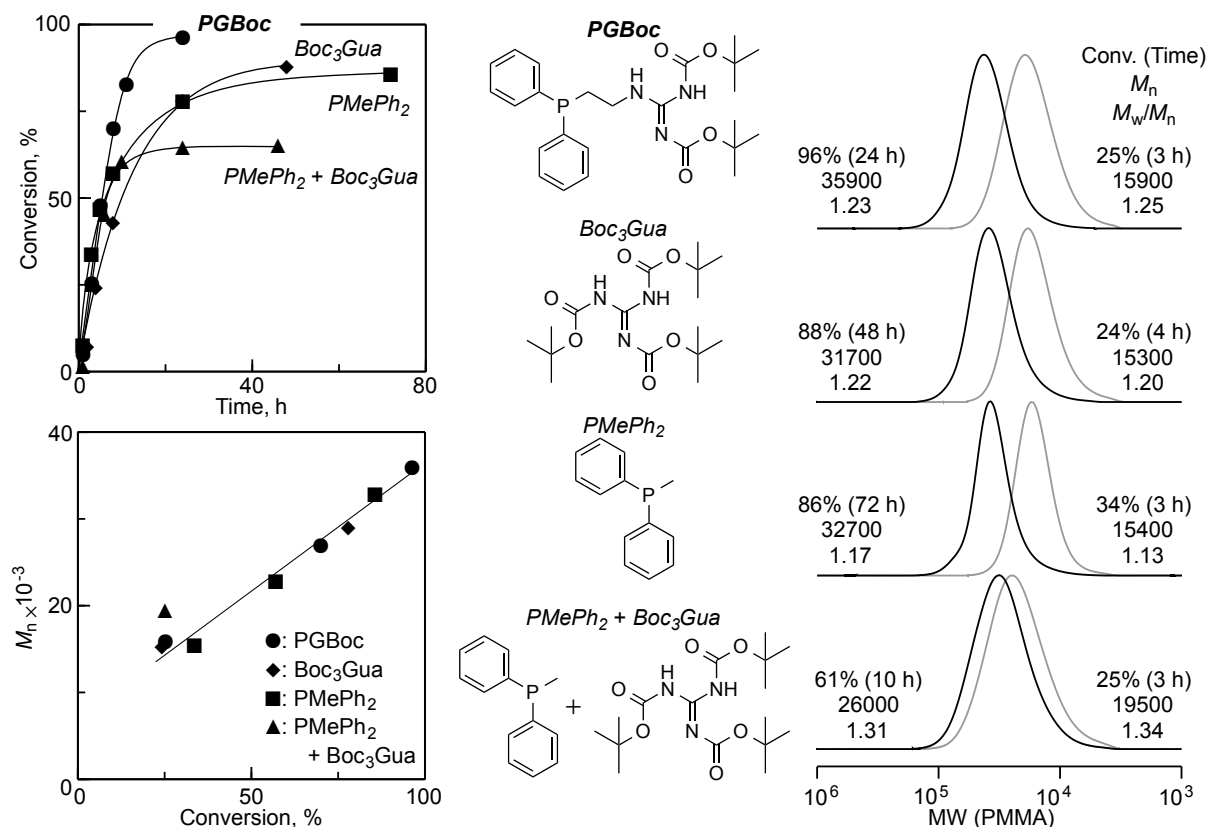


Figure 2. Chelation effect of **PGBoc** in iron catalyzed living radical polymerization of PEGMA in toluene at 60 °C: [PEGMA]₀ = 500 mM; [H-(MMA)₂-Br]₀ = 5.0 mM; [FeBr₂]₀ = 5.0 mM; [phosphine ligand]₀ = 0 or 10 mM; [Boc₃Gua]₀ = 0 or 10 mM.

3 Effect of the Ratio of PGBoc to FeBr₂

Three different amount of **PGBoc** (1, 2 or 3 equivalents to FeBr₂) were employed for iron-catalyzed polymerization of PEGMA to investigate the effect of the amount of **PGBoc** (Figure 3). As increasing the amount of **PGBoc**, the polymerization became faster but the molecular weight distributions of obtained polymers became a little broader, though the monomers smoothly consumed and the obtained polymers were basically controlled in all cases. In the following polymerizations, two equivalent of **PGBoc** to FeBr₂ was employed considering both polymerization rate and controllability.

