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Foreword by Dr. Hamaguchi

The President of Japan Science and Technology Agency

Molecular Technology is a newly developed research field supported through Japan Science and Technology Agency (JST) research funding programs. These programs aim to establish an innovative research field that harnesses the characteristics of molecules to enable new scientific and commercial applications. It is our great pleasure to publish this book, with the ambition that it will develop both an understanding of and further support for this new research field within the research and student community.

Molecular Technology as introduced in this book began in 2012 as a research area within JST's Strategic Basic Research Programs. JST is an advanced network-based research institution that promotes state-of-the-art R&D projects and leads the way in the co-creation of future innovation in tandem with wider society. JST develops a wide range of funding programs related to the promotion of scientific and technological innovation, which include strategy planning, target-driven basic research, and promotion of research and development.

Various research projects focused on Molecular Technology are currently underway within JST's Strategic Basic Research Programs, including

- the team-based research program "CREST (Core Research for Evolutionary Science and Technology)" and
- the individual research program "PRESTO (Precursory Research for Embryonic Science and Technology)."

Dr. Yamamoto (CREST) and Dr. Kato (PREST) manage the Molecular Technology research area as research supervisors.

In addition, JST's Strategic International Collaborative Research Program promotes research projects in the area of Molecular Technology, including ongoing cooperation with *L'Agence nationale de la recherche* (The French National Research Agency, ANR).

A wide range of researchers from the young to seniors across fields from green science, life science, and energy are participating in successful research aimed at establishing the new field of Molecular Technology. They are already producing excellent research results and it is our hope that these will develop into technologies capable of initiating a new era in energy and green and life sciences.

I encourage you to read not only researchers in related fields but also look more broadly to researchers working in other fields. Inspired by this book, I look forward to emerging new research fields and seeds toward future innovation.

Michinari Hamaguchi
Japan Science and Technology Agency
President

Foreword by Dr. Noyori

As an affiliated institution of the Japan Science and Technology Agency (JST), the Center for Research and Development Strategy (CRDS) navigates the latest global trends in science, technology, and innovation to aid the Japanese government in formulating its national strategies. *Molecular Technology* is the outcome of a research project born of a CRDS strategic proposal realized under the excellent editorial supervision of Hisashi Yamamoto and Takashi Kato. To them and to the scientists who have made major advances in molecular technology through their uninhibited research I extend my heartfelt congratulations and respect.

The significance of molecular science in all areas of scientific endeavor is certain to increase. Accurate understanding of molecular assemblies and molecular complexes is essential for comprehending the elaborate workings of natural phenomena and of the genesis and mechanisms of materials and life functions. Now, more than ever, science must be seen as a single entity, a comprehensive whole. Mathematical science and the most advanced technologies of observation and information help us explore the essence of materials and substances in a way that brings together all fields of science. It is the nature of molecular science to continually advance and expand. Using the metaphor of light, we can say that molecules behave in the manner of both "waves and particles."

The traditional separation of science into physics, chemistry, and biology no longer applies. Neither does it make any sense to maintain those seemingly self-contained subdivisions of organic chemistry, inorganic chemistry, physical chemistry, or polymer chemistry. So long as specialized groups and rigid educational systems cling to outdated perceptions, it is more important to encourage an "anti-disciplinary" type of science in which diverse fields converge rather than conventional interdisciplinary or transdisciplinary attempts to link diverse fields.

Molecular technology, while firmly grounded in fundamental scientific knowledge, aims for practical applications within contemporary society. Johann Wolfgang von Goethe once said, "Knowing is not enough; we must apply. Willing is not enough; we must do." Technology with no practical application is meaningless to society. Researchers should not hesitate to set their own themes and topics of exploration in academia where self-determination holds strong and creativity wins the highest respect. Researchers must show ingenuity in the pursuit of their chosen mission even as they fulfill their duty to pursue science-based technology

for society. Never forget that it is by no means advisable to function purely as a support for activities that industry should actually undertake on its own.

The creative outcomes of the Molecular Technology Project launched in 2013 in conjunction with new collaborations are certain to lead to a wide range of innovations and to make significant contribution to achieving the Sustainable Development Goals (SDGs) of the United Nations' 2030 Agenda.

Science is one; and the world is one. Those who will follow us have a responsibility to the world after 2030 and it is my hope that new generations will pioneer revolutionary molecular technology that will bring science and humanity ever closer together. Brain circulation and international collaboration are essential to achieve these goals. V.S. Naipaul, winner of the 2001 Nobel Prize in Literature, once noted that knowing what you wanted to write was three-quarters of the task of writing. Humanity's future is to be found in the unbounded imagination of the young and in its ability to support the challenges they undertake.

