Handbook of Stimuli-Responsive Materials

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Preface

Nature is a source of inspiration for the design and development of new materials that are capable of responding to stimuli in a controllable and predictable fashion. These attributes are often manifested by nature’s ability to reverse and to regenerate, commonly termed as stimuli-responsiveness. Although the concept of stimuli-responsiveness has been known for many years, the last decade, particularly, has witnessed a tremendous progress in this field. In 2002, the first International Symposium on Stimuli-Responsive Materials in Hattiesburg, USA, brought the international scientific community together and provided the first forum that has now matured into a major international conference that gathers scientists from around the world. Other conferences and meetings on similar topics followed, signifying strong scientific and technological interests in this continuously expanding field.

Inherent similarities as well as apparent differences between polymeric materials and entities produced by nature stimulated interest in stimuli-responsive polymeric materials. Although the similarities are obvious, with the common denominator being materials-functionality, what sets synthetic materials apart is their inability to respond to stimuli. Thus, significant interests and efforts are continuously directed toward synthesis of new materials and modification of the existing ones to achieve stimuli-responsive attributes. There are, however, significant challenges in mimicking of biological systems where structural and compositional gradients at various length scales are necessary for orchestrated and orderly responsive behaviors.

To tackle these challenges, numerous studies dealt with polymeric solutions, gels, surfaces and interfaces, but to lesser extent, with polymeric solids. These states of matter impose a different degree of restrictions on the mobility of polymeric segments or chains, thus making dimensional responsiveness more easily attainable for the systems with a higher solvent content and minimal energy inputs. Significantly greater challenges exist when designing chemically or physically cross-linked gels and solid polymeric networks that require maintaining their mechanical integrity. Restricted mobility within the network results from significant spatial limitations, thus imposing limits on obtaining stimuli-responsiveness. The challenge in designing these stimuli-responsive polymeric systems is to create
networks capable of inducing minute molecular, yet orchestrated changes that lead to significant physicochemical responses upon external or internal stimuli.

Setting up the stage with an overview of synthetic and physicochemical aspects of advanced stimuli-responsive materials, the first few chapters of this volume provide a comprehensive coverage of biologically responsive systems, ranging from glucose, enzyme, and antigen responses to electro-, magneto-ultrasound-, and photoresponsive polymers, followed by modeling of dynamic processes in self-oscillating gels. Subsequent chapters focus on recent advances in self-healing materials in the context of their dimensions as well as assemblies of sensing and responsiveness of chromogenic dyes in polymer matrices. Switchable surfaces and their design using a variety of chemistries and morphologies, where pH, temperature, and electromagnetic radiation are the primary stimuli are discussed in the context of mechano-mutable attributers, followed by strategies in designing and fabrication of layer-by-layer self-assembly responsive films. The final chapters focus on photorefractive and photochromic polymers in the context of their chemical design and physicochemical attributes leading to photoconductivity, electro-optical, and photochromic responses, followed by electrochemical approaches giving raise to electrografted and electrodeposited coatings.

This volume presents selected recent developments in stimuli-responsive materials and is not meant to be inclusive. As dynamics of stimuli-responsiveness, this field is also dynamically evolving and future volumes will disseminate other aspects as they are discovered. This provides an opportunity to identify the challenges and needs for future research. Although there has been significant progress in the synthesis of precisely controllable polymerization methods leading to well-defined macromolecular blocks with stimuli-responsive characteristics, understanding the physical–chemical aspects of these systems remains a challenge. The area of particular interest is the synthetic generation of larger scale objects with diversified shapes and compositional gradients that are capable of responses. In this context, control of responsive ranges, the effect of solvent–solute interactions, as well as mechano-rheological behavior as a function of stimuli need further understanding.

These relationships are particularly significant in micro- and nanofluidics as well as in other aspects of polymer rheology. Although recent advances in the development of colloidal dispersions at sub-nano-diameter levels are promising, colloidal nanoparticles with versatile morphologies, shapes, and bioactive attributes are of particular interest.

Polymeric interfaces, although extensively studied from the perspective of structure–property relationships, represent an unprecedented opportunity for the development of new multicomponent composite systems with stimuli-responsive characteristics in spatially confined environments. The main challenges are the control and measurement of surface and interfacial density and control of the chain length of anchoring nano-objects with variable length scale responsiveness. Development of materials with new self-healing mechanisms and precise selectivity and self-repairing characteristics are of great interest. Even more challenging will be networks that exhibit photochromic responsiveness. Stimuli-responsive
nanosurfaces will be particularly useful in the development of devices that resemble biologically active cilia with 3D actuation.