4 HEMA (Co)polymerization

HEMA is a functional monomer with hydroxyl group, and its (co)polymers are applied for functional polymer materials. However, iron-catalyzed (co)polymerizations of HEMA are difficult probably because many iron complexes are poisoned by hydroxyl group. The

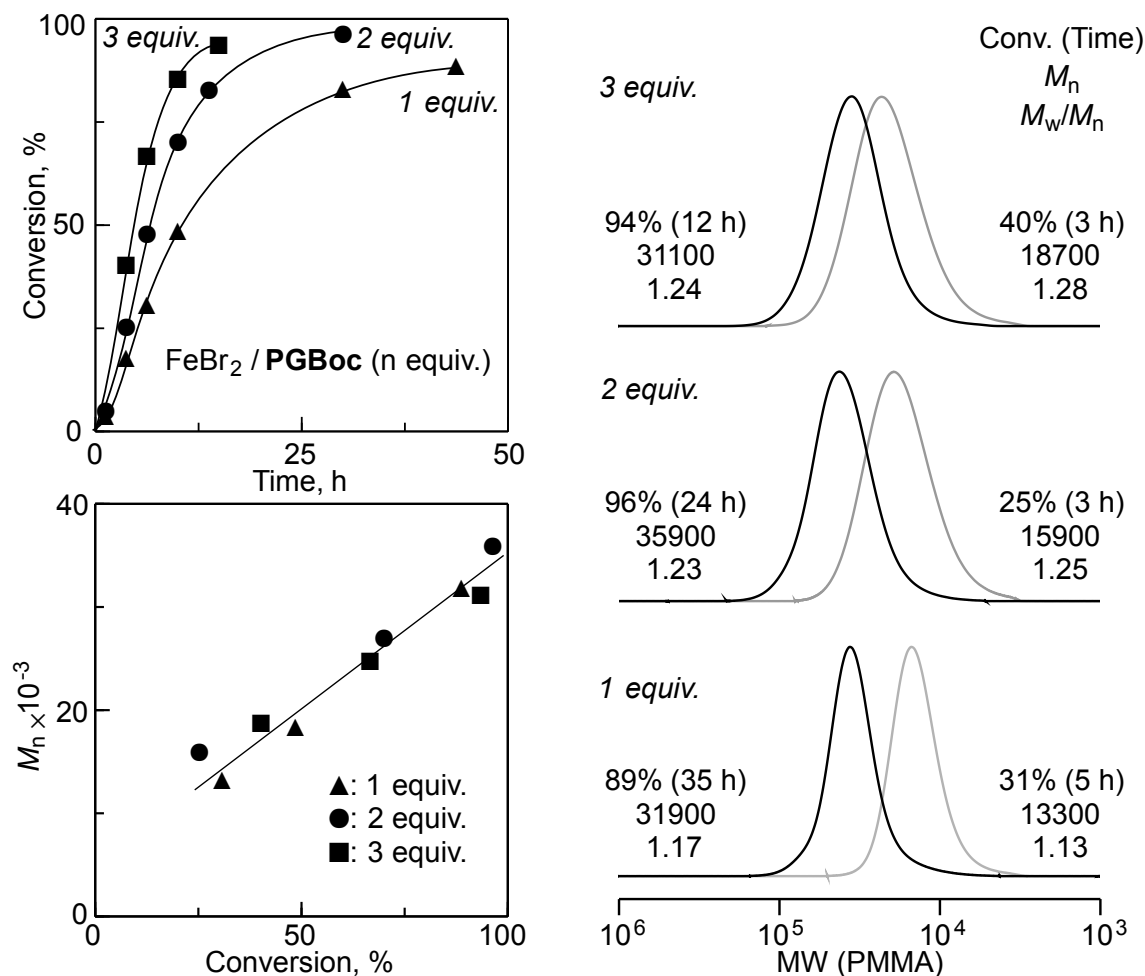


Figure 3. Effect of the amount of **PGBoc** in iron catalyzed PEGMA polymerization in toluene at 60 °C: [PEGMA]₀ = 500 mM; [H-(MMA)₂-Br]₀ = 5.0 mM; [FeBr₂]₀ = 5.0 mM; [PGBoc]₀ = 5.0–15 mM.