December 2017

Ryoji Noyori
Tokyo, Japan

Preface

Chemical science enables us to qualitatively change existing science and technology by purposefully designing and synthesizing molecules and creating the desired physical, chemical, and biological functions of materials and drugs at molecular level. In 2012, we have started a big funding project in Japan, "Molecular Technology" (Establishment of Molecular Technology toward the Creation of New Functions (CREST), and Molecular technology and new functions (PRESTO)), and numerous research groups in Japan have joined the project in diverse research areas. All of these are typical transdisciplinary research projects between chemistry and various research areas of science and technology. In other words, Molecular Technology is a brand-new scientific discipline. In principle, most of the proposed projects try to bridge the big gap between chemistry and other basic science and technology. We thus propose a good model for this bridge, which can make valuable contribution to human welfare.

Between JST and ANR, we initiated a number of international collaboration projects in molecular technology in 2014. Since then, 12 new collaboration projects have been started. The projects provide quite unique opportunity for collaboration between Japan and France and active research groups have participated with very close discussions on molecular technology between the two countries. We are sure this project will provide close contacts between the research groups of Japan and France for otherwise impossible discoveries. Overall, this international collaboration will be a new entry for even more important discoveries in future.

In 2016, we started the discussion to bring out a new and comprehensive book on molecular technology for the benefit of all the researchers in the world to provide typical and leading examples in molecular technology. Overall, researchers of 15 CREST, 50 PRESTO, and 12 INTERNATIONAL groups have contributed to this book. This book covers extremely diverse areas of molecular technology, from materials to pharmaceuticals.

Hisashi Yamamoto
Chubu University,
Supervisor of CREST

Takashi Kato
The University of Tokyo,
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Contents

1

Polymerization-Induced Self-assembly of Block Copolymer Nano-objects via Green RAFT Polymerization

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1.1 Introduction

Many biomolecules have specific three-dimensional structures in water or hydrophobic environments, and form higher order structures with high functions. To construct a highly functionalized and higher order structure with a synthetic polymer, it is necessary to examine the fundamental formulation to control the polymer's primary structure and to build the polymers up into a higher order structure. From this point of view, this chapter focuses on block copolymer synthesis as a *molecular technology* for self-organization. The key technology is *in situ* "polymerization-induced self-assembly (PISA)."

1.2 Block Copolymer Solution

Self-assembly of AB diblock, ABA, or ABC triblock copolymers to form a variety of macromolecular nanostructures is well known in both the solid state and in dilute solutions, with various prominent functions stemming from the structure [1–21]. In particular, amphiphilic AB diblock copolymers have been demonstrated to form a variety of self-assembled aggregate structures in dilute solutions, where the solvent preferentially solvates one of the blocks. Thus, the basic driving force for solution self-assembly is the solvophobic effect (hydrophobic effect in aqueous solution). These are well documented in other reviews [1–5]. For the amphiphilic AB diblock copolymer in a block-selective solvent, the precise nanostructure, i.e. morphology, is primarily a result of the inherent molecular curvature described by its mean curvature H and its Gaussian curvature K, which are given by the two radii of curvatures R_1 and R_2 in Figure 1.1. The curvature is related to the surfactant packing parameter, P, which is given by Eq. (1.1). The value of P depends on the relative core-block volume (v), the effective interfacial area (a_0) at the core–shell/solvent interface, and the chain length normal to the

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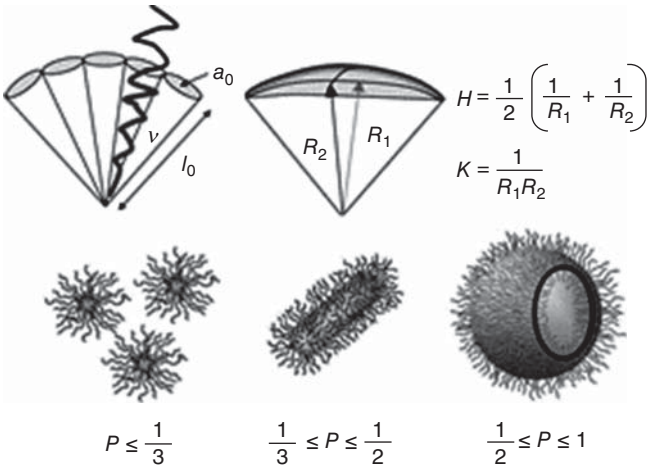


Figure 1.1 Various self-assemblies formed by solvophilic block copolymers in a block-selective solvent. The type of structure formed is due to the inherent curvature of the molecule, which can be estimated through calculation of its dimensionless packing parameter, *P*.

