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## Synthetic and Physicochemical Aspects of Advanced Stimuli-Responsive Polymers

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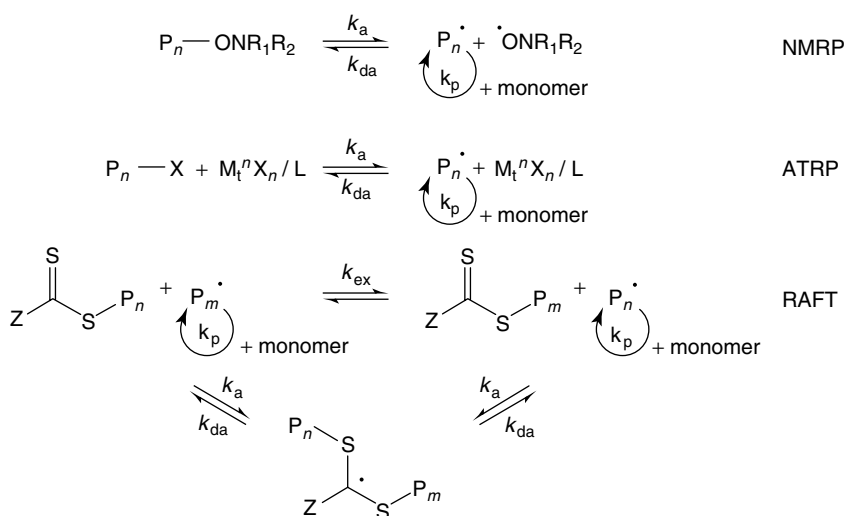
### 1.1

#### Introduction

Although the technological and scientific importance of functional polymers has been well established over the last few decades, currently much attention has been focused on stimuli-responsive polymers. This group of materials is of particular interest owing to their ability to respond to internal and/or external chemico-physical stimuli that is often manifested by the large macroscopic responses [1]. Stimuli-responsive polymers are also referred to as *smart*, *sensitive*, or *intelligent* polymers [2, 3], just to name a few. These terms are loosely used under the same stimuli-responsiveness umbrella attributed to selective polymer segments or the entire polymer backbones that exhibit stimuli-responsive characteristics. Notwithstanding the scientific challenges of designing stimuli-responsive polymers, the main technological interest is in the numerous applications ranging from reactive surfaces [4] to drug-delivery and separation systems [5], or from chemomechanical actuators [6] to other applications that have been extensively explored [7, 8].

In contrast to traditional polymers, in order to incorporate responsive components, it is necessary to copolymerize responsive blocks into a polymer or copolymer backbone [8]. For this reason, the preparation of well-defined block copolymers with different architectures is essential: for example, grafting amphiphilic blocks to a hydrophobic polymer backbone [9]. Using living anionic [10] and cationic polymerizations [11] as well as controlled radical polymerizations (CRPs) techniques [12], wide ranges of block copolymers were synthesized. However, the development of the CRP based on the concept of reversible chain termination minimizes the disadvantage of the free-radical polymerization, thus permitting the synthesis of well-defined block copolymer structures [13]. The growing demand for well-defined and functional soft materials in a nanoscale range has led to a significant increase of procedures that combine architectural control with the flexibility of incorporating functional groups. In view of these considerations, there has been a significant quest for elucidating a variety of controlled polymerization strategies, which resulted in nitroxide-mediated radical polymerization (NMRP) [14–16], atom transfer

radical polymerization (ATRP) [17, 18], and reversible addition fragmentation chain transfer (RAFT) procedures [19, 20]. While details for each synthetic route are readily available in the literature, Figure 1.1 illustrates the basic principles governing these reactions, which are capable of producing well-defined homo and block copolymers of different architectures in solutions and on surfaces [21, 22]. While each synthetic route has its own attributes, in general, free-radical polymerization processes can be conducted using homogeneous or heterogeneous conditions. Ring-opening metathesis polymerization (ROMP) also provides a unique means of synthesizing well-defined copolymers [23–25]. For example, ROMP of norbornene derivatives leads to precisely controlled polydispersity (PDI), backbone configuration, and tacticity [26]. In particular, Ru-based ROMP appears to be a highly beneficial route for synthesizing a broad spectrum of copolymers with biological relevance. Precisely controlled peptide-pendant copolymers [27] and amino acid functionalized norbornenes containing ester carboxy groups [28, 29] are the prime examples. Taking advantage of the versatility of the ROMP process, bioactive and therapeutic polymers were also developed [30], including stimuli-responsive betaines [31] and acid–base sensitive phenanthroimidazole-based [32] and thiol-functional [33] polymers. In addition, notable synthesis of tunable, temperature-responsive polynorbornenes with elastin peptide side chains was reported [34]. The first part of the chapter focuses primarily on homogeneous CRP, whereas the remaining sections outline heterogeneous colloidal synthesis and physicochemical aspects of stimuli responsiveness.



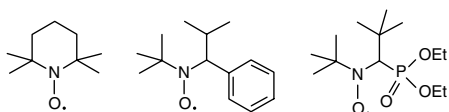
**Figure 1.1** General mechanisms for controlled radical polymerization (CRP).

## 1.2

### Controlled Free Radical Polymerization of Stimuli-Responsive Polymers

A CRP is a free-radical polymerization that displays a living character, that is, does not terminate or transfer, and is able to continue polymerization once the initial feed is exhausted by the addition of a monomer. However, termination reactions are inherent to a radical process, and modern CRP techniques seek to minimize such reactions, thus providing control over molecular weight and molecular weight distribution. More sophisticated CRP approaches incorporate many of the desirable features of traditional free-radical polymerization, such as compatibility with a wide range of monomers, tolerance of many functionalities, and facile reaction conditions. The control of molecular weight and molecular weight distribution has enabled access to complex architectures and site-specific functionality that were previously impossible to achieve via traditional free-radical polymerizations [35, 36].

The reversible deactivation of a growing radical chain can be achieved by stable (persistent) nitroxide radicals [37, 38]. Such radicals possess a structure similar to that of nitrogen monoxide. The single unpaired electron is delocalized over the nitrogen–oxygen bond. This delocalization as well as the captodative structure of the radical contributes to its stability. The deactivation occurs by the recombination of the radical chain end with such stable nitroxide. The formed C–O–N bond is thermolabile and can be cleaved at elevated temperatures (90–130 °C). Hence, the equilibrium between active and dormant species can be controlled by the reaction temperature. A recent major advance in nitroxide-mediated polymerization has been the development of a hydrido nitroxide, in which the presence of a hydrogen atom on the  $\alpha$ -carbon leads to a significant increase in the range of vinyl monomers that undergo controlled polymerization [39]. Several nitroxides have been synthesized and they are illustrated in Scheme 1.1. The initiation of the reaction can be achieved by common initiators, such as azo-bis(isobutyronitrile) (AIBN) or benzoyl peroxide (BPO). An alternative approach is to use the so-called iniferter, which has the initiating and terminating moiety combined in one molecule. Using multifunctional iniferters, unique polymer structures (e.g., block, star, or graft copolymers) can be formed [40–42]. For example, telechelic poly(*N*-isopropylacrylamides) (PNIPAAms) could be synthesized via nitroxide-mediated controlled polymerization by introducing defined end-group moieties. Various functional groups, linked to the central nitroxide-initiator via a triazole moiety resulting from the so-called azide/alkyne–“click” reactions, were



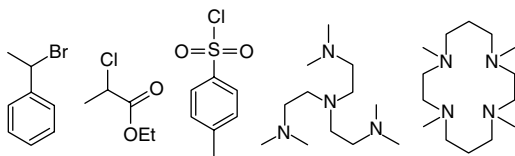
**Scheme 1.1** Selected nitroxides suitable for the controlled polymerization of vinyl monomers.

probed with *N*-isopropylacrylamides (NIPAAms) and *n*-butyl acrylate (nBA) as monomers in terms of efficiency and livingness [43].

