Thermo- and photo-responsive polymeric systems

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Since the first reported thermal phase transition of poly(*N*-isopropylacrylamide) by Heskin in 1968, this unique polymer has continued to gain popularity. Because of their potential applications in the field of biomedical science, various responsive polymeric systems, such as those induced by pH, salt, co-solvent, thermal, light, electric and magnetic field, have been synthesized and studied. This review reports on recent developments (over the last 10 years) of thermo- and photo-responsive homopolymers, copolymers, microgels, hydrogels and polymer brushes at interfaces, where the synthesis, physicochemical properties, and potential applications are highlighted. Although homopolymers and microgels undergo phase transitions upon the application of external stimuli, block copolymers, however, self-assemble into different nanostructures. Such reversible phase transitions and self-assembly behaviors have generated many robust structures that can be applied in coating industries, personal/home care, petroleum, drug/protein/DNA delivery and separation processes.

1. Introduction

Stimuli-responsive polymeric systems are polymers, whose solubility, volume, configuration and conformation can be reversibly manipulated by external stimuli, such as those involving chemical or physical signals.[1,2] The chemical signals, such as pH, metabolites, and ionic species alter the molecular interactions with polymeric chains and solutes. On the other hand, physical signals, such as temperature, light, shear, pressure, and electrical potential, alter the energies of chain dynamics and molecular interactions. These external stimuli modify the ionic interaction, hydrogen bonding, or hydrophobic interaction of the polymeric system giving rise to a reversible microphase separation or self-organization. Stimuli-responsive polymeric systems provide the possibility for fabricating tailorable "smart" functional materials, that find applications in controlled drug delivery, bio-separation, protein purification, personal care, industrial coatings, oil exploration, biological and membrane science, viscosity modifiers, colloid stabilization, surface modification and water remediation.[3–5] Due to their scientific and industrial importance, increasing efforts have been devoted to the investigation of various types of stimuli-responsive polymeric systems. Two recent monographs by McCormick and Urban provided a comprehensive overview on the behavior of stimuli-responsive polymers in solution and on surfaces,[6] where the most

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recent developments on stimuli-responsive polymeric systems were discussed, such as novel synthetic techniques, interesting physicochemical properties, commercial or potential applications in biological and chemical sciences.

One of the most common physical stimuli that controls the conformation and self-assembly of macromolecules is temperature. In aqueous solution, hydrophilic polymeric segments hydrate and exist in an extended conformation, while hydrophobic polymers are in their compact or precipitated form. Block copolymers containing both hydrophobic and hydrophilic segments (known as amphiphiles) self-assemble in solution to form aggregates of varying shapes and sizes, depending on their structures and compositions. For example, moderate to high molecular weight poly(*N*-isopropylacrylamide) (PNIPAM) is soluble in water at a temperature below the lower critical solution temperature (LCST) of 32 °C, and becomes insoluble beyond the LCST.[7] The existence of LCST is attributed to the disruption of water cages surrounding the NIPAM moieties, that induces the formation of inter- and intra- molecular hydrogen bonds between PNIPAM chains, which interferes with the free rotation of the molecules. The possibility of tuning the LCST by introducing suitable co-monomers with the desired functional characteristics will enhance and broaden the end-use applications of thermal-responsive polymeric systems. Since the pH-responsive polymeric system has been reviewed recently,[8] this review covers two important physical stimuli, thermo and photo, and their impact on the physical properties of homopolymers, block copolymers, microgels, hydrogels, and polymeric brushes. Some of the commonly used thermo-responsive polymers are summaraized in Scheme 1.

2. Recent development on the synthesis of stimuli-responsive polymers

Stimuli-responsive polymers can be synthesized through conventional radical polymerization, ionic or ring opening polymerization, depending on their chemical structures and final applications. Emulsion polymerization is one of the most popular synthetic routes to prepare vinyl based stimuli-responsive polymeric systems, where well-controlled particle size and size distribution can be readily attained. However, well-defined stimuli-responsive polymers with different structures and molecular weights can be produced by living polymerization techniques, such as anionic, ring opening, or "living"/controlled radical polymerizations. In this section, recent developments in emulsion and "living"/controlled radical polymerizations for producing various types of stimuli-responsive systems are described.

2.1 Emulsion polymerization

In contrast to bulk, solution and suspension polymerization, emulsion polymerization refers to a unique process that employs radical chain polymerization methodology to produce latexes with narrow particle size distribution. Such polymerization occurs within the monomer-swollen surfactant micelles, and the resulting molecular weight and size of the latex are dependent on the reaction parameters. During the course of polymerization, the molecular weight of the polymer can be increased without reducing the polymerization rate, thus both high molecular weight and high reaction rate can be attained simultaneously. The final product of an emulsion polymerization, referred to as latex, can in many instances be used directly without further purification.

