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# Nanoreactors for Polymerizations and Organic Reactions

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ABSTRACT: The aim of this Perspective is to use the knowledge of the underpinning kinetic and thermodynamic precepts that govern free-radical and "living" radical water-based heterogeneous polymerizations and apply this to small molecule organic reactions in nanoreactors. The difficulty in applying "living" radical polymerization to water-based heterogeneous systems has led to such an understanding, including partitioning of agents between the phases, nucleation of particles, and other phenomena including superswelling. This knowledge has allowed us to prepare polymers in heterogeneous systems with well-defined molecular weight distributions and particle size distributions. However, to overcome the physical chemistry constraints, researchers had to develop complex nanoreactor systems. For the field of small molecule organic reactions in heterogeneous systems to be industrially relevant and to grow rapidly, such physical chemistry precepts should be more greatly developed.

## Introduction

Nature has provided us with many examples of organic and polymer reactions in confined reaction environments.[1] A classical example is the synthesis of 100% *cis*-1,4-polyisoprene by the natural rubber tree (*Hevea brasiliensis*) in the form of rubber hydrocarbon polymer latex in water, which is used widely in tires, surgical gloves, and condoms.[2−4] Attempts to replicate the synthesis of polymers in water and attain the unique physical properties of natural rubber began during the First World War. It was not until the Second World War that serious efforts to replicate or replace natural rubber were undertaken on a scale similar to that of the Manhattan Project. After the war, heterogeneous polymerization (e.g., emulsion polymerization) developed into a widely accepted process for the industrial scale production of synthetic latexes consisting of polymer colloids particles on the nanoscale. The millions of tons of synthetic latex made today provide society with many essential products, including paints, paper coatings, carpet backing, adhesives, additives for concrete and bitumen, sealants, and adhesives. Synthetic nanoscaled polymer colloids are now finding wider applications in the biomedical area, ranging from diagnostics to drug and vaccine delivery.

Another significant advantage for carrying out free-radical polymerizations in nanoreactors (i.e., surfactant micelles) is the significantly faster rates of polymerization and much higher molecular weights that can range into the millions compared to either solution or bulk.[5] Primarily, this is due to the compartmentalization[3] and isolation of growing polymeric radicals, reducing the probability of bimolecular radical−radical termination.[4,6] It also became apparent that because water has a high specific heat capacity, the heat transfer through the continuous phase from these highly exothermic reactions is rapid.[3−5] Other advantages of carrying out heterogeneous polymerizations in water over solution or bulk include the following: (i) the solvent, water, is both environmentally friendly and cheap, (ii) the process can be used for a wide range of monomers under a wide range of reaction conditions, (iii) high conversions of polymer can be obtained with low monomer residuals, and (iv) high polymer solids (∼50 wt %) can be produced in a low-viscosity environment, which means that the polymer is easy to process. These advantages found in free-radical polymerization can too be adapted for other types of polymer and small molecule organic reactions.

The pioneering work of Breslow and Grieco in the 1980s, on the effects of water on the rates and selectivity of Diels−Alder reactions, led to many attempts to carry out various types of organic reactions in water.[7−11] However, for water to become the solvent of choice for industrial scale organic reactions, these reactions must be able to operate on a scale similar to or better than that achieved in organic solvents. These barriers are analogous to the implementation of heterogeneous polymerization back in the 1940s. It took many years to understand the kinetic and thermodynamic principles that involved the polymerization of hydrophobic monomers in water but allowed the synthesis of polymer nanoparticles with unique and interesting properties. Although there are now many examples of implementing small molecule reactions in nanoreactors, the knowledge of the physical chemistry of these systems is lacking. The aim of this Perspective is to provide the background to the kinetic and thermodynamic knowledge of heterogeneous free-radical and "living" radical polymerizations, give a brief overview of implementation of heterogeneous small molecule organic reactions in water, and finish by highlighting how such a knowledge of the physical chemistry could improved the design of heterogeneous systems for specific organic reactions. This Perspective is not intended to be a comprehensive review of the area but rather a discussion of influential papers that have impacted the field or have provided insight into the mechanisms for carrying out complex reactions in nanoreactors.

## Mechanism of Conventional Heterogeneous Free-Radical Polymerization

There are many types of heterogeneous polymerization systems that have been developed to produce polymer latex nanoparticles with controlled size, particle morphology, and molecular weight. In this paper, we will focus on those systems

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that have been tried in attempts to carry out successful heterogeneous "living" radical polymerizations as this will highlight how an understanding of the kinetic and thermodynamic precepts led the way to successful polymer nanoparticle synthesis. It was initially thought that with the discoveries of the three "living" radical polymerization methods (nitroxide-mediated,[12−14] ATRP,[15−17] and RAFT[18−20]) translation from solution to a heterogeneous system would be relatively simple. However, it required over 10 years of research from many groups around the world to not only understand the reasons for many failures but also produce polymer latexes with controlled size and molecular weight distributions. This mechanistic insight gained over these years therefore should provide a kinetic and thermodynamic platform into implementing more complex organic reactions in heterogeneous systems.

The main types of heterogeneous polymerizations are *ab initio* and seeded emulsion polymerization, mini- and microemulsions, and polymerizations in self-assembling and degassed systems.[21,22] Most monomers polymerized by these methods vary in their degree of hydrophobicity. Surfactants, usually consisting of amphiphilic molecules or macromolecules, form nanoscale micelles through the attractive hydrophobic interactions between the tails of the surfactant that, in the case where the surfactant headgroup is charged, are counterbalanced by the charge repulsion between the hydrophilic head groups and provide an ideal environment to solubilize the monomers in water. Micelles are dynamic colloidal aggregates that form above a critical concentration (denoted as the critical micelle concentration, cmc) and below this concentration exist as individual species. Because of the very dynamic nature of the surfactant molecules, these types of micelles are found to be polydisperse and strongly influenced by the type of monomer, salt concentration, and temperature.