ATRP was developed by designing a proper catalyst (a transition metal compound and a ligand), using an initiator with an appropriate structure and adjusting the polymerization conditions. As a consequence, molecular weight during polymerization increased linearly with conversion and the polydispersities were typical for a living process [44]. The ATRP reaction mixture is, hence, a multicomponent system consisting of an initiator (mostly alkyl halogenides or chlorosulfonic acids), a transition metal catalyst, a ligand, a monomer, and if necessary a solvent and other compounds (an activator or a deactivator). Examples of initiators are illustrated in Scheme 1.2. The most significant part is the choice of the suitable catalyst/ligand system, which determines the equilibrium between dormant and active species. In the majority of studies, Cu is used as the catalyst, but the use of ruthenium, rhodium, palladium, nickel, and iron has also been reported [44]. Depending on the metal center, the ligands are nitrogen or phosphor compounds with a broad structural variety.

The choice of the initiator should be such that fast and quantitative initiation occurs. Under these conditions, all polymer chains grow at the same time. This is one prerequisite to obtain precise control of the molecular weight and a low PDI. Typical alkyl halogenides as initiators possess an acceptor substituent in the  $\alpha$ -position to the C–X bond to weaken the C–X bond. In this case, a fast and selective transfer of the halogen atom from the initiator to the metal center can be achieved. In most cases, the halogen is chlorine or bromine.

ATRP can be performed in bulk as well as in solution. The use of a solvent is necessary if the polymer or catalyst complex is not soluble in the monomer. However, the solvent might have an influence on the ATRP process, changing the structure of the complex and enhancing its solubility, which is essential for establishing equilibrium between active and dormant species. The structure of the complex determines the rate and equilibrium of the transfer reaction. To control the polymerization, the transfer reaction between the solvent and the growing radical should not take place. The main advantage of ATRP is the tolerance of a variety of functional groups, enabling the polymerization of a large number of monomers under controlled conditions such as styrene, acrylate, methacrylate, acrylamide, and acrylonitrile derivatives. Currently, various efforts have been made to develop environmentally friendly ATRP processes [45].



**Scheme 1.2** Examples of initiators and ligands for ATRP.

For the synthesis of block copolymers, the reactivity of the macroinitiator has to be high enough to ensure fast reinitiation. However, the rate of reinitiation strongly depends on the halogen atom at the end of the macroinitiator. To maintain the controllability, a procedure for the halogen exchange has been developed [46]. The result of the formation of the second block also depends on the choice of the correct catalyst/ligand system. Hence, block formation has to be done in the correct order. For most systems, the catalyst complex as well as the solvent have to be tuned to fit the reactivity of the macroinitiator.

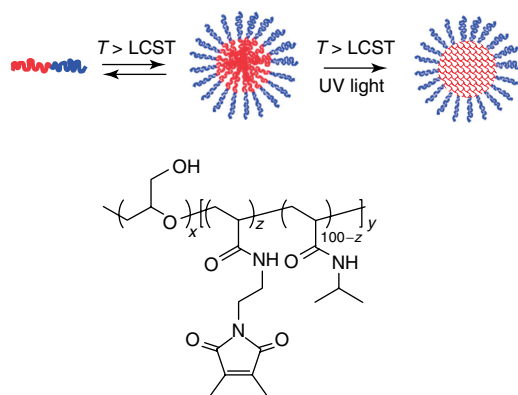
There are numerous examples using ATRP under different conditions (initiator, ligand, and catalyst) to form block copolymers based on substituted acrylates and methacrylates [47–53]. Amphiphilic random, gradient, and block copolymers of 2-(dimethylamino)ethyl methacrylate (DMAEMA) and *n*-butyl methacrylate (BMA) were synthesized by ATRP in water/2-propanol mixtures using a methoxy-poly(ethylene glycol) (MPEG) ( $M_n = 2000 \text{ g mol}^{-1}$ ) macroinitiator [54]. ATRP of dimethyl(1-ethoxycarbonyl)vinyl phosphate (DECVP) was performed in the presence of different catalyst systems and initiators, yielding polymers with controlled molecular weight and relatively low PDI ( $<1.5$ ). PDECVP dissolves in water below  $70^\circ\text{C}$ , but its critical solution temperature ( $T_c$ ) depends on the polymer concentration [55]. Low-molecular-weight hydroxyethyl methacrylate (HEMA) oligomers prepared by ATRP (target degrees of polymerization,  $DP_n$ , less than 20) exhibited water solubility over a wide temperature range (no cloud point behavior). Furthermore, for actual  $DP_n$ 's between 20 and 45, HEMA homopolymers exhibited inverse temperature solubility in dilute aqueous solution at pH 6.5, and their cloud points increased systematically as the  $DP_n$  was reduced. Statistical copolymerizations of HEMA with other comonomers such as glycerol monomethacrylate (GMA) and 2-hydroxypropyl methacrylate (HPMA) allowed the cloud point behavior to be manipulated. Finally, a range of novel HEMA-based block copolymers were synthesized, in which the HEMA block was either thermoresponsive or permanently hydrophilic, depending on its  $DP_n$  and the nature of the second block. Thus, diblock copolymer micelles with either hydroxylated cores or coronas could be prepared [56]. Poly(*N*-[(2,2-dimethyl-1,3-dioxolane)methyl]acrylamide) (PDMDOMAAM), a novel thermoresponsive polymer containing pendant dioxolane groups, was synthesized via ATRP. Water-soluble PDMDOMAAMs with controlled molecular weight and narrow molecular weight distribution were obtained. The  $T_c$  of PDMDOMAAM was finely tuned over a wide temperature range by the partial hydrolysis of the acid labile dioxolane side group to form diol moieties (PDMDOMAAM diols). Unlike the traditional way of controlling  $T_c$  by copolymerization, the advantage of this method is that a series of thermoresponsive polymers with different  $T_c$ s can be prepared from a single batch of polymers with comparable molecular weight profiles [57].

Using ATRP catalyst system of tris-(2-dimethylaminoethyl)-amine ( $\text{Me}_6\text{TREN}$ ) and Cu(I)chloride ( $\text{CuCl}$ ), well-defined PNIPAAm could be synthesized at room temperature [58]. Narrow-dispersed PNIPAAms with well-controlled molecular weights and with end groups of varying hydrophobicity were synthesized in 2-propanol using the corresponding chloropropionate and chloropropionamide

initiators. The choice of end groups affected the shape of the cloud point curves and the enthalpy of the phase transition [59]. A 2-chloropropionamide derivative featuring an azido group was used as the initiator to produce the end-functionalized PNIPAAm with an azido group. Subsequently, the “click” reaction between the azido end group and acetylene derivatives was demonstrated to produce PNIPAAm in which the end groups are modified by phenyl, 4-phenoxyphenyl, butyl, octyl, carboxylic acid, and hydroxymethyl groups. The resulting PNIPAAm derivatives show a  $T_c$  that ranges from 34.8 to 44.6 °C depending on the end group introduced [60]. Thermoresponsive polymers differing only in end functionalities induce phase transitions cooperatively only under dense-packed polymer brush conditions. This unique cooperative chain behavior in the hydrated micellar corona allows to regulate monodispersed micelle thermoresponse by blending well-defined diblock copolymers with thermoresponsive segments having hydrophobic and/or hydrophilic termini without any variations in critical micelle concentration (CMC) value or micelle size [61].

The syntheses of well-defined 7- and 21-arm PNIPAAm star polymers possessing  $\beta$ -cyclodextrin ( $\beta$ -CD) cores were achieved via the combination of ATRP and “click” reactions. A series of alkynyl terminally functionalized PNIPAAm (alkyne-PNIPAAm) linear precursors with varying  $DP_n$  were synthesized via ATRP of NIPAAm using propargyl 2-chloropropionate as the initiator. The subsequent “click” reactions of alkyne-PNIPAM with azido- $\beta$ -CD led to the facile preparation of well-defined 7- and 21-arm star polymers [62].