surface per molecule (l_0).

$$P = \frac{v}{a_0 l_0} = 1 + Hl_0 + \frac{Kl_0^2}{3} \tag{1.1}$$

The regions of spherical micelles are favored when $P \leq 0.33$, cylindrical micelles are produced when $0.33 < P \leq 0.50$, and vesicles are formed when $0.50 < P \leq 1.00$. Although vesicles are flexible bilayer aggregates, the planar bilayer of lamellae is ideally favored when $P = 1$. This concept was originally introduced by Israelachvili et al. [22, 23] to explain self-assembly of small-molecule surfactants, and was later extended to include diblock copolymer self-assembly by Antonietti and Förster [24].

In practice, morphology is controlled by various factors, especially for small-molecule amphiphiles. Assemblies such as spherical micelles, hexagonals, cubes, and lamellar lyotropic crystallines are highly dynamic with rapid exchange of molecules between micelles and the unimer state in solution. Thus, as shown in Figure 1.2, the packing geometry can be tuned by simply adjusting the surfactant concentration with the same solvent properties, i.e. without additives and at a constant temperature. Figure 1.2 shows an ideal phase sequence, which is only a very generalized picture, and the sequence may be different for some amphiphiles. However, this rapid exchange of molecules is very important to determine the structure and morphology of amphiphilic self-assembled aggregates [4, 23–25].

For many macromolecular amphiphiles, in contrast to small-molecule amphiphiles, the rate of exchange of unimers between colloidal aggregates and individual diblock copolymer chains can be negligible, leading to a range of kinetically frozen, i.e. nonergodic, structures. In other words, most amphiphilic

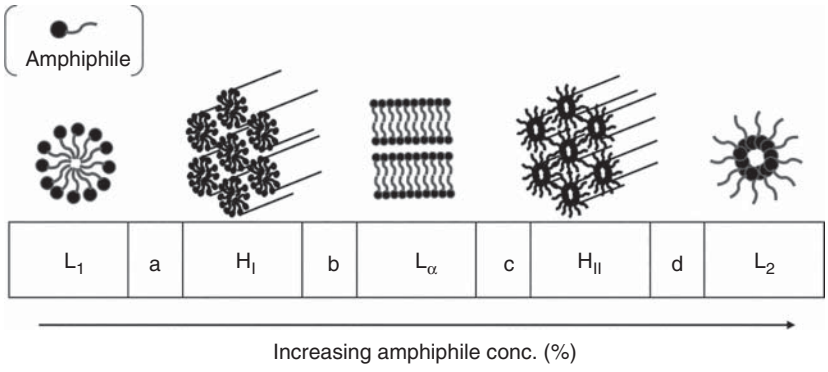


Figure 1.2 The "ideal" sequence of phases from L_1 to H_I to L_α observed upon increasing amphiphile concentration, in a binary small-molecular amphiphile–solvent system (ergodic system). Intermediate phases (a and b) are sometimes observed. The normal micellar structure is termed the L_1 phase. At higher concentrations, micelles can fill space efficiently to form a cubic phase by packing (a). Upon increasing the concentration further, the micelles change from spherical to rod-like ones. The rod-like micelles then pack into a hexagonal (H_I) phase. The H_I phase sometimes changes to a bicontinuous cubic or mesh structure phase (b), which is characterized by nonzero mean curvature and negative Gaussian curvature. The phase then changes to bilayers, which tend to stack into a lamellar phase (L_α). Lamellar phases can be found in different phase states including lamellar crystalline, lamellar gel, and lamellar fluid. When the solvent becomes the minority phase, inverse structures are formed such as the inverse hexagonal phase (H_{II}), inverse micellar liquid phase (L_2), and intermediates such as the inverse bicontinuous phase (c), and inverse micellar cubic phase (d).

block copolymers have been recognized for their many advantages, such as low critical micelle concentration, robust assemblies, and the ability to trap numerous different structures thanks to their kinetic stability due to slow kinetics [4, 26]. For example, this stability of the polymeric micelles is a very important issue for a drug (solubilizing substance) carrier for application in drug delivery systems (DDSs). This is because polymeric micelles can retain the loaded drug in the same morphology for a prolonged period of time even in a very diluted condition in the body [19, 20, 27]. In the early stages of research on DDS, kinetically frozen spherical micelles were used as the drug vehicle. Subsequently, worms (aka cylinders or filomicelles) were found to be better than spherical micelles due to their long circulation time *in vivo* [28, 29] and altered cell internalization pathway compared to spherical constructs [30]. As another example, complex polyprodrug amphiphiles were synthesized from block copolymer amphiphiles, which possess advantages of facile fabrication, high drug loading content and loading stability, active drug protection, blocked premature leakage, and on-demand controlled release [31]. Thus, it is no exaggeration to say that nanoparticles in the biomedical arena are being developed by utilizing the stability of the block copolymer self-organization. Hence, development of the formulation of various self-assemblies is essential and techniques for extracting unstable or metastable assemblies are strongly desired.