Enhanced mechanical integrity is essential to improve typically fragile polymeric gels and the balance between mechanical stability and rapid response times, reversibility, and processing conditions will be necessary for many new applications, in particular for biomedical systems. Further understanding of inclusive changes in polymer networks produced from natural building blocks, such as saccharides and aminoacids, nucleotides, and lipids will generate new avenues for regenerative medicine, where cell differentiation, membrane formation, neural network assemblies or other higher order hierarchical biocomponents may be produced.

Since dimensional changes in solid networks impose spatial and energetic limitations, design and formulation of heterogeneous structural features capable of charge transfer, ionization, or photoinduced conformational changes will be necessary. This can be achieved by combining in an orchestrated fashion low $T_g$ and multistimuli-responsive monomers into one copolymer backbone with controllable architecture. Molecular components that exhibit displacements responding to sunlight will be possible if we can control separation of charges which quickly recombine thousands or millions times faster than the molecular motion. This may possibly be accomplished by designing molecular architectures capable of separating charges so that the “frozen” energy is used for going back and forth from one equilibrium to another, while retaining mechanical network integrity. Rotaxanes, spyrpyrans, diarylethenes, fulgides, or azo-compounds represent selected examples of molecular entities that are capable of providing light-driven molecular motions. These processes should be reversible and self reassembling, with an infinitely high “fatigue factor,” that is the ability of infinitely long stimuli-responsiveness without physico-chemical changes. There are other possibilities as well – the challenge will be to control kinetics to achieve stimuli-responsiveness, and, to overcome the barriers of biocompatibility, biodegradability, and nontoxicity. Reversibility and speed of stimuli-responsiveness are essential in each of the states, especially for solid networks, and the design of suitable chemical structures to control metastable equilibrium energy states will formulate conditions for the design of orchestrated heterogeneous networks.

Synthetic materials capable of responses to external or internal stimuli represent one of the most exciting and emerging areas of scientific interest and have many unexplored commercial applications. While there are many exciting challenges facing this continually evolving field and there are a number of opportunities in design, synthesis, and engineering of stimuli-responsive materials, nature will continue to serve as a supplier of endless inspiration. We hope that this volume will provide the readers with comprehensive overviews of selected areas ranging from synthetic aspects of to theoretical and physical insights into this rapidly growing field and, at the same time, open up a dialogue for new ideas and explorations.

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1 Synthetic and Physicochemical Aspects of Advanced Stimuli-Responsive Polymers

Dirk Kuckling and Marek W. Urban

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 polynobornenes 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.

\[ P_n \xrightarrow{\text{ONR}_1R_2} P_n^+ + \text{ONR}_1R_2 \]

\[ P_n \xrightarrow{X + M_t^nX_n/L} P_n^+ + M_t^nX_n/L \]

\[ Z\text{-S}\text{-}P_n^+ + P_m^- \xrightarrow{k_{ex}} Z\text{-S}\text{-}P_m^- + P_n^+ \]

\[ Z\text{-S}\text{-}P_n^+ \xrightarrow{k_a} Z\text{-S}\text{-}P_n^- \]

\[ Z\text{-S}\text{-}P_m^- \xrightarrow{k_a} Z\text{-S}\text{-}P_m^+ \]

\[ P_n \xrightarrow{\text{monomer}} P_n^+ \]

\[ P_n^+ \text{NMRP} \]

\[ P_n^+ \text{ATRP} \]

\[ P_n^+ \text{RAFT} \]

Figure 1.1 General mechanisms for controlled radical polymerization (CRP).
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-bisisobutyronitrile (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](image-url)
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 α-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 acrylnitrile derivatives. Currently, various efforts have been made to develop environmentally friendly ATRP processes [45].

![Scheme 1.2](image-url)  
**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 (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 °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 (Me₆TREN) and Cu(I)chloride (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
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 β-cyclodextrin (β-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-β-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)-β-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
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

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

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**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 α,ω 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-carboxodithioic acid 4-vinylbenzyl ester with NIPAAm [78]. NIPAAm star polymers were prepared using the four-armed RAFT agent pentaerythritol-tetraakis(3-(S-benzyltrithiocarbonyl)-propionate) [79].

Acrylamides such as NIPAAm and N-ethylmethacrylamide (EMA) or acrylamides containing proline and hydroxyproline moiety, N-acryloyl-1-proline (A-Pro-OH) and N-acryloyl-4-trans-1-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-PDMAAmp–PNIPAAmq, with varying DPn,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
1.2 Controlled Free Radical Polymerization of Stimuli-Responsive Polymers

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 polymer-
ization. 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 intermolecu-
lar 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-\textit{block}-poly(sodium-4-stryrenesulfonate) [103], P2VP-\textit{block}-PAAc [104], and P2VP-\textit{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-\textit{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-\textit{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 HAuCl₄ in the presence of thermosensitive PNIPAAm. Although thiol end-capped PNIPAM (poly(N-isopropylacrylamide) is known as a \textit{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 \textit{in situ} via a facile approach. Heating the hybrid unimolecular micellar solutions leads to