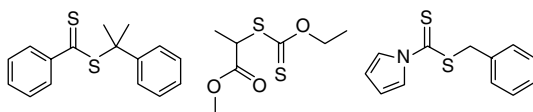
Water-soluble poly(glycidol) (PGL) macroinitiators for ATRP have been prepared and their ability to form block copolymers with NIPAAm and 4-VP has been proven [63, 64]. On the basis of such polymers, a new method for the synthesis of smart nanohydrogels under additives-free conditions and at high solid content was investigated. The new core-shell nanohydrogels with cross-linked PNIPAAm core and hydrophilic PGL shell were obtained by photo cross-linking of PGL-*block*-PNIPAAm copolymers above their phase transition temperature. Figure 1.2 depicts reactions leading to these polymers [65]. Several graft copolymers are described, such as Chitosan-*graft*-PNIPAAm [66] and PNIPAAm-*graft*-Poly(2-vinyl pyridine) (P2VP) polymers, in previous reports [67]. Both polymers show a temperature and pH-sensitive phase behavior in aqueous solutions. Thermo- and pH-responsive micellization of poly(ethylene glycol)- $\beta$ -P4VP-*b*-PNIPAAm in water was also studied. Micellization of the triblock copolymer, which was synthesized by sequential ATRP of 4VP and NIPAAm, occurred with combined stimulus of temperature and pH changes to form various morphological micelles [68]. Thermoresponsive materials with double-responsive AB-type diblock copolymers comprised of an NIPAAm segment and a poly(NIPAAm-co-(*N*-(hydroxymethyl) acrylamide) (HMAAm)) one were designed. Synthesized poly(NIPAAm-co-HMAAm)s showed sensitive thermoresponse, and the cloud point was completely tunable by the composition of HMAAm [69]. ATRP was also used to prepare thermosensitive cationic block copolymers of (3-acrylamidopropyl)-trimethylammonium chloride (AMPTMA) and NIPAAm with different block lengths [70]. Diblock copolymers poly(tetrahydrofuran-*block-tert*-butyl acrylate) (PTHF-*block*-PtBA) and



**Figure 1.2** Synthetic approach used for preparation of PGI/PNIPAAm core-shell nano-hydrogels.

poly(tetrahydrofuran-*b*-1-ethoxyethyl acrylate) (PTHF-*b*-PEEA) were successfully synthesized by the dual initiator 4-hydroxybutyl-2-bromoisobutyrate (HBBIB). The isobutyrate and alcohol function of HBBIB were used for the ATRP of tBA (or EEA) and the living cationic ring-opening polymerization of THF, respectively. Hydrolysis or thermolysis of the aforementioned diblock copolymers results in amphiphilic pH-responsive copolymers poly(tetrahydrofuran-*block*-poly(acrylic acid) (PTHF-*b*-PAA) [71]. Cleavable block copolymers can be synthesized by a simple combination of the homopolymers synthesized by ATRP. Complementary reactive functionalities can be incorporated in these block copolymers that allow for the incorporation of additional functionalities in a postpolymerization step [72].

The RAFT process involves conventional radical polymerization in the presence of a suitable chain transfer agent (CTA). The degenerative transfer between the growing radicals and the CTAs provides controlled chain growth. A wide range of structurally diverse CTAs has been reported including dithioesters, trithiocarbonates, dithiocarbamates, and dithiocarbonates (xanthates), which are illustrated in Scheme 1.3 [73]. The mechanism of the RAFT process is composed of the same three main steps as that of the conventional free-radical polymerization: initiation, propagation, and termination. Additionally, the propagation step in RAFT consists of two stages – the RAFT pre-equilibrium and the main RAFT equilibrium [35]. The first stage involves the activation of all added CTA along



**Scheme 1.3** Examples of thiocarbonylthio RAFT reagents.

with some degree of propagation, while the second stage consists of chain equilibrium and propagation. Because of the presence of the CTA and the subsequent degenerative transfer, the termination step is largely suppressed. The key to the structural control in the RAFT process is the careful selection of appropriate monomers, initiators, and CTAs. As polymers are synthesized by ATRP, the products from RAFT polymerization are colored due to the thiocarbonylthio end groups. However, these end groups can be readily removed by a posttreatment. A facile labeling technique was reported in which the telechelic thiocarbonylthio functionality of well-defined PNIPAAm prepared by room-temperature RAFT polymerization was first converted to the thiol and subsequently reacted with a maleimido-functional fluorescent dye [74]. Such an approach can be extended to the synthesis of hetero-telechelic  $\alpha,\omega$  biofunctionalized polymers [75, 76]. RAFT polymerization in the presence of a compound capable of both reversible chain transfer through a thiocarbonylthio moiety and propagation via a vinyl group led to highly branched copolymers by a method analogous to self-condensing vinyl copolymerization [77]. Highly branched PNIPAAm compounds were prepared by copolymerization of 3H-imidazole-4-carbodithioic acid 4-vinylbenzyl ester with NIPAAm [78]. NIPAAm star polymers were prepared using the four-armed RAFT agent pentaerythritoltetrakis(3-(*S*-benzyltrithiocarbonyl)-propionate) [79].

Acrylamides such as NIPAAm and *N*-ethylmethacrylamide (EMA) or acrylamides containing proline and hydroxyproline moiety, *N*-acryloyl-L-proline (A-Pro-OH) and *N*-acryloyl-4-*trans*-L-proline (A-Hyp-OH), were readily polymerized by the RAFT process [80]. The latter case afforded well-defined amino-acid-based polymers [81]. A-B-A stereoblock polymers with atactic PNIPAAm as a hydrophilic block (either A or B) and a nonwater-soluble block consisting of isotactic PNIPAAm were also synthesized using RAFT polymerizations [82–84]. Using RAFT it was possible to obtain amphiphilic block copolymers of PNIPAAm (hydrophilic) and poly(styrene) (PS) or poly(*tert*-butylmethacrylate) (PtBMA) as the hydrophobic compounds [85]. The design of bisensitive narrowly distributed block copolymers consisting of NIPAAm and acrylic acid (AAc) was also feasible [86]. RAFT homopolymerization of 2-(diisopropylamino)ethyl methacrylate (DPA) and 2-(diethylamino)-ethyl methacrylate (DEA) and their random copolymerization were investigated. The random copolymers of DPA-ran-DEA were synthesized and used as macro-CTA to prepare poly(DPA-ran-DEA)-*block*-poly(*N*-(2-hydroxypropyl) methacrylamide) amphiphilic block copolymers [87]. Other amphiphilic block copolymers consist of PNIPAAm and of positively charged first- and second-generation dendronized polymethacrylates [88]. Novel double hydrophilic multiblock copolymers of *N,N*-dimethylacrylamide (DMAAm) and NIPAAm, *m*-PDMAAm<sub>p</sub>-PNIPAAm<sub>q</sub>, with varying DP<sub>n</sub>s for PDMAAm and PNIPAAm sequences (p and q) were synthesized via consecutive RAFT polymerizations using polytrithiocarbonate as the CTA [89]. Thermosensitive association of a diblock copolymer consisting of poly(3-dimethyl(methacryloyloxyethyl) ammonium propane sulfonate) (PDMAEAPS), as an upper critical solution temperature (UCST) block, and poly(*N,N*-diethylacrylamide) (PDEAAm), as a lower critical



solution temperature (LCST) block, has been investigated. Micelles form at temperatures both below the UCST and above the LCST of the blocks [90].