In an *ab initio emulsion free-radical polymerization*[4,5,23−26] the reaction mixture contains the monomer (e.g., styrene, butyl acrylate, etc.), aqueous soluble free-radical initiator, micelle forming surfactant above its cmc (e.g., sodium dodecyl sulfate), and water. The polymerization mixture is then stirred or placed under different types of shear (homogenization or sonication) to form monomer swollen micelles ranging from 15 to 30 nm in diameter. In addition, there are large monomer droplets stabilized by surfactant. These monomer droplets are metastable and will coalesce upon cessation of shear. There are three intervals in an emulsion polymerization.[27−30] Polymerization occurs when an initiator-derived radical reacts with the monomer in the water phase and propagates to a critical chain length (of $z$ monomer units[31]) whereby its solubility in water diminishes and it enters a monomer-swollen micelle. These oligomeric radicals (or $z$-mer) are now located in a monomer-rich environment and rapidly propagate to form young "latex" particles. This stage of the emulsion polymerization is termed interval I (i.e., the nucleation stage for particles), and its end is defined by the disappearance of micelles due to the drop in the surfactant concentration in the water phase below its cmc. Particle growth continues via propagation with continuous replenishing of monomer from droplet reservoirs, maintaining the monomer concentration in the polymer particles high and constant—termed interval II. Interval III commences when there are no more monomer droplets present in the system, resulting in a concomitant decrease in monomer concentration in the growing particles with conversion. To obtain a narrow particle size distribution (PSD), a very high initiator concentration or high temperature is required to produce a high radical flux to nucleate and convert as many micelles as possible to particles.

In an emulsion polymerization, the propagating polymeric radical can undergo several fates at any stage of the polymerization.[4] For example, the polymeric radical can transfer to monomer to form a monomeric radical and a dead polymer chain. The monomeric radical can either (i) propagate with monomer present in the particle or (ii) exit the particle, via diffusion, and either terminate in the water phase or enter another particle and terminate the propagating polymeric radical present in that particle via instantaneous termination. The end result of transfer, entry, and exit events is the increase in the number of dead chains and a broader molecular weight distribution (MWD). It is these kinetic events that influence the rate of polymerization in an emulsion, which is given by

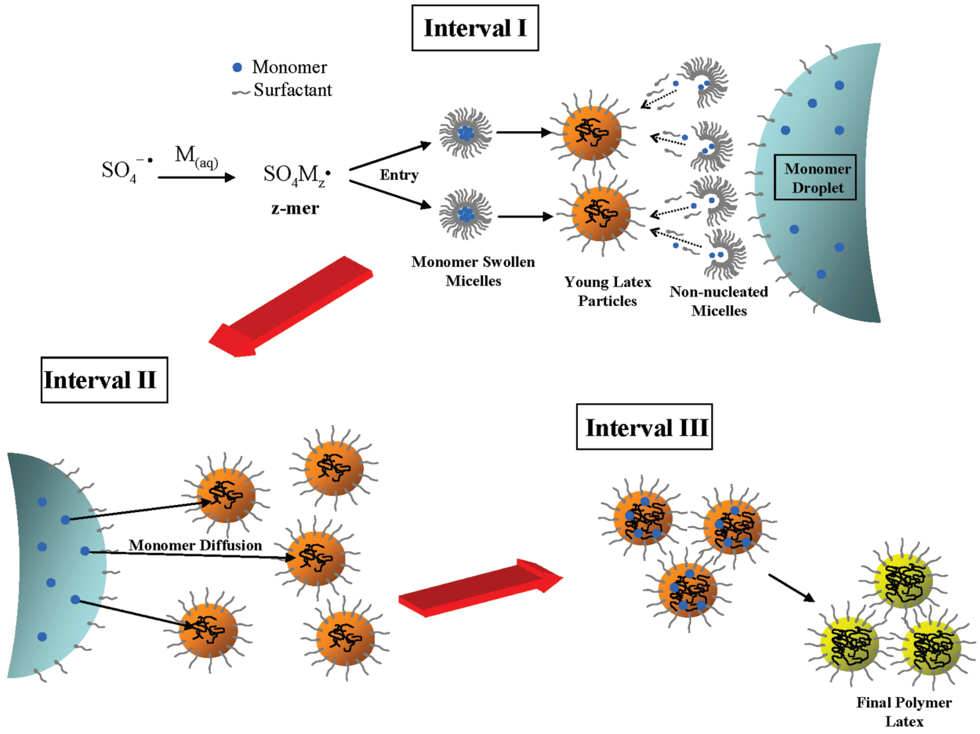
$$\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{k_p C_p \bar{n} N_c}{n_M^0 N_A} \tag{1}$$

where $x$ is monomer conversion, $k_p$ is the rate coefficient for propagation of monomer, $C_p$ is the concentration of monomer in the growing particles or micelles, $N_c$ is the number of particles per unit volume, $N_A$ is Avogadro's number, $\bar{n}$ is the average number of radicals per particle, and $n_M^0$ is the initial number of moles of monomer per unit volume in the reactor.

The three main factors controlling the rate of polymerization are $\bar{n}$, $N_c$, and $C_p$. The average number of radicals per particle is controlled by the entry rate of $z$-mer radicals into the growing particle and the size of the particle. If the particles are small, then an entry event into a particle already containing a polymeric radical will result in instantaneous termination. Such a system is denoted as zero−one, in which small particles can only exist with either one or zero radicals at any time. Larger particles result in pseudobulk kinetics in which more than one radical can reside in a particle. Obviously, the greater the number of particles, $N_c$, the faster the rate of polymerization. This is dependent upon the initial number of micelles and the initiator concentration. The concentration of monomer in the particle or micelles, $C_p$, is controlled exclusively by thermodynamic considerations of the system. More importantly, the concentration of monomer in the other phases, including the aqueous and droplet phases, needs to be considered.

