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**NANYANG
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**Functional Polymeric Assembly Materials via non-Transition
Metal Iodide Catalyzed Controlled Radical Polymerization**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2019

Functional Polymeric Assembly Materials via non-Transition Metal Iodide Catalyzed Controlled Radical Polymerization

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

A thesis submitted to the Nanyang Technological University in partial fulfilment of the requirement for the degree of Doctor of Philosophy

2019

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I hereby certify that the work embodied in this thesis is the result of original research done by me except where otherwise stated in this thesis. The thesis work has not been submitted for a degree or professional qualification to any other university or institution. I declare that this thesis is written by myself and is free of plagiarism and of sufficient grammatical clarity to be examined. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

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Authorship Attribution Statement

This thesis contains material from [2] paper(s) published in the following peer-reviewed journal(s) where I was the first author.

Chapter 2 is published as Sarkar, J.; Xiao, L.; Goto, A. Living Radical Polymerization with Alkali and Alkaline Earth Metal Iodides as Catalysts. *Macromolecules* **2016**, 49 (14), 5033-5042.

The contributions of the co-authors are as follows:

- Assoc. Prof. A. Goto provided the initial project.
- I performed all the experimental work and analysis at the Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Singapore.
- Assoc. Prof. A. Goto and Dr. L. Xiao provided guidance in the interpretation of the experimental data.
- I prepared the manuscript drafts. Assoc. Prof. A. Goto and Dr. L. Xiao edited and finalized the manuscript.

Chapter 3 is published as Sarkar, J.; Xiao, L.; Jackson, A. W.; van Herk, A. M.; Goto, A. Synthesis of transition-metal-free and sulfur-free nanoparticles and nanocapsules via reversible complexation mediated polymerization (RCMP) and polymerization induced self-assembly (PISA). *Polymer Chemistry* **2018**, 9 (39), 4900-4907. The work is reproduced by the permission of The Royal Society of Chemistry.

<https://pubs.rsc.org/en/content/articlelanding/2018/py/c8py01117f#!divAbstract>.

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- Assoc. Prof. A. Goto and Prof. A. M. van Herk designed the initial project.
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- Assoc. Prof. A. Goto, Prof. A. M. van Herk, Dr. A. W. Jackson, and Dr. L. Xiao provided guidance in the interpretation of the experimental data.
- Prof. A. M. van Herk research group performed the cryo-TEM analysis.
- I prepared the manuscript drafts. Assoc. Prof. A. Goto, Prof. A. M. van Herk, Dr. A. W. Jackson, and Dr. L. Xiao edited and finalized the manuscript.

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Abstract

Chapter 1 introduces the advantages and disadvantages of the well-known living radical polymerization (LRP) systems. The advantages of reversible complexation mediated polymerization (RCMP) over other LRPs have been discussed. The self-assembly methods of block copolymers for generating self-assemblies and their influencing parameters have been discussed in brief. The motivations and aims for the works in this Thesis are discussed.

In Chapter 2, Alkali metal iodides, NaI, KI, and CsI, and alkaline earth metal iodides, MgI_2 and CaI_2 , were systematically studied as catalysts. Among the five catalysts, NaI exhibited a particularly high reactivity. NaI is also amenable to styrene, acrylonitrile, and functional methacrylates. In addition to homopolymers, NaI also afforded well-defined block copolymers, telechelic polymers, and a star polymer. The high monomer versatility and accessibility to a wide range of polymer architectural designs are desirable features of this polymerization system.

In Chapter 3, NaI-catalyzed RCMP was combined with polymerization induced self-assembly (PISA) to generate self-assemblies. Poly(methacrylic acid) (PMAA) and poly(methyl methacrylate) (PMMA) were used as hydrophilic and hydrophobic segments, respectively, to generate self-assemblies. Micelles (nano-particles), worms (nano-cylinders), and vesicles (nano-capsules) were generated in ethanol at 5-9 wt% solid content.

In Chapter 4, biocompatible polymer nano-capsules (or vesicles) were prepared using aqueous emulsion PISA (polymerization induced self-assembly) catalyzed by NaI. The hydrophilic and hydrophobic monomers used in this study were poly(ethylene glycol) methyl ether methacrylate (PEGMA) and methyl methacrylate (MMA), respectively. Spheres and vesicles were generated depending on the degrees of polymerization (DPs) of the hydrophilic and hydrophobic segments in the block copolymers. The nano-capsules (or vesicles) were successfully obtained with relatively high (8-9%) solid concentrations. The encapsulation

property of the obtained vesicles was studied using a hydrophilic dye, i.e., Rhodamine-B. In a typical example loading capacity was 0.28% and the encapsulation efficiency 48%.

In Chapter 5, we carried out RCMP of a macromonomer, i.e., poly(dimethylsiloxane) methacrylate (PDMSM), and prepared a bottlebrush polymer via a grafting-through approach. The obtained bottlebrush polymer (PPDMSM-I) was further used as a macroinitiator in the polymerization of a divinyl crosslinkable monomer, i.e., ethylene glycol dimethacrylate (EGDMA), yielding a bottlebrush particle. For comparison, we also synthesized particle whose shell consisted of a linear (non-bottlebrush) polymer, i.e., poly(methyl methacrylate) (PMMA). In tetrahydrofuran (THF), above a critical overlapping concentration (5 wt%) of the particle, the viscosity of the PMMA particle significantly increased because of the entanglement of the linear shell polymers, and the viscosity of the PPDMSM particle became much lower than that of the PMMA particle, demonstrating a better lubrication property of the bottlebrush particle. The observed lower viscosity of the PPDMSM particle is ascribed to the entropic repulsion of the sterically hindered bottlebrush polymer shell.

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Table of Contents

Abstract	1
Acknowledgements	3
Chapter 1 Introduction.....	6
1.1 Nitroxide Mediated Radical Polymerization (NMP)	9
1.2 Reversible-Addition Fragmentation Chain Transfer (RAFT) Polymerization	10
1.3 Atom Transfer Radical Polymerization (ATRP)	11
1.4 Reversible Complexation Mediated Polymerization (RCMP)	12
1.5 Aim in Chapter 2.....	14
1.6 Self-Assembly of Block Copolymers.....	14
1.7 Polymerization Induced Self-Assembly (PISA).....	17
1.8 Aims in the Chapters 3 and 4.....	19
1.9 Bottlebrush Assembly.....	20
1.10 Aim in the Chapter 5.....	21
References.....	22
 Chapter 2 Living Radical Polymerization with Alkali and Alkaline Earth Metal Iodides as Catalysts.	 26
2.1 Introduction.....	27
2.2 Results and Discussion.	31
Experimental Proof of the Generation of R• from R–I with NaI.	31
Polymerizations of MMA with Five Different Catalysts Using 18-Crown-6- ether.....	32
Chain-End Fidelity.....	35
Polymerizations of MMA Using Diglyme.....	36
Increase in the Polymerization Rate	38

Toward Higher Molecular Weights	40
Use of Alkyl Iodide Formed In Situ	40
St, AN, and Functional Monomers	43
Block Copolymerizations	44
Telechelic Polymers and 3-Arm Polymer.....	46
2.3 Conclusions.....	49
2.4 Experimental Section	50
References.....	53

Chapter 3 Synthesis of Transition-Metal-Free and Sulfur-Free Nanoparticles and Nanocapsules via Reversible Complexation Mediated Polymerization (RCMP) and Polymerization Induced Self-Assembly (PISA)55

2.1 Introduction.....	56
2.2 Results and Discussion.	60
Synthesis of PMAA-I Macroinitiators.	60
PISA	61
Phase Diagram.....	64
Crosslinking	67
2.3 Conclusions.....	71
2.4 Experimental Section	72
References.....	75

Chapter 4 Synthesis of Nano-capsules using Aqueous Emulsion RCMP-PISA and their Encapsulation Study77

2.1 Introduction.....	78
2.2 Results and Discussion.	82
Synthesis of PPEGMA-I Macroinitiators.	82

PISA	83
Phase Diagram.....	87
Crosslinking of Assembly Structures	89
Encapsulation of Rhodamine-B Dye in Nano-capsules	91
2.3 Conclusions.....	96
2.4 Experimental Section	97
References.....	99

Chapter 5 Synthesis and Lubrication Property of Bottlebrush Polymer Particle..... 101

2.1 Introduction.....	102
2.2 Results and Discussion.	106
RCMP of PDMSM.....	106
Synthesis of PPDMSM-I Macroinitiator	107
Synthesis of Bottlebrush Polymer Particle.....	108
Synthesis of PMMA Particle	110
Viscosity of PPDMSM and PMMA Particles	111
2.3 Conclusions.....	113
2.4 Experimental Section	114
References.....	116

Chapter 6 Conclusions 118

Chapter 1. Introduction.

Polymer products are widespread in our daily lives and the latest technology. The properties of polymer materials such as mechanical, thermal, optical, and physiological properties strongly depend on the polymer structures such as molecular weights, molecular weight distributions, copolymerization sequences (e.g., random, gradient, and block sequences), and topologies (e.g., star, comb, and brush structures) (Figure 1.1). Hence, control of the polymer structures is a key issue for creating advanced materials. Thus, enormous effort has been dedicated to develop efficient methods for controlling the polymer structures in the last few decades.

Figure 1.1. Polymer structures.

Radical polymerization (RP) is important in academia and industry. Nearly 50% of polymer products are synthesized by RP in industry.¹ Unlike ionic polymerizations, RP does not require stringent removal of moisture and is compatible with polar solvents such as alcohols and water.² An important advantage of RP is its high monomer versatility.³ RP is applicable to a range of vinyl monomer families such as methacrylates, acrylates, and styrenics. RP is also

compatible with various functional groups and hence applicable to various functional monomers.⁴ Therefore, RP is much more widely employed than ionic polymerizations.

However, we are not able to control the polymer structures in conventional RP. Instead, we must use controlled radical polymerizations (called living radical polymerizations (LRP)), which is a useful and powerful technique to control the polymer structures and thereby enable the preparation of previously inaccessible polymers. LRP affords well-defined polymers with narrow molecular weight distribution (called low dispersity) and with sophisticated structures such as block, star, comb, and brush structures.⁵⁻⁸ The first LRP system was developed in 1990's. Since then, several useful LRP systems have been developed and have revolutionized synthetic polymer chemistry.

Scheme 1.1. Reversible activation (general Scheme).

LRP contains a monomer and a dormant chain (Polymer-X) (Scheme 1.1). X is a capping agent. Polymer-X is activated to the polymer radical (Polymer•) by thermal, photochemical, or chemical stimulus, depending on the kind of X. Polymer• propagates (reacts with monomers) until it is deactivated (capped with X) back to Polymer-X. If the polymer chain experiences a sufficiently large number of activation-deactivation cycles over a period of polymerization time, the polymer chain lengths becomes uniform as the polymer chains have nearly equal chances to grow. Thus, a sufficiently large number of activation and deactivation cycles are required for achieving low polydispersity.⁹ In LRP, the number-average molecular weight (M_n) (The unit of M_n is g/mol in my thesis) linearly increases with an increase in the monomer conversion. The molecular weight is predictable by controlling the monomer/initiator ratio. Block copolymers can be prepared by sequential monomer addition. The representative LRP systems include nitroxide mediated polymerization (NMP),^{10,11} atom

transfer radical polymerization (ATRP),¹²⁻¹⁵ and reversible addition-fragmentation chain transfer (RAFT) polymerization.¹⁶⁻¹⁹

1.1. Nitroxide Mediated Radical Polymerization (NMP).

In 1993, Georges et al. first reported the nitroxide mediated polymerization (NMP) yielding high molecular weight (as high as 150,000) polystyrenes with low dispersity ($\bar{D}$) (≤ 1.30).²⁰ NMP uses nitroxide as a capping agent (X). Georges et al. used TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) as a nitroxide (X). The dormant species (Polymer-TEMPO) reversibly dissociates to Polymer $\cdot$ at a high temperature (125 °C, typically). This system is mainly amenable to styrene monomer family.

Scheme 1.2. Mechanism of NMP.

Subsequently, new nitroxides such as *N*-(tert-butyl)-*N'*-(1-diethylphosphono-2,2'-dimethylpropyl)nitroxide (SG1)^{21,22} and 2,2,5-trimethyl-4-phenyl-3-azaheptane-3-oxyl (TIPNO)^{23,24} (Figure 1.2) were developed. These nitroxides enabled the controlled polymerizations of 1,3-dienes, acrylates, acrylonitrile, isoprene, and acrylamides in NMP.¹⁰ NMP was also utilized to synthesize complex architectures such as star, graft, cyclic, and hyperbranched polymers.²⁵

Figure 1.2. Examples of nitroxides used in NMP.

NMP is robust and useful for the synthesis of high molecular weight styrene and acrylates. However, NMP generally requires higher temperatures, and SG1 and TIPNO are expensive or need to be synthesized. NMP is generally difficult to use for methacrylate monomers.^{22,26,27}

Figure 1.3. General structure of RAFT agent.

1.2. Reversible-Addition Fragmentation Chain Transfer (RAFT) Polymerization.

Rizzardo and Moad et al. first reported the reversible-addition fragmentation chain transfer (RAFT) polymerization in 1998.¹⁸ The RAFT agent (R-X) consists of a leaving alkyl group (R), and a capping agent (X = SC(=S)Z) consisting a C=S bond and a stabilizing Z group (Figure 1.3). The X group includes dithioesters, dithiocarbamates, xanthates, and trithiocarbonates.^{18,28}

In the RAFT equilibrium, a growing Polymer[•] (P_n[•]) is added to the macro-RAFT agent and generates a radical intermediate. The intermediate undergoes fragmentation to generate a polymer radical, i.e., either P_n[•] or P_m[•]. When P_m[•] is generated the chain transfer (RAFT) is processed (Scheme 1.3).

Scheme 1.3. Mechanism of RAFT.

The RAFT polymerization is widely used. The RAFT polymerization is amenable to variety of monomers such as styrene, methacrylates, acrylates, vinyl ester, and acrylamides.²⁹ Homopolymers, block copolymers, star polymers, complex architectures, and chain-end functionalized polymers are easily obtainable with the RAFT polymerization.²⁸⁻³¹ The RAFT polymerization is used not only in homogeneous systems (bulk and solution polymerizations) but also in heterogeneous systems (emulsion and dispersion polymerizations).²⁹ RAFT polymerization was performed in continuous flow reactor.¹⁹ RAFT polymerization has been utilized for preparation of optoelectronic materials, delivery agent, and rheology control agents etc.¹⁹

The polymers produced in the RAFT polymerization contain sulfur (SC(=S)Z group) at the chain end, causing color and unpleasant odor. Also, not many RAFT agents are commercially available. Most of the RAFT agents need to be synthesized when necessary.

1.3. Atom Transfer Radical Polymerization (ATRP).

Atom transfer radical polymerization (ATRP) was developed independently by Sawamoto et al.¹⁴ and Matyjaszewski et al.¹² in the mid-1990s. They used ruthenium catalysts and copper catalysts, respectively, in their pioneering work. The ATRP system contains an alkyl halide (R-X, with X = chloride (Cl) or bromide (Br)) initiator, a transition metal halide (Mt^nX_n), a ligand (L) of the metal, and monomer. Polymer^{*} is generated from Polymer-X by the catalytic work of the catalyst/ligand (Mt^nX_n/L) complex. Polymer^{*} propagates until it receives the halide atom (X) from the $Mt^{n+1}X_{n+1}/L$ complex to generate Polymer-X (Scheme 1.4).

Scheme 1.4. Mechanism in ATRP.

Other transition metals such as iron and nickel have also been successfully utilized in ATRP.³² The copper-based catalysts are most frequently used in ATRP due to its high reactivity and good compatibility with functional groups. Bipyridine (bpy), dinonylbipyridine (dNbpy), and tris[2-(3,5-dimethyl-4-methoxy)pyridylmethyl]amine (TPMA) (Figure 1.4), for example, are used as efficient ligands.⁸ ATRP is amenable to styrene, acrylates, methacrylates, and acrylamides.¹³ The polymers prepared using ATRP are used in electronics, nano-composites, biomaterials, and so on.^{8,33} Functional groups can be attached at the chain end using functionalized initiators or post chain-end modifications, expanding the scope of applications of ATRP.

Figure 1.4. Examples of ligands used in ATRP.

Toxic metal catalysts are not environmentally benign and are not desirable in biological applications. In this regard, the catalyst loading has been reduced via activators regenerated electron transfer (ARGET) ATRP,³⁴ electronically mediated ATRP (*e*ATRP),³⁵ and supplemental activator and reducing agent (SARA) ATRP.³⁶ In photochemical ATRP, iridium and organic photo-catalysts were recently developed.³⁷

1.4. Reversible Complexation Mediated Polymerization (RCMP).

Organic catalysts have attracted great attention in the fields of organic chemistry and polymer chemistry. In the latter field, organic catalysts have been developed for anionic (group transfer) polymerizations and polycondensations (polyester synthesis).^{38,39} Our research group have developed an organocatalyzed LRP, i.e., reversible complexation mediated polymerization (RCMP). RCMP uses iodide as X and organic molecules as catalysts to induce reversible activation (Scheme 1.5). This is the first LRP system for the use of organic catalysts. Attractive features of RCMP include no use of special capping agents or expensive catalysts. The catalysts are relatively non-toxic, easy to handle, and amenable to a wide range of monomers and polymer structures. RCMP can serve as a useful method for various applications. Because of the low cost and the good compatibility with existing industrial manufacturing processes, RCMP is commercially used by Dainichiseika Color & Chemicals Mfg. Co. for producing block copolymers. The block copolymers are used as dispersants of pigments, affording high-quality inks.

Scheme 1.5. Reversible activation of RCMP.

This is a halogen bonding catalysis. Halogen bonding is strongest for iodides among iodides, bromides, and chlorides. Hence, RCMP uses alkyl iodides (R-I) as initiating dormant species. Using designed R-I initiators, RCMP has offered ABA triblock and CABC multi-block copolymers, star polymers, comb-shaped polymers, chain-end functionalized polymers, and polymer brushes on surfaces.^{40,41} A polymer (Polymer-I) obtained by RCMP possesses iodide at the chain end. The post-modification of the iodide chain-end to functional groups provided a range of chain-end functionalized polymers.⁴²

Scheme 1.6. Possible mechanism of reversible activation with iodide anion (I^-) catalyst.

The catalysts for RCMP include tertiary amines such as tributylamine²⁷ and *N,N,N',N'',N'''*-pentamethyldiethylenetriamine (PMDETA).⁴³ In 2013, organic salt such as tetrabutylammonium iodide ($\text{Bu}_4\text{N}^+\text{I}^-$) (BNI) was utilized as highly efficient catalysts in RCMP.⁴⁴ We suppose the following mechanism (Scheme 1.6). An iodide anion (I^- in the form of a salt A^+I^-) works as a catalyst to activate Polymer-I for generating $\text{Polymer}^{\bullet}$ and an iodide radical anion ($\text{A}^+\text{I}_2^{\bullet-}$) (Scheme 1.6a). The $\text{A}^+\text{I}_2^{\bullet-}$ is not a stable radical. Hence, two $\text{A}^+\text{I}_2^{\bullet-}$ species react with each other to produce A^+I^- and an A^+I_3^- , which are stable species (Scheme 1.6b). A^+I^- acts as an activator, whereas A^+I_3^- acts as a deactivator (Scheme 1.6c). $\text{Polymer}^{\bullet}$ can thus be deactivated by either $\text{A}^+\text{I}_2^{\bullet-}$ (Scheme 1.6a) or A^+I_3^- (Scheme 1.6c). This mechanism suggests that iodide anion (I^-) plays a key catalytic role. In the mentioned case, organic cations are used as counter cations (A^+). This finding expanded the monomer scope and molecular weight range in RCMP. RCMP is amenable to methacrylates, acrylates, styrene, and acrylonitrile. Besides iodide anion (I^-), azide, thiocyanate, and cyanate anions have also been

used as RCMP catalysts.⁴⁵ RCMP is controlled not only by thermal heating but also photo irradiation using light absorbing catalysts.⁴⁶⁻⁴⁸

1.5. Aim in Chapter 2.

Sodium iodide (NaI) is not an organic catalyst but it is among the most inexpensive inorganic salts. NaI is water-soluble and easy to separate from the reaction medium. Na is not a toxic metal. NaI is biologically safe and environmentally benign. NaI is soluble in polar media using crown ethers. NaI can be used for both polar and non-polar monomers. NaI catalyst can be removed easily by passing through a short alumina column. Therefore, NaI can be suitable for practical use. The existing organic catalysts such as BNI are not well dissolved in water or polar solvents. To address this problem, we have developed water-soluble sodium iodide (NaI) as an efficient catalyst for RCMP. The result will be discussed in the Chapter 2 in this Thesis.

A unique aspect of NaI catalyst is the good compatibility with both hydrophobic and hydrophilic monomers. Therefore, NaI catalyst opened up the synthesis of amphiphilic block copolymers that are not accessible with other RCMP catalysts. As useful applications of NaI catalyst, we studied the synthesis of amphiphilic block copolymers and creation of their self-assembly structures (micelles, worms, and vesicles), as described in Chapters 3 and 4 in this Thesis.

Figure 1.5. Amphiphilic block copolymer with water-soluble and water-insoluble segments.

1.6. Self-Assembly of Block Copolymers.

Amphiphilic block polymers with water-soluble and water-insoluble segments (Figure 1.5) self-assemble in selective solvents via spontaneous and thermodynamic process. Such self-assemblies have been used in, e.g., drug delivery, cosmetic, and sensing applications.⁴⁹⁻⁵²

LRP is a useful method for synthesizing well-defined amphiphilic block copolymers. Amphiphilic block copolymers can form spherical micelles,⁵³ worm-like micelles,⁵⁴ micellar

gels,⁵⁵ toroids,⁵⁶ and spherical vesicles.⁵⁷ These self-assemblies can be obtained by a post polymerization processing; namely, a prepared block copolymer is initially dissolved in a good solvent that commonly dissolves both segments, and subsequently a non-solvent selective for one segment is added to induce self-assembly.⁵⁸ The assemblies are formed by weak forces such as van der Waals interactions, hydrogen bonding, and electrostatic interactions. Therefore, these materials are soft and responsive to external stimuli such as pH, ionic strength, temperature, and redox potential.