Practically, the presence of surfactant is a major shortcoming of the emulsion polymerization process, as it may need to be removed at the end of polymerization. However, the removal of surfactant, either by dialysis or by desorption, might lead to coagulation or flocculation of the destabilized latexes. To solve this problem, surfactant-free emulsion polymerization (SFEP) has been adopted, where persulfate initiator was commonly used to generate a negatively charged surface. A characteristic of SFEP is that the particle number is generally smaller by up to two orders of magnitude compared to a typical emulsion polymerization, but the homogeneity of latexes is compromised. Other approaches include producing latexes with chemically bound surface-active groups using a reactive surfactant as the starting material or by introducing small amounts of water-soluble co-monomers. In addition, for water-insoluble or highly hydrophobic monomers, special techniques have to be adopted to produce stable emulsion systems, such as inverse emulsion polymerization and mini-emulsion polymerization.[9]

Typically, most stimuli-responsive polymers and microgels are synthesized by batch emulsion polymerization using water-soluble initiator, such as potassium persulfate (KPS) or ammonium persulfate (APS). PNIPAM latexes and microgels have been synthesized by emulsion polymerization, where linear high molecular weight PNIPAM chains with a viscosity averaged molecular weight of 2×10^6 have been produced. Near its LCST, PNIPAM chains undergo coil to globule transition to yield an insoluble compact latex particle. In the presence of small amounts of polymerizable crosslinker such as *N*,*N*′-methylenebisacrylamide (BIS), PNIPAM microgels of different sizes could be obtained. The swelling/deswelling characteristics could be controlled by varying the crosslinker content. In addition, many dual stimuli-responsive copolymers comprising of NIPAM and a second responsive monomer have been prepared using

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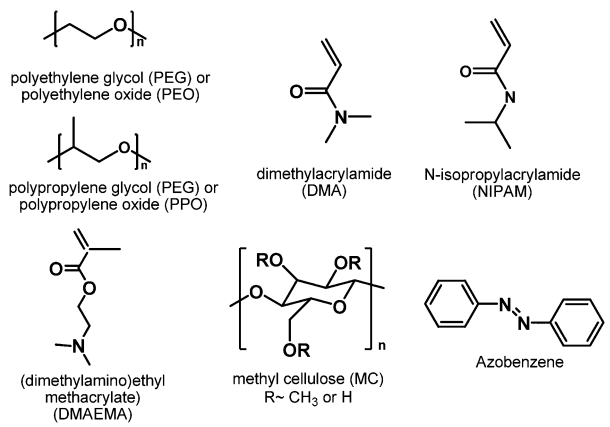
batch emulsion polymerization.[10] Based on the competitive reactivity ratio r_1 and r_2, the blockiness of the copolymer can be tailored, where r_1 and r_2 are defined as the ratios of the reaction constant of monomer 1 and monomer 1 (k_{11}) to that of monomer 1 and monomer 2 (k_{12}), *i.e.* $r_1 = k_{11}/k_{12}$.

To date, functional nanoscale particles with well-defined structures have gained increasing attention particularly in scientific and industrial communities. Seeded semi-batch emulsion polymerization under monomer starved feeding condition could be used to prepare well-defined nanoparticles of different structures.[11,12] The core-shell particles containing a poly(methyl methacrylate) (PMMA) core and a poly(methacrylic acid-*co*-ethyl acrylate) P(MAA-*co*-EA) shell have been successfully synthesized.[13a] The PMMA core or seed was first synthesized through conventional emulsion polymerization, and the second pre-emulsified monomers and small amounts of initiator were introduced slowly under monomer-starved feeding condition to grow the stimuli-responsive shell layer. Other systems, such as the PMAA core with a poly(*N*,*N*-diethylaminoethyl methacrylate) (PDEAEMA) shell, have recently been reported.[13b] In contrast to PMAA or polyacrylic acid (PAA) systems, such latex is swellable at low pH due to the protonization of amino groups. The core-shell particles containing a P(NIPAM-*co*-St) core and a PNIPAM shell have been synthesized using SFEP technique, where St is styrene. The feed ratio, stirring speed, and initiator concentration altered the thermo-responsive behavior, size and polydispersity of the core-shell particles.[14] In addition, seeded emulsion polymerization has also been used to prepare core-shell hybrid materials, and hollow nanocages could be produced by etching the metallic core after crosslinking the water-swellable shell layer.

2.2 "Living"/controlled radical polymerization

Free radical polymerization can be easily applied to prepare stimuli-responsive polymers. However, well-defined stimuli-responsive homopolymers and block copolymers with a low polydispersity index (PDI) can only be synthesized by a living polymerization process. Ring opening polymerization has been used to synthesize thermo-responsive polyethylene oxide (PEO), polypropylene oxide (PPO), and their tri-block copolymers, commercially known as Pluronic and Pluronic-R block copolymers.[15,16] Eisenberg and co-workers synthesized a series of asymmetric PAA containing block copolymers using anionic polymerization together with group protection chemistry and their aggregation behaviors in different selective solvents were elucidated. Block copolymers comprising of polystyrene-*b*-poly(*tert*-butyl acrylate) (PS-*b*-P*t*BA) were synthesized by sequential anionic polymerization of styrene followed by *tert*-butyl acrylate (*t*BA) using butyllithium as initiator in tetrahydrofuran (THF) under nitrogen environment at −78 °C. The P*t*BA blocks in the copolymers were then hydrolyzed to their acidic form by *p*-toluenesulfonic acid in toluene.[17] In addition, well-defined block copolymers of poly(*N*,*N*-dimethylaminoethyl methacrylate) (PDMAEMA) and PDEAEMA were synthesized by Armes and co-workers using the group transfer polymerization (GTP) technique.[18] Although these materials have been successfully prepared using living polymerization techniques, they often require stringent reaction conditions and are restricted to a limited number of relatively nonfunctional monomers. Therefore, the development of novel techniques to synthesize well-defined stimuli-responsive copolymers is of importance. In the 1990s, "living"/controlled radical polymerization was developed and used to prepare well-defined homo- or block copolymers under much simpler and less stringent reaction conditions. "Living"/Controlled radical polymerizations were achieved by minimizing normal bimolecular termination, thereby extending the lifetime of "living" polymers to much longer times, in the region of minutes or longer, through the introduction of dormant states in the propagating species. The "living" radical polymerization methods reported recently include stable free-radical polymerization (SFRP), atom transfer radical polymerization (ATRP), reversible addition fragmentation chain-transfer polymerization (RAFT), and others.[9] ATRP and NMP (nitroxide mediated polymerization, which is one type of SFRP) control chain growth by a reversible termination process step, while RAFT polymerization controls chain growth through reversible chain-transfer. The mechanisms of ATRP and RAFT are described in Scheme 2. Recently, "living" radical polymerizations have expanded rapidly, where a larger class of well-defined macromolecules were synthesized, resulting in the rapid proliferation of research in stimuli-responsive polymeric systems.[19]