The monomer concentration, $C_p$, within the particles is dependent upon the system to minimize the free energy. There

**Scheme 1. Three Intervals in an *ab Initio* Emulsion Polymerization**



are two opposing processes that determine $C_p$: the first is a process to lower the surface free energy to produce particles as small as possible and reduce $C_p$, and the second is lowering of the free energy for monomer mixing with polymer which acts to increase $C_p$ to the bulk monomer concentration value. This equilibrium is only reached when the system is monomer-rich. Morton derived the famous equation to describe the equilibrium swelling of polymer latex particles with monomer.[32] It should be noted that this equation is only valid for long polymer chains and cannot be used for small chains as in the case of “living” radical polymerizations. In this latter case, the superswelling theory[33] must be considered, which will be discussed later in this paper.

$$\ln(1-\phi_p)+\phi_p+\chi\phi_p^{\,2}+\frac{2\Gamma V_{sM}}{r_u RT}\phi_p^{\,1/3}=0 \qquad (2)$$

In this equation, $\Gamma$ is the interfacial tension between particles and water, $\phi_p$ is the volume fraction of polymer in the particles, $V_{sM}$ is the partial molar volume, $r_u$ is the unswollen radius of the particle, and $\chi$ is the Flory–Huggins interaction parameter This equation can be solved iteratively given values of $\chi$ and $r_u$ to yield $\phi_p$. Monomer concentration in the particles $C_p$ is therefore determined from the fraction of monomer in the particles $(1-\phi_p)$ divided by $V_{sM}$ (eq 3).

$$C_p=(1-\phi_p)/V_{sM} \qquad (3)$$

Parameters $\Gamma$ and $\chi$ are difficult to predict *a priori* for a polymer latex particle system and can only be determined from experiment. However, the Morton equation does provide a model to predict the swelling state of a polymer latex particle by its own monomer or different types of monomers. Figure 1 shows the effect of increasing the initial unswollen particle radius on $C_p$ for styrene swelling a polystyrene particle. It can be seen that the smaller the particle size, the lower the concentration of monomer within the particles. When the radius is greater than 20 nm, $C_p$ becomes relatively constant and close to 6 mol L$^{-1}$, which is close to the saturation monomer concentration in the particles determined from experiment.[34]

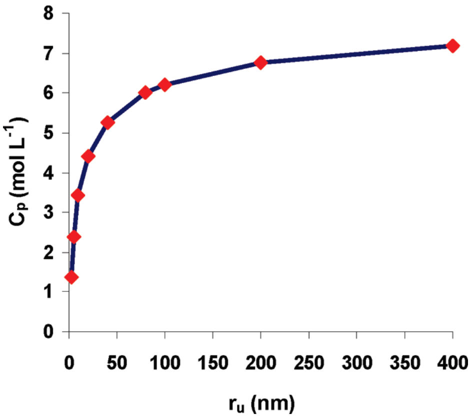


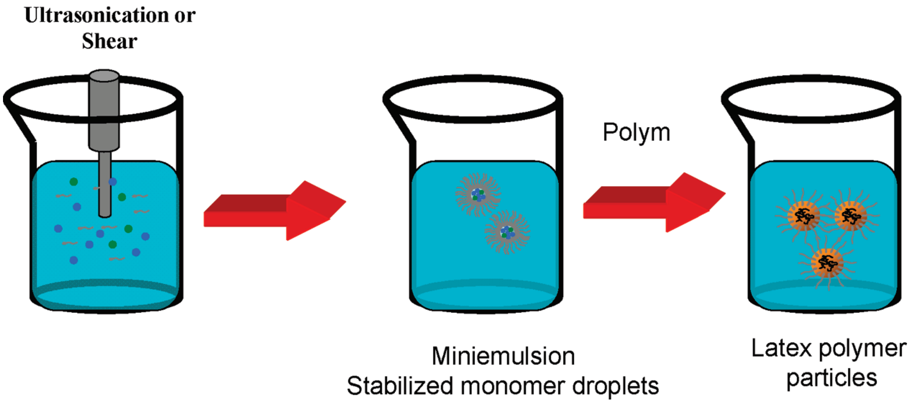
**Figure 1.** Equilibrium values of monomer concentration within particles, $C_p$, with unswollen radius, $r_u$, using the Morton equation (eq 2) and eq 3. The calculations used $\Gamma$ = 20 dyn cm$^{-1}$, $M_0$ = 104, $d_m$ = 0.878 g mL$^{-3}$, and $\chi$ = 0.45. This equation was solved iteratively given values to yield $\phi_p$. Equation 3 was then used to determine $C_p$.

Vanzo et al.[35] derived an equation (the Vanzo equation) to obtain a relationship between the saturation monomer concentration in the aqueous phase ($C_w^{sat}$) and the monomer concentration in the water phase at any time during the polymerization ($C_w$).[36]

$$\ln(1-\phi_p)+\phi_p+\chi\phi_p^{\,2}+\frac{2\Gamma V_{sM}}{r_u RT}\phi_p^{\,1/3}=\ln\frac{C_w}{C_w^{sat}} \qquad (4)$$

Equation 4 allows to predict partitioning of monomer between the aqueous phase and the polymer particles, providing $\Gamma$ and $\chi$ are known. However, most emulsion polymerizations are carried out using two or more monomers. An expression derived by Maxwell et al.[36,37] for a two monomer system is

**Scheme 2. Methodology for the Formation of Stable Miniemulsions**



given as follows:

$$\ln \phi_{\mathrm{p},i} + (1 - m_{ij})\phi_{\mathrm{p},j} + v_p + \chi_{ij}\phi_{\mathrm{p},j}{}^2 + \chi_{i\mathrm{p}}\phi_{\mathrm{p}}{}^2 + \phi_{p,j}\phi_{\mathrm{p}}(\chi_{ij} + \chi_{i\mathrm{p}} - \chi_{j\mathrm{p}}m_{ij}) + \frac{2V_{\mathrm{sM},i}\Gamma\phi_{\mathrm{p}}{}^{1/3}}{r_{\mathrm{u}}RT} = \ln \phi_{\mathrm{d},i} + (1 - m_{ij})\phi_{\mathrm{d},j} + \chi_{ij}\phi_{\mathrm{d},j}{}^2 = \ln\left[\frac{C_{\mathrm{w},i}}{C_{\mathrm{w},i}{}^{\mathrm{sat}}}\right] \quad (5)$$

where $\chi_{i,j}$ is the Flory−Huggins interaction parameter between monomer $i$ and $j$, $\chi_{i,\mathrm{p}}$ and $\chi_{j,\mathrm{p}}$ are the Flory−Huggins interaction parameters between monomer $i$ and $j$ and the polymer, respectively, and $m_{ij}$ is the ratio of the molar volume of monomer $i$ over monomer $j$. Under monomer saturation conditions the mole fraction of $i$ ($f_{i\mathrm{d}}$) and $j$ ($f_{j\mathrm{d}}$) in the droplets is shown to be respectively equal to the mole fraction of $i$ ($f_{i\mathrm{p}}$) and $j$ ($f_{j\mathrm{p}}$) in the polymer particles. An equation that allows one to predict the concentration of $i$ or $j$ in the particles can be derived assuming that the total monomer concentration in the particles is the sum of the individual monomer concentrations.[36,37]

$$C_{\mathrm{p}i} = f_{i\mathrm{d}}{}^2(C_{\mathrm{p}i}{}^{\mathrm{sat}} - C_j{}^{\mathrm{sat}}) + f_{i\mathrm{d}}C_j{}^{\mathrm{sat}} \quad (6)$$