Figure 1.6. Different self-assembly structures of amphiphilic AB block copolymers. Depending on the curvature of block copolymers, micelles, worm, and vesicles are formed from block copolymers. The packing parameter “ P ” depends on the a_0 , l_c , and v , where a_0 is the interfacial cross-sectional area, v is the volume of the hydrophobic segment, and l_c is the length of the cone consisting of the hydrophobic segment.

Theoretically, the self-assembly structure is determined by the volume fraction of hydrophilic and hydrophobic segments, the total degree of polymerizations (N) of the two segments, and the Flory-Huggins parameter (χ_{AB}) (Equation 1.1). The χ_{AB} shows the incompatibility between A and B segments.^{59,60} The χ_{AB} is defined as:

$$\chi_{AB} = \left(\frac{1}{k_B T} \right) \left[\epsilon_{AB} - \frac{1}{2} (\epsilon_{AA} + \epsilon_{BB}) \right] \quad \text{— (Equation 1.1)}$$

Here, k_B is the Boltzmann constant, T is the absolute temperature and ϵ_{AB} , ϵ_{AA} , and ϵ_{BB} are the three interaction energies associated with the A and B segments. The combination of N and χ_{AB}

provides the degree of segregation (χN) between the A and B segments. The self-assembly structures are determined by the volume fraction of hydrophobic and hydrophilic segments, and the χN values.⁶¹ The structure tends to change from spheres to worms to vesicles with an increase of the χN value in order to reduce the interface of the A and B segments.

A significant factor is the volume fraction of the two segments. The self-assembly structure depends on the curvature of the block copolymer,⁵⁰ and the curvature largely depends on the volume fractions. In water, when we fixed the degree of the polymerization (DP) of the hydrophilic segment and gradually increase the DP of the hydrophobic segment, the curvature will decrease and the assembly structure will change from spheres to worms to vesicles (Figure 1.6). The effect of the curvature on the assembly structure can be explained by the packing parameter (P). The “ P ” is defined by Equation 1.2.

$$P = \frac{v}{a_0 l_c} \quad \text{--- (Equation 1.2)}$$

Here a_0 is the interfacial cross-sectional area, v is the volume of the hydrophobic segment, and l_c is the length of the cone consisting of the hydrophobic segment. In general, spherical micelles are obtained when $P \leq 1/3$, cylindrical micelles (or worms) are obtained when $1/3 \leq P \leq 1/2$, and vesicles (or polymerosomes) are obtained when $1/2 \leq P$.⁵⁰ Other factors such as solvent quality, polymer concentration, pH, and ionic strength influence the curvature, the critical point of the micelle formation, and the thermodynamics and kinetics of the self-assembly process.^{60,62}

The post-polymerization processing is robust and generates various self-assemblies. However, a limitation of this method is that the self-assemblies can be obtained only in a very dilute condition. Namely, the polymer concentration should be less than 1 wt% in the solvent, typically.⁶³

1.7. Polymerization Induced Self-Assembly (PISA).

As an efficient method to overcome the limitation of the post-polymerization method, polymerization-induced self-assembly (PISA) (Figure 1.7) has been developed. PISA is an emerging technique taking place in block copolymerization for forming self-assemblies. In the first step, a hydrophilic monomer A is polymerized in a hydrophilic solvent. Then, a hydrophobic monomer B is added for the block polymerization. A growing polymer chain (A segment) changes from soluble to surface active, because a new block (B segment) is formed in the polymer chain creating an amphiphilic (AB block) structure. The generated amphiphilic polymers can then self-assemble in spherical micelles (particles), worm-like micelles (cylinders), and vesicles (capsules), depending on the solvents, temperatures, and molecular weights of the A and B segments (Figure 1.7). Thus, the polymerization induces self-assembly.

An important advantage of PISA is the high solid content. The polymer concentration can be increased up to 50 wt% in the solvent. Additionally, PISA enables one-pot syntheses of the different morphologies by just changing the molecular weights of the two block segments.

Figure 1.7. Illustration of PISA.

In principle, PISA can be performed using any types of LRP system.⁶⁴⁻⁶⁹ However, RAFT polymerization is mainly used for PISA, because of the limitation of amenable solvents and monomers in other LRP systems.⁷⁰⁻⁷² RAFT is suitable for PISA, because it is compatible with polar solvents such as water and alcohols and with a range of water-soluble and water-insoluble monomers.

RAFT-based emulsion and dispersion polymerizations are used in the PISA. Hawket et al.⁷³ and Armes et al.⁷⁴⁻⁷⁶ pioneered the emulsion-PISA and the dispersion-PISA, respectively. Subsequently, other researchers expanded the scopes of PISA. PISA is amenable to various monomer families (e.g., methacrylates, acrylates, and styrene), functional monomers (with acidic, basic, and neutral functionalities), solvents (e.g., polar, non-polar, ionic liquid, and CO₂), and experimental conditions (thermal or photochemical conditions).^{69-72,77,78}

In general, the final self-assembly structures obtained in PISA are determined by the factors valid for the post-polymerization method. However, for example, a PISA of benzyl methacrylate (BzMA) produced vesicles only when the DP of the (poly(lauryl methacrylate) (PLMA)) macroinitiator was low (DP = 17), as reported by Armes et al. The higher DP of the PLMA macroinitiator (DP = 37) generated only spheres.⁷⁹ The strong steric stabilization by the long PLMA segment prevented the sphere-sphere fusion, resulting in the termination of morphology conversion to worms and vesicles. A PISA of 2-hydroxypropyl methacrylate (HPMA) using a poly((2-methacryloyloxy)ethyl phosphorylcholine) (PMPC) macroinitiator generated only spheres below the 10 wt% solid content.⁷⁶ Worms and vesicles were obtained only above the 10 wt% solid content. PISA also generated a unique structure, i.e., a non-spherical “lumpy rod” assembly, in a crosslinking PISA system using ethylene glycol dimethacrylate (EGDMA) as a crosslinker.⁸⁰ A PGMA-PHPMA block copolymer vesicle was used as a macroinitiator in a PISA to generate a “framboidal vesicle”, in which BzMA was used as the third monomer, where PGMA is poly(glycerol methacrylate) and PHPMA is

poly(2-hydroxypropyl methacrylate).⁸¹ The framboidal vesicle was obtained because of the strong microphase segregation between PHPMA and PBzMA segments, where PBzMA is poly(benzyl methacrylate). Thus, the DPs of the segments, solid contents, monomers, and crosslinking can affect the final assembly structures in PISA.

The preparation of stimuli-responsive PISA assemblies has recently actively studied. Sumerlin et al. developed the polymerization induced thermal self-assembly (PITSA) using a thermally responsive poly(*N*-isopropylacrylamide) (PNIPAm) as a water-insoluble segment.⁸² The self-assemblies were generated only above the lower critical solution temperature (LCST) of the PNIPAm segment. Such assemblies were used for, e.g., deliveries as well as nanoreactor applications.⁷¹

1.8. Aims in the Chapters 3 and 4.

While RAFT polymerization is useful, it has some drawbacks. It uses expensive special sulfur compounds (dithioesters) as controlling agents. The obtained polymers possess sulfur moiety and have color and unpleasant odor. The obtained self-assemblies by the RAFT-PISA technique are not suitable to many applications such as medical, homecare, cosmetic, and food packaging applications, for which color and unpleasant odor are undesirable. In principle, other LRP systems such as NMP⁶⁴⁻⁶⁶ and ATRP^{67, 68} can also be used for PISA. These two systems have drawbacks such as the limited monomer scope and the requirement of high temperature (NMP) and the use of toxic heavy metal catalysts (ATRP).

We developed NaI-catalyzed RCMP in Chapter 2. NaI is not an organic catalyst, but it is among the most inexpensive catalysts and is suitable for practical use. Na is not a heavy metal. NaI is biologically safe, colorless, and odorless. The most prominent feature of NaI is its high solubility in water. The NaI catalyst is applicable to both water-insoluble and water-soluble monomers and polar (water and alcohol) solvents. Hence, NaI should be useful in PISA.

We aimed to use NaI-catalyzed RCMP in PISA and generate self-assemblies such as micelles, worms, and vesicles in ethanol.

Chapter 3 demonstrates the proof of the principle of the RCMP-PISA technique by using MMA and methacrylic acid (MAA) as hydrophobic and hydrophilic monomers, respectively, and ethanol as a solvent. In Chapter 4, in order to expand the scope of the RCMP-PISA, we used a bio-compatible monomer, i.e., poly(ethylene glycol) methyl ether methacrylate (PEGMA) as a hydrophilic monomer and water as a solvent. Water is greener than ethanol and the least expensive solvent. The obtained bio-compatible assemblies may be useful for practical applications. We also studied the encapsulation of external molecules in Chapter 4.

1.9. Bottlebrush Assembly.

A bottlebrush polymer is a polymer made of a backbone chain with a number of densely attached branch chains. Bottlebrush polymers are crosslinked to prepare a star like particle which is made of a distinct core and bottlebrushes are in the shell. This is known as a bottlebrush particle (Figure 1.8).

Figure 1.8. Structure of a bottlebrush particle.

Star like particles can be obtained by the arm-first approach.⁸³ In the arm-first approach, a polymer arm is synthesized first. The arm is used as a macroinitiator and crosslinked during a polymerization, generating a star architecture. As an advantage, because the arm is synthesized first, hence, the molecular weight of arm is well defined. A drawback is a possible difficulty in the purification of the obtained particles from the remaining unreacted arm

polymers. The arm-first approach successfully generated star like particles via ring opening metathesis polymerization (ROMP)^{84,85} and ATRP.⁸⁶⁻⁹⁰ Johnson et al. utilized the arm-first approach to prepare bottlebrush particles for the delivery applications.^{91,92} They utilized ROMP.

1.10. Aim in the Chapter 5.

The linear chain polymers undergo interpenetration and entanglement because of their random coil structures. The entanglement causes high viscosity and high friction in the solutions. In contrast, bottlebrush polymers are sterically hindered. They have steric repulsion with each other. Due to steric repulsion, the polymer chains do not undergo significant entanglement, resulting in low viscosity and excellent lubrication. Human body utilizes lubricin, i.e., a bottlebrush polymer, for lubrication in bone joint. Inspired by this, we prepared a synthetic bottlebrush via graft-through approach using a macromonomer, i.e., poly(dimethylsiloxane) methacrylate (PDMSM) using RCMP. This macromonomer provided super-hydrophobic bottlebrush due to the presence of the silicon segment with low surface energy. We further crosslinked the bottlebrushes to yield a lubricant bottlebrush particle, in which core was crosslinked and shell consisted of bottlebrushes.

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Chapter 2. Living Radical Polymerization with Alkali and Alkaline Earth Metal Iodides as Catalysts.

Abstract.

The generation of an alkyl radical ($R^\bullet$) from an alkyl iodide ($R-I$) with NaI playing a catalytic role was experimentally demonstrated. This catalytic reaction was exploited as an activation process for living radical polymerization. Alkali metal iodides, NaI, KI, and CsI, and alkaline earth metal iodides, MgI_2 and CaI_2 , were systematically studied as catalysts. 18-Crown-6-ether and a polyether, i.e., diethylene glycol dimethyl ether (diglyme), were utilized to solvate these catalysts in hydrophobic monomers. Among the five catalysts, NaI exhibited a particularly high reactivity. The polymer molecular weight and dispersity ($D = 1.2-1.4$) were well controlled with high conversions (e.g., 80–90%) in reasonably short periods of time (3–6 h) at mild temperatures (60–70 °C) in the polymerizations of methyl methacrylate. NaI is also amenable to styrene, acrylonitrile, and functional methacrylates. In addition to homopolymers, NaI also afforded well-defined block copolymers, telechelic polymers, and a star polymer. The high monomer versatility and accessibility to a wide range of polymer architectural designs are desirable features of this polymerization system.

2.1. Introduction.

Living radical polymerization (LRP) has made significant progress as a useful technique for the rational design of polymer architectures with predictable molecular weights and narrow molecular weight distributions.¹⁻¹⁶ LRP is based on the reversible activation of a dormant species (Polymer-X) to a propagating radical (Polymer•) (Scheme 2.1a). If the polymer chains exist mostly in the form of Polymer-X compared with the form of Polymer• and experience a number of activation-deactivation cycles over the period of the polymerization time, the polymer chains are given a nearly equal chance to grow, yielding low-polydispersity polymers (low-dispersity polymers).¹⁷⁻¹⁹ We developed two mechanistically different organocatalyzed LRP systems using iodine as a capping agent (X) and organic molecules as catalysts, i.e., reversible chain transfer catalyzed polymerization (RTCP)²⁰⁻²⁴ and reversible complexation mediated polymerization (RCMP).²⁵⁻³² In this paper, we focus on RCMP. Attractive features of RCMP include no use of special capping agents or expensive catalysts. RCMP catalysts are relatively non-toxic, easy to handle, and amenable to a wide range of monomers. RCMP may serve as a useful methodology for various applications.

The catalysts for RCMP include tertiary amines such as triethylamine (TEA).²⁵ RCMP involves the reversible complexation (RC) of Polymer-I with a catalyst (activator) to generate Polymer• and an •I-catalyst complex (deactivator) (Scheme 2.1b). Technically, RCMP is similar to normal atom transfer radical polymerization (normal ATRP)⁵⁻⁸ in that both include only a dormant species and an activator. Mechanistically, in RCMP, the degree of electron transfer from the catalyst to iodine ranges from full (redox) to partial (coordination) to nearly no transfer, depending on nature of the catalyst. Using TEA as a catalyst, theoretical calculation of the •I-catalyst complex suggests that the Mulliken charge of the catalyst (TEA) fragment is partially positive (δ +0.16) and that of the iodine moiety is negative to the same extent,

indicating that only partial charge transfer occurs from the catalyst to iodine through the coordination bond.²⁷ Note that RCMP is not a coordination polymerization but a radical polymerization. The term of coordination is used to describe the interaction between the catalysts and iodine. The propagating species in RCMP is a free radical.

(a) Reversible activation (general scheme)

(b) RCMP

Scheme 2.1. Reversible activation: (a) General scheme and (b) RCMP.

We recently utilized iodide anion (I^-) as a highly reactive catalyst for RCMP.²⁶ We utilized organic salts (A^+I^-) that contain organic counter cations, such as tetrabutylammonium iodide ($\text{Bu}_4\text{N}^+\text{I}^-$) and methyltributylphosphonium iodide ($\text{Bu}_3\text{MeP}^+\text{I}^-$). We suppose the following mechanism (Scheme 2.2). An iodide anion (A^+I^-) activates Polymer-I, generating $\text{Polymer}^{\bullet}$ and an I_2 radical anion ($\text{A}^+\text{I}_2^{\bullet-}$) (Scheme 2.2a). Because $\text{A}^+\text{I}_2^{\bullet-}$ is not a stable radical, two $\text{A}^+\text{I}_2^{\bullet-}$ species react with each other to produce A^+I^- and an I_3^- anion (A^+I_3^-), which are stable species (Scheme 2.2b). A^+I^- acts as an activator, whereas A^+I_3^- acts as a deactivator (Scheme 2.2c). $\text{Polymer}^{\bullet}$ can thus be deactivated by either $\text{A}^+\text{I}_2^{\bullet-}$ (Scheme 2.2a) or A^+I_3^- (Scheme 2.2c).

Scheme 2.2. Possible mechanism of reversible activation with a salt catalyst.

We previously used organic salts that contain organic counter cations, which expanded the scope of RCMP.²⁶ In this work, we pursued the use of alkali metal and alkaline earth metal cations as counter cations (A^+). A part of the results were previously published in our conference proceedings,²⁸ and four runs are cited in the present paper for discussion (entries 1 and 2 in Table 2.1 and entries 1 and 7 in Table 2.2 in the present paper), as explicitly noted in Tables 2.1 and 2.2. All other results in the present paper are new. Herein, we systematically studied NaI, KI, CsI, MgI_2 , and CaI_2 as catalysts for RCMP. These catalysts are not organic catalysts, but they are among the most inexpensive salts and may be suitable for practical use. These catalysts are also water-soluble and easy to separate from the reaction medium after polymerization. An important issue is the dissolution of alkali and alkaline earth metal iodides in hydrophobic monomers. We used 18-crown-6-ether and a polyether, i.e., diethylene glycol dimethyl ether (diglyme), to solvate these alkali and alkaline earth metal iodides (Figure 2.1). The studied monomers are methyl methacrylate (MMA), styrene (St), acrylonitrile (AN), and several functional methacrylates. We studied the homopolymerizations of these monomers and the preparation of diblock copolymers, a triblock copolymer, chain-end functional (telechelic) polymers, and a 3-arm star polymer, demonstrating high monomer versatility and accessibility to a wide range of polymer architectural designs. Among the five catalysts, NaI exhibited a particularly high reactivity, which is a notable feature of NaI. We also carried out a mechanistic

study to demonstrate the catalytic ability of NaI to generate an alkyl radical ($R^\bullet$) from an alkyl iodide ($R-I$) in a low-molar-mass model system.

Alkyl iodides

Catalysts

NaI KI CsI MgI_2 CaI_2

Ethers

Stabilization of metal cations by ethers

Figure 2.1. Structures of alkyl iodides, catalysts, and ethers used in this work and illustration of stabilization of metal cations by ethers.

2.2. Results and Discussion.

Experimental Proof of the Generation of R• from R-I with NaI.

A radical trap experiment^{26,33-36} was performed to demonstrate the generation of R• from R-I with NaI. We used 2-cyanopropyl iodide (CP-I) (Figure 2.1) as an R-I. We heated CP-I (10 mM), NaI (80 mM), 18-crown-ether (80 mM), and the radical trap 2,2,6,6-tetramethylpiperidiny1-1-oxy (TEMPO) (80 mM) at 70 °C in a mixture of toluene-*d*₈ (90%) and acetonitrile-*d*₃ (10%). 18-Crown-6-ether was used to solvate NaI. If CP-I reacts with NaI, the generated radical CP• is trapped by TEMPO, thereby yielding CP-TEMPO. Figure 2.2 shows the ¹H NMR spectra at time zero and 7 h. At 7 h, new signals appeared and matched the signals of pure CP-TEMPO.²⁶ The extent of the reaction of CP-I to CP-TEMPO was 89% (virtually quantitative). This result clearly demonstrates the generation of R• from R-I with NaI. In the absence of TEMPO, the reaction was reversible. Exploiting this reversible nature, we utilized NaI and other metal iodides as catalysts for RCMP, as described in subsequent sections.

Figure 2.2. ¹H NMR spectra (in the range of 0.5-2.5 ppm) of the solution of CP-I (10 mM), NaI (80 mM), 18-crown-6-ether (80 mM), and TEMPO (80 mM) heated at 70 °C for 0 and 7 h. The solvent was a mixture of toluene-*d*₈ and acetonitrile-*d*₃ (9:1).

Polymerizations of MMA with Five Different Catalysts Using 18-Crown-6-ether.

We studied the bulk polymerizations of MMA (8 M, 100 equiv) containing CP-I (80 mM, 1 equiv) as a low-mass dormant species, a metal iodide (40 mM, 0.5 equiv) as an activation catalyst, and 18-crown-6-ether as a solvating ligand of the metal cation at 70 °C. Alkali metal iodides NaI, KI, and CsI and alkaline earth metal iodides MgI_2 and CaI_2 were studied as catalysts. In the absence of 18-crown-6-ether, the catalysts were insoluble in MMA. Thus, we added 18-crown-6-ether (40 mM, same equivalent as the catalyst) to solvate the catalysts.

Figure 2.3 and Table 2.1 (entries 1-5) present the results. The monomer conversion was determined from the GPC peak area of polymer. The best result was obtained with NaI (Figure 2.3 (filled circles) and Table 2.1 (entry 1)), with which the monomer conversion reached 83% in a relatively short time of 4 h. Because the $[\text{MMA}]_0/[\text{CP-I}]_0$ ratio was set to 100 in this case, the degree of polymerization (DP) expected at a 100% monomer conversion is 100. The number-average molecular weight (M_n) agreed with the theoretical value ($M_{n,\text{theo}}$), and the dispersity (D) ($= M_w/M_n$) was approximately 1.2 from an early stage of polymerization, where M_w is the weight-average molecular weight. Importantly, D remained small (approximately 1.2) up to high conversions, illustrating the usefulness of the NaI catalyst. The relatively high polymerization rate R_p (conversion = 83% in 4 h) is also attractive. The R_p increased with an increase of the catalyst concentration (Figure 2.4), as expected from the activation-deactivation equilibrium (Scheme 2.1b).

No polymerization occurred in the absence of a catalyst (in the system containing only MMA and CP-I), meaning that the radical was generated because of the reaction of CP-I (and Polymer-I) with the catalyst. In RCMP, from a mechanistic point of view, not only reversible complexation (RC) (Scheme 2.1b) but also degenerative chain transfer (DT) (activation of

Table 2.1. Bulk Polymerizations of MMA with CP-I, Catalyst, and 18-Crown-6-ether.

entry	target DP ^a	catalyst	[MMA] ₀ /[CP-I] ₀ /[catalyst] ₀ /[crown ether] ₀ (mM)	T (°C)	t (h)	conv (%)	M _n (M _{n,theo} ^b)	<i>Đ</i>
1 ^c	100	NaI	8000/80/40/40	70	4	83	8200 (8300)	1.16
2 ^c	100	KI	8000/80/40/40	70	6	82	8500 (8200)	1.24
3	100	CsI	8000/80/40/40	70	8	32	4000 (3200)	1.17
4	100	MgI ₂	8000/80/40/40	70	8	0	—	—
5	100	CaI ₂	8000/80/40/40	70	8	7	1900 (700)	1.50
C1	100	none	8000/80/0/0 (with V65) ^d	70	3	86	8900 (8600)	1.77

^a Target degree of polymerization at 100% monomer conversion (calculated by [MMA]₀/[CP-I]₀). ^b Theoretical M_n calculated with [MMA]₀, [CP-I]₀, and monomer conversion. ^c Ref 28. ^d [V65]₀ = 10 mM.