Monomers composed of a (meth)acrylate moiety connected to a short poly(ethylene) glycol (PEG) chain are versatile building blocks for the preparation of smart biorelevant materials. Many of these monomers are commercial and can be easily polymerized by CRP, allowing the synthesis of well-defined PEG-based macromolecular architectures such as amphiphilic block copolymers, dense polymer brushes, or biohybrids. Furthermore, the resulting polymers exhibit fascinating solution properties in an aqueous medium. Depending on the molecular structure of their monomer units, nonlinear PEG analogs can be either insoluble in water, readily soluble up to 100 °C, or thermoresponsive [91, 92]. The bromine chain ends of well-defined poly(oligo(ethylene glycol) acrylate) (POEGA) prepared using ATRP were successfully transformed into various functional end groups (w-hydroxy, w-amino, and w-Fmoc-amino acid) via a two-step pathway: (i) substitution of the bromine terminal atom by an azide function and (ii) 1,3-dipolar cycloaddition of the terminal azide and functional alkynes (propargyl alcohol, propargylamine, and *N*-*R*-(9-fluorenylmethyloxycarbonyl)-L-propargylglycine) [93, 94]. By this “click” chemistry, even cyclic polymers could be prepared [95, 96].

Monomers bearing an activated ester group can be polymerized under various controlled polymerization techniques, such as ATRP, NMRP, and RAFT polymerization. Combining the functionalization of polymers via polymeric-activated esters with these controlled polymerization techniques generates possibilities to realize highly functionalized polymer architectures [97]. Block copolymers containing stimuli-responsive segments provide important new opportunities for controlling the activity and aggregation properties of protein–polymer conjugates. A RAFT block copolymer PNIPAAm-*block*-PAAc was conjugated to streptavidin (SA) via the terminal biotin on the PNIPAAm block. The aggregation properties of the block copolymer–SA conjugate were very different from those of the free block copolymer. The outer-oriented hydrophilic block of PAA shields the intermolecular aggregation of the block copolymer–SA bioconjugate at pH values where the –COOH groups of PAA are significantly ionized [98]. PNIPAAm with imidazole end groups can be used to separate a histidine-tagged protein fragment directly from a crude cell lysate [99].

Amphiphilic diblock copolymers undergo a self-assembly micellar process in solvents that are selective for one of the blocks [100]. By choosing selective conditions for each block, conventional micelles and so-called inverse micelles can be formed. Examples of the so-called schizophrenic micelles were reported [101]. In this case hydrophilic AB diblock copolymers can form micelles in an aqueous solution, in which the A block forms the inner core and inverted micelles (with the B block forming the inner core) [102]. A diblock copolymer with two weak polybases, (poly-[2-(*N*-morpholino)ethyl methacrylate-*block*-2- and (diethyl amino)ethyl methacrylate) (PMEMA-*block*-DEAEMA), forms stable micelles with DEAEMA cores by adjusting the pH value of the solution. The formation of inverted micelles (MEMA core) was achieved by a “salting out” effect by adding electrolytes to the aqueous solution.

The synthesis of polyampholytes by using P2VP as a basic block was reported in several papers, for example, P2VP-*block*-poly(sodium-4-styrenesulfonate) [103], P2VP-*block*-PAAc [104], and P2VP-*block*-PEO [100]. In this case, according to the corresponding pH value of the solution, it was possible to obtain precipitation, aggregation, or micellation. Recently, stimuli-responsive (pH-sensitive) block copolymers that self-assemble into vesicles without the addition of organic solvents have been reported [105]. Compared with pH-responsive materials, thermally responsive materials are advantageous for biological applications because of the stringent pH requirements in mammalian systems [106].

The behavior of double-responsive diblock copolymers of PNIPAAm-*block*-PAAc in aqueous solution is influenced by hydrogen-bonding interactions between the NIPAAm and AAc units [107]. This micellation behavior is often appealing to biomedical community for drug-delivery systems [108, 109]. Heterobifunctional block copolymers of PEG and PNIPAAm were synthesized by RAFT polymerization of NIPAAm using a macromolecular PEG-based CTA [110]. The synthesized block copolymers contained a carboxylic acid group from L-lysine at the focal point and a trithiocarbonate group at the terminus of the PNIPAAm block. The trithiocarbonate functionality was converted into a thiol group and used for conjugation of biotin to the end of the PNIPAAm block [111]. Alternatively, a biotinylated RAFT agent can be used [112]. Biotinylated copolymers that bind to the protein can be synthesized by ATRP as well [113, 114]. A series of well-defined PEO-*block*-PDMAEMA diblock copolymers were synthesized by ATRP techniques, followed by postpolymerization reactions to transform a portion of the tertiary amine groups of the PDMAEMA (poly(*N,N*-dimethylaminoethyl methacrylate)) into phosphorozwitterions. Antiparasitic drugs used for the treatment of Leishmania were incorporated into the copolymer aggregates [115].

Current trends in the field of optical sensing include the development of dual sensors that respond simultaneously and independently to different stimuli [116]. In recent years, dual optical sensors have been reported, for example, for temperature and pH value, which would be beneficial, for example, to monitor chemical reactions and for biological diagnostics. The dual-sensitive polymeric material prepared by RAFT shows responsiveness in a temperature range from 10 to 20 °C and a pH range from 1 to 7 [117]. Actively controlled transport that is thermally switchable and size selective in a nanocapillary array membrane can be obtained by grafting PNIPAAm brushes onto the exterior surface of an Au-coated polycarbonate track-etched membrane. PNIPAAm brushes with 10–30 nm (dry film) thickness were grafted onto the Au surface through surface-initiated ATRP using a disulfide initiator [118]. Gold nanoparticles were prepared by the reduction of HAuCl<sub>4</sub> in the presence of thermosensitive PNIPAAm. Although thiol end-capped PNIPAM (poly(*N*-isopropylacrylamide)) is known as a *macroligand effective* in stabilizing gold nanoparticles, this work showed that interactions between constitutive amides of PNIPAAm and gold are strong enough to protect gold nanoparticles against aggregation [119]. Highly stable hybrid unimolecular micelles with thermosensitive PNIPAAm shells incorporated with Ag nanoparticles were prepared *in situ* via a facile approach. Heating the hybrid unimolecular micellar solutions leads to

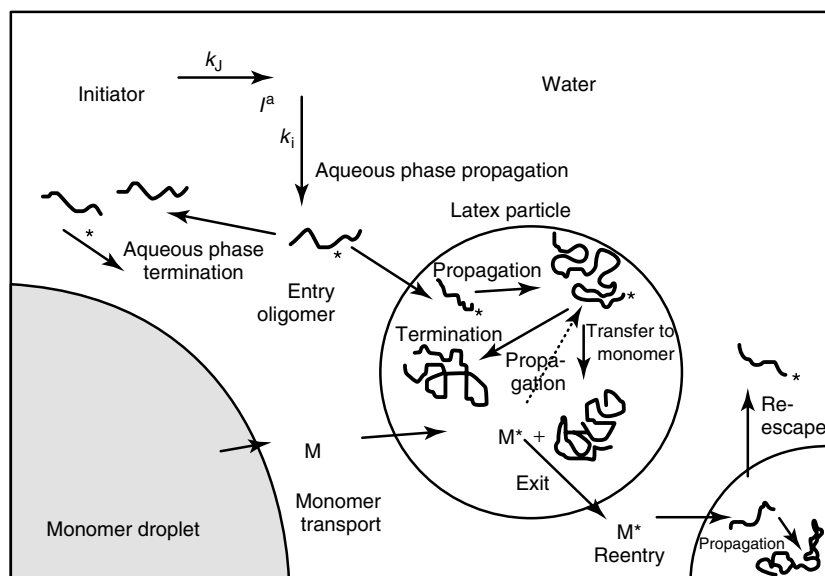
the shrinkage of the PNIPAM shell and allows for tuning the relative spatial distances between neighboring Ag nanoparticles. These novel hybrid unimolecular micelles might be potential candidates for applications in sensors, catalysis, and optic/electronic devices [120].