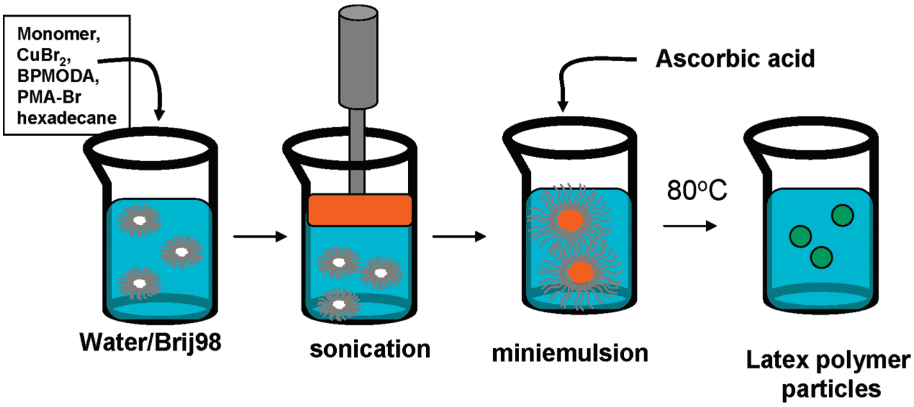
The equations above can be used as a predictive thermodynamic model, based on the classical Flory−Huggins theory, to determine the partitioning of monomer between the aqueous, droplet, and particle phases. Such a thermodynamic treatment provides an accurate measure of the rate of polymerization within the particles and can account for compositional drift in copolymer emulsion polymerizations. It should also be recognized that these equations can equally be used for small molecule organic reactions carried out within nanoreactors.

A *seeded emulsion polymerization*[4,5,23,34,38] begins with a reaction containing a "latex" that has been previously prepared with a well-defined particle size and PSD. Monomer, aqueous soluble initiator, and some additional surfactant are then added, and the polymerization initiated. The main locus of polymerization is in the seed particles, thus eliminating the nucleation period (or interval I in an *ab initio* polymerization), and therefore, one can start the polymerization in interval II or III. In other words, the seed particles act as nanoreactors and allow control over the rate of polymerization, the MWD, and more importantly the final particle size and distribution. To avoid additional or a second crop of particles through secondary nucleation (or homogeneous nucleation), the initial number of seeded particles must be high to increase the probability of entry into particles rather than growth of the radicals in the water phase to a water-insoluble species (reaching a $j_{\text{crit-mer}}$). These species collapse, swell with monomer, and grow in the same fashion as the other particles. Seeded particles in some cases can consist of a different polymer to that of the second polymer, which allows control of the particle morphology due to the chemical incompatibility of the seed polymer and the second polymer. However, for these polymerizations to be carried out successfully, the second monomer should effectively swell the seeded particles. Seeded emulsion polymerizations are also an ideal system to study the kinetics of heterogeneous polymerizations and allow kinetic parameters such as entry, exit, and termination to be determined.

A *miniemulsion polymerization*[5,23,39−42] begins with a reaction containing water-insoluble monomer, surfactant, costabilizer (e.g., hexadecane), water-soluble initiator, and water. The strict definition of miniemulsions is the formation of surfactant-stabilized monomer droplets of size ranging between 50 and 500 nm. The costabilizer is an important ingredient as it can limit the diffusion of monomer from the smaller particles to the larger ones (i.e., Ostwald ripening) and can provide additional surface stability against droplet coagulation depending on its chemical composition. The diffusion of monomer via the action of Ostwald ripening from small to larger droplets results in the growth of the larger droplets until they reach a critical size of usually greater than 500 nm, become buoyant, and then rise to form a single monomer phase at the top of the reaction vessel. Miniemulsions are typically formed through high shear by subjecting the system to ultrasonication, homogenizer, or microfluidizer. The high shear produces small monomer droplets stabilized by the surfactant and costabilizer. Polymerization of the system should result in each droplet becoming a particle (or one-to-one copy of droplets to particles, Scheme 2). In reality, there are fewer particles than droplets. This suggests that nucleation is an important consideration even in miniemulsions and, as will be described later, has implications on RAFT-mediated miniemulsion polymerizations. Once again, the number of droplets must be high to avoid secondary particle (homogeneous) nucleation. The number of particles therefore is strongly dependent upon the initiator concentration and suggests that nucleation is primarily via the monomer droplets and that only a fraction of droplets become particles.

A *microemulsion polymerization*[5,43,44] begins with a reaction containing water, monomer (few wt % to water), surfactant, water-soluble initiator, and cosurfactant that should be low molecular weight alcohol. Microemulsions are thermodynamically stable due to a low interfacial tension that compensates for the dispersion entropy. The droplet sizes are much smaller than miniemulsion droplets, and the reaction mixtures are usually transparent. Consequently, the number of droplets is very high, and as such the resulting "latex" contains only a few polymer chains per particle, sometimes equal or close to one. (Conventional *ab initio* emulsion polymerizations, on the other hand, produce particles that contain many polymer chains per

Scheme 3. "Living" Radical Polymerizations in Miniemulsions Using AGET ATRP



particle.) The amount of surfactant and cosurfactant required to obtain microemulsions is usually extremely high (with monomer to surfactant ratios ranging from 0.3 to 1), thus limiting their use in biomedical applications or for the production of large quantities of a pure well-defined polymer. However, very small "latex" particles are formed, ranging between 20 and 40 nm. The mechanism of microemulsions is believed to occur via the continuous nucleation of droplets over time, and thus the number of particles increases with conversion. This is a result of the high surfactant and thus high micelle concentration, in which nucleation is preferential in the micelles rather than particles.