Figure 2.3. Plots of (a) $\ln([M]_0/[M])$ vs t and (b) M_n and M_w/M_n vs conversion for the MMA/CP-I/catalyst/18-crown-ether systems in bulk (70 °C): [MMA]₀ = 8 M; [CP-I]₀ = 80 mM; [catalyst]₀ = 40 mM; [18-crown-ether]₀ = 40 mM, and for the MMA/CP-I/V65 system in bulk (70 °C): [MMA]₀ = 8 M; [CP-I]₀ = 80 mM; [V65]₀ = 10. The symbols and catalysts are indicated in the figure.

Polymer-I by Polymer[•])⁹ occurs in the activation process. However, the contribution of DT is minor. Figure 2.3 (open circle) and Table 2.1 (entry C1) show the pure DT system (iodine transfer polymerization) that did not contain a catalyst (RC) but did contain 2,2'-azobis(2,4-dimethylvaleronitrile) (V65) as a radical initiator (DT). Only large *Đ* values (> 1.7) were

observed in this pure DT system, which clearly indicates that the regulated polydispersity in RCMP arises primarily from the work of the catalyst (RC) with only a small contribution from DT. In the MMA polymerization, the degenerative chain transfer constant (C_{tr}) is as small as 2.6 at 80 °C³⁷ and 1.6 at 90 °C.²⁵

Figure 2.4. Plots of (a) $\ln([M]_0/[M])$ vs t and (b) M_n and M_w/M_n vs conversion for the MMA/CP-I/NaI/18-crown-ether systems in bulk (70 °C): $[MMA]_0 = 8$ M; $[CP-I]_0 = 80$ mM; $[NaI]_0 = 20$ -80 mM; $[18\text{-crown-6-ether}]_0 = 20$ -80 mM. The symbols and concentrations are indicated in the figure.

KI also served as an efficient catalyst for controlling M_n and achieving low $\bar{D}$ (Figure 2.3 (filled squares) and Table 2.1 (entry 2)). KI resulted in slightly slower polymerization than NaI because of the partially undissolved KI with 18-crown-6-ether and some effects of the counter cation. CsI resulted in much slower polymerization because CsI was not dissolved effectively with 18-crown-6-ether (Figure 2.3 (filled triangles) and Table 2.1 (entry 3)). The cavity size of 18-crown-6-ether is 2.6–3.2 Å,³⁸ which is large enough to capture Na^+ (atomic size = 1.94 Å) and K^+ (2.66 Å) but not Cs^+ (3.34 Å), explaining the different solubilities of NaI, KI, and CsI. 18-Crown-6-ether was used in this experiment because it is the largest crown-ether that is easily accessible. Besides the solubility issue, the counter cation may affect the catalytic activity of iodide anion. The metal cation and iodide anion are present in the

dissociated and associated forms under equilibrium. The dissociated iodide anion is more basic (not stabilized by the cation) and may be a more powerful catalyst than the associated iodide anion. The equilibrium depends on the cation. The basicity of the associated iodide anion also depends on the cation. Thus, the counter cation may affect the polymerization performance.

MgI₂ and CaI₂ did not work as effective catalysts (Figure 2.3 (open triangles and open squares) and Table 2.1 (entries 4 and 5)). MgI₂ and CaI₂ were virtually insoluble in MMA with 18-crown-6-ether. The cavity size (2.6–3.2 Å) of 18-crown-6-ether is large enough to capture Mg²⁺ (1.44 Å) and Ca²⁺ (1.98 Å) but this crown ether is not powerful enough to solvate these densely charged 2+ cations. Moreover, I₂²⁻ is the anion for MgI₂ and CaI₂ and might not facilitate effective catalysis compared to I⁻ (for NaI, KI, and CsI).

Chain-End Fidelity.

A polymer obtained with the NaI catalyst was analyzed by NMR to examine the livingness (chain-end fidelity) of this polymerization. The polymer obtained after 70 min in Figure 2.3 (filled circles) was reprecipitated in hexane and further purified by preparative GPC to remove any traces of impurities. The M_n and D determined by GPC calibrated with standard poly(methyl methacrylate)s (PMMA)s were 4500 and 1.15, respectively, before the purification, and 4600 and 1.13, respectively, after the purification. After the purification, the polymer was subjected to 500 MHz ¹H NMR analysis (Figure 2.5). The methyl protons (a, a', and a'') at the side chain appeared at 3.55-3.76 ppm. The main peak at 3.55-3.62 ppm and its shoulder peak at 3.62-3.64 ppm were assigned to the monomer units (a) in the middle of the chain (the shoulder peak at 3.62-3.64 ppm may be due to a chain-end penultimate unit). The down-field-shifted peak at 3.73-3.76 ppm was assigned to the ω -terminal chain-end unit (a') adjacent to iodine. Such a down-field shift for the ω -terminal chain-end unit was reported for PMMA-bromide.³⁹ From the peak area and the M_n determined by GPC, the fraction of the iodine chain end was calculated to be ~100% (with $\pm 8\%$ experimental error). (A small amount

of dead polymer should be generated via radical-radical termination, because this polymerization is a radical polymerization. The result suggests that the amount of dead polymer was small in this case.) The peak at 3.64-3.68 ppm was due to the α -terminal chain-end unit (a'') adjacent to the 2-cyanopropyl (CP) group. This NMR analysis demonstrates good livingness (high chain-end fidelity) of this polymerization.

Polymerizations of MMA Using Diglyme.

18-Crown-6-ether can effectively dissolve NaI and KI but is expensive. Thus, we attempted using diglyme (Figure 2.1) as an ether. Diglyme, which is a linear polyether with a structure similar to that of an 18-crown-6-ether cut in half, is inexpensive and environmentally friendly and is therefore widely used as a solvent for radical polymerization in industry.

Figure 2.5. ^1H NMR spectrum (CDCl_3) of PMMA-I obtained from CP-I and purified with preparative GPC ($M_n = 4600$ and $\bar{D} = 1.13$ after purification). The polymerization condition is given in Table 2.1 (entry 1) and Figure 2.3 (filled circles) for 70 min.

Figure 2.6. Plots of (a) $\ln([M]_0/[M])$ vs t and (b) M_n and M_w/M_n vs conversion for the MMA/CP-I/catalyst/diglyme systems (70 °C): $[MMA]_0 = 8$ M; $[CP-I]_0 = 80$ mM; $[catalyst]_0 = 40$ mM; $[diglyme]_0 = 660$ mM ($[MMA]_0/[diglyme]_0 = 90/10$ wt%). The symbols and catalysts are indicated in the figure.

Figure 2.6 and Table 2.2 (entries 1-5) show the results with CP-I (80 mM), a catalyst (40 mM), and diglyme (660 mM). The studied catalysts are NaI, KI, CsI, MgI₂, and CaI₂. The concentration of 660 mM of diglyme (17 equivalents to catalyst) corresponds to 10 wt% of diglyme (and 90 wt% of MMA) in the polymerization solution. NaI was completely dissolved at the polymerization temperature of 70 °C. With NaI, $\bar{D}$ was small (1.2–1.3), demonstrating the usefulness of diglyme as an ether. The other four catalysts were not well dissolved with diglyme and led to much smaller R_p values. These results illustrate the high efficiency and usefulness of NaI compared with the other four studied catalysts. Therefore, NaI was studied in the subsequent experiments.

Table 2.2. Polymerizations of MMA with CP-I, V65, Catalyst, and Diglyme (MMA/Diglyme = 90/10 wt%).^a

entry	target DP ^b	catalyst	[MMA] ₀ /[CP-I] ₀ /[V65] ₀ /[catalyst] ₀ (mM)	<i>T</i> (°C)	<i>t</i> (h)	conv (%)	<i>M_n</i> (<i>M_{n,theo}</i> ^c)	<i>Đ</i>
1 ^d	100	NaI	8000/80/0/40	70	8	57	5300 (5700)	1.27
2	100	KI	8000/80/0/40	70	8	14	2200 (1400)	1.41
3	100	CsI	8000/80/0/40	70	8	0	–	–
4	100	MgI ₂	8000/80/0/40	70	8	13	1500 (1300)	1.20
5	100	CaI ₂	8000/80/0/40	70	8	7	1300 (700)	1.18
6	100	NaI	8000/80/0/40	80	6	65	6300 (6500)	1.33
7 ^d	100	NaI	8000/80/0/40	60	8	25	2900 (2500)	1.55
8	100	NaI	8000/80/5/40	60	6	96	8900 (9600)	1.21
9	100	NaI	8000/80/10/40	60	3.5	98	8600 (9800)	1.20
10	200	NaI	8000/40/5/40	60	6	97	18300 (19400)	1.24
11	300	NaI	8000/27/5/40	60	7	76	22000 (23000)	1.33

^a [diglyme]₀ = 660 mM. ^b Target degree of polymerization at 100% monomer conversion (calculated by [MMA]₀/[CP-I]₀). ^c Theoretical *M_n* calculated with [MMA]₀, [CP-I]₀, and monomer conversion. ^d Ref 28.

Increase in the Polymerization Rate.

In comparison with 18-crown-6-ether, diglyme led to slower polymerization: the conversion reached 57% after a relatively long time of 8 h at 70 °C (Figure 2.6 (filled circles) and Figure 2.7 (filled circles), same data in both figures). Thus, in the diglyme system, we elevated the temperature from 70 °C to 80 °C (Figure 2.7 (filled squares)). The *R_p* indeed increased by a factor of approximately 1.5, but *Đ* became larger with time after 4 h. This result is possibly because of a side reaction, i.e., elimination of HI (hydroiodic acid) from the polymer chain end that significantly occurs at high temperatures.

Figure 2.7. Plots of (a) $\ln([M]_0/[M])$ vs t and (b) M_n and M_w/M_n vs conversion for the MMA/CP-I/(V65)/NaI/diglyme systems: $[MMA]_0 = 8$ M; $[CP-I]_0 = 80$ mM; $[V65]_0 = 0, 5$, or 10 mM; $[NaI]_0 = 40$ mM; $[diglyme]_0 = 660$ mM ($[MMA]_0/[diglyme]_0 = 90/10$ wt%). The symbols, $[V65]_0$, and temperatures are indicated in the figure.

An effective way to overcome this slow polymerization was the addition of a small amount of an azo initiator V65 (Figure 2.7 (open symbols) and Table 2.2 (entries 8 and 9)). Azo initiators are often used to decrease the deactivator concentration and hence effectively increase R_p in other LRP systems such as ATRP and nitroxide-mediated polymerization.¹⁷⁻¹⁹ As Figure 2.7 shows, compared with the system without V65 at 70 °C (filled circles), the addition of V65 dramatically increased R_p by a factor of approximately two with 5 mM of V65 (open triangles) and approximately four with 10 mM of V65 (open circles), even at a lower temperature of 60 °C. Compared with the system without V65 at 60 °C (filled triangles), the addition of V65 increased R_p by a factor of as much as fifteen. The addition of small amounts of V65 did not significantly affect M_n or D despite the significant increase in R_p . The conversion reached 98% in a relatively short time of 3.5 h even at a mild temperature of 60 °C. Diglyme is among the most inexpensive polyethers. The use of such a common polyether as well as the small D achievable even at high conversions may be highly useful.

Figure 2.8. Plots of (a) $\ln([M]_0/[M])$ vs t and (b) M_n and M_w/M_n vs conversion for the MMA/I₂/V65/NaI/diglyme systems (60 °C): [MMA]₀ = 8 M; [I₂]₀ = 20–40 mM; [V65]₀ = 50–100 mM; [NaI]₀ = 40 mM; [diglyme]₀ = 660 mM ([MMA]₀/[diglyme]₀ = 90/10 wt%). The symbols and reaction conditions are indicated in the figure.

Toward Higher Molecular Weights.

We targeted higher DPs of 100, 200, and 300 at 100% monomer conversion in the polymerizations of MMA (Table 2.2 (entries 8, 10, and 11)). We obtained low-dispersity ($\mathcal{D}$ = 1.2–1.3) polymers with high conversions (76–96%) in reasonable periods of time (6–7 h).

Use of Alkyl Iodide Formed In Situ.

Instead of a preformed isolated R–I (e.g., CP–I as studied above), we can employ molecular iodine (I₂) and an azo compound (R–N=N–R) as the starting compounds; then, the R–I formed *in situ* can be used for the polymerization. We previously showed that this (I₂/azo) method is effective for RTCP^{20–24} and RCMP.²⁶ The I₂/azo method was originally developed by Lacroix-Desmazes et al. for ITP^{37,40,41} and may be practically useful because of the general long-term instability of R–I during storage.

Table 2.3. Polymerizations of MMA with I₂, V65, NaI, and Diglyme (MMA/Diglyme = 90/10 wt%).^a

entry	target DP ^b	catalyst	[MMA] ₀ /[I ₂] ₀ /[V65] ₀ / [NaI] ₀ (mM)	<i>T</i> (°C)	<i>t</i> (h)	conv (%)	<i>M_n</i> (<i>M_{n,theo}</i> ^c)	<i>Đ</i>
1	100	NaI	8000/40/90/40	60	6	98	9200 (9800)	1.18
2	100	NaI	8000/40/100/40	60	5	98	7900 (9800)	1.19
3	200	NaI	8000/20/50/40	60	5	97	15600 (19400)	1.23

^a [diglyme]₀ = 660 mM. ^b Target degree of polymerization at 100% monomer conversion (calculated by [MMA]₀/(2[I₂]₀)). ^c Theoretical *M_n* calculated with [MMA]₀, [I₂], and monomer conversion.

We adopted this I₂/azo method to NaI (Figure 2.8 and Table 2.3). Figure 2.8 (filled circles) and Table 2.3 (entry 1) show the polymerization of MMA (8 M) with I₂ (40 mM), V65 (90 mM), and NaI (40 mM) at 60 °C. V65 affords the alkyl radical R•, and R• reacts with I₂ to yield R–I. Virtually no polymerization occurred for 2.5 h, during which time R• had predominantly reacted with I₂ (rather than the monomer), and R–I had accumulated. Because the efficiency of V65 to produce free R• is approximately 0.6-0.7 and approximately 65% of V65 decomposes for 2.5 h at 60 °C, 90 mM of V65 (in this study) can yield about 80 mM of free R• and hence about 80 mM (theoretical amount) of R–I for 2.5 h. After this period, the polymerization proceeded smoothly due to the catalytic work of NaI and the continuous supply of radicals from the remaining amount of V65. The conversion reached 98% for 6 h. The *M_n* agreed well with *M_{n,theo}*, and *Đ* remained small (approximately 1.2) throughout the polymerization. The *R_p* further increased with an increase of V65 from 90 mM to 100 mM (Figure 2.8 (filled squares) and Table 2.3 (entry 2)). The polymerization was complete in a shorter time of 5 h (98% conversion) while maintaining small *Đ* values. This method was effective for a higher target DP of 200 (Figure 2.8 (filled triangles) and Table 2.3 (entry 3)) and is simple to execute.

Notably, Lacroix-Desmazes et al. successfully obtained low-dispersity (*Đ* ≤ 1.2)⁴¹ polymers with relatively high conversions in reverse iodine transfer polymerization (RITP) of

MMA using I₂ and azobis(isobutyronitrile) (AIBN) in toluene at 80 °C. RITP does not contain a catalyst and purely proceeds with DT. The $\bar{D}$ becomes smaller with monomer conversion as experimentally observed.³⁷ In theory, in bulk ITP, $\bar{D}$ is given by $\bar{D} = 1 + (1/C_{\text{ex}})(2-c)/c + 1/x_n$,^{17-19,42} where c is the fractional monomer conversion and x_n is the number-average degree of polymerization and may reach 1.38-1.63 at a full conversion ($c = 1$) as an ideal limit with $C_{\text{ex}} = 1.6$ -2.6 for MMA.^{25,37} In the present RCMP system (Figure 2.7), $\bar{D}$ was small (≤ 1.2) from an early stage of polymerization because of the catalytic work of NaI. $\bar{D}$ also remained small up to high conversions, showing the usefulness of the NaI catalyst.

Lacroix-Desmazes et al. also successfully utilized NaI (in combination with potassium persulfate (KPS)) as a source of I₂ in RITP of *n*-butyl acrylate, while $\bar{D}$ was larger than 1.5.⁴³ In our polymerization (RCMP), NaI is used as a catalyst. The combination of RITP (NaI/KPS method) and RCMP to exploit both roles of NaI would be interesting to study in the future.

Table 2.4. Polymerizations of Several Monomers with CP-I, Azo Initiator, and Catalyst.

entry	monomer	target DP ^a	Azo initiator	Catalyst	solvent ^b	[M] ₀ / [CP-I] ₀ /[azo] ₀ / [catalyst] ₀ (mM) ^c	T (°C)	t (h)	conv (%)	M_n^d ($M_{n,\text{theo}}^e$)	$\bar{D}^d$
1	AN	200	none	KI	diglyme / EC	8000/40/0/160	75	24	100	17000 (12000)	1.34
2	AN	100	AIBN	KI	EC	8000/80/0.5/160	75	5	100	12000 (6000)	1.32
3	St	100	AIBN	NaI	diglyme	8000/80/30/40	80	15	89	6700 (9300)	1.30
4	LMA	200	V65	NaI	diglyme	8000/40/20/160	60	5	100	33000 (45000)	1.26
5	BzMA	400	V65	NaI	diglyme	8000/20/5/40	60	5	84	50000 (59000)	1.26
6	DMAEMA	100	V70	NaI	diglyme	8000/80/20/80	50	5	87	10000 (14000)	1.30
7	HEMA	100	V70	NaI	diglyme	8000/80/20/80	50	2	93	15000 (12000)	1.26
8	PEGMA	100	V70	NaI	water	8000/80/20/160	40	2	100	17000 (30000)	1.31

^a Target degree of polymerization at 100% monomer conversion (calculated by $[M]_0/[CP-I]_0$). ^b Diglyme/EC = 10/50 wt% for entry 1, EC = 50 wt% for entry 2, diglyme = 10 wt% for entries 3-7, and water = 20 wt% for entry 8. ^c M = monomer. ^d PMMA-calibrated GPC values for entries 1, 2, and 4-8, and polystyrene-calibrated GPC value for entry 3. ^e Theoretical M_n calculated with $[M]_0$, $[CP-I]_0$, and monomer conversion.

St, AN, and Functional Monomers.

Table 2.4 shows the polymerizations of AN (entries 1 and 2), St (entry 3), and functional methacrylates with lauryl (LMA), benzyl (BzMA), dimethylamino (DMAEMA), hydroxyl (HEMA), and polyethylene glycol (PEGMA) groups (entries 4-8), using an isolated alkyl iodide CP-I. Table 2.5 shows the polymerizations of these monomers using the I₂/azo method. In all studied cases (Tables 2.4 and 2.5), the polymerization was regulated with high conversions ($\geq 75\%$). These results clearly demonstrate the high monomer versatility of the NaI catalyst. The polymerization of PEGMA was carried out in water (solvent) (Table 2.4 (entry 8) and Table 2.5 (entry 7)). NaI was soluble in the studied water/PEGMA solution (20/80 wt%) without adding diglyme. A relatively low temperature of 40 °C was set to suppress possible side reactions such as the elimination of HI from the polymer chain end, which can readily occur in water. Because the previously studied RCMP catalysts are not compatible with water, the use of NaI as a catalyst opens up the possibility of aqueous polymerizations, which will be studied further in the future.

Table 2.5. Polymerizations of Several Monomers with I₂, Azo Initiator, and Catalyst.

entry	monomer	target DP ^a	Azo initiator	catalyst	solvent ^b	[M] ₀ /[I ₂] ₀ /[azo] ₀ /[catalyst] ₀ (mM) ^c	T (°C)	t (h)	conv (%)	M _n ^d (M _{n,theo} ^e)	D ^d
1	AN	100	V70	KI	EC	8000/40/50/160	75	24	100	18000 (6000)	1.30
2	St	100	AIBN	NaI	diglyme	8000/40/80/40	80	15	95	7200 (9900)	1.34
3	LMA	200	V70/V65	NaI	diglyme	8000/20/(35/10)/10	65	5	79	27000 (40000)	1.26
4	BzMA	200	V65	NaI	diglyme	8000/20/60/40	60	5	89	34000 (30000)	1.20
5	DMAEMA	100	V70	NaI	diglyme	8000/40/40/80	50	5	100	20000 (16000)	1.46
6	HEMA	100	V70	NaI	diglyme	8000/40/80/10	50	3	100	21000 (15000)	1.36
7	PEGMA	100	V70	NaI	water	8000/40/120/20	40	5	75	19000 (22000)	1.31

^a Target degree of polymerization at 100% monomer conversion (calculated by $[M]_0/(2[I_2]_0)$). ^b EC = 50 wt% for entry 1, diglyme = 10 wt% for entries 2 and 4-6, diglyme = 25 wt% for entry 3, and water = 20 wt% for entry 7. ^c M = monomer. ^d PMMA-calibrated GPC values for entries 1 and 3-7 and polystyrene-calibrated GPC value for entry 2. ^e Theoretical M_n calculated with $[M]_0$, $[I_2]_0$, and monomer conversion.

Table 2.6. Diblock Copolymerizations from PMMA-I ($M_n = 4600$ and $M_w/M_n = 1.13$) in Diglyme.

entry	monomer	target DP ^a	Azo initiator	catalyst	$[M]_0/[PMMA-I]_0/[azo]_0/[catalyst]_0$ (mM) ^b	T (°C)	t (h)	conv (%)	M_n^c ($M_{n,theo}^d$)	$\bar{D}^c$
1	BzMA	200	V65	NaI	8000/40/10/40 ^e	60	4.5	72	30000 (31000)	1.33
2	HEMA	100	V65	NaI	8000/80/80/80 ^e	60	3	75	12000 (14000)	1.31
3	St	100	AIBN	NaI	8000/80/30/40 ^e	80	13	99	12000 (15000)	1.35

^aTarget degree of polymerization at 100% monomer conversion (calculated by $[M]_0/[PMMA-I]_0$). ^bM = monomer.