highly active catalysis of FeBr₂/PGBoc encouraged the author to employ the catalyst for copolymerization of PEGMA and HEMA in toluene at 60 °C (Figure 4, Table 1 Entry 1–3). As a result, the monomers were smoothly consumed and the molecular weight distributions of obtained copolymers were narrow (M_w/M_n = 1.27–1.35), though consumption of HEMA was faster than that of PEGMA. This faster consumption in nonpolar solvent had been previously observed²⁶ probably due to hydrogen bonding of HEMA.

On the other hand, trivalent iron bromide (FeBr₃) was also reported with phosphine ligands as active catalysts for living radical polymerization without reducing agents.^{32,34–36} Thus, FeBr₃ also employed with PGBoc for copolymerization of HEMA and PEGMA (Entry 4–5). The obtained copolymer had narrower molecular weight distributions (M_w/M_n = 1.14–1.27) compared to that with FeBr₂-based catalyst, though the polymerization became slower.

Table 1. Iron Catalyzed (Co)polymerization of HEMA with PGBoc at 60 °C

Entry	[HEMA] ₀ /[PEGMA] ₀ /[Init] ₀ /[Cat] ₀ ^a (mM)	Solvent	Fe ^b	Time (h)	Conv. (%) (HEMA/PEGMA)	M _n ^c	M _w /M _n ^c
1	500/500/10/10	Toluene	Fe ^{II}	3	47/21	12200	1.35
2				8	67/35	15100	1.29
3				12	75/41	16800	1.27
4			Fe ^{III}	6	22/7	7000	1.14
5	2000/-/40/10	Toluene/EtOH	Fe ^{III}	30	40/14	10400	1.27
6				10	20	3100	1.21

^aInitiator: H-(MMA)₂-Br Catalyst: FeBr_n/**PGBoc** (2equiv.). ^bFe^{II}: FeBr₂. Fe^{III}: FeBr₃. ^cBy size-exclusion chromatography calibrated with PMMA standards.

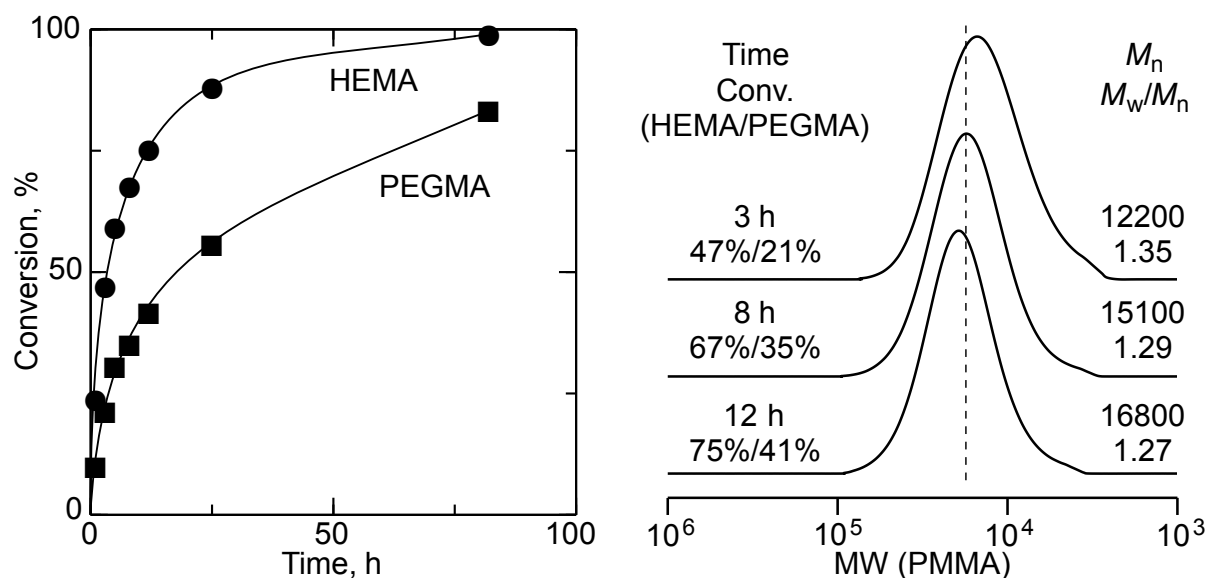


Figure 4. Iron-catalyzed copolymerization of HEMA and PEGMA with **PGBoc** in toluene at 60 °C: [HEMA]₀ = 500 mM; [PEGMA]₀ = 500 mM; [H-(MMA)₂-Br]₀ = 10 mM; [FeBr₂]₀ = 10 mM; [**PGBoc**]₀ = 20 mM.