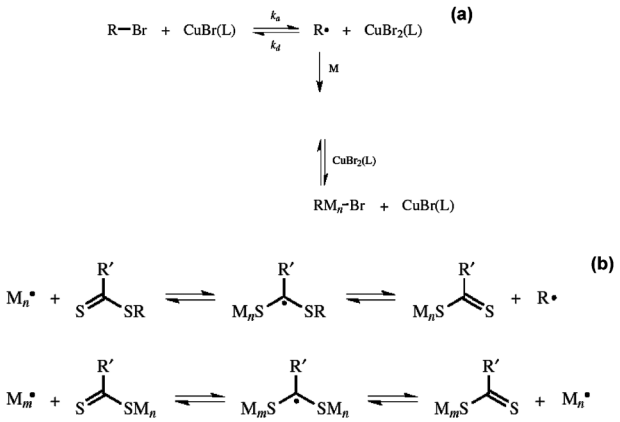
Because of the slow deactivation in conjunction with fast activation and loss of bromine end-groups through a cyclization reaction involving nucleophilic Br displacement by penultimate amide nitrogen, PNIPAM could not be successfully synthesized by NMP and ATRP.[20] Similarly, the controlled polymerization of *N*,*N*-dimethylacrylamide (DMA) by ATRP was difficult, due plausibly to three reasons: (1) deactivation of ATRP catalyst bound to monomeric or polymeric amide groups, (2) substitution of halide from propagating chain ends by amide groups, and (3) low values of ATRP equilibrium constant. However, it was only very recently that such challenges in the synthesis of DMA and NIPAM *via* ATRP were addressed by utilizing stronger coordinating ligands and more stable initiators, such as alkyl chlorides. Recently, well-defined PNIPAM has been successfully synthesized using different chloro-initiators in isopropanol associated with Me_6TREN catalyst.[21] In a DMF and water mixture at room temperature, PNIPAM was synthesized through ATRP using ethyl 2-chloropropionate (ECP) as the initiator and CuCl/*tris*(2-dimethylaminoethyl)-amine (Me_6TREN) as the catalyst.[22] The



Scheme 1 Chemical structures of monomers and polymers described in this review.

reaction obeyed first order reaction kinetics and up to 92% conversion resulted in a polymer with a molecular weight of more than 20 K and M_w/M_n of 1.19. The pyrenyl PNIPAM (Py-PNIPAM) was also synthesized using CuCl/Me_6TREN in a DMF/water mixture.[23] The end –Cl group of PNIPAM remained stable and active as evident from the formation of block copolymers with DMA. The well-defined biotinylated PNIPAM was synthesized through the synthetic scheme shown in Scheme 3 using the CuCl/$CuCl_2$/Me_6TREN catalyst in DMSO at room temperature.[24] Similarly, photo-sensitive azobenzene containing methacrylate could be synthesized using the CuCl/PMDETA catalyst system, however the degree of polymerization was low.[25]

In comparison, RAFT has been successfully used to synthesize various stimuli-responsive polymeric systems, especially for preparing block copolymers of NIPAM and *N*-hydroxysuccinimide methacrylate (NHSMA).[26] This approach was first introduced in 1998 by Rizzardo and co-workers, and is arguably the most versatile "living" radical polymerization technique in terms of monomer selection and reaction conditions.[27] The polymerization can be performed in a variety of solvents, including water, by simply charging an appropriate quantity of a suitable RAFT chain-transfer agent (CTA) to a standard free radical polymerization reaction mixture. The polymerization can then be conducted using a conventional initiator such as a peroxide or azobisisobutyronitrile (AIBN). The critical factor of a RAFT process is in the choice of RAFT chain-transfer agent.[28] RAFT chain-transfer agents, such as cumyldithiobenzoate, reversibly transfers a labile end-group (a dithioester end-group) to a propagating chain. The end-group originating from the chain-transfer agent is reversibly exchanged between different propagating chains. The transfer reaction in RAFT is not a one-step transfer of labile end-groups, but it involves radical addition to a thiocarbonyl group of dithioester to form an intermediate radical that fragments to yield a new dithioester and radical. Details on the RAFT polymerization and CTA selection can be obtained from well-documented sources.[9,28] PNIPAM has been successfully polymerized *via* RAFT using either benzyl dithiobenzoate or benzyl and cumyl dithiocarbamate as chain-transfer agents.[29,30] Schilli *et al.* disclosed the benzyl and cumyl dithiocarbamate mediated polymerization of NIPAM in 1,4-dioxane at 60 °C.[29] Ganachaud *et al.* reported the successful solution polymerization of NIPAM initiated by AIBN in the presence of benzyl dithiobenzoate (in benzene) and cumyl dithiobenzoate (in 1,4-dioxane) at 60 °C.[30] 2-Dodecylsulfanylthio-carbonyl sulfanyl-2-methyl propionic acid, a trithiocarbonate RAFT CTA, in conjunction with a room-temperature azo initiator 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile), in DMF, at 25 °C, provided the right conditions for the homopolymerization of NIPAM that boar all the characteristics of a "living" polymerization.[31] Ray and co-workers demonstrated the ability to control the tacticity in RAFT polymerizations of NIPAM *via* the addition of a suitable Lewis acid, such as $Sc(OTf)_3$ or Y(OTf).[32] The telechelic hydrophobically modified PNIPAM (HM-PNIPAM) samples with *n*-octadecyl termini were obtained by RAFT polymerization of NIPAM in 1,4-dioxane in the presence of *S*-1-*n*-octadecyl-*S*′-(α,α′-dimethyl-α″-*N*-*n*-octadecylacetamide) trithiocarbonate as the chain-transfer agent.[33] The di- and tri-block copolymers of PEO and NIPAM