### 1.3

#### Synthesis of Stimuli-Responsive Colloidal Dispersions

Colloidal dispersions represent one of the technologically important heterogeneous polymerization systems. Although colloidal particles have been synthesized for over five decades, complexities involved in synthetic aspects are related to their water-dispersive characteristics as well as the resulting particle morphologies. While the latter will determine film properties after and during colloidal particle coalescence, the former will affect solution characteristics. A schematic diagram illustrating reactions leading to the formation of colloidal particles is shown in Figure 1.3. While synthetic challenges arise from the complexity of synthetic conditions to accommodate a variety of monomers, there are opportunities for producing colloidal entities with a variety of shapes and morphologies.

The primary synthetic methods utilized for generating colloidal dispersions are suspension and emulsion polymerizations. Suspension polymerization occurs when monomers are suspended as a noncontinuous phase in a continuous aqueous medium and organic-soluble initiators facilitate polymerization by diffusion into the monomer droplets. Surfactants are typically utilized as stabilizing agents; however,



**Figure 1.3** Schematic diagram illustrating principles of emulsion polymerization.

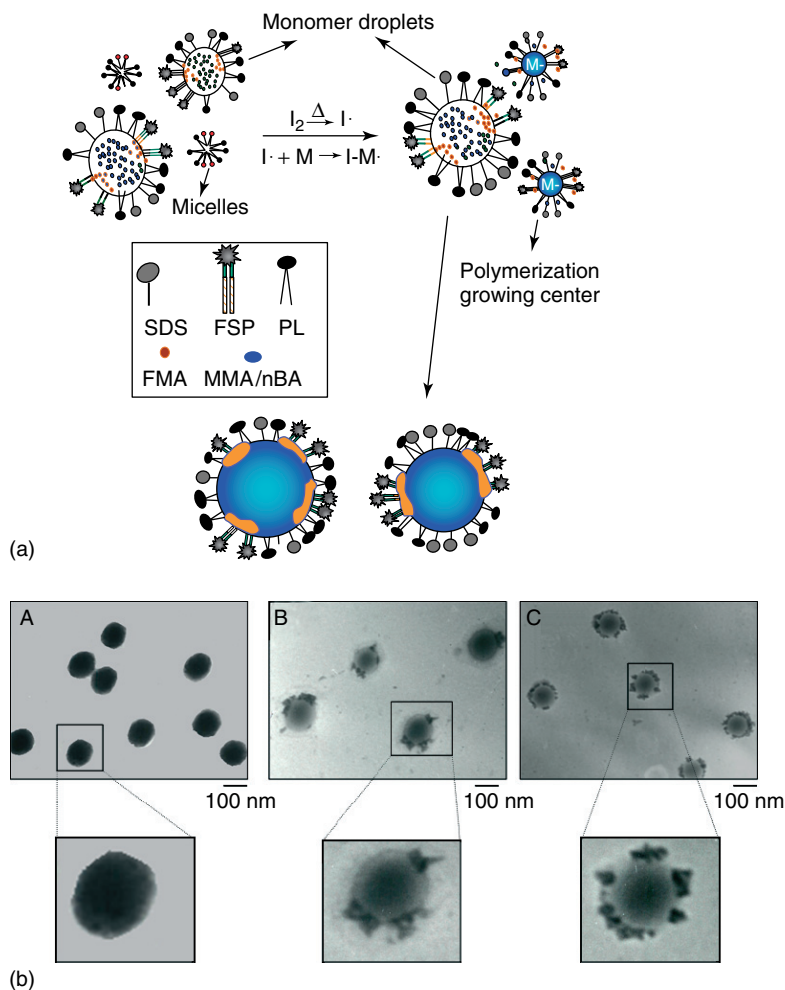
their concentration levels are too low to form micellar structures. Polymeric particles obtained by suspension polymerization range in size from 50 to 500 nm. Without proper agitation, the suspended particles remain in the continuous phase for a time period which may vary, depending upon experimental conditions.

Colloidal dispersions can also be synthesized using emulsion polymerization. Although similar to suspension polymerization, emulsion polymerization produces colloidal dispersions of typically smaller sizes while having increased stability within the continuous phase. As shown in Figure 1.3, emulsion polymerization proceeds through a free-radical polymerization process where monomers are polymerized in the presence of surfactant molecules suspended in an aqueous medium. The mechanism of the formation of polymer particles proceeds by two simultaneous processes. The first step is micellar nucleation that takes place when radicals (primary or oligomeric) enter from the aqueous phase into the micelles, followed by a homogeneous nucleation, which occurs when solution-polymerized oligomeric radicals become insoluble and are ultimately stabilized by free surfactant. When the concentration of surfactant molecules surpasses the CMC, highly ordered micellar structures are formed serving as polymerization loci for monomer molecules that have diffused through the continuous phase from the larger monomer droplets. At the same time, a water-soluble initiator is cleaved either thermally or photochemically, which initiates polymerization in the hydrophobic core of the micelle. As monomer continues to diffuse from the droplets and polymerize within micelles, surfactant molecules may be adsorbed from other micelles, solution, and monomer droplets [121–123]. Upon exhaustion of the monomer droplets, the reaction ceases, which is referred to as monomer starvation condition.

Emulsion polymerization reactions are typically conducted as a batch, semi-continuous, or continuous process. In a batch polymerization, water, initiator, surfactant, and monomer are incorporated into the reactor at the same time, and the cleavage of the initiator begins the polymerization process. This process provides limited control over particle nucleation and particle growth. For this reason, semicontinuous processes have been developed, providing better control over reaction conditions. During this process, one or more of monomers are polymerized over an extended period of time. To achieve control over the polymerization process, a small fraction of pre-emulsion, often referred to as a *seed*, can be utilized to induce polymerization, followed by the controlled addition of the remainder of the pre-emulsion. As discussed earlier, molecular weight can be controlled using CRP approaches discussed above, and colloidal size and shape control are major challenges. Dispersing agents are another significant component, which serve the dual purpose: stabilization of polymerization loci as well as stabilization of polymerized colloidal particles in an aqueous medium. One can envision that synthesis of larger sizes may be challenging if the glass transition temperature ( $T_g$ ) of the copolymer is very low, particles may coagulate and precipitate out. Thus, from this prospective, an access of the free volume may not be beneficial, but as will be seen later, it will certainly help facilitating stimuli responsiveness [124, 125].

Because of the facile control of reaction kinetics, emulsion polymerization has found many applications and is often categorized according to the size of the resulting particles. While the most common are macroemulsions in the particle range of greater than 1  $\mu\text{m}$  [126], miniemulsions are 50–200 nm [127, 128], and microemulsions are 10–100 nm [126]. Although there is a significant size overlap among these dispersions, there are major stability differences. While miniemulsions are generated by vigorous stirring and/or ultrasonication and are generally unstable, microemulsions are synthesized by spontaneous reactions of suitable monomers and are thermodynamically stable. For the latter, therefore, the monomers and their concentrations, dispersants, as well as other components must be carefully chosen to achieve desirable particle sizes. The use of reversible addition fragmentation chain transfer inverse microemulsion polymerization (RAFT-IMEP) resulted in the synthesis of well-controlled polymers retaining CTA functionality, which was accomplished by the design of pseudo-three-component phase diagrams consisting of hydrophilic monomer *N,N*-dimethylacrylamide, water, hexanes, nonionic surfactants, and a cosurfactant [129]. In contrast, using inverse miniemulsion photoinitiated polymerization of poly(*N*-isopropylacrylamide), high-quality composite quantum dot microspheres were also prepared [130]. Since the synthesis of hollow polymeric capsules offers the possibility of nano- or microreactors for a variety of applications, hollow polymeric capsules containing a hydrophilic liquid core were obtained in a simple one-pot miniemulsion process without the use of a sacrificial core and consist of polyurea, polythiourea, or polyurethane shells made by polycondensation at the interface of the droplets [131]. In addition, cross-linked nanoparticles of a random copolymer composed of methylmethacrylate (MMA), 4-vinylbenzyl chloride (VBC), and divinylbenzene (DVB) were also synthesized using RAFT miniemulsion polymerization in aqueous solutions [132]. Use of amphiphilic macro-RAFT agents in miniemulsion polymerization has been reported frequently. For example, RAFT-controlled/living *ab initio* emulsion polymerization by amphiphilic macro-RAFT self-assembly was reported [133] along with encapsulation of hydrophobic or hydrophilic pigments by emulsion polymerization using butyl acrylate/AAC random macro-RAFT copolymers [134]. In addition, poly(ethylene oxide) (PEO) macro-RAFT agent was used as both a stabilizer and a control agent in styrene polymerization in aqueous dispersed systems [135, 136]. Well-defined monodisperse NCs were also synthesized via this method [137]. In addition, PEO-RAFT interfacial inverse miniemulsion polymerization to synthesize the nanocapsules in a one-step process was reported [138].