^c PMMA-calibrated GPC values with THF-GPC for entries 1 and 3 and DMF-GPC for entry 2. ^dTheoretical M_n calculated with $[M]_0$, $[PMMA-I]_0$, and monomer conversion. ^e diglyme = 10 wt% for entries 1 and 3 and diglyme = 40 wt% for entry 2.

Table 2.7. Triblock Copolymerization of LMA and MMA.

Block	monomer	target DP ^a	reaction condition	T (°C)	t (h)	conv (%)	M_n^b ($M_{n,theo}^c$)	$\bar{D}^b$
1st	LMA	200	$[LMA]_0/[EMA-II]_0/[V65]_0/[NaI]_0$ (mM) = 8000/40/20/40 (10wt% diglyme)	60	3	69	25000 (35000)	1.32
			After purification				26000	1.29
2nd	MMA	200	$[MMA]_0/[PLMA-II]_0/[NaI]_0$ (mM) = 8000/40/40 (50wt% diglyme)	70	24	100	33000 (46000)	1.28

^a Target degree of polymerization at 100% monomer conversion (calculated by $[LMA]_0/[EMA-II]_0$ or $[MMA]_0/[PLMA-II]_0$). ^b PMMA-calibrated GPC values. ^c Theoretical M_n calculated with $[LMA]_0$, $[EMA-II]_0$, and monomer conversion or $[MMA]_0$, $[PLMA-II]_0$, and monomer conversion.

Block Copolymerizations.

Exploiting the living character, we performed block copolymerizations (Figure 2.9 and Table 2.6). Starting from the purified poly(methyl methacrylate)-iodide (PMMA-I) macroinitiator ($M_n = 4600$ and $\bar{D} = 1.13$) presented in Figure 2.5, the polymerizations of BzMA and HEMA yielded well-defined methacrylate/methacrylate block copolymers (Figures 2.9a and 2.9b and Table 2.6 (entries 1 and 2)). Figures 2.9a and 2.9b show the full molecular weight distributions (GPC chromatograms). A large fraction of the macroinitiator chains were extended to block copolymers, which confirms high block-efficiency due to the high chain-end fidelity, as demonstrated above (Figure 2.5). These successful syntheses of hydrophobic/hydrophobic and hydrophobic/hydrophilic block copolymers suggest good

accessibility of this NaI system to a variety of block copolymers. The polymerization of St starting from the same PMMA-I also yielded a relatively low-dispersity block copolymer ($\bar{D} = 1.35$) (Figure 2.9c and Table 2.6 (entry 3)), although a noticeable amount of the macroinitiator remained, as observed in the GPC chromatogram. In addition to the alkyl mono-iodide (CP-I) used above, we employed an alkyl di-iodide EMA-II (Figure 2.1) to prepare an A-B-A triblock copolymer (Figure 2.9d and Table 2.7). We used LMA as the first block monomer (B segment monomer) and obtained a polymer with $M_n = 26000$ and $\bar{D} = 1.29$ after purification. The subsequent polymerization of MMA (A segment monomer) yielded a low-dispersity MMA-LMA-MMA triblock copolymer with $M_n = 33000$ and $\bar{D} = 1.28$. This triblock copolymer is a hard-soft-hard triblock copolymer and may have applications in elastomers, for example.

Figure 2.9. GPC chromatograms before (dashed lines) and after (solid lines) the block copolymerizations in Tables 2.6 and 2.7. (a)-(c) corresponds to entries 1-3 in Table 2.6, respectively, and (d) corresponds to Table 2.7.

Telechelic Polymers and 3-Arm Polymer.

Chain-end functional (telechelic) polymers were prepared by using functional alkyl iodides, i.e., HEMA-I with a hydroxyl group (Figure 2.1) and IHE with a triethoxysilyl group (Figure 2.1), in the polymerizations of MMA. Figures 2.10 to 2.12 and Table 2.8 (entries 1 and 2) show the results. An azo initiator (V65) was not used in this case to obtain pure chain-end functional polymers. 18-Crown-6-ether was used instead of diglyme to attain sufficiently fast polymerization even without an azo initiator. Figure 2.10 shows the ^1H NMR spectrum of the polymer synthesized from HEMA-I (monomer conversion = 58%) and purified with a preparative GPC ($M_n = 5900$ and $D = 1.32$ after purification). The signal of $\text{CH}_2\text{CH}_2\text{OH}$ (4.1 ppm) in the initiating moiety is clearly observed, demonstrating the introduction of the hydroxyl group at the chain end. The chain-end functionality can be estimated from the relative peak areas of this initiating moiety and the monomer units. We calculated the number of monomer units (= 56) using the M_n determined by GPC and estimated the chain-end functionality to be 92% (with $\pm 10\%$ experimental error). Figure 2.11 shows the ^1H NMR spectrum of the polymer synthesized from HEMA-I (monomer conversion = 78%) and purified with a preparative GPC ($M_n = 8400$ and $D = 1.38$ after purification). The chain-end functionality can be estimated from the relative peak areas of this initiating moiety (peak **e**) and the monomer units (peak **a**, **a'**, and **a''**). We calculated the number of monomer units (= 81) using the M_n determined by GPC and estimated the chain-end functionality to be 100% (with $\pm 10\%$ experimental error). IHE also afforded a low-dispersity telechelic polymer ($M_n = 8300$ and $D = 1.30$ after purification) with high chain-end functionality of 89% (with $\pm 10\%$ experimental error) with a high monomer conversion of 74% (Figure 2.12). Thus, telechelic polymers with virtually quantitative chain-end functionalities were obtained. In addition to linear polymers, we also successfully prepared a 3-arm star polymer ($M_n = 28000$ and $D = 1.23$) from an alkyl tri-iodide EMA-III (Figure 2.1) in the polymerization of MMA (Table 2.8 (entry

3)). These results clearly demonstrate the accessibility of the NaI system to a wide range of polymer architectural designs (di-block, tri-block, telechelic, and star polymers).

Table 2.8. Polymerizations of MMA from Some Alkyl Iodides R-I.

entry	target DP ^a	R-I	catalyst	[MMA] ₀ /[R-I] ₀ /[catalyst] ₀ /[18-crown-6-ether] ₀ (mM)	T (°C)	t (h)	conv (%)	M _n (M _{n,theo} ^b)	Đ
1	100	HEMA-I	NaI	8000/80/40/40	70	3	58	5800 (5800)	1.33
							(after purification) ^c	5900	1.32
						6	78	8200 (7800)	1.39
							(after purification) ^c	8400	1.38
2	100	IHE	NaI	8000/80/40/40 ^d	70	7	74	8100 (7400)	1.30
							(after purification) ^c	8300	1.30
3	300	EMA-III	NaI	8000/27/40/40	70	6	82	28000 (25000)	1.23

^a Target degree of polymerization at 100% monomer conversion (calculated by [MMA]₀/[R-I]₀). ^b Theoretical M_n calculated with [MMA]₀, [R-I]₀, and monomer conversion. ^c Purified with preparative GPC. ^d Addition of I₂ (4 mM).

Figure 2.10. ¹H NMR spectrum (acetone-*d*₆) of PMMA-I obtained from HEMA-I and purified with preparative GPC (*M*_n = 5900 and *Đ* = 1.32 after purification). The polymerization condition is given in Table 2.8 (entry 1 for 3 h).

Figure 2.11. ^1H NMR spectrum (acetone- d_6) of PMMA-I obtained from HEMA-I and purified with preparative GPC ($M_n = 8400$ and $D = 1.38$ after purification). The polymerization condition is given in Table 2.8 (entry 1 for 6 h).

Figure 2.12. ^1H NMR spectrum (acetone- d_6) of PMMA-I obtained from IHE and purified with preparative GPC ($M_n = 8300$ and $D = 1.30$ after purification). The polymerization condition is given in Table 2.8 (entry 2).

2.3. Conclusions.

The catalytic role of NaI in generating $R^\bullet$ from $R-I$ was experimentally demonstrated. Based on this proof, NaI, KI, CsI, MgI_2 , and CaI_2 were used as catalysts in RCMP with the addition of 18-crown-6-ether and diglyme. Among the five catalysts, NaI exhibited a particularly high reactivity. The amenable monomers encompass MMA, St, AN, and functional methacrylates. Well-defined diblock, triblock, telechelic and 3-arm star polymers were synthesized. The accessibility to such a wide range of polymer designs is a highly desirable feature of this polymerization. NaI is easy to handle (insensitive to air), and the NaI/diglyme system is inexpensive. These features may be attractive for practical uses.

2.4. Experimental Section.

Materials.

Methyl methacrylate (MMA) (>99.8%, Tokyo Chemical Industry (TCI), Japan), styrene (St) (>99%, TCI), acrylonitrile (AN) (>99%, Kanto Chemical, Japan), lauryl methacrylate (LMA) (>95%, TCI), benzyl methacrylate (BzMA) (>98%, TCI), *N,N*-dimethylaminoethyl methacrylate (DMAEMA) (>98.5%, TCI), 2-hydroxyethyl methacrylate (HEMA) (>95%, TCI), and poly(ethylene glycol) methacrylate (PEGMA) (average molecular weight = 300) (98%, Aldrich) were purified through an alumina column. 2-Cyanopropyl iodide (CP-I) (>95%, TCI), NaI (>99.5%, Kanto), KI (>99.5%, Kanto), CsI (99.9%, Aldrich), CaI₂ (99%, Aldrich), MgI₂ (98%, Aldrich), 2,2'-azobis (2,4-dimethyl valeronitrile) (V65) (95%, Wako Pure Chemical, Japan), 2,2'-azobis(2-methylpropionitrile) (AIBN) (98%, Wako), 2,2'-azobis(4-methoxy-2,4-dimethyl valeronitrile) (V70) (95%, Wako), iodine (I₂) (>98%, TCI), diethylene glycol dimethyl ether (diglyme) (>99%, TCI), 18-crown-6-ether (>98%, TCI), and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (>98%, TCI) were used as received. Ethylene glycol bis(2-iodoisobutyrate) (EMA-II), glycerol tris(2-iodoisobutyrate) (EMA-III), 2-hydroxyethyl 2-iodo-2-phenylacetate (PhEOH-I) (>90%), 2-hydroxyethyl 2-iodoisobutyrate (HEMA-I) (>98%), and 6-(2-iodo-2-isobutyloxy)hexyltriethoxysilane (IHE) (>95%) were provided through the courtesy of Godo Shigen Co., Ltd. (Japan) and used as received.¹

Measurements.

The GPC analysis was performed on a Shodex GPC-101 liquid chromatograph (Tokyo, Japan) equipped with two Shodex KF-804L mixed gel columns (300 × 8.0 mm; bead size = 7 μm; pore size = 20–200 Å). The eluent was tetrahydrofuran (THF) or dimethyl formamide (DMF) at a flow rate of 1.0 mL/min (THF) or 0.8 mL/min (DMF) (40 °C). Sample detection and quantification were conducted using a Shodex differential refractometer RI-101 calibrated

with known concentrations of polymer in solvent. The monomer conversion was determined from the peak area. The column system was calibrated with standard polystyrenes and poly(methyl methacrylate)s (PMMAs).

The NMR spectra in Figure 2.2 were recorded on a Bruker BBF0400 spectrometer (400 MHz) (Germany) at ambient temperature; ^1H : spectral width 4000.00 Hz, acquisition time 8.192 sec, and pulse delay 1.000 sec. The NMR spectra in Figures 2.4, 2.9, 2.S2, and 2.S3 were recorded on a Bruker AV500 spectrometer (500 MHz) at ambient temperature; ^1H : spectral width 5000.00 Hz, acquisition time 6.554 sec, and pulse delay 1.000 sec.

Some polymers were purified with a preparative GPC (LC-918, Japan Analytical Industry, Tokyo) equipped with JAIGEL 1H and 2H polystyrene gel columns (600×40 mm; bead size = 16 μm ; pore size = 20-30 (1H) and 40-50 (2H) Å). Chloroform was used as eluent at a flow rate of 14 mL/min (room temperature).

Reaction of CP-I, NaI, 18-Crown-6-Ether, and TEMPO (Figure 2.2).

A mixture of toluene- d_8 (1.8 mL), acetonitrile- d_3 (0.2 mL), CP-I (10 mM), NaI (80 mM), 18-crown-6-ether (80 mM), and TEMPO (80 mM) was heated in a Schlenk flask at 70 °C for 7 h under an argon atmosphere with magnetic stirring and subsequently quenched to room temperature. The mixtures before and after the heat treatment were analyzed by ^1H NMR.

Polymerization.

In a typical run, a mixture of monomer (3 mL), an alkyl iodide initiator, a catalyst, and an ether was heated in a Schlenk flask at 40-80 °C under an argon atmosphere with magnetic stirring. After a prescribed time t , an aliquot (0.1 mL) of the solution was taken out by a syringe, quenched to room temperature, diluted by THF or DMF to a known concentration, and analyzed by GPC.

Preparation of PMMA-I for Block Copolymerizations.

A mixture of MMA (4 mL (8 M)), CP-I (80 mM), NaI (40 mM), and 18-crown-6-ether (40 mM) was heated in a Schlenk flask at 70 °C for 70 min under an argon atmosphere with magnetic stirring, yielding a PMMA-I with $M_n = 4500$ and $\bar{D} = 1.15$ (monomer conversion = 38%) (before purification). The reaction mixture was diluted with THF and passed through a short alumina column to remove NaI. After purification by reprecipitation from cold hexane and with the preparative GPC, a PMMA-I with $M_n = 4600$ and $\bar{D} = 1.13$ was obtained and used as a macroinitiator for the block copolymerization (Figures 2.9a, 2.9b, and 2.9c and Table 2.6).

Preparation of I-PLMA-I for Triblock Copolymerization.

A mixture of LMA (1.8 mL (8 M)), EMA-II (40 mM), NaI (40 mM), V65 (20 mM), and diglyme (10 wt%) was heated in a Schlenk flask at 60 °C under an argon atmosphere for 3 h with magnetic stirring, yielding an I-PLMA-I with $M_n = 25000$ and $\bar{D} = 1.32$ (monomer conversion = 69%) (before purification). The reaction mixture was diluted with THF and passed through a short alumina column to remove NaI. After purification by reprecipitation from acetonitrile, an I-PLMA-I with $M_n = 26000$ and $\bar{D} = 1.29$ was obtained and used as a macroinitiator for the block copolymerization (Figures 2.9d and Table 2.7).

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Chapter 3. Synthesis of Transition-Metal-Free and Sulfur-Free Nanoparticles and Nanocapsules via Reversible Complexation Mediated Polymerization (RCMP) and Polymerization Induced Self-Assembly (PISA).

Abstract.

NaI-catalyzed reversible complexation mediated living radical polymerization (RCMP) was combined with polymerization induced self-assembly (PISA) to generate self-assemblies. Poly(methacrylic acid) (PMAA) and poly(methyl methacrylate) (PMMA) were used as hydrophilic and hydrophobic segments, respectively, to generate self-assemblies. Micelles (nano-particles), worms (nano-cylinders), and vesicles (nano-capsules) were generated in ethanol at 5-9 wt% solid content. The self-assemblies were also fixed (crosslinked) by using a cross-linkable divinyl monomer, i.e., ethylene glycol dimethacrylate (EGDMA), as a co-monomer in the hydrophobic segment. NaI-catalyzed RCMP is a heavy-metal-free and sulfur-free synthetic method. The nano-particles, cylinders, and capsules obtained through the RCMP/PISA process are highly attractive for biomedical, healthcare, cosmetics, and agrochemical release applications.

3.1. Introduction.

Amphiphilic block polymers with water-soluble and water-insoluble segments self-assemble in selective solvents.¹⁻³ The self-assemblies can be spherical micelles, worm-like micelles, micellar gels, toroids, and spherical vesicles, depending on the solvents, temperatures, and fractions (molecular weights) of hydrophilic and hydrophobic segments. Such self-assemblies are extensively used to create advanced materials for, e.g., drug delivery, cosmetics, and energy applications. Living radical polymerization (or reversible deactivation radical polymerization) is an efficient method for synthesizing well-defined amphiphilic block copolymers.⁴⁻¹⁴ The self-assemblies can be obtained by using pre-synthesized block copolymers; a pre-synthesized block copolymer is dissolved in a good solvent that commonly dissolves both hydrophilic and hydrophobic segments, and then a non-solvent that selectively precipitates one segment is added to induce self-assembly. A limitation of this method is that the self-assemblies can be obtained in dilute conditions; the polymer concentration is usually less than 1 wt% in the solution.

Polymerization-induced self-assembly (PISA) has been developed as an efficient method to overcome this limitation.¹⁵⁻⁴⁵ Reviews on PISA are available.²⁴⁻³³ PISA affords high colloidal stability of the generated self-assemblies even at high polymer concentrations (high solid contents) (up to 50 wt%).^{23,24,31}

Although the term PISA was coined only a few years ago, the phenomenon itself dates from the initial efforts to conduct living radical polymerizations in emulsion polymerization. In 2002, an effective *ab initio* emulsion polymerization under reversible addition-fragmentation chain transfer (RAFT) control was published,¹⁵ where initially an acrylic acid block was grown under RAFT control and then this water-soluble RAFT oligomer was used for subsequent polymerization of butyl acrylate, growing the PISA-formed micelles further into solid latex particles. The amphiphilic RAFT oligomers organized themselves in micelles

and the poly(butyl acrylate) particles were grown to a 60 nm size. Later, a full mechanistic description was given including heat traces of the reaction¹⁶ and a full calorimetric study.¹⁷

The group of Armes initially focused on aqueous dispersion polymerization of 2-hydroxypropyl methacrylate combined with a poly(glycerol monomethacrylate)-based macro RAFT agent.¹⁸ In a similar work using a poly(2-(methacryloyloxy)ethylphosphorylcholine)-based macro RAFT agent, he constructed a full phase diagram which contained besides spheres also worms and vesicles.¹⁹ Spherical micelles (particles), worms (cylinders), and vesicles (capsules) are generated, depending on the solvents, temperatures, and molecular weights of the A and B segments. As one of the pioneers of living radical polymerizations in aqueous media, Charleux et al. worked on PISA.²⁰ Also the group of Pan performed a similar work,^{21,22} e.g., in dispersion polymerization in methanol,²¹ at this point he coined this approach the polymerization-induced self-assembling and reorganization (PISR).

RAFT polymerization is used for PISA in many cases.^{15–35} Water, ethanol, *n*-alkanes, and ionic liquids, for example, are used as solvents. Atom transfer radical polymerization (ATRP),^{36–38} nitroxide mediated polymerization (NMP),^{39–41} sulfur-free addition-fragmentation chain transfer (AFCT) polymerization,^{42,43} and living anionic polymerization⁴⁴ are also used for PISA. Arguable another example of PISA is the formation of micelles through ultrasonically splitting a water-soluble polymer into two radicals that are then grown into block copolymers through polymerization with a water insoluble monomer in emulsion polymerization, again leading to micelles and latex particles.⁴⁵ Most commonly RAFT is used in PISA though. While RAFT polymerization is useful, it uses sulfur compounds, causing colour and unpleasant odor in the products. ATRP uses transition metals (heavy metals). The use of a sulfur-free and heavy-metal-free technique is preferable for biomedical, healthcare, cosmetics, and agrochemical release applications.

We developed reversible complexation mediated living radical polymerization (RCMP) that uses an alkyl iodide (R-I) as an initiator (initiating dormant species) and iodide anion (I^-) as a catalyst.⁴⁶⁻⁵⁰ This polymerization is attractive because no special capping agents or no expensive catalysts are required. RCMP is based on the reversible activation of a dormant polymer-iodide species (Polymer-I) to a propagating radical (Polymer $^\bullet$) by a catalytic role of I^- (Scheme 3.1). I^- is used in the form of salts such as sodium iodide (NaI).⁴⁸ NaI is a highly active catalyst and is amenable to a variety of monomers. Na is not a heavy metal. NaI is biologically safe, colourless, and odourless. NaI is inexpensive and attractive for practical use. An important feature is that the NaI catalyst is highly soluble in hydrophilic solvents such as water and ethanol and is amenable to both hydrophilic and hydrophobic monomers. Therefore, the NaI catalyst is suitable to PISA.

Scheme 3.1. Reversible activation of RCMP.

In the present work, we combined RCMP with PISA to provide a heavy-metal-free and sulfur-free synthesis technique of micelles (particles), worms (cylinders), and vesicles (capsules). Ethanol was used as a non-toxic solvent. We used poly(methacrylic acid) (PMAA) as a hydrophilic segment and poly(methyl methacrylate) (PMMA) as a hydrophobic segment (Scheme 2) to generate self-assemblies. We comprehensively studied the self-assembly structures (morphologies) with different degrees of polymerization (DPs) of the PMAA and PMMA segments and constructed a phase diagram. Crosslinking is extensively used to fix the self-assembly structures.^{26,51,52} Radical crosslinking of divinyl monomers and epoxy-amine chemistry are used, for example. In the present work, we also synthesized fixed self-assemblies using a divinyl monomer as a co-monomer in the hydrophobic B segment.

Scheme 3.2. Synthesis of PMAA-PMMA block copolymers.

3.2. Results and Discussion.

Synthesis of PMAA-I Macroinitiators.