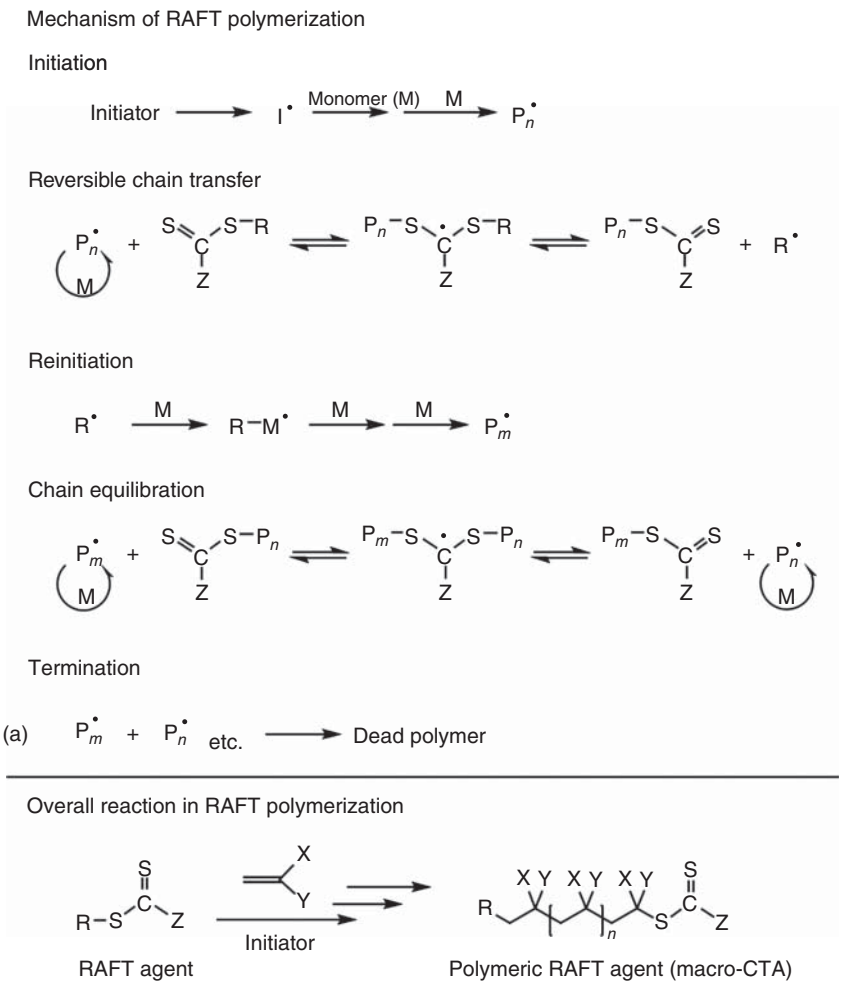
1.3 Synthesis of Block Copolymers via RAFT Polymerization

In general, controlled/living polymerization refers to chain polymerization without termination and chain-transfer reaction. Since Szawrc discovered living anionic polymerization in 1956 [32, 33], the process has been used in various polymerization mechanisms. In 1962, the first reports on block copolymer self-assembly were published [34]. The advent of controlled/living free-radical polymerization (CRP) [35–38] based on the reversible deactivation of the propagating radicals has revolutionized the domain of polymer chemistry and opened the door to the possibility of designing new polymer architectures and creating new materials with targeted properties. A number of fundamental block copolymers for the assemblies mentioned above have been recently synthesized using controlled/living polymerization techniques, especially CRP.

As for CRP, atom transfer radical polymerization (ATRP) [37–40], nitroxide-mediated polymerization (NMP) [41, 42], iodine transfer polymerization (ITP) [43, 44], organotellurium-mediated radical polymerization (TERP) [45, 46], cobalt-mediated radical polymerization (CMRP) [47], reversible addition–fragmentation chain-transfer (RAFT) polymerization [48–50], and reversible chain-transfer-catalyzed polymerization [51, 52] are well known. For almost all polymerizations, the abovementioned PISA has been adopted. Examples of these include ATRP [53–55], NMP [56], ITP [57], and TERP [58, 59]. However, the vast majority of reports at present have focused on the RAFT process, which results in block copolymer formation and self-assembly. Well-documented reviews of this field have been published by Armes and coworkers [60–62], Pan and coworkers [63], Charleux et al. [64], Lowe [65], etc. Incidentally, the author is also one of the coworkers of Prof. Armes.