Compared to homogeneous bulk or solution media, it might be a bit more complicated and challenging, but certainly beneficial, to extend ATRP to aqueous dispersions, thus opening avenues for commercial production of latex particles [139–141]. A new efficient initiation system, activators generated by electron transfer (AGET), significantly “face-lifted” the ATRP for heterogeneous systems [142–144], where instead of using activating Cu(I) catalyst that is sensitive to air, a higher oxidation state catalyst derived from a Cu(II) complex was utilized. Using this approach, thermally responsive random copolymers of di(ethylene glycol) methyl ether methacrylate (M(EO)2MA) and oligo(ethylene glycol)



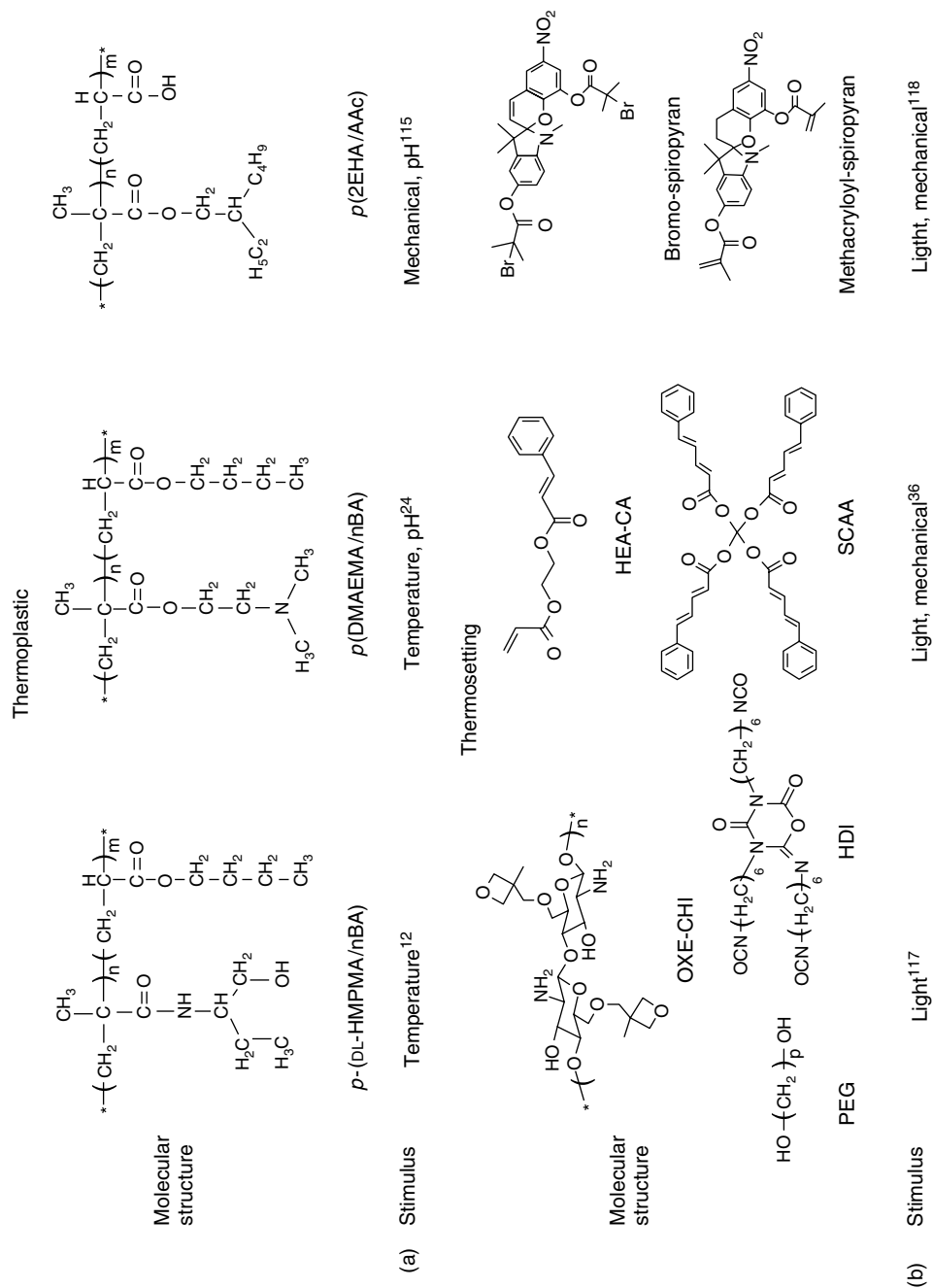
**Figure 1.4** (a) Schematic diagram illustrating formation of mixed unimodal micelles and polymerization of non-spherical *p*-MMA/*n*BA/FMA colloidal particles; (b) TEM images of *p*-MMA/*n*BA (A); *p*-MMA/*n*BA/FMA (B and C).

methyl ether methacrylate (OEOMA) ( $M_n \cong 300$  or 475) with varies compositions were successfully synthesized via AGET ATRP in miniemulsion at 65 °C [145].

Heterogeneity of the colloidal reactions imposes several synthetic limitations. For example, the use of low-surface-tension monomers, such as fluoromonomers, has been a challenge. However, the use of biologically active phospholipids (PLs) as a dispersing agent provides synthetic conditions under which *p*-methyl methacrylate/*n*-butyl acrylate/heptadecafluorodecyl methacrylate (*p*-MMA/*n*BA/FMA) copolymer colloidal dispersions containing up to 15% w/w

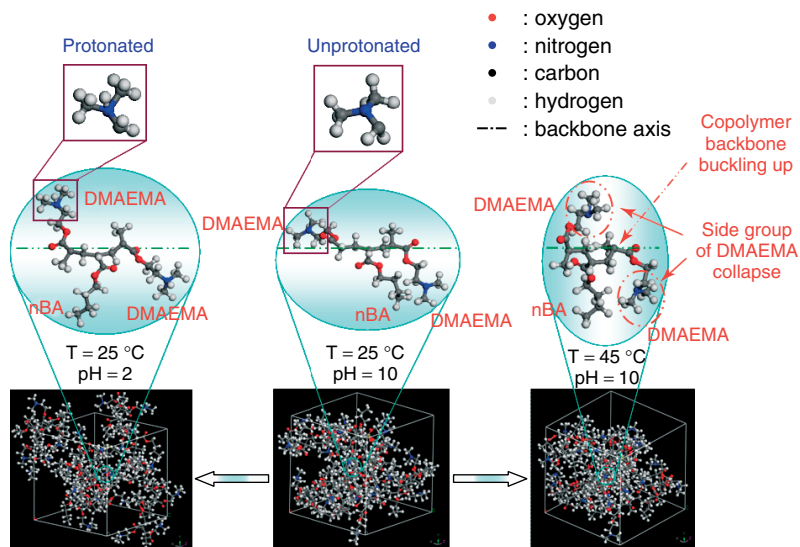
of heptadecafluorodecyl methacrylate (FMA) were copolymerized. These particles exhibit nonspherical particle morphologies and the choice of 1,2-dilauroyl-sn-glycero-3-phosphocholine (DLPC) was dictated by the fact that combining this PL with SDS/FSP surfactants results in the reduction of the overall surface tension of the aqueous phase from 72 to about 1–5 mN m<sup>-1</sup> [146]. These conditions appear to be essential during polymerization of F-containing colloidal particles because lower surface tension not only facilitates efficient monomer transport to the polymerization loci but also provides stability of colloidal particles after synthesis. As shown earlier [147], DLPC in the presence of sodium dioctyl sulfosuccinate (SDOSS) forms unimodal micelles and consequently monodispersed particles are produced. In contrast, hydrogenated soybean phosphatidylcholine (HSPC) PL in the presence of SDOSS forms bimodal distribution of particles. Thus, the choice of the PL is crucial [148]. When monomers diffuse through an aqueous phase to the nucleation site, the reduced surface tension and monomer starvation conditions facilitate transport of higher quantities and polymerization of FMA into *p*-MMA/*n*BA particles. This is schematically illustrated in Figure 1.4. As MMA and *n*BA monomers initially migrate to the polymerization site, and upon initiation polymerize at the reactive site, monomer starvation conditions force FMA to migrate to the reactive site and diffuse to *p*-MMA/*n*BA copolymer core, which is facilitated by the presence of PL, which lowers the surface tension such that colloidal particles containing hydrophobic-lipophobic entities of *p*-FMA are stable and thus do not coagulate.