Scheme 2 Mechanisms describing the (a) ATRP; and (b) RAFT processes.

were synthesized through RAFT in THF using PEO capped with one or two dithiobenzoyl groups as a macromolecular chain-transfer agent (macro-CTA).[34] Similarly, PEO-based macro-CTA was also employed to polymerize DMA *via* the RAFT process.[35] Such macro-CTA was then used to mediate the statistical copolymerization of DMA and a reactive monomer *N*-acryloxysuccinimide (NAS), forming a di-block copolymer of PEO-*b*-(DMA-*s*-NAS). Subsequent chain extension with NIPAM produced a thermally responsive PEO-*b*-(DMA-*s*-NAS)-*b*-NIPAM tri-block copolymer. In addition, the water-soluble di-block copolymer was prepared from sodium 2-(acrylamido)-2-methylpropanesulfonate (NaAMPS) and NIPAM using 4-cyanopentanoic acid dithiobenzoate as CTA.[36] McCormick and co-workers reported on the synthesis of well-defined di-block copolymers of NIPAM and DMA in aqueous media at room temperature using the VA-44 initiator as shown in Scheme 4.[37]

3. Physicochemical properties and applications of stimuli-responsive polymers

The physical properties of stimuli-responsive polymer systems could be tailored by manipulating various stimuli-responsive parameters. By controlling external stimuli, chain conformation, configuration, and solubility can be manipulated. For block copolymers, they may self-assemble in solution to produce aggregates of different sizes and morphologies. Similarly, the swelling/deswelling of microgels and hydrogels alters their surface properties with respect to changes in the external stimuli. Such "intelligent" properties of soft matters are attractive for applications in life sciences and chemical industries. In the following sections, the effects of temperature and light on the physicochemical properties of responsive polymers are described and discussed.

3.1 Thermal-responsive polymeric systems

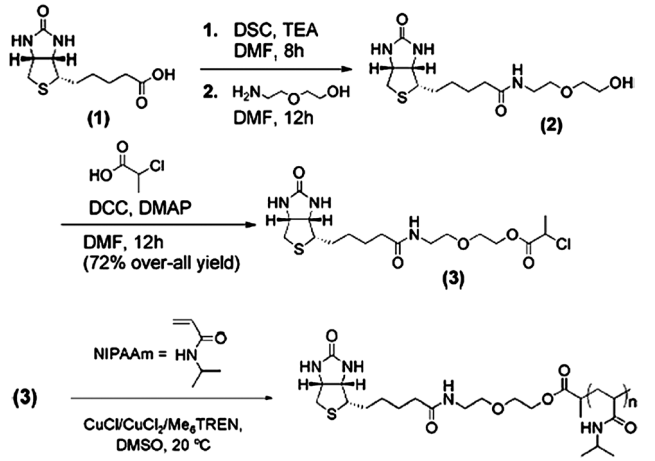
When polymers are dissolved in a solvent, they could be either soluble/swellable or precipitated on the basis of their solvent-polymer interactions, as described by the Flory–Huggins interaction parameter χ or the second virial coefficient A_2.[38] However, χ and A_2 are dependent on polymer characteristics, solvents, and

prevailing conditions. At Flory Θ temperature, $\chi \sim 1/2$ and $A_2 \sim 0$. For a good solvent, $\chi < 1/2$ and $A_2 > 0$, while for a poor solvent, $\chi > 1/2$ and $A_2 < 0$. In some uncharged polymers that form hydrogen bonds with water at room temperature, the solubility of these polymers in water decreases with increasing temperature. Beyond a critical temperature, known as the lower critical solution temperature (LCST), the polymers become insoluble. For polymeric gel system, the volume phase transition temperature (VPTT) is widely used to describe such transition instead of LCST since such polymers swell instead of dissolving in solution. Polyethylene glycol (PEG) or PEO is one such water-soluble polymer that possesses a LCST greater than 90 °C. (Note PEG and PEO are chemically synonymous, but historically PEG has been commonly used to refer to oligomers and polymers with a molecular mass below 20 000 g/mol, while PEO is used for polymers with a molecular mass greater than 20 000 g/mol.) They are synthesized through ring opening polymerization, and have found diverse applications in biological sciences, personal care products, and industrial additives.[39] The enhancement on the hydrophobicity of alkyl segments results in the reduction of LCST, for example, polypropylene glycol (PPG) possesses a much lower LCST (ranging from ~20 to 40 °C) than PEG, depending on its molecular weight.[40] Pluronic and Pluronic-R block copolymers of PEO and PPO are commercially available polymeric surfactants that exhibit temperature dependent phase characteristics. In addition, block copolymers of poly(butylene-oxide) (PBO) and PEO have also been reported.[41] The synthesis and self-assembly behavior of these block copolymers can be found in several reviews and book chapters.[15,16] There are, however, other categories of polymers (for example poly-betaines) that possess an upper critical solution temperature (UCST) in aqueous solution, where the polymers become water-soluble as the temperature is increased.[42] The salting-in and salting-out encountered by polyelectrolyte or polyampholyte systems in a salt solution will have an impact on the LCST and UCST.