We prepared PMAA-I hydrophilic macroinitiators using NaI-catalyzed RCMP (Table 3.1). PMAA has been used as the hydrophilic segment in RAFT-based PISA.⁵³⁻⁵⁵ A mixture of methacrylic acid (MAA) (50 eq, monomer), 2-iodo-2-methylpropionitrile (CP-I (Scheme 3.2)) (1 eq, initiating dormant species), 2,2'-azobis (2,4-dimethylvaleronitrile) (V65) (1.67 eq, azo initiator), NaI (1 eq, catalyst), and water (50 wt%, solvent) was heated at 45 °C for 1.2 h (Table 3.1 (entry 1)). We intentionally stopped the polymerization at a low monomer conversion (26%) for a short time (1.2 h) to retain iodide at the chain end. The high iodide-chain-end fidelity of the macroinitiator was demonstrated by the high block efficiency as presented below. The obtained polymer was purified by reprecipitation in diethyl ether (non-solvent). We analysed the polymer with gel permeation chromatography (GPC) using tetrahydrofuran (THF) as an eluent, for which the polymer was methylated with (trimethylsilyl)diazomethane to generate PMMA-I. We obtained a PMAA-I with $M_n = 1700$ (DP = 20) and $\bar{D} (= M_w/M_n) = 1.15$ (after the purification), where M_n is the number-average molecular weight, DP is the degree of polymerization, $\bar{D}$ is the dispersity, and M_w is the weight-average molecular weight. (The M_n value of PMAA-I (1700) was calculated from that of the methylated polymer PMMA-I (2000), considering the molecular weights of the MAA (86) and MMA (100) monomer units, where MMA is methyl methacrylate.) Similarly, we obtained PMAA-I polymers with DP = 11 and 5 (Table 3.1 (entries 2 and 3)). These PMAA-I polymers were used as hydrophilic macroinitiators in the following PISA experiments.

Table 3.1. Synthesis of PMAA-I Macroinitiators.

entry	[MAA] ₀ /[CP-I] ₀ / [V65] ₀ /[NaI] ₀ (mM) ^a	<i>T</i> (°C)	<i>t</i> (h)	Conv (%)	<i>M_n</i> ^b	DP ^b	<i>D</i> ^b
1	8000/160/266/160	45	1.2	26	1700	20	1.15
2	8000/160/266/160	45	0.7	15	900	11	1.12
3	8000/160/266/160	45	0.5	11	400	5	1.12

^a Solution polymerization in 50 wt% water (solvent). ^c The *M_n*, DP, and *D* values of PMAA-I after purification (reprecipitation). PMAA-I was methylated to PMMA-I, which was analyzed with THF-GPC. The *M_n* values (e.g., 1700 in entry 1) listed in the table for PMAA-I were calculated from those (e.g., 2000 in entry 1) determined for PMMA-I, considering the molecular weights of MAA (86) and MMA (100) monomer units.

PISA.

We used MMA as a hydrophobic monomer and ethanol as a solvent to conduct PISA. We heated a mixture of MMA (300 eq, monomer), PMAA-I (DP = 20) (1 eq, macroinitiator), V65 (1.5 eq, azo initiator), NaI (1.5 eq, catalyst), and ethanol (solvent) at 60 °C (Figure 3.1 and Table 3.2 (entry 11)). The solvent was 90 wt%, and the total amount of the macroinitiator and monomer was 10 wt% (macroinitiator/monomer = 0.5/9.5). The solid content was to be 10% after a full (100%) conversion of MMA. The GPC curves show that a large fraction of the macroinitiator chains smoothly extended to block copolymers, indicating high block-efficiency (Figure 3.1a). The polymerization reached a relatively high monomer conversion, i.e., 75%, at 14 h (Figure 3.1b). The *M_n* increased with the monomer conversion, and the *D* was 1.14–1.40 (Figure 3.1c). A deviation of *M_n* at a later stage of polymerization is ascribed to an increase in the number of chains originated from V65 (azo initiator). After 1.4 h, self-assemblies were generated, because the PMMA segment became long enough to be insoluble in ethanol. In the following, PMAA_x-PMMA_y denotes a block copolymer with *x* DP of PMAA and *y* DP of PMMA.

After the reaction, to the reaction solution (ethanol), an aqueous solution of NaHCO₃ (0.9 equivalents to the COOH group) and KCl was added (reaction solution/aqueous solution = approximately 1/5), which is a stock solution. This treatment stabilized the self-assemblies and prevented their aggregation upon storage at room temperature. Without this treatment, after cooling from the reaction temperature 60 °C, the self-assemblies gradually aggregated and

precipitated. This treatment was required for the nature of the polymer (PMAA-PMMA) but not for the nature of the synthetic method (RCMP). The stock solution was used for the subsequent transmission electron microscope (TEM) and dynamic light scattering (DLS) analyses described below.

At 14 h, PMAA₂₀-PMMA₁₈₀ (with 180 DP of PMMA) was generated and self-assembled to vesicles, as the TEM image shows (Figure 3.1d). The TEM sample was prepared by dropping the solution on a TEM grid and drying it under vacuum. We compared the dried TEM samples prepared from the original ethanol reaction solution (Figure 3.1e) and the treated aqueous solution (Figure 3.1d). No morphology difference was observed, supporting that the aqueous treatment did not affect the morphology in this study. We also froze the treated solution with liquid ethane and conducted a cryogenic TEM (cryo-TEM) analysis. The cryo-TEM (in situ frozen sample) (Figure 3.1f) and normal TEM (dried sample) (Figure 3.1d) images showed similar morphologies, supporting that the morphology was unchanged upon drying. These results support that the dry TEM images of the stock solutions that will be discussed below are close to the actual assembly structures generated during the polymerization. Although we did observe the expected morphologies in both TEM and cryo-TEM, they do not represent the only morphologies in the system. This could partially be due to sample preparation and because of morphology changes immediately after the reaction. More direct support was obtained by crosslinking experiments, as discussed below, in which the morphologies were fixed by crosslinking in situ during the polymerization. The crosslinking result supported that the morphologies (sphere, worm, and vesicle) observed with TEM below were truly generated during the polymerization but not generated during the aqueous treatment or the TEM sample preparation.

Table 3.2. PISA of MMA with PMAA-I, NaI, and V65 (in 90% ethanol) at 60 °C.

Entry	DP of PMAA	[MMA] ₀ /[PMAA-I] ₀ / [NaI] ₀ / [V65] ₀ (mM) ^a	<i>t</i> (h)	Conv (%)	DP of PMMA ^b	<i>D</i> ^b
1	5	8000/133/40/40	0.3	30	10	1.10
			0.6	50	22	1.10
			1	64	33	1.32
			1.5	79	40	1.39
2	5	8000/80/40/40	1.5	71	65	1.34
			2.5	80	86	1.39
3	5	8000/53/40/40	3	69	107	1.49
4	5	8000/40/40/40	3	82	177	1.45
5	11	8000/160/40/40	1	48	20	1.18
6	11	8000/80/40/40	1.5	51	42	1.20
			2	72	65	1.36
			2.3	80	77	1.35
7	11	8000/53/40/40	3	70	95	1.41
			6	83	186	1.40
8	20	8000/80/40/40	1	34	30	1.10
			1.6	58	60	1.25
			2	68	70	1.34
9	20	8000/53/40/40	3.5	70	85	1.30
			4	76	95	1.36
			4.8	80	134	1.45
10	20	8000/40/40/40	5	73	150	1.43
			5.2	82	160	1.44
11	20	8000/27/40/40	10	68	170	1.39
			14	75	180	1.40

Entry	Code of Block Copolymer	<i>f</i> _{PMMA} A	Hydrodynamic Diameter ^c (nm)	DLS Size Distribution Index	Assembly Structure ^d	Code in Figures 3.2 and 3.3
1	PMAA ₅ -PMMA ₁₀	0.70	-	-	Soluble	
	PMAA ₅ -PMMA ₂₂	0.84	28	0.100	S	A
	PMAA ₅ -PMMA ₃₃	0.88	70	0.060	W	
	PMAA ₅ -PMMA ₄₀	0.90	106	0.080	W	B
2	PMAA ₅ -PMMA ₆₅	0.94	154	0.060	V	
	PMAA ₅ -PMMA ₈₆	0.95	184	0.080	V	C
3	PMAA ₅ -PMMA ₁₀₇	0.96	200	0.140	V	
4	PMAA ₅ -PMMA ₁₇₇	0.98	440	0.220	V	D
6	PMAA ₁₁ -PMMA ₂₀	0.68	-	-	Soluble	
	PMAA ₁₁ -PMMA ₄₂	0.82	43	0.105	S	E
	PMAA ₁₁ -PMMA ₆₅	0.87	138	0.120	W	F
	PMAA ₁₁ -PMMA ₇₇	0.89	159	0.176	W+V	
7	PMAA ₁₁ -PMMA ₉₅	0.91	297	0.126	V	G
	PMAA ₁₁ -PMMA ₁₈₆	0.95	375	0.360	V	H
8	PMAA ₂₀ -PMMA ₃₀	0.64	-	-	Soluble	
	PMAA ₂₀ -PMMA ₆₀	0.78	50	0.100	S	I
	PMAA ₂₀ -PMMA ₇₀	0.80	80	0.106	S	
9	PMAA ₂₀ -PMMA ₈₅	0.83	110	0.268	W	J
	PMAA ₂₀ -PMMA ₉₅	0.85	121	0.200	W	K
	PMAA ₂₀ -PMMA ₁₃₄	0.89	150	0.215	W+V	
10	PMAA ₂₀ -PMMA ₁₅₀	0.90	211	0.168	V	L
	PMAA ₂₀ -PMMA ₁₆₀	0.90	380	0.300	V	M
11	PMAA ₂₀ -PMMA ₁₇₀	0.91	390	0.369	V	
	PMAA ₂₀ -PMMA ₁₈₀	0.91	465	0.450	V	N

^a The mixture of MMA, PMAA-I, NaI, and V65 at the described concentration was diluted with ethanol (ethanol content = 90 wt%). ^b DP and *D* were determined by THF-GPC after methylation of the PMAA segment. ^c The DLS peak top value. ^d S = sphere, W = worm, and V = vesicle.

The dynamic light scattering (DLS) analysis shows that the hydrodynamic size (DLS peak top) of the assembly was 465 nm (Table 3.2 (entry 11)). The contour length of this block copolymer (200 units) is 50 nm. The assembly size (465 nm) was much larger than twice (100 nm) of the contour length, indicating that the assembly was not a micelle but a vesicle. The solid content was 7.6 wt% (0.5 wt% from the original macroinitiator and 7.1 wt% from the PMMA segment generated in the polymerization). Thus, this RCMP-PISA system successfully yielded nano-capsules at a relatively high solid content.

Figure 3.1. (a) GPC chromatograms, (b) plot of $\ln([M]_0/[M])$ vs t and (c) plots of M_n and M_w/M_n vs monomer conversion for the MMA/PMAA-I/NaI/V65/ethanol system (60 °C): $[MMA]_0 = 8$ M; $[PMAA-I]_0 = 27$ mM; $[NaI]_0 = 40$ mM; $[V65]_0 = 40$ mM; ethanol = 90 wt% (Table 3.2 (entry 11)). (d-f) TEM image of the vesicles generated at 14 h ((d) is the same TEM image as that in part N in Figure 3.3).

Phase Diagram.

We used PMAA-I macroinitiators with three different DPs (5, 11, and 20), varied the DP of the PMMA segment (from 0 to 186), and constructed a phase diagram (Table 3.2 and Figures. 3.2 and 3.3). The solid content was 5-9 wt% in this diagram except for the soluble phase (2-5 wt% solid contents). We optimized the polymerization conditions of MMA to generate the assemblies at >50% monomer conversions (Table 3.2).

Figure 3.2. Phase diagram of the self-assemblies generated in the PISA process for PMAA-PMMA (Table 3.2). The solid content was 5-9 wt% (except the soluble phase). W + V denotes a mixture of worms and vesicles.

Using the PMAA₅-I macroinitiator with DP = 5, we carried out a series of PISA experiments with varying the DP of the PMMA segment (at DP of PMAA = 5 in the horizontal axis in Figure 3.2). The generated block copolymer was soluble for PMAA₅-PMMA₁₀ with a short PMMA segment (DP = 10). As the DP of the PMMA segment increased, the block copolymer self-assembled to micelles (spheres) for PMAA₅-PMMA₂₂ (DP = 22), worms for PMAA₅-PMMA₄₀ (DP = 40), and vesicles for PMAA₅-PMMA₈₆ (DP = 86) (Figure 3.2). The assembly structure changed from micelles to worms to vesicles with an increase of the hydrophobic (PMMA) fraction, as illustrated in the TEM images (parts A, B, and C in Figure 3.3). The hydrodynamic size of the sphere (28 nm) determined with DLS (Table 3.2 (entry 1)) was close to twice (15 nm) of the contour length of PMAA₅-PMMA₂₂, which is consistent with the sphere structure observed with TEM (part A in Figure 3.3). The hydrodynamic size of the vesicle (184 nm) (Table 3.2 (entry 2)) was much larger than twice (45 nm) of the contour length of PMAA₅-PMMA₈₆, agreeing with the vesicle structure observed with TEM (Figure 3.3C). A further increase in the DP of the PMMA segment (PMAA₅-PMMA₁₇₇ (DP = 177)) led to an increase in the vesicle size (440 nm) (Table 3.2 (entry 4)) and also an increase in the thickness of the shell, as observed with TEM (part D in Figure 3.3). Thus, we obtained nano-capsules with different sizes and different shell thicknesses.

Figure 3.3. TEM images of the self-assemblies generated in the PISA process (Table 3.2 and Figure 2), where A = PMAA₅-PMMA₂₂, B = PMAA₅-PMMA₄₀, C = PMAA₅-PMMA₈₆, D = PMAA₅-PMMA₁₇₇, E = PMAA₁₁-PMMA₄₂, F = PMAA₁₁-PMMA₆₅, G = PMAA₁₁-PMMA₉₅, H = PMAA₁₁-PMMA₁₈₆, I = PMAA₂₀-PMMA₆₀, K = PMAA₂₀-PMMA₉₅, L = PMAA₂₀-PMMA₁₅₀, and N = PMAA₂₀-PMMA₁₈₀.

Using the PMAA₁₁-I and PMAA₂₀-I macroinitiators with DP = 11 and 20, respectively, we varied the DP of the PMMA segment (parts E–N in Figures 3.2 and 3.3). The assembly structure changed from micelles to worms to vesicles with an increase of the hydrophobic fraction, as observed with the PMAA₅-I macroinitiator with DP = 5. The assembly structure basically depended on the fractions of the hydrophilic and hydrophobic segments in the block copolymer, because the assembly structure depends on the curvature at the hydrophilic-hydrophobic interface. The structure is empirically related to the mass fraction.⁵⁶ Thus, the mass (weight) fraction of the PMMA segment in the block copolymer is defined as f_{PMMA} . As a rough estimate, the block copolymer was soluble with $f_{\text{PMMA}} < 0.75$ and formed spheres with $f_{\text{PMMA}} = 0.75\text{--}0.85$, worms with $f_{\text{PMMA}} = 0.85\text{--}0.9$, and vesicles with $f_{\text{PMMA}} > 0.9$ in this studied system. The boundary between the phases may not be very sharp. There may be broad transition

zones between the phases, as the DLS size distribution index tended to be large at the boundary (Table 3.2). The sizes of the spheres, worms, and vesicles tended to be larger with an increase of the DP of the block copolymer, as expected. Therefore, we obtained spheres (28–80 nm), worms (70–138 nm), and vesicles (154–465 nm) of different sizes using the macroinitiators with different DPs (Table 3.2).

Crosslinking.

In the mentioned experiments, we used a non-crosslinkable monomer MMA in the second block, and the generated assembly structures were not fixed. To fix the assembly structures, we used a cross-linkable divinyl monomer, i.e., ethylene glycol dimethacrylate (EGDMA), as a co-monomer of MMA in the second block.

In the mentioned experiments using the PMAA₂₀-I macroinitiator with DP = 20, we obtained spheres for PMAA₂₀-PMMA₆₀ (part I in Figures 3.2-3.4 and Table 3.2 (entry 8)), worms for PMAA₂₀-PMMA₈₅ (part J in Figures 3.2 and 3.4 and Table 3.2 (entry 9)), and vesicles for PMAA₂₀-PMMA₁₆₀ (part M in Figures 3.2 and 3.4 and Table 3.2 (entry 10)). These assemblies decomposed in a strongly basic condition (pH > 12) with sodium hydroxide (NaOH). The DLS analysis (Figure 4) showed that the spheres (50 nm), worms (110 nm), and vesicles (380 nm) decomposed to single polymer chains (2, 3, and 5 nm, respectively) in the basic condition.

Figure 3.4. DLS curves before (dashed lines) and after (solid lines) the addition of an aqueous NaOH solution for (a) PMAA₂₀-PMMA₆₀, (b) PMAA₂₀-PMMA₈₅, and (c) PMAA₂₀-PMMA₁₆₀ (Table 3.2 (entries 8-10)). TEM images before the addition of the NaOH solution for PMAA₂₀-PMMA₆₀ (part I), PMAA₂₀-PMMA₈₅ (part J), and PMAA₂₀-PMMA₁₆₀ (part M).

We carried out the same experiments but used a mixture of MMA and EGDMA (Table 3.3) instead of pure MMA. Relatively small molar fractions (4.8-9.1%) of EGDMA were used in order for the crosslinking to take place after the assembly structures are generated. The EGDMA fraction was set smaller in the order of spheres (9.1%), worms (6.5%), and vesicles (4.8%) to delay the crosslinking point at a larger DP of the second segment. Figure 3.5 shows the TEM images of spheres with PMAA₂₀-(PMMA/PEGDMA)₆₀ (part O), worms with PMAA₂₀-(PMMA/PEGDMA)₈₅ (part P), and vesicles with PMAA₂₀-(PMMA/PEGDMA)₁₆₀ (part Q). We treated these crosslinked assemblies in a basic condition (pH > 12) with NaOH. Unlike the non-crosslinked assemblies, the crosslinked assemblies did not decompose in the basic condition, as the DLS analysis shows (Figure 3.5). With this basic treatment, the hydrodynamic size became slightly larger from 73 nm to 79 nm for the sphere, from 102 nm to 106 nm for the worms, and from 400 nm to 470 nm for vesicles (Table 3.3), because the carboxylic acid turned to the ionic form and the PMAA segment became extended due to the electronic repulsion. TEM images (parts R, S, and T in Figure 3.5) showed no change in morphologies with the basic treatment. Regarding the TEM image of the vesicles, while the

shell of the vesicle was dark before the basic treatment (part Q in Figure 3.5), the inside of the vesicle was dark after the basic treatment (part T in Figure 3.5). This is because NaOH (sodium ion) was incorporated inside the vesicle with the basic treatment. Therefore, the opposite contrast was observed. Thus, we successfully obtained the stable (fixed) assemblies.

Figure 3.5. DLS curves before (dashed lines) and after (solid lines) the addition of NaOH for (a) PMAA₂₀-(PMMA/PEGDMA)₆₀, (b) PMAA₂₀-(PMMA/PEGDMA)₈₅, and (c) PMAA₂₀-(PMMA/PEGDMA)₁₆₀ (Table 3.3). TEM images before and after the addition of NaOH for PMAA₂₀-(PMMA/PEGDMA)₆₀ (parts O and R), PMAA₂₀-(PMMA/PEGDMA)₈₅ (parts P and S), and PMAA₂₀-(PMMA/PEGDMA)₁₆₀ (parts Q and T).

Importantly, the morphologies (sphere, worm, and vesicle) observed with TEM were the same with (Figure 3.5) and without (Figure 3.4) the crosslinking. For the crosslinking systems, we fixed the morphologies that were generated in situ in the polymerization. This result clearly evidences that the morphologies discussed above for the non-crosslinked were also truly generated during the polymerization but not generated during the TEM sample preparation.

Table 3.3. PISA of a mixture of MMA and EGDMA with PMAA₂₀-I, NaI, and V65 (in 90% ethanol) at 60 °C.

Entry	[MMA] ₀ /[EGDMA] ₀ /[PMAA ₂₀ -I] ₀ /[V65] ₀ /[NaI] ₀ (mM) ^a	<i>t</i> (h)	Code of Block Copolymer ^b	DLS Hydrodynamic Diameter (nm) ^c	DLS Size Distribution Index	Assembled Structure ^d	Code in Figure 3.5
1	7270/730/80/40/40	1.6	PMAA ₂₀ -(PMMA/PEGDMA) ₆₀	73	0.100	S	O
	(after adding aq NaOH)			79	0.164	S	R
2	7480/520/53/40/40	3.5	PMAA ₂₀ -(PMMA/PEGDMA) ₈₅	102	0.143	W	P
	(after adding aq NaOH)			106	0.108	W	S
3	7620/380/40/40/40	5.2	PMAA ₂₀ -(PMMA/PEGDMA) ₁₆₀	400	0.400	V	Q
	(after adding aq NaOH)			470	0.414	V	T

^a The mixture of MMA, EGDMA, PMAA₂₀-I, NaI, and V65 at the described concentration was diluted with ethanol (ethanol content = 90 wt%). ^b DP of (PMMA/PEGDMA) in entries 1, 2, and 3 in Table 3.3 corresponds to DP of PMMA in entries 8 (1.6 h), 9 (3.5 h), and 10 (5.2 h) in Table 3.2, respectively. ^c The DLS peak top value.

^d S = sphere, W = worm, and V = vesicle.

3.3. Conclusions.

The combination of NaI-catalyzed RCMP and PISA successfully generated micelles, worms, and vesicles of PMAA-PMMA block copolymers. The assembly structure changed from micelles ($f_{\text{PMMA}} = 0.75\text{--}0.85$) to worms ($f_{\text{PMMA}} = 0.85\text{--}0.9$) to vesicles ($f_{\text{PMMA}} > 0.9$) with an increase of the hydrophobic fraction. The assembly structures were also fixed by using the cross-linkable divinyl monomer (EGDMA). RAFT and ATRP use sulfur compound as a RAFT agent and heavy metals as a catalyst, respectively. The RCMP-based PISA is a heavy-metal-free and sulfur-free process and hence may be attractive for biomedical, healthcare, cosmetics, and agrochemical release applications, for example.

3.4. Experimental.

Materials.

Methyl methacrylate (MMA) (>99.8%, Tokyo Chemical Industry (TCI), Japan), methacrylic acid (MAA) (>99%, TCI), ethylene glycol dimethacrylate (EGDMA) (98%, Sigma Aldrich), iodo-2-methylpropionitrile (CP-I) (>95%, TCI), NaI (>99.5%, Kanto), 2,2'-azobis(2,4-dimethyl valeronitrile) (V65) (95%, Wako Pure Chemical, Japan), and (trimethylsilyl)diazomethane (10% in hexane) (TCI) were used as received. Although inhibitor was not removed in this work, inhibitor can be removed by distillation or passing through a short alumina column.