## Mechanism of "Living" Radical Emulsion Polymerization

"Living" radical polymerization (LRP) has emerged as the most versatile technique to produce polymers with controlled MWD and architecture. In solution and bulk systems, the most used living radical techniques are (i) reversible addition−fragmentation chain transfer (RAFT),[45−51] (ii) atom transfer radical polymerization (ATRP),[52−57] (iii) nitroxide-mediated polymerization (NMP),[58−62] and (iv) metal-catalyzed radical polymerization (e.g., single electron transfer LRP),[63−68] which have been used to make new, interesting, and smart polymeric materials. The versatility of these polymerization techniques is attributed to the vast number of monomers capable of polymerizing effectively, a wide range of acceptable solvents and the ability to conduct polymerizations at ambient temperature. "Living" radical polymerization has offered the polymer scientist an avenue for preparing polymers with effectively uniform chain lengths parallel to that of an organic chemist's synthesis of organic compounds.

For LRP to find widespread use in industry, especially in the coatings area, these polymerizations must be easily carried out in heterogeneous systems. Initially, it was thought that taking this technology from bulk or solution to heterogeneous systems would be simple. However, partitioning of the monomer and agents, which act to control the "living" behavior, between the droplets, particles, and aqueous phase has made controlling the molecular weight and particle size distribution significantly more complex than originally anticipated. The three "living" radical techniques have been applied under heterogeneous conditions in suspension, dispersion, *ab initio* emulsion, seeded emulsion, and miniemulsion using water as the reaction medium. There have been a number of recent reviews of the techniques in dispersed media.[69−72]

Nitroxide-mediated polymerization has been shown to produce a controlled and narrow MWD in miniemulsions and seeded styrene polymerizations, but due to the sensitive nature of the kinetics and thermodynamics of heterogeneous systems, correct reaction conditions need to be selected in order to gain optimal control over rate, MWD, and colloidal stability. In particular, the partitioning of the nitroxide and alkoxyamines between the water and organic phases is a critical issue. Similarly, partitioning is a major consideration in ATRP for both the ligand and the copper(II) complex. By controlling the partitioning of the copper/ligand complexes by altering the hydrophobicity of the ligand, Chambard et al.[73] showed that ATRP emulsions could produce well-defined polymer chains. The use of a less hydrophobic ligand resulted in poor control of the MWD with PDIs close to 2. Increasing the hydrophobicity of the ligand gave good control over the molecular weight and PDI as a direct result of an increase in the copper(II)/Ligand deactivating species within the particles. There was also a concomitant decrease in the rate of polymerization due to the persistent radical effect.

NMP and ATRP are affected by the troublesome partitioning of the small deactivating species over the two phases, which complicates the kinetics by altering the relative concentrations of active, persistent, and dormant species inside the growing particle.[74,75] If the persistent species moves into the water phase, it will slow down the growth of aqueous phase radicals, hampering radical entry, while at the same time decreasing the rate of polymerization. Control of molecular weight at the main locus of polymerization (i.e., inside the particle) will be decreased because of the decrease in deactivating species. It has also been suggested that the persistent radical effect, which adds to the control in bulk and solution polymerizations, will cause a significantly greater rate of retardation due to the increased local persistent radical concentration inside the particles.[76]

Recently, Matyjaszewski and co-workers[77] developed a new initiating system to carry out ATRP in miniemulsions (termed AGET ATRP). By confining all the reagents to the miniemulsion monomer droplets, the polymerizations were well controlled. The ligand used was hydrophobic which acts to confine the copper species within the growing particles (Scheme 3). It was also shown that a two step *ab initio* emulsions can be carried out in the presence of droplets.[78] This work was based on earlier work for NMP by Nicolas et al.[79] In this case, a microemulsion was formed and polymerization initiated. Soon after the formation of polymer, a large amount of monomer was fed into the reaction mixture to produce well-defined polymer chains.

Transport and partitioning of active species in the different phases has not only restricted the use of NMP and ATRP to mini- or microemulsions but also played a similar role in RAFT. *Ab initio* and seeded RAFT emulsion polymerizations failed to produce well-controlled MWDs and PSDs due to transport problems of monomer or other compounds (e.g., RAFT agent) from monomer droplet reservoirs to the growing particles.[80] In many cases, a red layer from the color of the RAFT agent was found on the top of the polymerization mixture. Miniemulsions solved the transport problem as each droplet is an isolated bulk nanoreactor, in which all components are located within the droplet but in some cases the red layer still appeared.[81] The drawbacks of miniemulsions are (a) the difficulty in isolating pure polymer product due to the high levels of surfactant (and some cases the high levels of hexadecane used to reduce Oswald ripening) and (b) the PSDs are broad with little or no control over the particle size. Other methods of growing amphiphilic diblock copolymers *in situ* led to poor control of the chain length polydispersity ( > 1.4, while below 1.2 is considered "good control"), broad PSDs,[82,83] and very long polymerization times.[84−86] Recent work by Charleux and co-workers have show that through the use of a amphiphilic poly(ethylene oxide) macro-RAFT stabilizer well-controlled dispersion polymerizations were obtained at much faster rates of polymerization.[87,88]

Several phenomena were observed when using the RAFT-mediated miniemulsion polymerizations indicating a deviation from the idealized theory when the miniemulsion was stabilized by an ionic surfactant.[89] Inefficient droplet nucleation, a steadily rising polydispersity over the reaction time, and the appearance of a separate organic phase after initiation were all indications of particle instability. A distinct difference between standard polymerizations and those that involve highly active RAFT agents comes from the fact that in RAFT polymerization there is a time interval early in the reaction where oligomers dominate the molecular weight distribution. The presence of large quantities of oligomers is believed to be the major culprit behind the destabilization observed through a detrimental interaction with the ionic surfactant of the miniemulsion.[89] Conductivity measurements verified the increase of free surfactant in the aqueous phase over the course of reaction. Despite this, results showed clear indication of "living" character with a linear evolution of molecular weight until roughly 40% monomer conversion, after which the molecular weight showed contributions from initiator-derived chains. Lansalot et al.[90] showed that they could find conditions where colloidal stability was observed when using SDS. However, the polydispersity found in their experiments ranged between 1.7 and 2, suggesting that these systems gave nonideal RAFT polymerization.