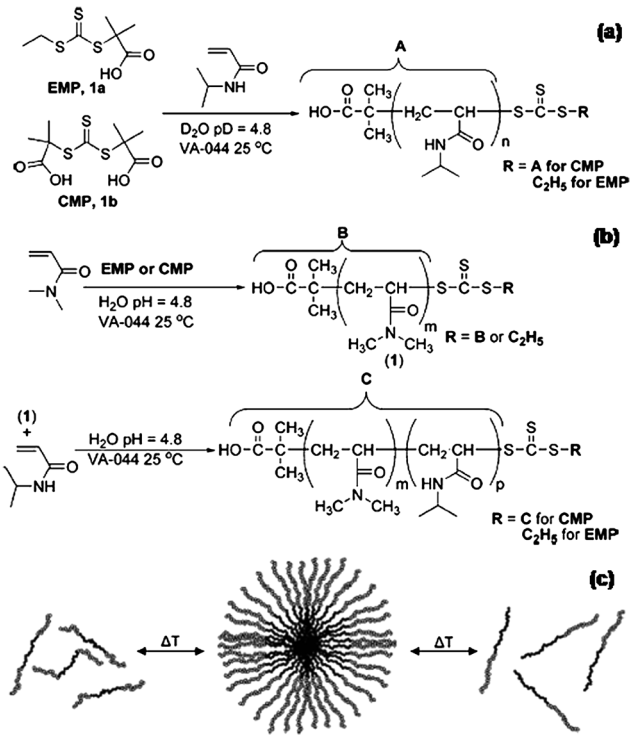
3.1.1 Thermo-responsive homopolymers and copolymers. PNIPAM is one of the most studied thermal-responsive polymers due to its sharp phase transition temperature and biocompatibility. Several review articles on PNIPAM have been published since 1990.[2] PNIPAM undergoes a liquid–solid phase transition near its LCST of around 32 °C, which is attributed to a shift in the distribution of hydrophobic and hydrogen-bond interactions. High molecular weight PNIPAMs undergo a stable single-chain coil-to-globule transition when the temperature is increased beyond its LCST.[43] Such phase separation could be exploited for the purification of amino acids, proteins, nucleic acids, and cells.[44] Recent studies have focused on the application of this thermal-responsive polymer in various disciplines, such as in targeted drug delivery,[45] nanotechnology,[46] and microfluidics.[47] Unlike other PNIPAM samples, it was reported that PNIPAMs produced from ATRP showed a stronger tendency to sediment above their LCST, and hence they could be useful systems for investigating aggregation and colloidal stability phenomena.[21]

The hydrophobic modification or copolymerization of PNIPAM with other monomers will have an impact on the LCST. The incorporation of a hydrophilic monomer, such as acrylic acid, sodium acrylate, acrylamide, *N*-methyl-*N*-vinylacetamide, *N*-vinylacetamide, and *N*-vinyl-*2*-pyrrolidinone, increases the thermal phase transition temperature,[48,49] while the reverse is true when hydrophobic monomers (*e.g.* di-*n*-propylacrylamide, di-*n*-octylacrylamide or di-dodecylacrylamide) were used.[50] Such an effect is more significant for a low molecular weight system. The LCST for the liquid–solid phase transition was found to be 21.7, 24.8, 26.5, and 29.3 °C for Py–PNIPAMs with M_n of 3000, 3400, 4200, and 5000, respectively.[23] It is evident that the LCST decreased significantly with decreasing M_n. The LCST of 21.7 °C for Py–PNIPAM with a M_n of 3000 Da could be effectively raised by introducing β-cyclodextrin (β-CD). The LCST was found to remain constant at 26 °C when the molar ratio of [β-CD]/[Py–PNIPAM] exceeded 2/1, suggesting the formation of β-CD and pyrene inclusion complexes, which disrupt the formation of PNIPAM precipitates, thereby raising the LCST. For hydrophobically modified PNIPAM, the cloud point temperatures decreased significantly with increasing polymer concentration. However, the temperature for the PNIPAM coil-to-globule transition (29 to 31 °C) was modified slightly by the solution concentration and polymer molecular weight due to the coexistence of the association of hydrophobic *n*-octadecyl terminal groups and the hydration of PNIPAM chains.[33] Cholesterol has been grafted to random copolymers of NIPAM and *N*-hydroxylmethylacrylamide, where irregular shaped micellar aggregates were formed in aqueous solution.[51] These random copolymers could be used for the delivery of hydrophobic drugs. The conjugates of PNIPAM and proteins have been proposed for applications in biotechnology.[52] In addition, the strong affinity between biotin and naturally occurring proteins, such as avidin and streptavidin was also exploited.[24,53]