CRP addresses the philosophy of green chemistry summarized in the 12 main principles that were established by Anastas and Warner in 1998 [66]. CRP meets the criteria of atom economy, and is thus a "green" polymerization [67]. In fact, RAFT polymerization is arguably the most versatile process since it is performed without a metal catalyst, is tolerant to a wide variety of reaction conditions and functionalities, and can be performed on existing conventional free-radical polymerization setups (Scheme 1.1) [48–50]. However, there is a problem of the resulting polymers having undesirable color and odor [68]. RAFT proceeds via a degenerative transfer process and relies on the use of compounds employed as chain-transfer agents such as thiocarbonylthio compounds. The R group initiates the growth of polymeric chains, and the Z group activates the thiocarbonyl bond toward radical addition and stabilizes the resultant adduct radical.

Using such CRP techniques including RAFT polymerization, diblock copolymers for an amphiphile are generally synthesized in good solvent (or bulk) for both blocks. After purification, the desired self-assembly is usually achieved by post-polymerization processing, where solvent quality affects the solubility of the core-forming block. Examples also include self-assemblies in mixtures of good and selective solvents [1–23, 69] and assemblies by stimulus [70–72]. Pioneering work was conducted by Eisenberg's group over the past two decades,



$$M_{n,\,calcd} = \frac{\text{Monomer consumed}}{\text{Chain initiated}}$$

$$\approx \frac{[\text{monomer}]_0}{[\text{RAFT}]_0} \times M_{monomer} \times \text{convn} + M_{RAFT} \qquad (1.2)$$

(b)

Scheme 1.1 The generally accepted mechanism of RAFT polymerization.

which has established a dominant paradigm for processing block copolymer assemblies in which a common solvent (tetrahydrofuran [THF]) is gradually decreased in quality for one block by addition of a selective solvent (methanol), driving the copolymer to aggregate, as in polystyrene-*b*-poly(acrylic acid) (PSt-*b*-PAA) [12, 13]. Frozen assemblies can also be formed from the block polymer. The formulation is performed as follows. The block copolymer prepared by living anionic polymerization is dissolved in good solvent, *N*,*N*-dimethyl

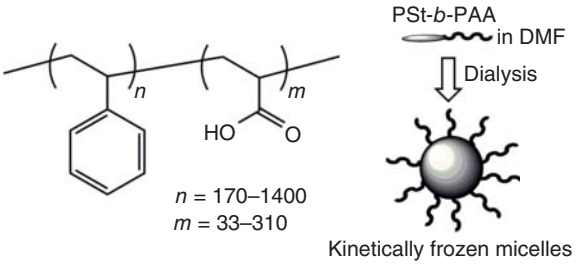


Figure 1.3 Frozen assembly formation using PSt-*b*-PAA prepared by dialysis against distilled water from DMF solution. The core radii are scaled as $r_{core} \sim N_{PSt}^{0.4} N_{PAA}^{-0.15}$ (where N_{PSt} and N_{PAA} are the lengths of the blocks).

formamide (DMF), and then is slowly dialyzed against water (Figure 1.3) [14]. While these assemblies may temporarily be in equilibrium at the onset of aggregation, further addition of the non-solvent pushes the critical aggregation concentration toward zero and drives the solvophobic block to solidify, locking the copolymer into one of a wide range of possible morphologies. However, such processing allows the attainment of only kinetically stable assemblies partly because the polymerization temperature is below the glass transition temperature (T_g) of the second block [73], which is typically conducted in highly dilute solutions (<1% solids concentration). Thus, efficient synthesis of block copolymer self-assemblies with well-defined morphologies in concentrated aqueous solution is widely recognized to be a difficult technical challenge. In addition, it is also a formidable challenge to obtain different morphologies without changing the solvent composition from an identical block copolymer that is kinetically frozen.

1.4 Polymerization-Induced Self-assembly

1.4.1 PISA Using RAFT Process: Emulsion and Aqueous Dispersion Polymerization

To overcome the abovementioned technical challenges, polymerization formulations have been developed using the RAFT process. Initially, Gilbert and coworkers focused on *ab initio* RAFT emulsion polymerization using water-insoluble monomers such as methyl methacrylate and styrene with an amphiphilic macromolecular RAFT agent (the so called "macro-chain-transfer agent [CTA]") [74]. The amphiphilic macro-CTA can mediate polymerization in both aqueous and organic phases, and is prepared with a water-soluble monomer such as acrylic acid (AA) and a hydrophobic monomer such as *n*-butyl acrylate (BA). The resulting hydrophobic moiety is an oligomer, which forms rigid micelles with a poly(acrylic acid) shell (RAFT-containing seeds). Thus, the self-assembly approach relies on micellar particle nucleation via self-assembly of amphiphilic macro-CTA. This is a very efficient formulation to induce the formation of kinetically trapped spheres (Figure 1.4).