Furthermore, the FeBr₃/**PGBoc** catalyst also enabled homopolymerization of HEMA in toluene/ethanol (9/1, v/v): the obtained polymer was very controlled ($M_w/M_n = 1.21$), though the monomer conversion was low (Entry 6).

The author believes that the iron catalysts with **PGBoc** enable more active and controlled HEMA polymerization by further optimization of the polymerization conditions.

Conclusion

In this chapter, the guanidine-based P-N chelate ligand (**PGBoc**) was combined with iron bromide (FeBr_2 or FeBr_3), and the complexes allowed iron-catalyzed living radical polymerization of functional monomers (PEGMA and HEMA). The FeBr_2 -based complex showed high activity in copolymerization of HEMA/PEGMA (1/1) [Conv. 75%/41% (HEMA/PEGMA) in 12 h, $M_w/M_n = 1.27$] as well as homopolymerization of PEGMA (Conv. 96% in 24 h, $M_w/M_n = 1.23$). In Addition, FeBr_3 /**PGBoc** improved controllability in HEMA (co)polymerization sufficient to obtain HEMA homopolymer with narrow MWD ($M_w/M_n = 1.21$). The author believes the highly active and robust iron catalysis contributes to environmentally benign synthesis of functional materials

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LIST OF PUBLICATIONS

Part I

Chapter 1

“Design of a Hydrophilic Ruthenium Catalyst for Metal-catalyzed Living Radical Polymerization: Highly Active Catalysis in Water”

Keita Nishizawa, Makoto Ouchi, Mitsuo Sawamoto

RSC Adv., **2016**, 6, 6577-6582.

Chapter 2

“Water-Soluble Ruthenium Catalyst with Polyethylene Glycol (PEG) for Highly Active Aqueous Living Radical Polymerization”

Keita Nishizawa, Makoto Ouchi, Mitsuo Sawamoto

to be submitted.

Chapter 3

“Guanidine-Embedded Phosphine Ligands for Active Metal-Catalyzed Living Radical Polymerization in Water”

Keita Nishizawa, Yusuke Fukuzaki, Makoto Ouchi, Mitsuo Sawamoto

Submitted for publication

Chapter 4

“Ruthenium-Catalyzed Living Radical Polymerization of Methacrylic Acid in Water: Direct Controlled Polymerization of Acidic Monomer”

Keita Nishizawa, Makoto Ouchi, Mitsuo Sawamoto

to be submitted.

Part II

Chapter 5

“Phosphine-Ligand Decoration toward Active and Robust Iron Catalysts in LRP”

Keita Nishizawa, Makoto Ouchi, Mitsuo Sawamoto

Macromolecules **2013**, *46*, 3342–3349.

Chapter 6

“Guanidine-Based P-N Chelate Ligand for Iron-Catalyzed Living Radical Polymerization”

Keita Nishizawa, Makoto Ouchi, Mitsuo Sawamoto

to be submitted.

Other Publications

- 1 “Shuttling Catalyst for Living Radical Miniemulsion Polymerization: Thermoresponsive Ligand for Efficient Catalysis and Removal”

Elijah Bultz, Makoto Ouchi, Keita Nishizawa, Michael F. Cunningham, Mitsuo Sawamoto

ACS Macro Letters **2015**, *4*, 628-631.

- 2 “Living CO₂ Switchable Latexes Prepared via Emulsion ATRP and AGET Miniemulsion ATRP”

Xin Su, Keita Nishizawa, Elijah Bultz, Mitsuo Sawamoto, Makoto Ouchi, Philip G. Jessop, Michael F. Cunningham

Submitted for publication

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