Measurements.

PMAA-I and PMAA-PMMA-I were methylated for the GPC analysis.⁵⁷ PMAA-I (purified by reprecipitation) (15 mg) or PMAA-PMMA-I (not purified but dried after the polymerization) (15 mg) was dissolved in tetrahydrofuran (THF) (1 mL). (Trimethylsilyl)diazomethane (1.5 equivalents to the COOH group) was added into the solution. The solution was stirred overnight at room temperature and analyzed with GPC. The GPC analysis was performed on a Shodex GPC-101 liquid chromatograph (Tokyo, Japan) equipped with two Shodex KF-804L mixed gel columns (300 × 8.0 mm; bead size = 7 μ m; pore size = 20–200 Å). The eluent was THF at a flow rate of 1.0 mL/min. Sample detection was conducted using a Shodex differential refractometer RI-101. The column system was calibrated with standard poly(methyl methacrylate)s (PMMA)s.

The NMR spectra were recorded on a Bruker (Germany) AV500 spectrometer (500 MHz) and Bruker BBFO400 spectrometer (400 MHz) at ambient temperature. DMSO-*d*₆ (Cambridge Isotope Laboratories (CIL), USA) and D₂O (CIL) were used as the solvents for the NMR analysis.

Transmission electron microscopy (TEM) images were obtained on a JEM-1400 transmission electron microscope (JEOL, Japan) operated at 100 kV. The TEM grid was carbon-coated on 200 mesh (copper) (Ted Pella, USA).

The cryogenic transmission electron microscopy (cryo-TEM) image was obtained in a FEI Titan Krios equipped with an auto sampler and a field emission gun (FEG) and performed under 300 kV. The image was captured with a Falcon II camera (4*4) with magnification of 29,000 and pixel size of 2.873 Å. The vitrification of the sample was performed using a vitrification robot (FEI Vitrobot Mark IV, Hillsboro, OR, USA). A 5 μ L stock solution was poured on a grid (Quantifoil, R2/2, Holey Carbon film) which was freshly glow-discharged before use at 20 mA for 60 s. An excess sample was blotted away with filter paper at room temperature, in 100% humidity, in a blotting time of 2 s, and with a blotting force of 1. Then it was vitrified in liquid ethane and immediately transferred to a cryo-holder.

The dynamic light scattering (DLS) measurement was carried out on a Malvern Zetasizer Nano ZSP (Worcestershire, UK). The test angle for the DLS analysis was 173° (backscattering detection). Water was used as the solvent.

Preparation of PMAA-I Macroinitiator.

A mixture (2 g) of MAA (8 M), CP-I (160 mM), V65 (266 mM), NaI (160 mM), and water (50 wt% of the mixture) was heated in a Schlenk flask at 45 °C under argon atmosphere with magnetic stirring. The reaction mixture was diluted with 1 mL ethanol. The polymer was reprecipitated in diethyl ether and dried under vacuum.

PISA.

A mixture (1.5 g) of MMA (8 M), PMAA-I (27 mM), NaI (40 mM), V65 (40 mM), and ethanol (90 wt% of the mixture) was heated in a Schlenk flask at 60 °C under argon atmosphere with magnetic stirring. After the prescribed time t , an aqueous solution (50 μ L) of NaHCO₃

(0.9 equivalents to the COOH group) was added to the reaction mixture. An aliquot (0.1 mL) of the solution was dried under vacuum, methylated, and analyzed with GPC. Another aliquot (0.1 mL) was diluted with DMSO- d_6 (0.9 mL) and analyzed with ^1H NMR for obtaining the monomer conversion. Another aliquot (0.1 mL) was diluted with an aqueous solution (0.5 mL) of KCl (1 mM), which is a stock solution. The stock solution (50 μL) was further diluted with water (0.6 mL) and analyzed with DLS. The stock solution (10 μL) was also dropped on a TEM grid, dried under vacuum, and analyzed with TEM.

3.5. References.

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Chapter 4. Synthesis of Nano-capsules using Aqueous Emulsion RCMP-PISA and their Encapsulation Study.

Abstract.

Biocompatible polymer nano-capsules (or vesicles) were prepared using aqueous emulsion PISA (polymerization induced self-assembly) catalyzed by NaI. The hydrophilic and hydrophobic monomers used in this study were poly(ethylene glycol) methyl ether methacrylate (PEGMA) and methyl methacrylate (MMA), respectively. Spheres and vesicles were generated depending on the degrees of polymerization (DPs) of the hydrophilic and hydrophobic segments in the block copolymers. The nano-capsules (or vesicles) were successfully obtained with relatively high (8-9%) solid concentrations. The spheres and vesicles were crosslinked using a divinyl monomer (ethylene glycol dimethacrylate (EGDMA)) as a comonomer of MMA, proving the in situ generation of those self-assemblies during the polymerization. The encapsulation property of the obtained vesicles was studied using a hydrophilic dye, i.e., Rhodamine-B. In a typical example loading capacity was 0.28% and the encapsulation efficiency 48%.

4.1. Introduction.

Nano-capsules (or vesicles) (Figures 4.1a) are polymer materials with confined cavity. The polymer shell layer is a bilayer of an amphiphilic block copolymer with hydrophobic and hydrophilic segments. In water, both outer and inner surfaces of the shell are hydrophilic. The inside of the bilayer is hydrophobic. Therefore, the material can encapsulate hydrophilic molecules in the cavity and hydrophobic molecules in the shell layer (Figure 4.1b). The material is widely used as a delivery vehicles in cosmetics¹ and in drug delivery.² Extensive researches are dedicated to develop bio-compatible nano-capsules with high solid concentrations and high loading capacity of guest molecules for possible commercialization.

Figure 4.1. Illustration of (a) empty nano-capsule and (b) guest molecule loaded nano-capsule.

Nano-capsules and other self-assembly structures are obtainable by the self-assembly of pre-synthesized block copolymers^{3,4} or by the in situ formation of self-assembly during the polymerization, the latter of which known as polymerization induced self-assembly (PISA) technique.⁵⁻¹⁵ PISA is advantageous over the post polymerization self-assembly in that PISA enables a high solid content (high capsule content) in water because of high colloidal stability of the capsules.

Chapter 3 demonstrated the successful combination of NaI-catalyzed reversible complexation mediated polymerization (RCMP) with PISA for generating self-assemble

structures such as micelles, worms, and vesicles in ethanol with relatively high (5-9%) solid concentrations. The advantages of RCMP over other controlled radical polymerization systems such as nitroxide mediated polymerization (NMP), reversible addition-fragmentation chain transfer (RAFT) polymerization, and atom transfer radical polymerization (ATRP) are the use of inexpensive and nontoxic organic molecules as catalysts and no use of special capping agents. Hence, RCMP is fairly biologically and environmentally safe. Chapter 3 used block copolymers containing poly(methacrylic acid) (PMAA) as a hydrophilic segment and poly(methyl methacrylate) (PMMA) as a hydrophobic segment. Despite the successful generation of the self-assembly structures, the instability of the obtained self-assembly structures upon long-term storage was a major issue due to the acid functionality of the hydrophilic segment (PMAA). The hydrogen bonding and electrostatic interaction between the acid groups caused the aggregation of the self-assembly structures and decreased their stability. Furthermore, PMAA (hydrophilic segment) is not a bio-compatible segment. To address these issues, in this chapter (Chapter 4), we attempted to synthesize stable vesicles with a bio-compatible segment. We also used water instead of ethanol as a solvent. Water is greener and the least expensive solvent, which is useful for industrial applications.

PISA in water (aqueous PISA) has been mainly conducted using RAFT-based dispersion polymerization (where the second-block monomer is dissolved in water) and emulsion polymerization (where the second-block monomer is not dissolved in water).¹² Due to the limited range of monomers amenable to the aqueous dispersion polymerization, the aqueous emulsion polymerization has been more extensively studied. Hawket et al. reported a pioneering work of aqueous PISA using emulsion polymerization.^{16,17} They utilized acrylic acid and *n*-butyl acrylate as hydrophilic and hydrophobic monomers, respectively. Subsequently, Charleux et al. reported aqueous emulsion PISA with several hydrophilic monomers such as acidic,¹⁸ basic,¹⁹ neutral,²⁰ and acrylamide²¹ and several hydrophobic

monomers such as acrylates,²¹ methacrylates,^{20,22} and styrene²³ for generating nano-spheres (micelles). In 2009, Charleux et al. for the first time succeeded to generate non-spherical structures using aqueous emulsion polymerization.²⁴ They exploited poly(acrylic acid)-co-poly((ethylene oxide) methyl ether acrylate) as a hydrophilic segment and polystyrene as a hydrophobic segment. The assembly structures (spheres, worms, and vesicles) depended on the weight ratio of hydrophilic and hydrophobic segments. The stirring speed and pH of the solution were also important for determining the assembly structures.²⁵ Most of the aqueous emulsion PISA reported so far generated the kinetically preferred sphere morphology. Only few reports are available for the generation of non-spherical structures such as worms and vesicles using aqueous emulsion PISA.^{23,25-28} Therefore, it is worth attempting to establish an aqueous emulsion PISA system that can generate vesicles with relatively high solid concentrations and to test the loading of guest molecules in obtained vesicles.

In this chapter, we synthesized spheres (particles) and vesicles (capsules) via aqueous emulsion RCMP-PISA. We used poly(poly(ethylene glycol) methyl ether methacrylate) iodide (PPEGMA-I) as a hydrophilic macroinitiator in an emulsion polymerization of methyl methacrylate (MMA) (a hydrophobic monomer) to generate self-assemblies. We used water unlike the previous chapter (Chapter 3) using ethanol. MMA is insoluble in water. Hence, it is an emulsion system. PPEGMA is bio-compatible. The obtained particle may find applications in biomedical, food, and personal care use. The self-assembly structures depended on the degrees of polymerization (DPs) of hydrophilic and hydrophobic segments. We constructed the phase diagram. The spheres and vesicles were also crosslinked using a divinyl monomer (ethylene glycol dimethacrylate (EGDMA)) as a co-monomer of the hydrophobic monomer MMA.

The loading of guest molecules in PISA-generated assemblies have been studied by, e.g., Boyer et al.,²⁹⁻³¹ Pan et al.,^{32,33} Armes et al.,^{34,35} and An et al.³⁶ for delivery and nano-

reactor applications. Boyer et al. first reported the encapsulation of guest molecule, i.e., Nile Red during the nanoparticle generation in the PISA.³¹ The encapsulation of silica nanoparticles inside the core of the nano-capsules were reported by Armes et al. using similar approach.³⁴ They added the silica nanoparticle solution in the PISA solution. During the chain extension with the second monomer, the vesicle is generated with the hydrophilic cavities which is suitable for encapsulating the silica nanoparticles. The morphology was intact in presence of these additives. Using similar approach, we tested the encapsulation of a hydrophilic guest molecule, i.e., Rhodamine-B (Rh-B) in the obtained vesicles. We have selected the Rh-B because: (a) it is highly soluble in water and (b) it has strong UV-Vis absorption which allows easy quantification. In this chapter, the loading efficiency and encapsulation efficiency were studied in our capsules.

4.2. Results and Discussion.

Synthesis of PPEGMA-I Macroinitiator.

PPEGMA-I macroinitiators were prepared using reversible complexation mediated polymerization (RCMP) (Scheme 4.1). We used tetrabutylammonium iodide (BNI) as a catalyst.³⁷ An in situ generated alkyl iodide (R-I) was utilized as an initiator instead of an isolated R-I. Namely, we used iodine (I_2) and an azo compound, i.e., 2,2-azobis(2,4-dimethylvaleronitrile) (an azo initiator) (V65) ($R-N=N-R$), to in situ generate an R-I. V65 generated the alkyl radical ($R^\bullet$) which reacted with I_2 to generate R-I. This I_2 /azo method was developed for ITP by Lacroix-Desmazes et al.³⁸ and utilized for RCMP by our research group.^{37,39}

Scheme 4.1. Synthetic procedure of PPEGMA_x-PMMA_y.

We heated a mixture of poly(ethylene glycol) methyl ether methacrylate (PEGMA) (average molecular weight = 300) (8 M, monomer), I_2 (40 mM), V65 (160 mM), BNI (80 mM, catalyst), and ethanol (20 wt%, solvent) at 60 °C for 3.5 h (Table 4.1 (entry 1)). At 3.5 h, the monomer conversion reached 75%. The synthesized polymer was purified by reprecipitation using a mixture of hexane and diethyl ether (1:1 (v/v)) as a non-solvent. The number-average molecular weight (M_n) and dispersity ($\mathcal{D}$) ($= M_w/M_n$) of the purified PPEGMA-I were 27000 and 1.31, respectively, where M_w stands for weight-average molecular weight. These values are PMMA-calibrated GPC values. Taking the molecular weight of the monomer (300) into account, the degree of polymerization (DP) of the polymer was estimated to be 90. Similarly, we synthesized other two PPEGMA-I macroinitiators with DPs of 46 and 33 with relatively

high (70-73%) monomer conversions (Table 4.1 (entries 2 and 3)). These PPEGMA-I polymers were utilized as water soluble macroinitiators for the emulsion polymerization of methyl methacrylate (MMA) in water.

Table 4.1. Synthesis of PPEGMA-I Macroinitiators using PEGMA, I₂, V65, and BNI in 20 wt% Ethanol.

entry	[PEGMA] ₀ /[I ₂] ₀ /[V65] ₀ /[BNI] ₀ (mM) ^a	<i>T</i> (°C)	<i>t</i> (h)	Conv. ^b (%)	<i>M_n</i> ^c	DP ^c	<i>D</i> ^c
1	8000/40/160/80	60	3.5	75	27000	90	1.31
2	8000/80/320/80	60	3.5	73	13800	46	1.21
3	8000/160/640/80	60	4	70	9900	33	1.16

^a Solution polymerization in 20 wt% ethanol (solvent). ^b Monomer conversions were calculated from ¹H NMR analyses. ^c The *M_n*, DP, and *D* values of PPEGMA-I were PMMA-calibrated GPC values after purification (reprecipitation).

PISA.

We utilized PPEGMA₉₀-I (DP = 90) as macroinitiator for this experiment. In the following, PPEGMA_x-PMMA_y symbolizes a block copolymer with *x* DP of PPEGMA and *y* DP of PMMA. Previously, Zhu et al. exploited PPEGMA macro-RAFT agent for aqueous emulsion PISA of MMA to produce spherical particles.⁴⁰ They utilized semi batch monomer addition method. In the present work, we utilized a batch system (containing the whole amount of monomer at the onset of polymerization). We used MMA as a hydrophobic monomer. We heated a mixture of MMA (5 g, 8 M, monomer), PPEGMA₉₀-I (3.38 g, 20 mM, macroinitiator), 4,4-azobis(4-cyanovaleric acid) (V501) (40 mM, azo initiator), NaI (160 mM, catalyst), and water (75.4 g, 90 wt%, solvent) at 60 °C (Table 4.2 (entry 3)). The total amount of the monomer and macroinitiator was fixed at 10 wt% (monomer/macroinitiator = 6/4) of the total mixture. The solid content is 4% (macroinitiator) at a zero monomer conversion and will reach 10% (macroinitiator + monomer converted to polymer) at a full (100%) monomer conversion. The pH of the solution was adjusted to 7 by adding sodium bicarbonate (NaHCO₃).

Figure 4.2. (a) GPC chromatograms, (b) plot of $\ln([M]_0/[M])$ vs t , and (c) plots of M_n and M_w/M_n vs monomer conversion for the MMA/PPEGMA₉₀-I/NaI/V501/water system (60 °C): $[MMA]_0 = 8$ M; $[PPEGMA-I]_0 = 20$ mM; $[NaI]_0 = 160$ mM; $[V501]_0 = 40$ mM; water = 90 wt% (Table 4.2 (entry 3)). (d) TEM image of the vesicles generated at 4 h (the same TEM image as that in image I in Figure 4.4).

The GPC chromatograph shows that most of the macroinitiator chains successfully extended to block copolymers (Figure 4.2a). This result indicated high block-efficiency. A relatively high monomer conversion (83%) was achieved at 4 h (Figure 4.2b, Table 4.2 (entry 3)). The M_n was increased with an increase in the monomer conversion. The $\bar{D}$ value (1.27-1.50) was relatively low in the whole course of polymerization (Figure 4.2c, Table 4.2 (entry 3)). The experimental M_n values deviated from the theoretical values, because the experimental values of the block copolymer (PPEGMA-PMMA) are PMMA-calibrated GPC values. At 1.2 h, the DP of the PMMA segment was 15 and a self-assembly was generated because the PMMA segment is long enough to be insoluble in water (Table 4.2 (entry 3)).

Table 4.2. Aqueous Emulsion PISA of MMA with PPEGMA-I, V501, and NaI in 90 wt% Water at 60 °C.

Entry	DP of PPEGMA	[MMA] ₀ /[PPEGMA-I] ₀ / [V501] ₀ (mM) ^a	<i>t</i> (h)	Conv (%)	DP of PMMA ^b	<i>D</i> ^b
1	33	8000/20/160/40	1.2	35	21	1.17
			1.8	43	31	1.21
			2.3	50	49	1.21
			2.8	57	61	1.21
			3.8	67	91	1.24
2	46	8000/20/160/40	1	20	16	1.31
			1.5	30	26	1.32
			2	35	34	1.31
			2.5	41	42	1.32
			3	54	58	1.28
			3.5	66	78	1.26
3	90	8000/20/160/40	5	75	140	1.35
			1.2	20	15	1.27
			1.8	28	25	1.27
			2.3	35	35	1.27
			2.8	60	110	1.42
			4	83	480	1.50

Entry	Symbol of Block Copolymer	<i>f</i> _{PMMA}	Hydrodynamic Diameter ^c in DLS (nm)	Size Distribution Index in DLS	Assembly Structure ^d	Code in Figs. 4.3 and 4.4
1	PPEGMA ₃₃ -PMMA ₂₁	0.18	30	0.124	S	A
	PPEGMA ₃₃ -PMMA ₃₁	0.24	39	0.134	S	
	PPEGMA ₃₃ -PMMA ₄₉	0.33	60	0.284	S	
	PPEGMA ₃₃ -PMMA ₆₁	0.38	110	0.352	S + V	B
	PPEGMA ₃₃ -PMMA ₉₁	0.48	158	0.366	V	C
2	PPEGMA ₄₆ -PMMA ₁₆	0.13	60	0.113	S	D
	PPEGMA ₄₆ -PMMA ₂₆	0.16	75	0.137	S	
	PPEGMA ₄₆ -PMMA ₃₄	0.20	85	0.143	S	
	PPEGMA ₄₆ -PMMA ₄₂	0.23	93	0.127	S	
	PPEGMA ₄₆ -PMMA ₅₈	0.30	100	0.210	S + V	E
	PPEGMA ₄₆ -PMMA ₇₈	0.36	135	0.329	S + V	
3	PPEGMA ₄₆ -PMMA ₁₄₀	0.50	165	0.284	V	F
	PPEGMA ₉₀ -PMMA ₁₅	0.05	35	0.243	S	G
	PPEGMA ₉₀ -PMMA ₂₅	0.08	45	0.203	S	
	PPEGMA ₉₀ -PMMA ₃₅	0.12	65	0.196	S	
	PPEGMA ₉₀ -PMMA ₁₁₀	0.30	100	0.139	S+V	H
	PPEGMA ₉₀ -PMMA ₄₈₀	0.64	370	0.590	V	I

^a The mixture of PPEGMA-I, NaI, and V501 was diluted with water (water content = 90 wt%) and mixed with MMA at the described concentration. ^b DP and *D* were recorded using DMF-GPC after drying. ^c The size was the DLS peak-top value. ^d S = sphere and V = vesicle.

We obtained different PPEGMA₉₀-PMMA_y block copolymers at different polymerization times (up to 4 h (monomer conversion = 83%)), where y is the DP of PMMA. At each sampling time, a small portion of the reaction mixture was taken out from the reactor vessel, divided in three parts. The first part was dried and subjected to GPC analysis. The second part was diluted with DMSO-*d*₆ and performed the ¹H NMR analysis. The third part was diluted by 50 times with water. This solution was used as the stock solution for the subsequent dynamic light scattering (DLS) and transmission electron microscope (TEM) studies.

We prepared TEM samples by casting a drop of the stock solution on TEM grid, followed by drying in vacuum. Figure 4.2d shows the TEM image of the self-assembly structure for PPEGMA₉₀-PMMA₄₈₀ obtained after 4 h polymerization, for example. In this case, we observed vesicles. The self-assembly structures may change during the dilution and drying process in the preparation of TEM samples. However, as described below, the crosslinking experiments (fixation of self-assembled structures by in situ crosslinking during the polymerization) supported that the observed morphologies were really generated during the polymerization but not during the dilution or drying process.

The contour length of PPEGMA₉₀-PMMA₄₈₀ is 143 nm. The average diameter of the vesicles obtained with PPEGMA₉₀-PMMA₄₈₀ was 370 nm in a swollen state in water, as measured with dynamic light scattering (DLS) (Table 4.2 (entry 3)). The diameter (370 nm) is larger than the twofold (286 nm) of the contour length (143 nm) of the copolymer. Therefore, the self-assembled structure was a vesicle but not a sphere. After 4 h, the total solid concentration reached 9% in which 4% was due to the macroinitiator and additional 5% was due to the PMMA segment generated during the polymerization. Thus, we obtained vesicles with a relatively high (9%) solid content.

Figure 4.3. Phase diagram of the self-assembled structures generated in the aqueous emulsion PISA process of PEGMA-PMMA (Table 4.2). The solid content was 4-9 wt%. S + V denotes a mixture of spheres and vesicles.

Phase Diagram.

We constructed a phase diagram using a series of hydrophilic PPEGMA-I macroinitiators with different DPs (33, 46, and 90). The monomer/macroinitiator ratio in PISA was fixed to 400. We varied the DPs (from 16 to 480) of the hydrophobic PMMA segment with different monomer conversions (from 20% to 83%). We observed spheres and vesicles, depending on the DPs of the PPEGMA and PMMA segments. In the phase diagram, the solid content was 4-9% (Figures 4.3 and 4.4, Table 4.2).