Charleux and coworkers have made considerable progress toward this important scientific objective utilizing various emulsion polymerization formulations. A water-soluble polymer precursor is chain-extended by polymerizing a water-immiscible monomer via living radical polymerization including RAFT so

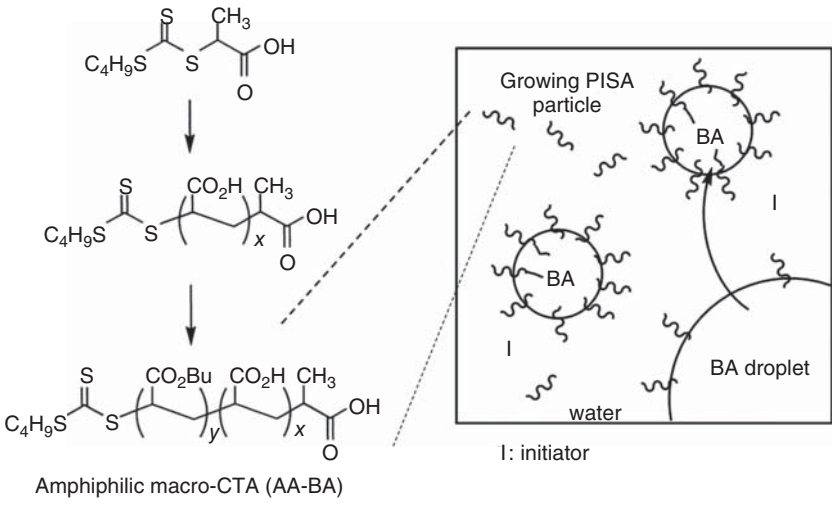


Figure 1.4 AA-BA-RAFT macro-CTA for RAFT emulsion polymerization of styrene or methyl methacrylate and the *ab initio* RAFT emulsion polymerization model of styrene.

as to produce an amphiphilic diblock copolymer *in situ* [75–78]. This approach leads to PISA and can produce diblock copolymer nanoparticles in the form of spheres, worms, or vesicles, with the final copolymer morphology being dictated primarily by the relative volume fractions of the hydrophilic and hydrophobic blocks. The best advantage of RAFT emulsion polymerization is that many hydrophobic (water-insoluble) monomers are available, unlike the RAFT aqueous dispersion polymerization described below. However, their formation mechanism is complicated because macro-CTA must be sufficiently hydrophobic for micellar nucleation to dominate; otherwise, particles may form mainly via homogeneous nucleation [79, 80].

In contrast to RAFT emulsion polymerization, RAFT dispersion polymerization is a much simpler formulation for self-assembly since the initial reaction solution is homogeneous and block copolymer architecture, such as the packing parameter of the solvent, can be directly applied. An important prerequisite for such formulations is the selection of a water-miscible monomer, which, when polymerized, forms a water-insoluble polymer. Normally, this would simply lead to macroscopic precipitation. However, when using a reactive steric stabilizer (macro-CTA), stable colloidal dispersions can be obtained if an appropriate colloid stability mechanism prevails [81]. This typical formulation using aqueous dispersion polymerization is shown in Figure 1.5.

The first report of RAFT aqueous dispersion polymerization was published by Hawker and coworkers, who prepared poly(*N*,*N*′-dimethylacrylamide)–poly(*N*-isopropylacrylamide) diblock copolymer (PDMA-*b*-PNIPAM) nanoparticles from PDMA macro-CTA with the aid of microwave irradiation, with the further addition of a bis(acrylamide) cross-linker during the *N*-isopropylacrylamide (NIPAM) polymerization to produce thermoresponsive nanogels as shown in Figure 1.6 [82]. Similar nanogels were prepared in the same year by Charleux