Poly(*N*-isopropylacrylamide-*co*-vinylpyrrolidone) P(NIPAM-*co*-VP) of similar composition and chain length but different monomer distributions on the backbone were synthesized through free radical polymerization.[54] Due to the hydrophilic character of PVP, the coil to globule transition temperature was found to exceed 32 °C. The folding characteristics of NIPAM copolymers were affected by the synthesis temperature, where blocky sequences forming denser globules were obtained at higher reaction temperatures. The thermal-sensitive *N*-isopropylacrylamide (NIPAM)–*N*-propylacrylamide (NPAM)–vinyl pyrrolidone (VP) terpolymers (PNINAVP) were prepared by varying feed ratios using free radical copolymerization.[55] The sol–gel transition behaviors of different PNINAVP were examined. It was found that the transition temperature, time and rheological properties of PNINAVP solutions were strongly dependent on the copolymer composition and the presence of radiopaque agent. The sol–gel transition of copolymer solutions occurred reversibly within 1 min when subjected to temperature fluctuations. The incorporation of Iohexol (a radiopaque agent) increased the transition time and temperature of PNINAVP solutions. The formation of bulk hydrogel containing Iohexol and copolymer mixtures could contribute to the development of a new temperature-sensitive polymer-based embolic agent as evident from the *in-vitro* embolic model experiment. Three terpolymers of AA, NIPAM, and cinnamoyloxyethyl acrylate (CEA) were synthesized, and such terpolymers were responsive to temperature, UV, pH, and ionic strength.[56] The copolymers can be photo-crosslinked by irradiation with UV light at



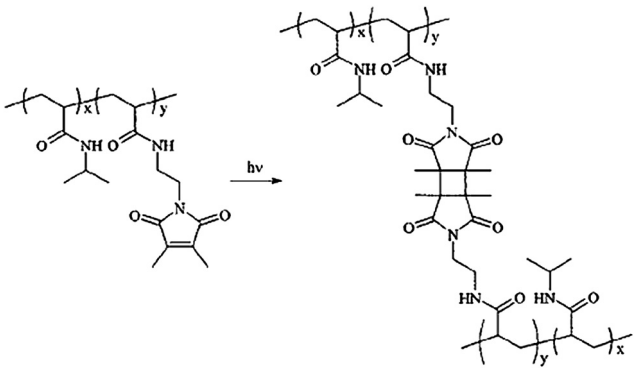
Scheme 3 Synthesis of biotinylated PNIPAM using ATRP. Reproduced from ref. 24 © Royal Society of Chemistry.



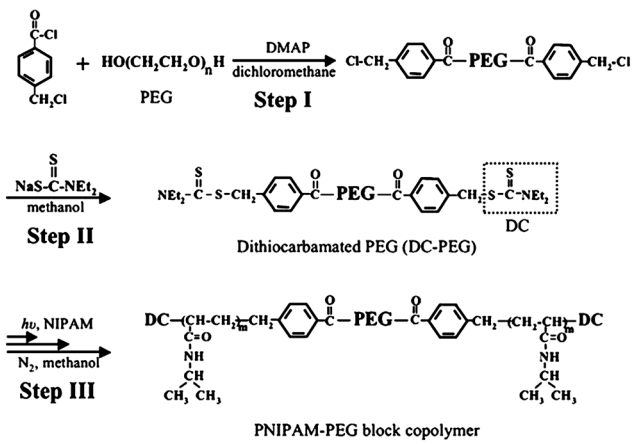
Scheme 4 (a) Aqueous room temperature RAFT polymerization of NIPAM. (b) Preparation of di- and tri-block copolymers of DMA and NIPAM *via* aqueous room temperature RAFT. (c) Temperature responsive reversible micellization of PDMA-*b*-PNIPAM. Reproduced from ref. 37 © American Chemical Society.

300 nm, and the hydrophobicity of the polymers can be increased by reducing pH or by irradiation (Scheme 5). Photo-crosslinkable co- and terpolymers comprising of NIPAM, 2-(dimethylmaleimido)-*N*-ethylacrylamide (DMIAM) as the chromophore, and DMA was prepared by free radical copolymerization.[57] The phase transition temperature decreased with increasing amounts of DMIAM, to 24.7 °C, where it then increased with increasing DMA content to 59.5 °C. These polymers could be efficiently converted to gel-like networks by UV irradiation in the presence of a photosensitizer, such as thioxanthone. Investigation on the swelling properties of its thick films indicated that the phase transition temperature was slightly influenced by photo-crosslinking reaction. However, by decreasing the film thickness, the phase transition temperature shifted towards higher temperatures due to the confinement effect of the substrate.