It was thought that destabilization could be similar to that observed for ATRP in the presence of SDS, and therefore, ionic surfactants were substituted for a nonionic surfactant (e.g., Brij 98).[81] This allowed well-defined polymer (PDI $<$ 1.2) to be prepared with no stability problems. However, retardation compared to polymerization without a RAFT agent was found. This was prescribed to be due to termination of the intermediate radical species, which lowered the propagating radical concentration considerably.[91] Although the rate is significantly reduced by intermediate radical termination, this termination step should have little or no effect on the MWD since the amount of RAFT dormant chains lost through intermediate termination is less than 5%. It was also found that a wide range of monomers could be polymerized with controlled MWDs and could be further used to prepare block copolymers with low polydispersities ( $<$ 1.2).[81] One major advantage of the RAFT process is that acidic monomers can be used, which provide very efficient stability of the polymer latex particles. For example, using Brij 98 (nonionic surfactant), a block copolymer of polyEHMA-*block*-poly(methyl methacrylate-*co*-methacrylic acid) was prepared.

A destabilization theory to explain the observations in miniemulsions was described by Luo et al.[33] They argued that the growing particles in a LRP would have a lower chemical potential than non-nucleated droplets due to the "superswelling" effect of small oligomers. This would result in monomer transfer from high to low chemical potential, where monomer would swell the growing particles until equilibrium was reached. The authors suggested that by simply increasing the costabilizer level the problems found when using ionic stabilizers would be eliminated. Ugelstat and co-workers[92] showed that polymer particles can swell up to 5 times their unswollen volume in the presence of small hydrophobic molecules. They also showed[92,93] that polymer particles consisting of oligomers can swell as much as 100 times their volume. Further work[94] by carrying out minemulsions with higher levels of surfactant and costabilizer (hexadecane) tentatively supported the Luo et al.[33] postulate. The "superswelling" theory is becoming more widely accepted as the thermodynamic reason for poor control in RAFT-mediated dispersion polymerizations and was used by Urbani et al.[95] to describe their results. The authors commented that by utilizing a nonionic surfactant such as Brij98 "superswelling" could be avoided due to the surfactant's lower efficiency[96] (i.e., it can stabilize a larger surface area than for example SDS) and also hinder monomer transportation.[33] Luo and Cui[97] used the "superswelling" theory to aid in the experimental design to produce well-defined polymer using RAFT in the presence of high amounts of SDS and initiator. However, deviation from theory was observed when high molecular weights were targeted analogous to the Urbani et al.[95] results. In this case, although $M_n$ increased linearly with conversion and was close to that calculated, the PDI values ranged between 1.5 and 1.8. The authors suggested that the high PDI values were not a result of the colloidal stability but were most probably a result of a heterogeneous distribution of RAFT agent among the particles formed at different nucleation times. Therefore, according to the "superswelling" theory, an increase in the nucleation rate should lead to lower PDIs, which was found by Urbani et al.[95]

Charleux and co-workers[98] showed that diblock amphiphilic copolymers could function to stabilize conventional *ab initio* emulsion polymerizations. This work led to the synthesis of "latex" particle via a self-assembly process.[82] The initiator (4,4′-azobis(4-cyanopentonoic acid)) was added to a solution of poly(acrylic acid)(PAA) macro-RAFT agent in water. The mixture was brought to the reaction temperature and butyl acrylate fed into the reaction to maintain the monomer concentration below the saturation concentration of BA in the water phase. The BA units added to the PAA macro-RAFT agent to form a diblock copolymer, and when the number of BA units was high enough, the diblock would self-assemble into small PAA-stabilized nanoparticles, where the core consisted of PBA. The monomer would then swell the hydrophobic PBA region and polymerization would continue with growth of the particles. There was a linear increase in $M_n$ with conversion, and the PDI increased from approximately 1.25 (10% conversion) to 1.5 (70% conversion). The increase in PDI with conversion for the higher molecular weight polymerizations could possibly be explained by the "superswelling" phenomenon.

Very recently, a new nanoreactor approach was taken to carry out RAFT heterogeneous polymerizations.[99,100] A diblock copolymer consisting of poly(*N*-isopropylacrylamide-*b*-dimethylacrylamide) (P(DMA$_{49}$-*b*-NIPAM$_{106}$)) was used to construct the nanoreactor.[100] At room temperature the diblock was water-soluble, and when the reaction mixture, including monomer, MacroCTA (PNIPAM$_{18}$-SC(=S)SC$_4$H$_9$), and initiator, was heated above the LCST of PNIPAM block (~32 °C) to the polymerization temperature of 70 °C, nanoparticles instantaneously formed with the MacroCTA located inside (see Scheme 4). Polymer chains were formed rapidly with the predicted molecular weights and with very narrow molecular weight distributions (polydispersity indexes below 1.1). In addition, the particle size distribution was very narrow, and by altering the weight ratio of monomer to MacroCTA, the average size could be changed in a linear fashion. This represents the first successful RAFT heterogeneous polymerization where the molecular weight and particle size distributions were narrow and importantly can be controlled independently of each other.[100] The diblock nanoreactor can be separated from the new polymer latex