Combination of stimuli-responsive components with other monomers that provide higher free volume content is one of the prerequisites for preparing stimuli-responsive colloidal particles that form solid films. For example, in thermoplastic materials, it is desirable to copolymerize lower  $T_g$  components with stimuli-responsive species, as shown in Figure 1.5a. In thermosetting materials illustrated in Figure 1.5b, incorporation of an entity that responds to electromagnetic stimuli is a common approach and the challenge is to make stimuli-responsiveness reversible, and lower  $T_g$  facilitates spatial conditions for responsiveness because the presence of localized “voids” provides space for polymer chain rearrangements. Following this concept, poly(*N*-(DL)-(1-hydroxymethyl) propylmethacrylamide/*n*-butyl acrylate) (*p*(DL-HMPMA/*n*BA)) [12] and poly(2-(*N,N'*-dimethylamino)ethyl methacrylate/*n*-butyl acrylate) (*p*(DMAEMA/*n*BA)) [24] colloidal particles were synthesized, which upon coalescence retain their stimuli responsive properties. This is facilitated by the presence of low  $T_g$  *n*BA components. The temperature responsiveness is controlled by DL-HMPMA or DMAEMA components, while the lower  $T_g$  *n*BA component provides sufficient free volume for copolymer chain rearrangements. One interesting macroscopic phenomenon resulting from these combinations of monomers is detectable 3D changes observed in *p*(DL-HMPMA/*n*BA) and *p*(DMAEMA/*n*BA) films. While *p*(DL-HMPMA/*n*BA) shrink in the  $x$ – $y$  plane and expand in the thickness (–) directions, *p*(DMAEMA/*n*BA) films shrink in all the directions at elevated temperatures. Such reversible dimensional differences in *p*(DL-HMPMA/*n*BA) and *p*(DMAEMA/*n*BA) copolymer films are attributed to preferential orientational



**Figure 1.5** Examples of molecular structures of thermoplastic (A) and thermosetting (B) stimuli-responsive monomers.

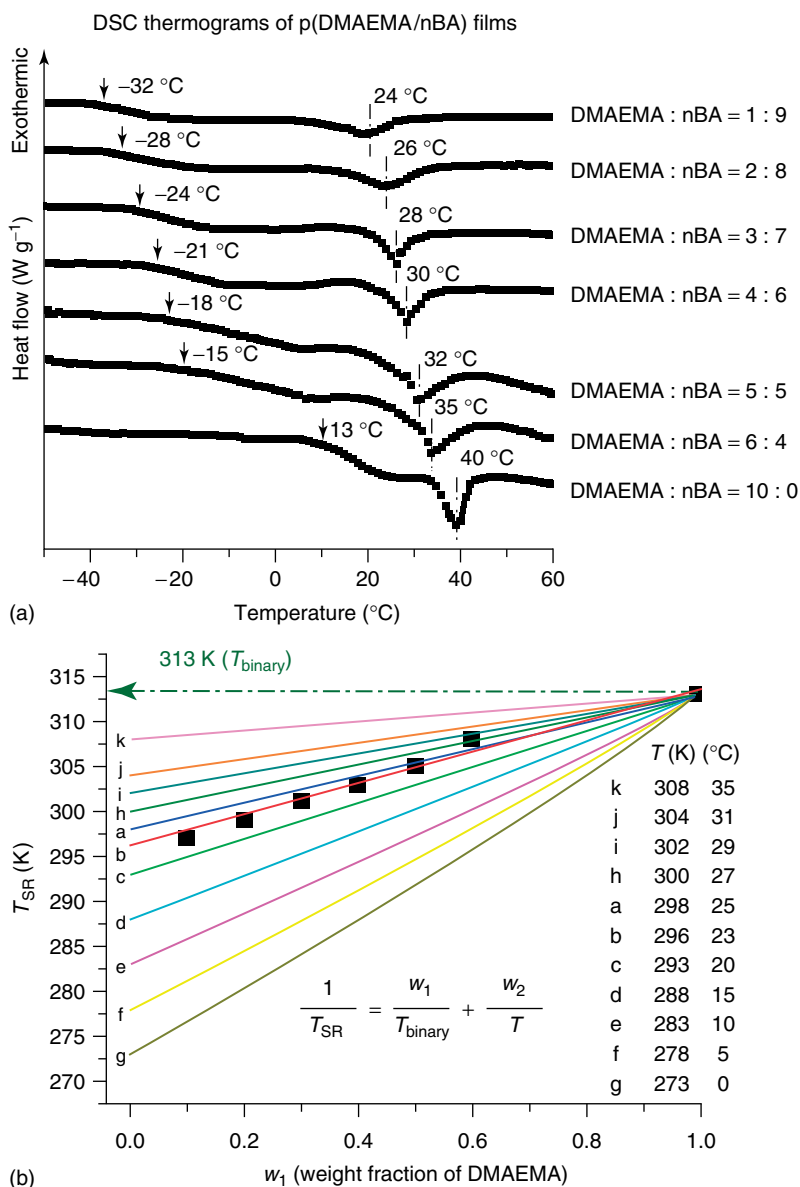




**Figure 1.6** Computer simulation results of:  $p(\text{DL-HMPMA}/\text{nBA})$  (A) and  $p(\text{DMAEMA}/\text{nBA})$  (B).

changes of the side groups, as amide side groups in DL-HMPMA form preferential inter-/intramolecular interactions with itself or butyl ester pendant groups of nBA units, as compared to the ester side groups in DMAEMA. As a result, orientations of the side groups in  $p(\text{DL-HMPMA}/\text{nBA})$  changes from preferentially parallel to perpendicular, which is responsible for the expansion in the  $z$  direction. Computer modeling results, shown in Figure 1.6, also confirmed the dimensional changes resulting from the buckling of copolymer backbone and a collapse of the DL-HMPMA or DMAEMA components leading to macroscopic volume changes of the entire network.

Designing polymer systems with different surface energy components afford another method to create responsive solid networks. Generally, in multicomponent networks, the component with a low surface energy is located at the top surface, while the component with the high surface energy is hidden beneath. Following this concept, poly(2-ethylhexyl acrylate/acrylic acid) ( $p(2\text{EHA}/\text{AAc})$ ) [115] elastomers were developed, in which aliphatic portions with the low surface energy components are located at the top layer. Upon pressure load, chain rearrangements occur, which allow the high surface energy chains (acid portion) to migrate to the surface; this process is facilitated by hydrogen-bonding that leads to enhanced adhesion. Copolymers with long perfluoroalkyl and alkyl side chains are another example [119], which at low temperatures, phase separate perfluoroalkyl chains into liquid crystalline domains at the top layer, thus resulting in a low surface energy. At elevated temperatures, the liquid crystal domains become disordered and the perfluoroalkyl side chains mix with the aliphatic chains, which results in the increase in surface energy and the sharp decrease in tacticity.