PNIPAM block copolymers could reversibly form micelles in response to changing solution temperature, but the micellar sizes and phase transition temperatures are dependent on the structure and composition of the copolymers.[37] The tri-block copolymers of NIPAM and other polyacrylamide derivatives have been synthesized by RAFT. Although these block copolymers still exhibited thermo-responsive behavior, their LCSTs were different from that of PNIPAM homopolymer.[58] In the PNaAMPS-*b*-PNIPAM system, the NIPAM blocks associated into micellar aggregates at temperatures greater than the LCST. The micellar aggregates assumed an elongated or spherical core-corona morphology induced by inter-micellar association of individual micelles.[36] In aqueous solution, PEO-*b*-P(DMA-*s*-NAS)-*b*-PNIPAM tri-block copolymer formed micelles when the solution temperature was raised beyond the LCST of PNIPAM.[35] Incorporation of NAS units into the tri-block copolymer allowed for the facile formation of uniform shell crosslinked micelles by reacting with di-functional primary amines in aqueous media. The block copolymers of PEG and PNIPAM with different structures were synthesized by iniferter-based photopolymerization of dithiocarbamylated PEGs (DC-PEG) under ultraviolet irradiation (Scheme 6).[59] The LCST of these polymers varied from 31 to 34 °C and decreased with increasing PNIPAM block length or with the formation of branched architecture. The tri-block copolymer of PPO and NIPAM was synthesized using ATRP associated with ceric ion redox system.[60] Due to the different LCSTs of PNIPAM and PPO, the thermal-responsive block copolymers exhibited a two-stage phase transition temperature. The dual-responsive core-shell corona micelles were observed for P(*t*BA-*co*-AA)-*b*-PNIPAM synthesized by ATRP using CuCl/Me_6TREN catalyst.[61] At pH 5.8 and at 25 °C, the block copolymer self-assembled into spherical core-shell micelles comprising of a hydrophobic P*t*BA core and a PAA/PNIPAM hydrophilic shell. Increasing temperature induced the conversion of the core-shell micelles to core-shell-corona (CSC) micelles with P*t*BA cores, surrounded by a collapsed PNIPAM layer and a PAA corona. By reducing the pH at 25 °C, PAA chains collapsed onto the core to form CSC micelles comprising of P*t*BA core, PAA shell and PNIPAM corona (Fig. 1). The block copolymer of PNIPAM and PMMA was synthesized using the semi-telechelic amino-PNIPAM and semi-telechelic carboxylic-PMMA, which were synthesized by telomerization with 2-amino ethanethiol hydrochloride (AET) and 3-mercaptopropionic acid (MPA) as telogens. End groups of PMMA-COOH were transformed to activated ester groups by reacting with *N*-hydroxysuccinimide (NHS). Block copolymers of PNIPAM-*b*-PMMA were obtained *via* a condensation reaction between the amino end-groups of PNIPAM and the activated terminal PMMA end-groups in the presence of dicyclohexylcarbodiimide (DCC).[62] In aqueous system, core-shell nanoscale micelles with an averaged size of 190 nm were formed in solution. Such micelles possessed fast/slow



Scheme 5 Photo crosslinking reaction of NIPAM containing copolymers. Reproduced from ref. 57 © American Chemical Society.



Scheme 6 Schematics for the preparation of PNIPAM and PEG block copolymer. Reproduced from ref. 59 © Elsevier Ltd.

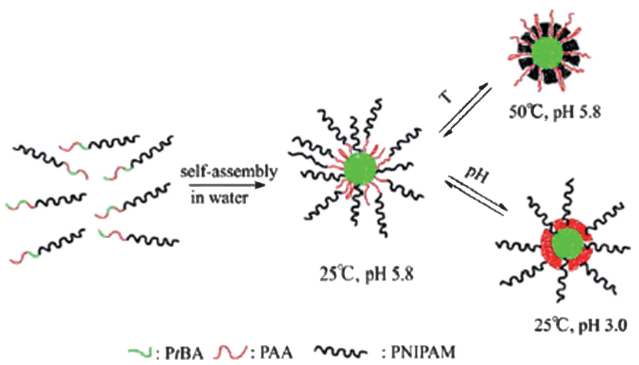


Fig. 1 Schematic illustration of the thermo- and pH-responsive micellization of P(*t*BA-*co*-AA)-*b*-PNIPAM. Reproduced from ref. 61 © Elsevier Ltd.

thermal-responsive switching behaviors suitable for drug release based on the temperature-responsive structural changes of the micellar shell structure. The block copolymer of PNIPAM-*b*-PAA was synthesized through RAFT in methanol using 1-cyanoethyl-2-pyrrolidone-1-carbodithioate as the chain-transfer agent.[63] The block copolymers formed micelles in aqueous solution depending on pH and temperature. The solution behavior was found to be strongly influenced by hydrogen bonds between NIPAM and AA blocks. The formation of hydrogen bonds between NIPAM and AA units within the aggregates were evident from both FTIR and Raman spectra. PAA is interesting since its characteristics change with both pH and ionic strength. At pH < 4 and temperatures exceeding the LCST, precipitation occurred due to the protonation of carboxylate groups, which reduced the solubility of the block copolymer in water. At pH > 4 and temperature exceeding the LCST, the block copolymers self-assembled into micelles consisting of a PNIPAM core and deprotonated PAA shell. At pH < 4 and temperature lower than the LCST, micelles also formed in solution with a PAA core and a PNIPAM corona, while at pH < 4 and T > LCST, the polymer became hydrophobic and formed large aggregates or gel in solution. Conjugation of drugs or proteins to PNIPAM-*b*-PAA generated thermo- and pH-responsive entities that can be manipulated by external stimuli. It was obvious that such a copolymer is sensitive to pH, temperature, solvent and block length, where the applications of such polymers in bio-adhesion, bio-separation, drug delivery and tissue engineering are being considered. pH responsive micelles have been applied for the delivery of drugs to tumors, inflamed tissues, or endosomal compartments, where a lower pH than in normal tissue is encountered. A novel double hydrophilic PDEA-*b*-PAA-*b*-PDEA tri-block copolymer was synthesized by sequential anionic polymerization and the modification of poly(*tert*-butyl acrylate) (P*t*BA) middle block by selective hydrolysis and neutralization to its ionic functions.[64] At low temperature and high pH, the polymeric chains existed as unimers, while at temperatures above the LCST of PDEA (poly-diethylacrylamide), a sol–gel transition was evident due to the formation of a three-dimensional transient network comprising crosslinked hydrophobic PDEA bridged by negatively charged PAA chains. The observed gelation temperature of 60 °C was about 20 °C higher than the LCST of PDEA. The sol–gel transition and the rheological properties of the physical gel were strongly influenced by the presence of salt. Addition of salt not only reduced the LCST of PDEA, but also induced electrostatic screening of negatively charged PAA chains.