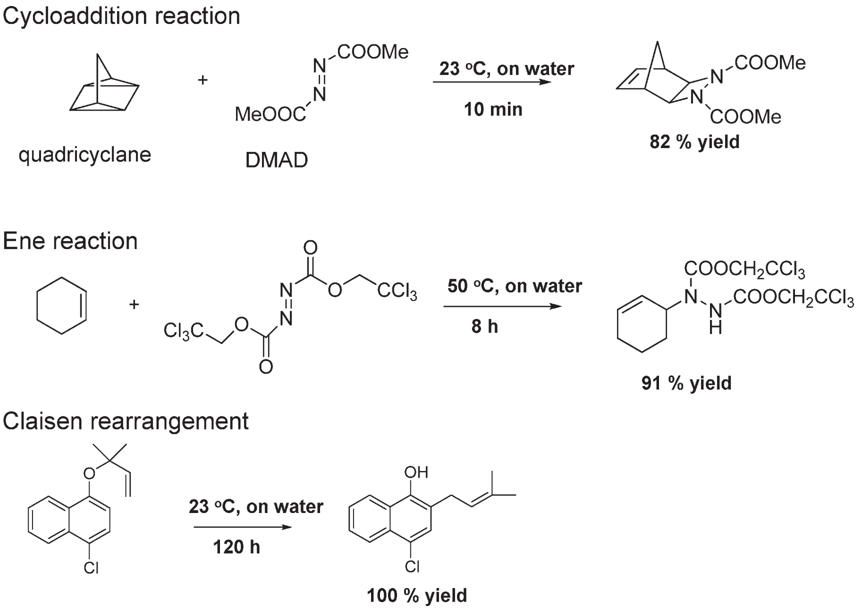
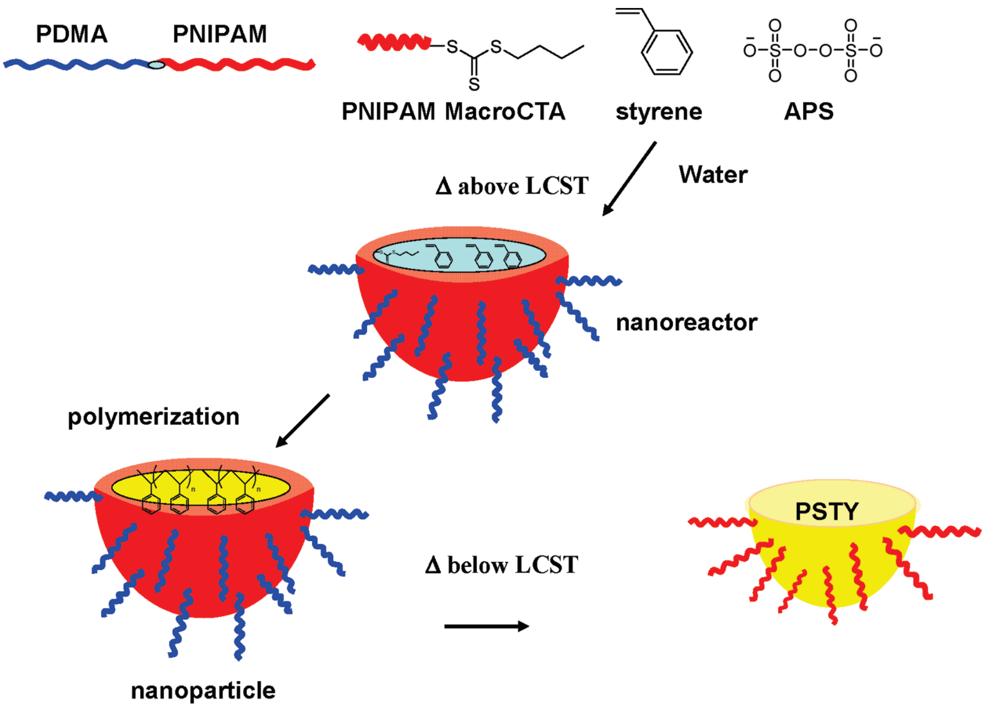


**Figure 2.** Organic reactions carried out “on” water with significant rate enhancement.[115]

**Scheme 4. Novel Designer Thermoresponsive Nanoreactors for RAFT-Mediated Heterogeneous Polymerizations in Water**



particles by cooling below the LCST. The latex particles are stabilized by the PNIPAM on the MacroCTA, and the P(NIPAM-*b*-DMA) diblock becomes water-soluble. It was found that at the beginning of the polymerization only a small fraction of monomer could swell into the nanoreactors. After a few percent conversion and through “superswelling” of the small oligomers the rest of the monomer swell into the nanoreactors, representing a 6-fold volume increase over the theoretical swelling volume according to the Morton equation.

## Nanoreactors in Small Molecule Organic Reactions

The description of free-radical and “living” radical polymerizations in nanoreactors given above has shown the complexities of implementing polymer reactions in heterogeneous systems. Although the initial work showed little in the way of success in “living” heterogeneous systems, the intensive research over the past decade has overcome the initial impediments to produce polymer latex particles with well-defined polymer chain length, morphology, and particle size. Confining the reactants to a small volume was also the key to rapidly producing polymers of commercial interest. This confinement or compartmentalization of reactants has found widespread use in small hydrophobic molecule organic reactions.[1,101,102] The breakthrough in carrying out organic reactions in heterogeneous systems (i.e., in the presence of surfactant-type micelles) was the observed control over the enantioselectivity in asymmetric hydrogenations catalyzed by chiral rhodium(I) complexes due to the specific interactions with the surfactant micelles.[103] The field expanded to include a wide variety of other reactions including Diels–Alder reactions,[104−106] aldol reactions,[107,108] allylation reactions,[109] and Heck[110] and Suzuki[111,112] coupling reactions. Organic reactions in water-based heterogeneous systems have been extensively reviewed.[1,101,102,113,114]

Sharpless and co-workers[115] showed that a significant rate enhancement for the cycloaddition reaction of quadricyclane (a liquid) and diethyl azodicarboxylate (DEAD, a solid) "on" water could be obtained (Figure 2). The reactants (at ~10 wt %) were mixed in ice water and vigorously stirred, and the reaction was completed in 10 min rather than the 2 days in, for example, toluene. They also carried out ene, Diels−Alder, aromatic Claisen rearrangement, and nucleophilic opening of an epoxide reaction "on" water. This heterogeneous system defied the well-known precept that "substances do not interact unless dissolved". The authors suggested that perhaps the surface tension energetics at oil−water interface play a dominant role but suggested still more work was required to fully elucidate the mechanism. These reactions have commercial relevance as they can be used on industrial scales. It would be interesting to understand the partitioning of the reactants and products in the system and how this influences the rate of reaction. If these reactions were carried out in mini- or microemulsions stabilized with surfactant, would one observe retardation or enhancement of rate and would such a system provide insight into the role of the oil−water interface in such organic reactions?