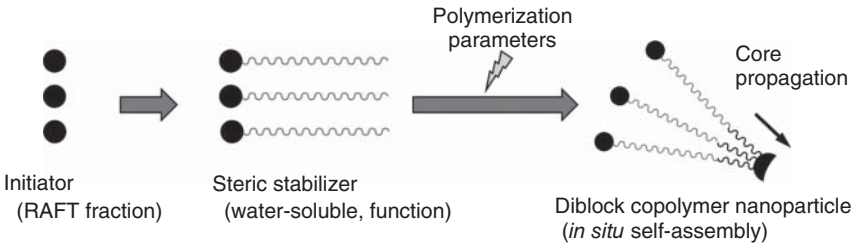


Figure 1.5 Typical formulation using aqueous dispersion polymerization: a soluble diblock copolymer is initially obtained after the second block copolymerization from a steric stabilizer block, but at some critical degree of polymerization the growing second block becomes water insoluble, which causes *in situ* self-assembly to form a micellar nanoparticle. Upon further polymerization, various morphologies can be formed depending on the polymerization parameters. The primary structural feature governing the final nanoparticle morphology is the packing parameter, i.e. the relative volume fractions of the constituent blocks.

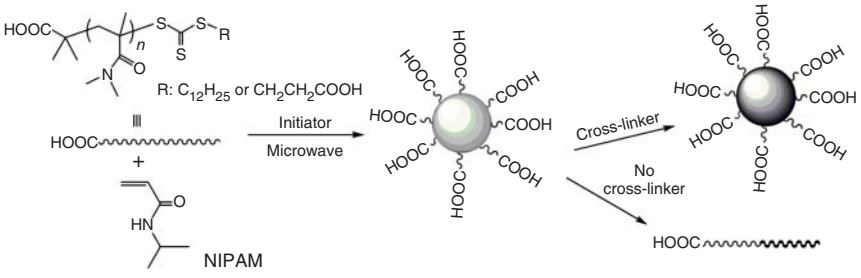


Figure 1.6 Initial research on RAFT aqueous dispersion polymerization of NIPAM for the synthesis of nanogels.

and coworkers using NMP instead of RAFT polymerization [83]. NMP is also a metal-free polymerization but is available to only a small number of monomers [42].

Recent synthetic advances in RAFT aqueous dispersion polymerization now allow spherical micelles, stable or metastable worm-like micelles or vesicles, and nonspherical strange assemblies composed of well-defined AB diblock copolymers to be prepared directly in concentrated aqueous solution as described in detail later [84–87]. However, there is a limited number of suitable core monomers that possess the requisite "water-miscible monomer" and "water-insoluble polymer" characteristics for the RAFT aqueous dispersion polymerization. This is a pressing issue to solve.

In the case of RAFT dispersion polymerization in a variety of media such as alcohols including alcohol/water mixtures, some core monomers including commodity styrenes can be utilized. The first research on this was reported by Zeng and Pan [88]. Representative examples of other media are polar media [88], nonpolar media [89], ionic liquids [90], and supercritical CO_2 [91]. Reviews of RAFT dispersion polymerization in nonaqueous media are shown in Refs. [64, 65].

1.4.2 Reagents for RAFT Aqueous Dispersion Polymerization

Aqueous dispersion (precipitation) polymerization is a heterogeneous polymerization process carried out in the presence of a polymeric stabilizer in a reaction medium using a water-soluble initiator. Thus, in RAFT aqueous dispersion polymerization, a highly hydrated macro-CTA as a steric stabilizer is needed for high dispersion stability with good blocking efficiency. Suitable reagents are listed in Sections 1.4.2.1–1.4.2.3.

1.4.2.1 RAFT Agents

The structure of the RAFT agent is not crucial because most hydrophilic macro-CTAs prepared by RAFT polymerization can be utilized and its influence on a polymer of sufficient molecular weight seems to be small. However, RAFT polymer chain ends are often susceptible to hydrolysis when RAFT polymerizations are conducted in water. In particular, dithiobenzoates are more susceptible to *in situ* hydrolysis than trithiocarbonates [92]. However, commonly used RAFT agents such as dithiobenzoates and trithiocarbonates are available for aqueous dispersion polymerization giving high monomer conversions and good blocking efficiencies. This may be because polymerization proceeds in a waterless field, i.e. a hydrophobic core. As dispersion polymerization progresses, the growing second block becomes a water-insoluble block, which causes *in situ* self-assembly to form a micellar nanoparticle. Thus, the penetration of monomers into the hydrophobic core gradually becomes more difficult, which causes the molecular weight distribution to become larger than in homogeneous polymerization. Since the macro-CTA is required to have high hydrophilicity, carboxylic RAFT agents are often used. However, ionization of the carboxylic acid end group on a shell block derived from the RAFT agent occasionally induces a morphology transition [93].