In the PISA of MMA using PPEGMA₃₃-I (DP = 33 in the horizontal axis in Figure 4.3), the DP of PMMA segment (in the vertical axis in Figure 4.3) increased from 21 to 91 with an increase in the polymerization time (Table 4.2 (entry 1)). The self-assembly structure was spheres for PPEGMA₃₃-PMMA₂₁ (with a small DP of PMMA) and changed to vesicles for PPEGMA₃₃-PMMA₉₁ (with a large DP of PMMA) through a mixed phase of spheres and vesicles (for PPEGMA₃₃-PMMA₆₁) (with a middle DP of PMMA), as observed in the TEM

Figure 4.4. TEM images of the self-assemblies obtained in the aqueous emulsion PISA process (Table 4.2 and Figure 4.3), where A = PPEGMA₃₃-PMMA₃₁, B = PPEGMA₃₃-PMMA₆₁, C = PPEGMA₃₃-PMMA₉₁, D = PPEGMA₄₆-PMMA₂₆, E = PPEGMA₄₆-PMMA₇₈, F = PPEGMA₄₆-PMMA₁₄₀, G = PPEGMA₉₀-PMMA₂₅, H = PPEGMA₉₀-PMMA₁₁₀, and I = PPEGMA₉₀-PMMA₄₈₀.

images (A, B, and C in Figure 4.4). PPEGMA₃₃-PMMA₂₁ and PPEGMA₃₃-PMMA₃₁ were self-assembled to micelles (spheres). The diameters of the spheres determined in the DLS were 30 and 39 nm, respectively (Table 4.2 (entry 1)). The diameters were comparable with the twofold (26 and 32 nm, respectively) of the contour length of the block copolymers (13 and 16 nm, respectively), which is consistent with the sphere structure. PPEGMA₃₃-PMMA₆₁ generated a mixture of spheres and vesicles as a boundary phase. For PPEGMA₃₃-PMMA₉₁, the diameter

(158 nm) of the obtained structure was larger than the twofold (62 nm) of the contour length of the block copolymer (31 nm), which is consistent with vesicle structure.

In general, the colloidal stability of the self-assembled structures increases with an increase of the molecular weight of the polymers. Thus, we used other two macroinitiators PPEGMA₄₆-I and PPEGMA₉₀-I with higher DPs (Table 4.2 (entries 2 and 3)). Similar to PPEGMA₃₃-I, the structure changed from spheres to vesicles through the mixed phase with an increase of the DP of the PMMA segment for both macroinitiators (Figures 4.3 and 4.4 (images D-I)). In principle, hydrophilic and hydrophobic mass fractions in the block copolymers determine the morphologies, as discussed in previous chapter (Chapter 3). The f_{PMMA} represents the mass (weight) fraction of the PMMA segment in the PPEGMA-PMMA block copolymer. In the present system, as a rough estimate, PPEGMA-PMMA forms micelles at $f_{\text{PMMA}} < 0.30$, a mixture of micelles and vesicles at $0.30 < f_{\text{PMMA}} < 0.46$, and vesicles at $f_{\text{PMMA}} > 0.46$. With an increase in the DPs of the PMMA segment, the size of the assembly structures increased from 30-93 nm (spheres) to 158-370 nm (vesicles) in the studied cases (Table 4.2). Unlike, the PMAA-PMMA system in the previous chapter (Chapter 3), we did not observe worms in the present system. Vesicles were obtained in water with relatively high (8-9%) solid concentrations, which were used to test the encapsulation of guest molecules, as described below.

Crosslinking of Assembly Structures.

In order to fix the assembly structures, a cross-linkable divinyl monomer, i.e., ethylene glycol dimethacrylate (EGDMA) was copolymerized with MMA (a non-crosslinkable monomer) in PISA.

As mentioned above, PPEGMA₃₃-PMMA₃₁ (Figures 4.3-4.5 (image A) and Table 4.2 (entry 1)) generated spheres and PPEGMA₃₃-PMMA₉₁ (Figures 4.3-4.5 (image C) and Table 4.2 (entry 1)) generated vesicles. These non-crosslinked assemblies were treated with

tetrahydrofuran (THF) solvent. The assemblies were decomposed because both the PPEGMA and PMMA segments were soluble in THF. DLS curves show that spheres (42 nm) and vesicles (158 nm) decomposed to single linear block copolymers (1.5 and 3.5 nm, respectively) (Figure 4.5 (parts a and b)).

Figure 4.5. DLS curves before (dashed lines) and after (solid lines) the addition of a tetrahydrofuran (THF) solvent for (a) PPEGMA₃₃-PMMA₃₁ and (b) PPEGMA₃₃-PMMA₉₁ (Table 4.2 (entry 1)). TEM images before the addition of THF solvent for PPEGMA₃₃-PMMA₃₁ (image A) and PPEGMA₃₃-PMMA₉₁ (image C).

We replaced pure MMA with a mixture of MMA and EGDMA (Table 4.3) for these PISA experiments (PPEGMA₃₃-PMMA₃₁ (spheres) and PPEGMA₃₃-PMMA₉₁ (vesicles)). We used a small amount of EGDMA (9.1% to fix the spheres and 6.5% to fix the vesicles) to prevent the crosslinking at an early stage of polymerizations. Therefore, the crosslinking occurred only after the formation of self-assembled structures. We obtained similar structures, i.e., spheres for PPEGMA₃₃-(PMMA/PEGDMA)₃₁ (Figure 4.6 (image J)) and vesicles for PPEGMA₃₃-(PMMA/PEGDMA)₉₁ (Figure 4.6 (image K)). These assemblies were treated with THF. The spheres showed virtually no change in the DLS curves before and after the THF treatment (Figure 4.6a, Table 4.3 (entry 1)), meaning that the spheres did not decompose. No change of the structure was also confirmed with TEM image (Figure 4.6 (image L)). The vesicles showed a partial decomposition by the THF treatment, as a new peak (4 nm) of the

single linear polymers was observed along with the original peak (158 nm) of the vesicles in the DLS analysis (Figure 4.6b, Table 4.3 (entry 2)). A part of the polymer chains was not chemically crosslinked (but physically assembled) and released from the vesicles in the THF solution. However, the structures of the vesicles perfectly retained. Almost no change in the DLS peak for the vesicles, and the vesicle structures were clearly observed with TEM (Figure 4.6 (image M)). Thus, the spheres and vesicles were successfully crosslinked. Importantly, the obtained crosslinked structures (spheres and vesicles) were the same as the non-crosslinked structures, clearly confirming that the structures observed with TEM for the non-crosslinked systems were truly generated during the polymerization.

Figure 4.6. DLS curves before (dashed lines) and after (solid lines) the addition of THF for (a) PEGMA₃₃-(PMMA/PEGDMA)₃₁ and (b) PEGMA₃₃-(PMMA/PEGDMA)₉₁ (Table 4.3). TEM images before and after the addition of THF for PEGMA₃₃-(PMMA/PEGDMA)₃₁ (images J and L) and PEGMA₃₃-(PMMA/PEGDMA)₉₁ (images K and M).

Encapsulation of Rhodamine-B Dye in Nano-capsules.

The encapsulation of a guest molecule was studied using PPEGMA₉₀-I macroinitiator (with a large DP), because a higher DP of hydrophilic segment provides a higher colloidal stability of the vesicles. A hydrophilic dye Rh-B was used as a guest molecule.

Table 4.3. Aqueous Emulsion PISA of a Mixture of MMA and EGDMA with PPEGMA₃₃-I, V501, and NaI in 90 wt% Water at 60 °C.

Entry	[MMA] ₀ /[EGDMA] ₀ /[PPEGMA ₃₃ -I] ₀ /[V501] ₀ /[NaI] ₀ (mM) ^a	<i>t</i> (h)	Symbol of Block Copolymer ^b	Hydrodynamic Diameter in DLS (nm) ^c	Size Distribution Index in DLS	Self-assembled Morphology ^d	Image in Figure 4.6
1	7270/730/20/40/160	1.8	PPEGMA ₃₃ -(PMMA/PEGDMA) ₃₁	42	0.199	S	J
	(after adding THF)			46	0.158	S	L
2	7480/520/20/40/160	3.8	PPEGMA ₃₃ -(PMMA/PEGDMA) ₉₁	156	0.288	V	K
	(after adding THF)			4 & 158	0.566	V	M

^a The mixture of PPEGMA-I, NaI, and V501 was diluted with water (water content = 90 wt%) and mixed with MMA and EGDMA at the described concentration. ^b DP of PMMA in PPEGMA₃₃-PMMA₃₁ and PPEGMA₃₃-PMMA₉₁ in entry 1 (1.8 h and 3.8 h, respectively) in Table 4.2 and DP of (PMMA/PEGDMA) in entries 1 (1.8 h) and 2 (3.8 h) in Table 4.3 were same. ^c The size was the DLS peak-top value. ^d S = sphere and V = vesicle.

Table 4.4. Encapsulation of Rh-B Dye in Nano-capsules Generated in an Aqueous Emulsion PISA of MMA with PPEGMA₉₀-I, V501, and NaI in 90 wt% Water at 60 °C.

[MMA] ₀ /[PPEGMA ₉₀ -I] ₀ /[NaI] ₀ /[V501] ₀ /[Rh-B] ₀ (mM) ^a	<i>t</i> (h)	Conv (%)	DP of PMMA ^b	<i>D</i> ^b	Hydrodynamic Diameter in DLS (nm) ^c	Size Distribution Index in DLS	Assembly Structure ^d	EE (%) ^e	LC (%) ^f
8000/20/160/40/15	4.5	83	520	1.60	420	0.820	V	48	0.28

^a The mixture of PPEGMA-I, NaI, Rh-B, and V501 was diluted with water (water content = 90 wt%) and mixed with MMA at the described concentration. ^b DP and *D* were recorded using DMF-GPC after drying. ^c The size was the DLS peak-top value. ^d V = vesicle. ^e EE is encapsulation efficiency. ^f LC is loading capacity. concentration was measured with respect to initial concentration.

We performed the same polymerization as Table 4.2 (entry 3) (non-crosslinked system) but using a Rh-B containing water (15 mM, 0.8 eq with respect to macroinitiator) instead of pure water as a solvent. After 4.5 h, the polymerization was stopped with an 83% monomer conversion (Table 4.4). The *D* (1.60) of the block copolymer using a Rh-B containing water was larger than that (1.50) using pure water, meaning that Rh-B slightly affected the polymerization (Table 4.4). The DP of PMMA segment was 520.

Figure 4.7. TEM images of empty vesicles generated from PEGMA₉₀-PMMA₄₈₀ (image I) and Rhodamine-B dye loaded vesicles generated from PEGMA₉₀-PMMA₅₂₀ (image N).

After the polymerization, 1 g of the reaction mixture was diluted with 3 g pure water and subsequently dialyzed with water for 84 h. Figure 4.7 (image N) shows the vesicles after the dialysis. The core is dark, suggesting that Rh-B (dye) was successfully loaded inside the core of the vesicles. Figure 4.7 (image I) shows the vesicles prepared in pure water. The core is brighter than the shell, suggesting the core is empty. This result clearly demonstrated the successful loading of Rh-B. The size distribution index of the vesicle became significantly broader when the [Rh-B]₀ was increased from 0 to 15 mM. This result also indicated the encapsulation of the Rh-B inside the vesicle during the PISA.³⁴

For more quantitative discussion, we carried out a UV-Vis analysis (Figure 4.8). We added acetone to the solutions before and after dialysis (3.5/1 (acetone/solution)). The vesicles were decomposed with the addition of acetone, releasing Rh-B from the vesicle to the solution, because acetone is a good solvent for both PEGMA and PMMA segments. The UV-Vis spectra of the acetone solutions (Figure 4.8) showed the absorption of Rh-B with a peak top at 546 nm. The absorbance at the peak top before the dialysis was 0.582 (Figure 4.8 (red line)), and that after the dialysis was 0.297 (Figure 4.8 (blue line)). We also analyzed the supernatant of the dialyzed solution which was obtained by careful centrifugation for removing the vesicles from the solution, showing almost no absorption spectrum (Figure 4.8 (black line)). This means that

the observed absorption (absorbance = 0.297) resulted from the loaded Rh-B in the vesicle (not from the supernatant). Thus, the encapsulation efficiency (the molar ratio of the encapsulated Rh-B to the initially added Rh-B) was calculated to be 48% ($= 0.297/0.582$).

Figure 4.8. UV-Vis spectra of the solution before dialysis (red line), dialyzed solution (blue line), and supernatant after centrifugation of the dialyzed solution (black line).

The average diameter of the Rh-B loaded vesicles was 420 nm, as determined by the DLS analysis (Table 4.4). The average shell thickness of the vesicles was 25 nm as a rough estimate from the TEM images. This means that the radius of the outer shell is 210 nm and that of the inner shell is 185 nm; namely, a vesicle contains 68% ($= 185^3/210^3$) core cavity and 32% polymer shell in volume. The weight fraction of polymer was 9% in the solution (4% PPEGMA and 5% PMMA), and here we assume the density of the polymer shell to be 1.18 g/cm³, which is the density of bulk PMMA (25 °C). Then we calculate the volume ratio to be 22.5% core cavity (water), 10.6% shell (polymer), and 66.9% outer media (water). It follows that a Rh-B containing water was supposed to be distributed in the core cavity in 25.2% ($22.5/(22.5 + 66.9)$) and the outer media in 74.8%. The observed 48% encapsulation exceeds the 25.2% encapsulation expected on the water-volume basis distribution of Rh-B. This result suggests that Rh-B was encapsulated not only in the cavity but also in the shell layer to some extent. Previously, Zhang et al. reported the maximum encapsulation efficiency via physical entrapment during PISA was 24%.⁴¹ They encapsulated BSA protein into the PPEGMA-

P(HPMA-DMAEMA) block copolymer vesicles, where HPMA is 2-hydroxypropyl methacrylate and DMAEMA is 2-(dimethylamino)ethyl methacrylate. In our typical experiment, the enhance encapsulation would be due to the aromatic moiety of Rh-B which may have affinity to the hydrophobic polymer shell in this particular case. Due to encapsulation of Rh-B in both the core and shell layer, 48% encapsulation efficiency was obtained.

In this study, we used 0.044 g Rh-B, 48% of which was encapsulated. The total weight of the polymer was 7.525 g. The loading capacity was calculated to be 0.28% ($= 0.021/7.525$).

4.3. Conclusion.

Nano-particles (spheres) and nano-capsules (vesicles) were successfully prepared in NaI-catalyzed aqueous emulsion PISA of MMA using PPEGMA-I macroinitiators. Nano-capsules were generated when $f_{\text{PMMA}} > 0.46$. This system is attractive because the PPEGMA segment located on the inner surfaces and outer surfaces of the shell is bio-compatible, water is green and the least expensive solvent, and the nano-capsules are obtainable with relatively high (8-9%) solid concentrations. The nano-capsules were also crosslinked. Rh-B was successfully encapsulated with a 48% encapsulation efficiency and a 0.28% loading capacity, demonstrating the effective use of the obtained capsules as containers of guest molecules.

4.4. Experimental Details.

Materials.

4,4'-azobis(4-cyanovaleric acid) (V501) (95%, Wako Pure Chemical, Japan), and Rhodamin-B (Rh-B) (TCI, >95%), and other chemicals were used as received. The details of other chemicals were mentioned in the experimental details of Chapters 2 and 3 (Sections 2.4 and 3.4).

Measurements.

The GPC, DLS, NMR, and TEM measurements were performed using same instrument as mentioned in Chapter 3 (Section 3.4). GPC was equipped with same columns as Chapter 3 and columns were calibrated with standard poly(methyl methacrylate)s (PMMA)s. For the GPC analysis, dimethyl formamide (DMF) was used as an eluent and flow rate was 0.8 ml/min.

Shimadzu UV-3600 (Japan) instrument was used to record the UV-Vis absorption spectra. We used quartz cuvette with 1cm optical path length for recording the absorption spectra in room temperature.

Preparation of PPEGMA-I Macroinitiator.

A mixture (12.5 g) of PEGMA (8 M), Iodine (I₂) (40 mM), V65 (160 mM), BNI (80 mM), and ethanol (20 wt% of the mixture) was heated in a Schlenk flask at 60 °C under argon atmosphere with magnetic stirring. The reaction mixture was dilute with 2 mL ethanol. The synthesized polymer was purified by reprecipitation using a mixture of hexane and diethyl ether (1:1 (v/v)) as a non-solvent.

PISA.

A mixture (83.8 g) of MMA (8 M), PPEGMA-I (20 mM), V501 (40 mM), NaI (160 mM), and water (90 wt% of the mixture) was heated in a glass reactor at 60 °C under argon

atmosphere with mechanical stirring. The pH of the solution was adjusted to 7 by adding 1 g of a 1 M aqueous sodium bicarbonate (NaHCO_3) solution. Toluene (0.5 g) was used as an external standard for calculating the monomer conversion. An aliquot (0.1 mL) of the solution was dried under vacuum and analyzed with GPC. ^1H NMR analysis was performed like previous Chapter 3 (Section 3.4.). Another aliquot (0.1 mL) was diluted with 5 mL water. This solution was used as the stock solution for the subsequent dynamic light scattering (DLS) and transmission electron microscope (TEM) studies.

Encapsulation of Rhodamine-B Dye in Nano-capsules.

A mixture (83.8 g) of MMA (8 M), PPEGMA-I (20 mM), V501 (40 mM), NaI (160 mM), Rh-B (15 mM), and water (90 wt% of the mixture) was heated in a glass reactor at 60 °C under argon atmosphere with mechanical stirring. The pH of the solution was adjusted to 7 by adding 1 g of a 1 M aqueous sodium bicarbonate (NaHCO_3) solution. The GPC and NMR analyses were performed as described in PISA. An aliquot (1 mL) was taken out, diluted with 3.5 mL of acetone, and analyzed with UV-Vis spectrophotometer. Another aliquot (2 mL) of the solution was taken out, diluted with 6 mL of water, and dialyzed with water for 84 h using cellulose dialysis tube (Orange Scientific, MWCO: 6000-8000). Water was changed in every 6 h. An aliquot (0.1 mL) of the dialyzed solution was diluted with 1 mL water and analyzed with DLS and TEM. An aliquot (1 mL) of the dialyzed solution was diluted with acetone (3.5 mL) and analyzed with UV-Vis spectroscopy. Another part of the dialyzed solution (5 mL) was centrifuged for 8 minutes using 8000 rpm and supernatant was collected in 4 cycles. The resultant supernatant (1 mL) was diluted with acetone (3.5 mL) and analyzed with UV-Vis spectrophotometer. The absorbance value was used to calculate the loading capacity (LC) and encapsulation efficiency (EE). The LC and EE were calculated using the following definitions: $\text{LC} = (\text{amount of loaded dye} / \text{amount of polymer}) \times 100\%$ and $\text{EE} = (\text{amount of loaded dye} / \text{total amount of dye}) \times 100\%$.³²

4.5. References.

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Chapter 5. Synthesis and Lubrication Property of Bottlebrush Polymer Particle.

Abstract.

A bottlebrush polymer is unique in its shape and exhibits a lubrication property. In this chapter (Chapter 5), a bottlebrush polymer was synthesized using reversible complexation mediated polymerization (RCMP) via a grafting-through approach. We carried out RCMP of a macromonomer, i.e., poly(dimethylsiloxane) methacrylate (PDMSM), and prepared a bottlebrush polymer. The obtained bottlebrush polymer (PPDMSM-I) was further used as a macroinitiator in the polymerization of a divinyl crosslinkable monomer, i.e., ethylene glycol dimethacrylate (EGDMA), yielding a bottlebrush particle. The core of the particle was crosslinked and the shell consisted of a bottlebrush polymer. For comparison, we also synthesized a particle whose shell consisted of a linear (non-bottlebrush) polymer, i.e., poly(methyl methacrylate) (PMMA). In tetrahydrofuran (THF), the PPDMSM particle showed slightly lower viscosity than the PMMA particle in a low particle concentration region. Above a critical overlapping concentration (5 wt%) of the particle, the viscosity of the PMMA particle significantly increased because of the entanglement of the linear shell polymers, and the viscosity of the PPDMSM particle became much lower than that of the PMMA particle, demonstrating a better lubrication property of the bottlebrush particle. The observed lower viscosity of the PPDMSM particle is ascribed to the entropic repulsion of the sterically hindered bottlebrush polymer shell.

5.1. Introduction.

A bottlebrush polymer is a polymer consisting of a backbone chain with a number of attached branch chains (Figure 5.1). When the density of the branch chain is low (the number of the branch chain is small), the branch chains take random-coil conformations and the backbone chain is flexible (Figure 5.1). Thus, the polymer is star shaped. As the density of the branch chain increases, the branch chains are forced to take extended conformations because of the steric hindrance of neighbouring branch chains, and hence the backbone chain is also extended (Figure 5.1). Thus, the polymer is bottlebrush-shaped. The conformation is like worm or cylindrical.^{1,2}

Figure 5.1. Conformations of bottlebrush polymers.

Bottlebrush polymer (called bottlebrush hereafter) has drawn attraction, particularly since the 1980s.^{3,4} Bottlebrushes were assembled to create new types of assembly materials. Due to their unique shapes, these materials were utilized for efficient sensing and drug delivery in biological systems.⁵⁻⁸ Bottlebrushes were also utilized in various materials such as elastomer,^{9, 10} coating materials,¹¹ photonic crystal,¹² and nanoporous materials.¹³

From a theoretical point of view, linear polymer chains can easily be interpenetrated and entangled one another because of their random coil structures. This entanglement causes high viscosity and high friction in the polymer solution. In contrast, bottlebrush polymers are sterically hindered and have steric repulsion among one another (Figure 5.2). Because of this steric repulsion, the polymer chains are not entangled significantly, resulting in low viscosity and low friction (i.e., excellent lubrication). Importantly, this is entropic repulsion but not enthalpy repulsion (such as electronic charge repulsion) and hence does not depend on solvents. The branch chains are already extended, and the further extension of the branch chains

caused by the interpenetration significantly loses their possible number of conformations, penalizing the conformational entropy. Therefore, bottlebrushes will not interpenetrate one another.