Micellar systems can function to concentrate the reactants within a nanoenvironment and orientate reactants to alter the stereo- and regioselectivity of the product. Hydrophobic effects play a dominant role in the orientation and are analogous to the catalytic effects of enzymes in biological systems. The hydrophobic attractive forces between reactants allow the reactants to be in contact for longer periods of time than in solution, resulting in kinetic enhancement of the rate. As the microviscosity of the micelles is much greater than in homogeneous solutions, the reactants have a lower degree of translational freedom, which controls the regioselectivity.[116] Preorientation of the reactants at or close to the stern layer of the ionic micelle has allowed the formation of products with regioselectivity through photochemical reactions. In organic solvents, anthracene photocoupling reactions gave 91% head-to-tail addition in benzene and 50% head-to-head in methanol. When these reactions were carried out in the presence of potassium dodecanoate micelles, 98% of the product formed was head-to-head addition (Figure 3).[117] This methodology has also been used to control the regioselectivity for cycloaddition reactions, in which the reagents were surfactant-like. Therefore, the design of the nanoreactors must account for each individual reaction and the objective of that reaction and the physical properties of the reactants and products.

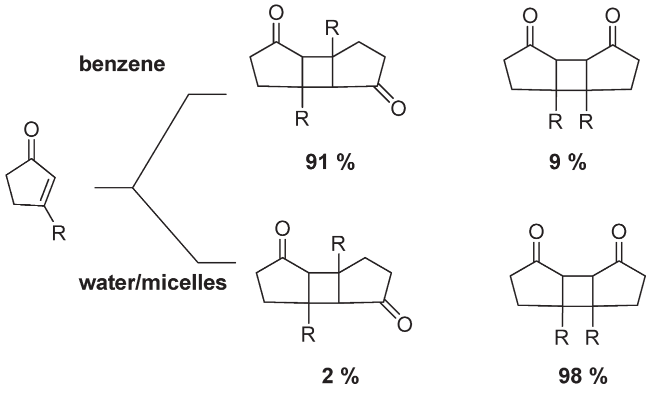


**Figure 3.** Micellar nanoreactors used to control the stereo- and regiospecific reactions through preorientation of the reactants.[117]

The ability to precisely design the chemical composition and chain length of polymers through "living" radical polymerization now allows researchers to tune the properties and self-assembly behavior of, for example, amphiphilic block copolymers of polystyrene and poly(acrylic acid).[48,54,118−121] The range of polymer architectures has now greatly increased with the new types of "click" reactions, which are selective and near quantitative. The 3D self-assembled structures range between spheres, vesicle, and rods, all of which have the capacity to act as nanoreactors for organic reactions.[122−128] The main advantage of polymeric self-assembled systems is their stability over surfactant-based micelles.

Weberskirch and co-workers[129] have used amphiphilic polymeric micelles to encapsulate active metal catalysts to synthesize enantiopure epoxides and diols from racemic starting compounds (Figure 4). This hydrolytic kinetic resolution (HKR) was a duel action process involving the electrophilic epoxide and nucleophilic water, catalyzed by Co$^{III}$(salen) complexes bound to the polymer side chains. The epoxide reagents were chosen to be hydrophobic, and the success of the reaction relied on the high concentration of reagent and Co$^{III}$ localized within the polymeric micelles. Water was excluded from the core, allowing the catalyst to achieve high conversions with enantioselectivity. Of commercial interest is that the polymer−Co$^{III}$ (micelles−catalyst) could be recycled four consecutive times without loss of enantioselectivity. A similar polymer was used but with a differently attached pendant, N-heterocyclic carbenes, as ligands for palladium, resulting in nanoparticles between 10 and 30 nm in size.[130] These polymer-based catalysts were used for the C−C coupling Heck reactions. The Heck reaction is an important reaction in the pharmaceutical industry and for producing conducting polymers. Reactions between iodobenzene and styrene resulted in high conversions within 5 h with 80% formation of *trans*-stilbene. With each subsequent cycle, the conversions decreased slightly by 7% and the formation of *trans*-stilbene decreased down to 68%.

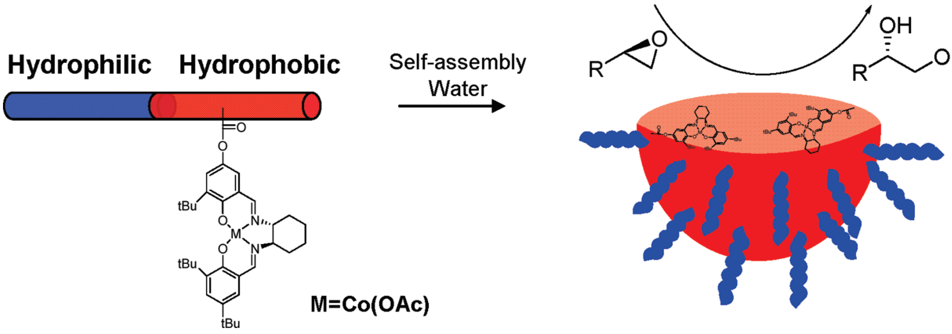


**Figure 4.** Amphiphilic polymeric micelles used the hydrolytic kinetic resolution (HKR) to synthesize enantiopure epoxides and diols from racemic starting compounds.[129]

## Conclusion and Outlook

This Perspective has provided the thermodynamic and kinetic principles that allow free-radical polymerizations to be carried out in heterogeneous systems. Applying "living" radical polymerization to heterogeneous (emulsions) has not been as easy as anticipated. The thermodynamics of such systems plays an influential role on the kinetics of polymerization and the resulting control of both rate and molecular weight distribution. Partitioning of the monomer and other agents between the droplets, aqueous phase, and particles needs to be first determined, as this can influence the equilibrium between dormant and active chains. Another major consideration is the "superswelling" in which the particles swell in the presence of oligomeric chains, found after the first few percent conversion in a "living" radical polymerization, to greater than 6 times their initial volume. This can change the very nature of heterogeneous system.

Applying this knowledge to the synthesis of small molecules using a variety of important organic reactions is still at its infancy, with little information on the physical chemistry of the systems and little or no perspective on the design of heterogeneous systems for specific organic reactions. A mechanistic understanding of the system taken from a holistic point of view will certainly enable the field to grow rapidly. With the ever expanding range of polymers and polymer architectures, the design of thermo- or pH-responsive polymer nanoreactors will play a more influential role in heterogeneous organic and polymer reactions.

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