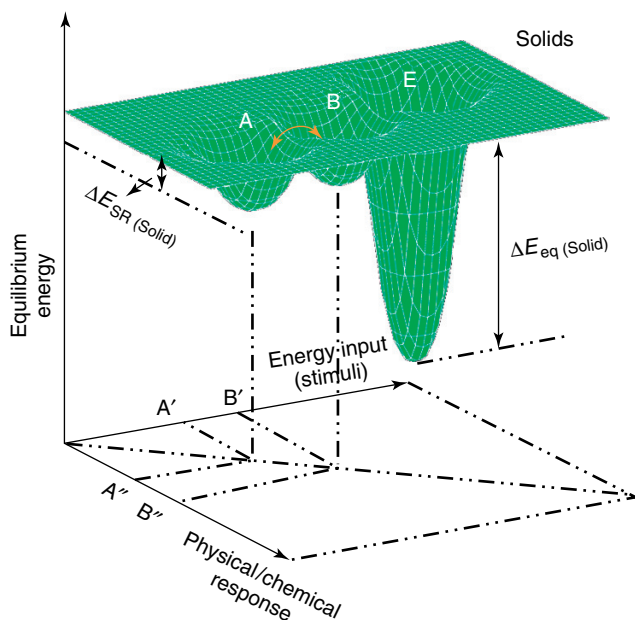


**Figure 1.7** DSC thermograms of p(DMAEMA/nBA) copolymer films recorded for different DMAEMA/nBA weight ratios (A); Experimental  $T_{\text{SR}}$  values obtained from DSC measurements which allowed  $T_{\text{SR}}$  predictions for different  $T$  values plotted as a function of  $w_1$  :  $1/T_{\text{SR}} = w_1/T_{\text{binary}} + w_2/T$ .

The first example of stimuli-responsive stratification of polymeric films, which would alter properties across the film thickness, was demonstrated on polyurethanes [149]. Other studies on colloidal dispersions also demonstrated that it is possible to control surface and interfaces responsiveness [150–154]. Heterogeneous stimuli-responsive polymer networks can also be generated by stratification across the film thickness [155]. Poly(methyl methacrylate/*n*-butyl acrylate/heptadeca-fluorodecylmethacrylate) (*p*(MMA/*n*BA/FMA) [154] colloidal dispersions is one example where the presence of bioactive dispersing agents PLs facilitates fluoromonomer copolymerization. These dispersions upon coalescence result in phase separation, where the FMA phase stratifies near the surface, thus resulting in ultralow static and kinetic coefficients of frictions, and MMA and *n*BA phases reside near the substrate. The degree of FMA stratification depends on the external temperature stimuli, which provides an opportunity for adjusting the film surface properties. Recent studies have shown that it is possible to entirely synthesize fluoro-surfactant free colloidal dispersions [156]. A similar process was utilized in the synthesis of colloidal particles that exhibit acorn shapes [157]. On the other hand, stimuli-responsive SS cross-linked redox responsive star polymer gels can be synthesized using ATRP in which SS cross-linked stars cleave under reducing conditions to form SH-functionalized soluble stars [158].

Stratification of the dispersing agents, such as SDOSS and PL during the film-formation processes, represents another stimuli-responsive heterogeneous network, where migration of individual species to the film–air (F–A) or film–substrate (F–S) interfaces is highly dependent on the external temperature, pH, and ionic strength. Furthermore, stratification of PLs leads to the formation of well-organized surface crystalline entities referred to as *surface-localized ionic clusters* (SLICs). Spectroscopic experiments combined with *ab initio* calculations [159] demonstrated that PL molecules recognize the MMA and *n*BA monomer boundaries along the copolymer backbone.

As mentioned above, the presence of free volume facilitates spatial conditions for polymer chain rearrangements. This is reflected in the  $T_g$  changes being controlled by the copolymer compositional changes. If stimuli-responsiveness results in conformational changes, these rearrangements should exhibit an endothermic character. This hypothesis has led to the observation of compositional dependence of new endothermic stimuli-responsive transition ( $T_{SR}$ ) [160] for stimuli-responsive polymeric solids [161]. As shown in Figure 1.7a, in addition to the lower  $T_g$  facilitating chain rearrangements, a series of DSC thermograms of *p*(DMAEMA/*n*BA) copolymer films recorded for different DMAEMA/*n*BA copolymer compositions show  $T_{SR}$ . As seen, similar to copolymer composition-dependent  $T_g$  transitions, the  $T_{SR}$  transitions also shift to higher temperatures as the amount of the stimuli-responsive DMAEMA component increases in the DMAEMA/*n*BA copolymer. On the basis of these experimental data, the following empirical relationship was established:  $1/T_{SR} = w_1/T_{binary} + w_2/T_{form}$  or  $1/T_{SR} = w_1(1/T_{binary} - 1/T) + 1/T$ , where  $T_{SR}$  is the temperature of the stimuli-responsive transition,  $T_{binary}$  is the temperature of the stimuli-responsive homopolymer in a binary polymer–water equilibrium,  $w_1$  and  $w_2$  ( $w_2 = 1 - w_1$ ) are weight fractions of each component in the copolymer,



**Figure 1.8** The relationship between equilibrium energy, stimuli energy input, and physical/chemical response in polymer solids.

and  $T$  is the film-formation temperature. As shown in Figure 1.7b, similar to the Fox equation [162] that allows predictions of the  $T_g$  for random copolymers, this relationship allows  $T_{SR}$  transition predictions in stimuli-responsive compositional solid films formed at different temperatures. While the  $T_g$  represents endothermic transitions due to segmental motion of the entire polymeric networks, for the  $T_{SR}$  to occur, free volume must be such that the local rearrangements of stimuli-responsive components are possible.

Because of spatial limitations resulting from a limited access of free volume, creating stimuli-responsive solid polymeric networks using colloidal processes represents a great challenge. For a given stimuli-responsive polymeric system, Figure 1.8 illustrates the relationship between the equilibrium energy ( $z$  axis), stimuli energy input ( $x$  axis), and chemical/physical response ( $y$  axis). Similar to polymeric gels, the minimum energy at equilibrium ( $E$ ) provides stability of the network, whereas metastable energy states  $A$  and  $B$  facilitate stimuli responsiveness. In polymeric solids, the  $\Delta E_{eq(solid)}$  at equilibrium is significantly greater compared to solutions, surfaces, and gels, thus resulting in a greater network integrity due to tightly entangled or cross-linked polymeric chains. As a consequence, the  $T_g$  is also relatively higher compared to other states. However, in solid polymeric networks, the entropic term ( $\Delta S$ ) does not contribute significantly to stimuli responsiveness because spatial mobility in these tighter networks is restricted. Polymer

conformational changes as well as packing of responsive segments are significant contributors to the stimuli-responsive properties, and thermoplastic [163–165] and thermosetting [166–169] stimuli-responsive components of solids networks illustrated in Figure 1.5 represent only a fraction of what will become available in the future. There is an endless list of future applications and technologies that will take an advantage of these materials [170, 171].

## 1.4

### Summary

Although the field of stimuli-responsive polymers is relatively new, and there are many recent advances being made, in particular in their synthesis, there are numerous opportunities available in creating new materials with stimuli-responsive attributes or in engineering unique nano-objects and devices in highly complex environments. Precise synthetic steps leading to an exact placement of a given monomer in a polymer backbone or as side groups have always been a challenge, and recent advances in ATRP, RAFT, and NMRP have created unprecedented opportunities for the creation of new stimuli-responsive polymers with well-defined molecular architectures. Furthermore, developments of colloidal synthesis resulting in different shape particles and copolymer morphologies provided an opportunity for new technological advances where stimuli-responsive attributes are maintained not only in solutions but also in a solid phase.

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