Figure 5.2. Crosslinked-particle consisting of bottlebrush polymers in the shell.

Human body utilizes bottlebrush polymers such as Lubricin to acquire lubrication.¹⁴ Inspired by the natural bottlebrushes, we aimed to synthesize synthetic bottlebrush. Bottlebrushes can be prepared in three ways, i.e., grafting-from,^{15,16} grafting-to^{16,17} and grafting-through^{16,18} approaches. The grafting-through approach uses a so-called macromonomer (polymer with a polymerizable vinyl monomer group at the chain end). The backbone chain length can be controlled by the initiator-to-macromonomer ratio in living polymerizations. An important advantage is its high and uniform graft density; namely, all backbone repeating units have a branch chain.¹⁶ In this work, we utilized grafting-through approach to synthesize bottlebrushes.

The recent development of controlled radical polymerization (living radical polymerization (LRP)),^{16,19,20} Suzuki polycondensation,^{16,21} and controlled ring opening metathesis polymerizations enabled the synthesis of well-defined bottlebrushes with sophisticated structures.²² For LRP, atom transfer radical polymerization (ATRP),^{23,24} reversible addition-fragmentation chain transfer (RAFT) polymerization,²⁵ and nitroxide

mediated polymerization (NMP)²³ were used. In this work, we used reversible complexation mediated polymerization (RCMP) for the synthesis of a bottlebrush. The advantages of RCMP method are the use of inexpensive and nontoxic organic molecules as catalysts and no use of special capping agents.

Scheme 5.1. Synthetic route of bottlebrush polymer particle.

In this work, we used poly(dimethylsiloxane) methacrylate (PDMSM) (Scheme 5.1) as a macromonomer and carried out a RCMP of PDMSM to obtain a bottlebrush. This macromonomer contains a silicon segment with low glass transition temperature and low surface energy and hence can provide super-hydrophobic bottlebrush.

We further utilized the obtained bottlebrush, i.e., poly(poly(dimethylsiloxane) methacrylate) iodide (PPDMSM-I), as a macroinitiator in the polymerization of a crosslinkable divinyl monomer, i.e., ethylene glycol dimethacrylate (EGDMA (Scheme 5.1)). Both this PPDMSM and PEGDMA polymer segments are soluble in toluene. Through this polymerization, the bottlebrushes were crosslinked to yield a bottlebrush particle, in which core was crosslinked and the shell consisted of bottlebrushes. This assembly is generated via crosslinking, not via self-assembly. This assembly is not similar as Chapters 3 and 4. In ATRP, this (arm-first) approach was used for the star polymer preparation.^{26,27} This is the first report of bottlebrush polymer particle (crosslinked-assembly material) synthesis using RCMP. There is no use of heavy transition metal catalyst which may be attractive for skin care industry.

The viscosity of the particles depends on the size and morphology of the particles.²⁸ For comparison, we also prepared a core-crosslinked particle whose shell consisted of linear (non-bottlebrush) poly(methyl methacrylate) (PMMA) chains. The viscosity of the bottlebrush and non-bottlebrush particles in tetrahydrofuran (THF) was studied. The bottlebrush particle showed a lower viscosity, which may find applications for lubrication coatings and smooth cosmetic particles.

5.2. Results and Discussion.

RCMP of PDMSM.

We used PDMSM (average molecular weight = 900) as a macromonomer and 2-iodo-2-methylpropionitrile (CP-I (Scheme 5.1)) as an alkyl iodide (R-I) initiator. We used tetraoctylammonium iodide (ONI) as a highly active catalyst, which was required for this macromonomer. We heated a mixture of PDMSM (8 M, 50 equiv.), CP-I (160 mM, 1 equiv), V65 (an azo compound, 200 mM, 1.3 equiv.), and ONI (80 mM, 0.5 equiv.) at 60 °C. A large amount of V65 was used to increase the rate of polymerization.

Table 5.1. RCMP of PDMSM with CP-I, ONI, and V65 at 60 °C.

entry	[PDMSM] ₀ /[CP-I] ₀ /[ONI] ₀ /[V65] ₀ (mM)	<i>T</i> (°C)	<i>t</i> (h)	conv (%) ^a	<i>M</i> _n ^b	<i>Đ</i> ^b
1	8000/160/80/200	60	0.6	24	10000	1.12
			1.1	47	19000	1.17
			2	75	27000	1.22
			3	85	31000	1.28
			4.5	93	34000	1.27
2	8000/266/80/200	60	4.5	85	19000	1.18
	(after Purification)				19000	1.17

^aThe monomer conversion was calculated with ¹H NMR. ^b*M*_n and *Đ* were determined using PMMA-calibrated GPC.

Figure 5.3 and Table 5.1 (entry 1) show the result of the polymerization. The polymerization was relatively fast, and the monomer conversion reached 93% for 4.5 h. The number-average molecular weight (*M*_n) increased with an increase in the monomer conversion. The dispersity (*Đ*) (= *M*_w/*M*_n) was as low as 1.12 to 1.28 in the whole course of polymerization, where *M*_w is the weight-average molecular weight. Thus, the polymerization of PDMSM was well controlled via RCMP.

Figure 5.3. Plots of (a) $\ln([M]_0/[M])$ vs t and (b) M_n and M_w/M_n vs monomer conversion for the PDMSM/CP-I/ONI/V65 system in bulk (60 °C); [PDMSM]₀ = 8 M; [CP-I]₀ = 160 mM; [ONI]₀ = 80 mM; and [V65]₀ = 200 mM.

Synthesis of PPDMSM-I Macroinitiator.

We prepared a PPDMSM-I with a relatively small degree of polymerization as a macroinitiator for the subsequent polymerization. A mixture of PDMSM (8 M, 30 equiv.), CP-I (266 mM, 1 equiv.), V65 (200 mM, 0.8 equiv.), and ONI (80 mM, 0.3 equiv.) was heated at 60 °C for 4.5 h. A high (85%) monomer conversion was achieved (Table 5.1 (entry 2)). The M_n and $\bar{D}$ of the obtained polymer were 19000 and 1.18, respectively. The polymer was purified by reprecipitation using a mixture of methanol and diethyl ether (2:1 (v/v)) as a non-solvent. The M_n and $\bar{D}$ of the purified polymer were 19000 and 1.17, respectively. We utilized the purified polymer as a macroinitiator for the preparation of the bottlebrush particle (Scheme 5.1).

Preparation of Bottlebrush Polymer Particle.

We prepared the bottlebrush particle via an arm-first approach. We used the mentioned PPDMSM-I as a macroinitiator, a divinyl monomer EGDMA as a crosslinkable monomer, and toluene as a solvent.

Table 5.2. Polymerization of EGDMA with PPDMSM-I, BNI, and V65 in 70 wt% Toluene.

entry	[EGDMA] ₀ /[PPDMSM-I] ₀ /[BNI] ₀ (mM) ^a	<i>T</i> (°C)	<i>t</i> (h)	conv (%) ^b	<i>M_n</i> ^c	<i>Đ</i> ^c	Hydrodynamic Size (nm) ^d
1	160/20/80	70	36	80	57000		
	After addition of [V65] ₀ = 40 mM ^e	60	8	85	63000		
	(after Purification)				84000	1.22	22

^a Solution polymerization in 70 wt% toluene. ^b The monomer conversion was calculated with ¹H NMR from the decay of the amount of EGDMA. ^c *M_n* and *Đ* were determined using PMMA-calibrated GPC. ^d The size was the DLS Peak-top value. ^e The amount of V65 used with respect to the initial amount of EGDMA.

We heated a mixture of EGDMA (160 mM, 8 equiv.), PPDMSM-I (20 mM, 1 equiv.), BNI (80 mM, 4 equiv.), and toluene (70 wt% of total mixture) at 70 °C for 36 h. We used 8 equiv. of the monomer with respect to the initiator (1 equiv.). A small amount of EGDMA was used to avoid the inter-particle crosslinking during the particle generation. A large (70 wt%) amount of toluene was also used to prevent the inter-particle crosslinking. The particle was generated for 36 h (80% monomer (EGDMA) conversion), as shown in the GPC chromatogram (Figure 5.4a (dashed line), Table 5.2). The GPC chromatogram shows that 64% of the macroinitiator was converted to bottlebrush particle. This result suggests a relatively low chain-end fidelity of the macroinitiator. This would be because of the use of a relatively large amount of V65 to increase the polymerization rate in the synthesis of the macroinitiator. Also, because of the bulkiness of PPDMSM, the C-I bond at the chain end is weakened, which might cause a relatively low stability of the PPDMSM-I macroinitiator during the purification. The peak-top molecular weight of the obtained particle determined by PMMA-calibrated GPC was 57000 (Table 5.2), where PMMA is poly(methyl methacrylate).

In order to further densely crosslink the particle core, V65 (40 mM, 2 equiv. with respect to initial PPDMSM-I) was added after the mentioned 36 h polymerization, and the mixture was heated for another 8 h at 60 °C (Table 5.2). V65 generated radicals and consumed the remaining pendant vinyl groups in the core for dense crosslinking. The peak-top molecular weight of the obtained particle was 63000 (Table 5.2), according to PMMA-calibrated GPC. These values were virtually unchanged before and after the V65 treatment, suggesting that the inter-particle crosslinking was negligible during the V65 treatment. The mono-modal peak (in the particle part) was observed in the GPC chromatogram (Figure 5.4a (solid line)).

We separated bottlebrush particle from the macroinitiator by the following steps. In order to remove the catalyst (BNI), we diluted the reaction mixture with THF, centrifuged, collected the supernatant, and dried. THF was a non-solvent of BNI. The dried polymer was washed with a mixture of diethyl ether and methanol (1:1 (v/v)), centrifuged (with 3000 rpm rotation for 90 sec), and the pellet was collected. The pellet was washed with the same solvent mixture and dried in five cycles. Figure 5.4b (solid line) suggests that there was no trace of macroinitiator. Thus, we obtained pure crosslinked bottlebrush particle. The M_n and $\bar{D}$ of the pure particle were 84000 and 1.22, respectively.

Figure 5.4. (a) GPC chromatograms of PPDMSM-I (short dash line), PPDMSM particle after 36 h (dash line), and PPDMSM particle after 44 h (solid line) for the synthesis of bottlebrush particle (Table 5.2). (b) GPC chromatograms and (c) DLS curves of PPDMSM-I (short dash lines) and purified crosslinked particle (solid lines). (d) TEM image of purified bottlebrush particle.

The dynamic light scattering (DLS) peak-tops of the macroinitiator (Figure 5.4c (dash line)) and the bottlebrush particle (Figure 5.4c (solid line)) were 8 nm and 22 nm, respectively. The diameter (22 nm) of the bottlebrush particle was slightly larger than the twofold (16 nm) of the macroinitiator (8 nm). This increment was due to the addition of EGDMA monomer

units in the core. This result reasons the formation of particle. The observed hydrodynamic size of the particle also indicates that the inter-particle coupling was almost negligible. The transmission electron microscopy (TEM) image showed that each particle was independent (not aggregated) (Figure 5.4d). The particle size was different between the DLS and TEM analyses because the swollen state of the particles in THF was observed with DLS whereas the dry state was observed with TEM.

Scheme 5.2. Synthetic procedure of PMMA particle.

Synthesis of PMMA Particle.

For comparison, we also used a linear PMMA-I macroinitiator in the polymerization of EGDMA and obtained a non-bottlebrush particle (Scheme 5.2). The shell consisted of linear PMMA chains. Table 5.3 shows the synthesis of the macroinitiator. We obtained a PMMA-I ($M_n = 21000$ and $\bar{D} = 1.22$ after purification) with a similar molecular weight to the bottlebrush PPDMSM-I ($M_n = 19000$ and $\bar{D} = 1.18$).

Table 5.3. Preparation of PMMA-I Macroinitiator.

entry	[MMA] ₀ /[CP-I] ₀ /[BNI] ₀ /[V65] ₀ (mM)	<i>T</i> (°C)	<i>t</i> (h)	conv (%) ^a	<i>M_n</i> ^b	$\bar{D}$ ^b
1	8000/20/80/5	60	2.5	60	21000	1.22

^aThe monomer conversion was obtained from GPC peak area. ^b M_n and $\bar{D}$ were determined using PMMA-calibrated GPC after purification.

We used the PMMA-I as a macroinitiator in the polymerization of the EGDMA (Table 5.4). After 24 h, the GPC chromatogram showed that 75% of the macroinitiator was converted to the crosslinked particle (Figure 5.5a). The particles were purified similarly but using a mixture of dichloromethane (DCM) and methanol (1/4.8 (v/v)) for washing out the

macroinitiator from the particle. The M_n and D values of the purified particle measured by PMMA-calibrated GPC were 145000 and 1.11, respectively (Table 5.4). The DLS peak-top value was 20 nm (Figure 5.5c). The size (20 nm) was similar to that (22 nm) of the bottlebrush particle.

Table 5.4. Preparation of Linear PMMA Particle using PMMA-I, EGDMA, and BNI in 70 wt% Toluene.

entry	[EGDMA] ₀ /[PMMA-I] ₀ /[BNI] ₀ (mM) ^a	<i>T</i> (°C)	<i>t</i> (h)	conv (%) ^b	M_n ^c	D ^c	Hydrodynamic Size (nm) ^d
1	160/20/80	70	24	70	131000	1.17	
	(after Purification)				145000	1.11	20

^a Solution polymerization in 70 wt% toluene. ^b The monomer conversion was calculated with ¹H NMR analysis. ^c M_n and D were determined using PMMA-calibrated GPC. ^d The size was the DLS Peak-top value.

Figure 5.5. (a) GPC chromatograms of PMMA-I (dash line) and PMMA particle (solid line) for the synthesis of non-bottlebrush particle (Table 5.4). (b) GPC chromatograms and (c) DLS curves of PMMA-I (dash lines) and purified PMMA particle (solid lines).

Viscosity of PPDMSM and PMMA Particles.

As mentioned above, we prepared the bottlebrush (PPDMSM) and non-bottlebrush (PMMA) particles with similar sizes. We measured the viscosity of the two particles in THF at different particle concentrations, i.e., 1, 2.5, 5, 8, and 10 wt%. Figure 5.6 shows the results of the viscosity. For both particles, the viscosity increased with an increase in the particle concentration. At low (1-2.5%) concentrations of the particle, the viscosity of the PMMA particle was slightly higher than that of the PPDMSM particle. Above a critical overlapping concentration (5 wt%), the viscosity of the PMMA particle significantly increased and became much higher than that of the PPDMSM particle. This result clearly demonstrates a better lubrication property of the bottlebrush particle. The significant increase in the viscosity for the PMMA particle is ascribed to the entanglement of the linear shell polymers. In contrast, the

bottlebrush particle showed a lower viscosity because of the entropic repulsion of the sterically hindered bottlebrush shell, as explained in Introduction.

Figure 5.6. Plot of viscosities vs particle concentration in THF: PPDMSM particle (square) and PMMA particle (circle).

5.3. Conclusions.

We successfully synthesized the PPDMSM bottlebrush particle with the crosslinked core and the PPDMSM bottlebrush shell. In THF, the PPDMSM particle showed slightly lower viscosity than the non-bottlebrush PMMA particle in a low (1-2.5%) particle concentration region. Above a critical overlapping concentration (5 wt%), the viscosity of the PMMA particle significantly increased because of the entanglement of the linear shell chains, and the viscosity of the PPDMSM particle became much lower than that of the PMMA particle. This result clearly demonstrates the better lubrication property of the bottlebrush particle because of the steric repulsion. This is an entropic repulsion and does not depend on solvents. The bottlebrush particles may find applications in lubrication coatings and cosmetics.

5.4. Experimental.

Materials.

Poly(dimethylsiloxane) methacrylate (average molecular weight = 900) (Shin-Etsu Silicone (Japan), 90%), and tetraoctylammonium iodide (ONI) (98%, TCI) were used as received. The details of other used materials in this work were mentioned in Chapters 2 (Section 2.4) and 3 (Section 3.4).

Measurements.

Polymers were analyzed in Shimadzu LC-2030C Plus liquid chromatograph (Kyoto, Japan) gel permeable chromatography. The eluent was THF. The columns, detector, and measurements details were similar as Chapter 2 (Section 2.4). The ^1H NMR, DLS, and TEM were performed in same instrument as mentioned in Chapters 3.

Viscosity was measured using Brookfield DV-III Ultra Programmable Rheometer equipped with LV set2 spindle.

Controlled Polymerization of PDMSM.

The procedure is similar as “Polymerization” in Chapter 2 (Section 2.4).

Synthesis of PPDMSM-I Macroinitiator.

A mixture of PDMSM (2.0 g, 8 M), CPI (266 mM), V65 (200 mM), and ONI (80 mM) was heated in oil bath for 4.5 h under argon atmosphere with magnetic stirring. The reaction mixture was diluted with 1 mL THF, reprecipitated from a mixture of methanol and diethyl ether (2:1 (v/v)), and dried. The M_n and $\bar{D}$ of the purified polymer 19000 and 1.17, respectively. The purified polymer was used as a macroinitiator for the preparation of bottlebrush particle.

Preparation of Bottlebrush Particle.

A mixture of EGDMA (0.1 g, 160 mM), PPDMSM-I (20 mM), BNI (80 mM), and toluene (70 wt% of total reaction mixture) was heated in a reaction tube in oil bath at 70 °C for

36 hours under argon atmosphere with magnetic stirring. After 36h, an aliquot (0.1 mL) of the reaction mixture was taken out by a syringe, quenched to room temperature, diluted by THF to a known concentration, and analyzed by GPC. Another aliquot (0.1 mL) of the solution was taken out by a syringe, diluted with CDCl_3 , and analyzed by ^1H NMR. The peak-top molecular weight was 57000 using PMMA-calibrated GPC. After 36 h, V65 (40 mM, 2 equiv. with respect to initial PPDMSM-I) was added and heated for another 8 h at 60 °C. Similarly, the aliquots were taken out and analyzed with GPC and ^1H NMR. The peak-top molecular weight was 63000 using PMMA-calibrated GPC. The mixture was diluted with THF, centrifuged, and supernatant was collected, and dried. The dried polymer was washed with a mixture of diethyl ether and methanol (1:1 (v/v)), centrifuged (with 3000 rpm rotation for 90 sec), and the pellet was collected. The pellet was washed with the same solvent mixture and dried in five cycles. The M_n and D of the purified particle were 84000 and 1.22, respectively. We dissolved 40 mg of the purified particle in 1 ml THF and used this solution as a stock solution for DLS and TEM analyses.

Preparation of PMMA-I Macroinitiator.

The procedure is similar as “Preparation of PMMA-I for Block Copolymerizations” in Chapter 2 (Section 2.4).

Preparation of linear PMMA Particle.

A mixture of EGDMA (0.1g, 160 mM), PMMA-I (20 mM), BNI (80 mM) and toluene (70 wt%) was heated at 70 °C for 24 hours under argon atmosphere with magnetic stirring. The polymer was reprecipitated from hexane and dried. The dried polymer was washed with a mixture of dichloromethane (DCM) and methanol (1:4.8 (v/v)) for five times. The M_n and D of the purified particle were 146000 and 1.11, respectively. 40 mg of the purified polymer was dissolved in 1 ml THF and performed the DLS analysis.

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Chapter 6. Conclusions.

In Chapter 2, we successfully utilized alkali and alkaline earth metal iodides such as NaI, KI, CsI, MgI₂, and CaI₂ as catalysts in RCMP. NaI exhibited the higher reactivity. NaI was amenable to methacrylates, styrene, and acrylonitrile monomers. It is also amenable to the synthesis of diblock, triblock, telechelic, and 3-arm star polymers. The attractive feature of NaI iodide is soluble in water. NaI is compatible with both hydrophilic and hydrophobic monomers. As useful applications of NaI catalyst, we studied the synthesis of amphiphilic block copolymers and creation of their self-assemble structures (micelles, worms, and vesicles) in Chapters 3 and 4.

In Chapter 3, we successfully developed the NaI-catalyzed RCMP-PISA using MAA and MMA as hydrophilic and hydrophobic monomers, respectively, and ethanol as a solvent. We successfully obtained micelles, spheres, and vesicles of PMAA-PMMA block copolymers. A cross-linkable monomer, i.e., EGDMA was used to fix the assembly structures. In Chapter 4, in order to expand the scope of the RCMP-PISA, we used a bio-compatible monomer, i.e., PEGMA as a hydrophilic monomer and water as a solvent. We successfully obtained nano-capsules with relatively high (8-9%) solid concentrations. Rh-B was successfully encapsulated with a 48% encapsulation efficiency and a 0.28% loading capacity, demonstrating the effective use of the obtained nano-capsules as containers of guest molecules. This system is attractive because PEGMA located inner and outer surfaces of nano-capsules is bio-compatible, and water is green and least expensive. In summary, the RCMP-based PISA is metal-free and sulfur-free process and obtained nano-capsules are well containers of guest molecules. Hence, this system may be attractive for biomedical, healthcare, cosmetics, and agrochemical release applications.

In Chapter 5, we successfully utilized ONI-catalyzed RCMP to synthesize a PPDMSM bottlebrush polymer. We utilized this bottlebrush to prepare a bottlebrush particle with the

crosslinked core and PPDMSM bottlebrush on the shell. We compared the viscosity of this particle with respect to a PMMA non-bottlebrush particle. In THF, above the 5 wt% particle concentrations, the non-bottlebrush particle showed higher viscosity than the bottlebrush particle because of the entanglement of linear shell chains. Due to steric repulsion, the bottlebrush particle exhibited the excellent lubrication property. This repulsion is entropic repulsion and does not depend on the solvent. Hence, the bottlebrush particle may find applications in lubrication coatings and cosmetics.

RCMP has advantages. But, polymerizations of acrylamides and vinyl acetate monomers are still challenging using RCMP. Design and development of the new RCMP catalyst for expanding the monomer scope will be interesting to study in future. RCMP-PISA is environmentally and biologically safe. In future, stimuli-responsive PISA assemblies can be prepared using RCMP-PISA for delivery and nano-reactor applications.