1.4.2.2 Steric Stabilizer (Macro-CTA, Shell)

The macro-CTA plays both the role of a steric stabilizer block and the function of the resulting block copolymer. In RAFT aqueous dispersion polymerization, a wide range of steric stabilizers are used as shown in Figure 1.7. Most CTAs for shell structures are well documented for both aqueous dispersion and emulsion polymerization [61]. Among them, functional examples include zwitterionic poly(2-(methacryloyloxy)ethylphosphorylcholine) (PMPC) with biocompatibility and enhanced salt tolerance [84, 85, 94], nonionic poly(ethylene oxide) (PEO) with biocompatibility [87, 95], and anionic poly(ammonium 2-sulfatoethyl methacrylate) with the ability to include particles within inorganic crystalline hosts [96], which is used in a 2:1 v/v ethanol/water mixture.

1.4.2.3 Monomers (Core)

The choice of an appropriate monomer is difficult for aqueous dispersion polymerization. Literature examples include NIPAM [82], *N*,*N*′-diethylacrylamide (DEAA) [97], 2-methoxyethyl acrylate (MEA) [87, 98, 99], 2-hydroxypropyl methacrylate (HPMA) [84–86, 93, 95, 96], and di(ethylene glycol) methyl ether methacrylate (DEGMA) [100] as shown in Figure 1.8. These monomers

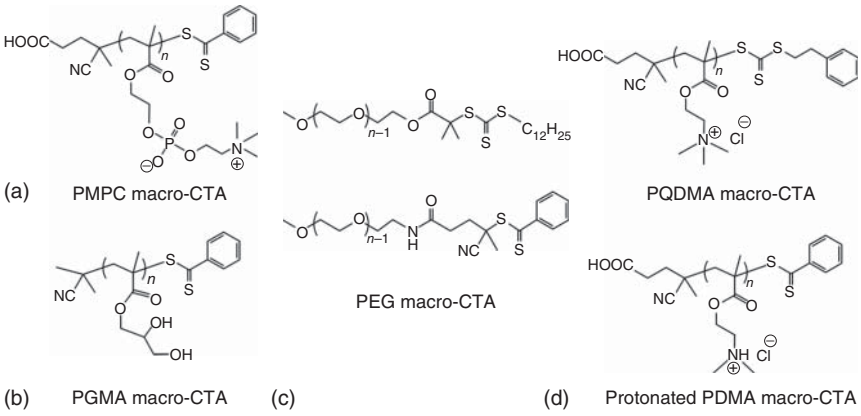


Figure 1.7 Representative macro-CTAs for RAFT aqueous dispersion polymerization: (a) PMPC, (b) PGMA, (c) polyethylene glycol (PEG), and (d) PQDMA or protonated PDMA.

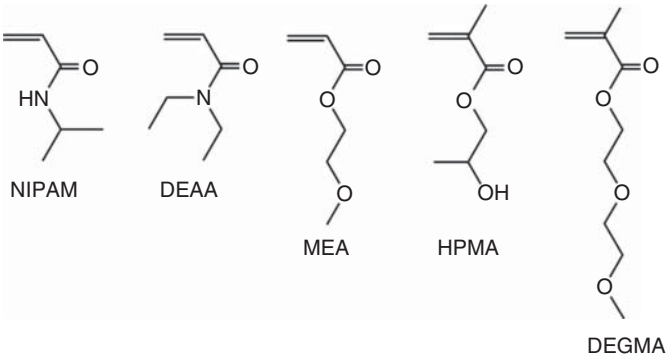


Figure 1.8 Representative monomers for RAFT aqueous dispersion polymerization.

possess the requisite "water-miscible monomer" and "water-insoluble polymer" characteristics. Strictly speaking, since these monomers have a weakly hydrophobic nature, they produce thermoresponsive polymers that have an appropriate hydrophilic/hydrophobic balanced side chain. For example, lower critical solution temperatures (LCSTs) are approximately 32, 33, under 0, around 0, and 26 °C for NIPAM [101], DEAA [102, 103], MEA [99], HPMA [104], and DEGMA [100, 105], respectively. Since these polymers are synthesized above the LCST, the requisite "water-miscible monomer" and "water-insoluble polymer" characteristics of dispersion polymerization are fulfilled. The weakly hydrophobic nature of the core-forming block leads to interesting thermoresponsive behavior for the assemblies. For example, worms form free-standing gels at room temperature but undergo reversible degelation upon cooling as a result of a worm-to-sphere transition [106, 107]. Analogous thermoresponsive worm gels have also been reported by Monteiro and coworkers [108, 109]. An and coworkers reported tunable sized nanogels using poly(ethylene glycol) methyl ether acrylate prepared via PISA [99, 100], analogous to the initial RAFT aqueous dispersion of NIPAM [82].