3.1.2 Thermo-responsive microgels. The crosslinking of linear PNIPAM chains can be accomplished by either introducing small amounts of crosslinker during the polymerization process or by introducing a multi-functional monomer followed by post-crosslinking process. When the chains are crosslinked to form a colloidal gel, PNIPAM-based microgels exhibited thermal responsiveness *via* a reversible deswelling volume phase transition characteristic at between 32 and 35 °C. PNIPAM microgel systems display dramatic changes in particle size, surface charge density, and water content over a small temperature range of 5 to 10 °C. The volume transition equilibrium and the interaction potential between PNIPAM particles dispersed in water were investigated using thermodynamic perturbation theory combined with light-scattering and spectrometer measurements.[65] A novel phase diagram of PNIPAM nanoparticles dispersed in water was documented (Fig. 2). The aqueous dispersions of PNIPAM exhibited phase transitions at both high and low temperatures. The phase behavior of PNIPAM microgel dispersion resembled that of hard spheres below the

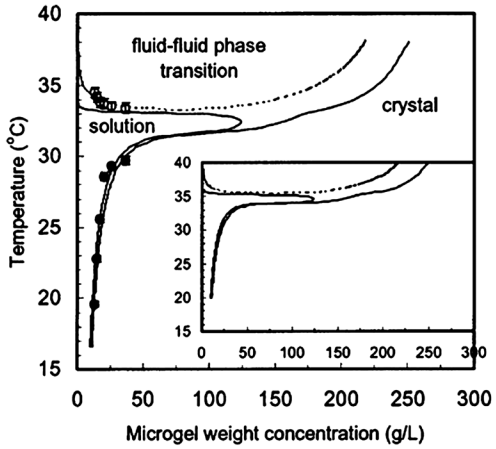


Fig. 2 The phase diagram of aqueous dispersions of PNIPAM particles determined from turbidity measurements (symbols) and from the thermodynamic perturbation theory with an empirical correction of temperature (lines). The filled and open circles represent the melting and the second phase-separation temperatures, respectively. The inset shows the predicted phase diagram without any adjustable parameters. Reproduced from ref. 65 © The American Physical Society.

volume-phase transition temperatures. However, at higher temperatures, the phase separation is driven by van der Waals attractions and the metastable liquid–liquid and the liquid–solid equilibrium coexisted.

Colloidal NIPAM-AA microgels with different amounts of acrylic acid were synthesized using the SFEP technique.[66] The microgels exhibited a two-step volume phase-transition with increasing acrylic acid content. The volume phase transition of colloidal NIPAM-AA microgels depended on the effective charge density within the polymeric network. Hydrogen bonding should be taken into consideration for describing this two-step volume phase transition observed for these colloidal microgels. Another interesting phenomenon is the reversible formation of well-defined aggregates at low pH and high salt conditions. The balance between hydrophobic and electrostatic forces controls the swelling equilibrium of colloidal particles. In addition, the contribution of Donnan osmotic pressure with increasing amounts of acrylic acid resulted in a higher swelling capacity of NIPAM-AA copolymeric microgels than that observed in neutral PNIPAM microgels. The microgel composed of NIPAM and *N*-isopropyl-maleamic acid (NIPMMA) together with BIS crosslinker (*N*,*N*′-methylene-*bis*-acrylamide) was synthesized.[67] Due to the existence of carboxyl groups in the NIPAM-NIPMMA microgels, they also possessed significant pH sensitivity. The microgels exhibited enhanced pH-responsiveness with increasing NIPAM content, while the volume-phase transition temperature (VPTT) of NIPAM remained unchanged, which was attributed to the existence of continuous NIPAM sequences in the NIPAM-NIPMMA microgel system. The microgels containing NIPAM and vinylacetic acid (VAA) were synthesized using emulsion polymerization and exhibited a host of novel swelling responses compared to equally functionalized microgels prepared using conventional acrylic acid or methacrylic acid comonomers.[10] Ionization induced a much larger swelling (three times) response in VAA-NIPAM microgels than in a conventional MAA-NIPAM system. The highly responsive and tunable ionization and swelling profiles observed for VAA-NIPAM were consistent with the tendency of VAA to act as a chain-transfer agent, resulting in the incorporation of a large number of well-separated VAA units on highly mobile chain ends at or near the microgel surface. Both copolymerization kinetics and experimental observations indicated that AA and MAA tended to form blocks within the NIPAM-rich polymer chains comprising the microgel.[68] This unique NIPAM-rich core/carboxyl-terminated oligomer shell morphology allowed VAA-NIPAM microgels to ionize over a much narrower pH range. When fully protonated, VAA-NIPAM copolymer microgels possessed sharp, and highly responsive thermal deswelling profiles that were similar to those of non-functionalized PNIPAM microgels. However, when fully ionized, the volume phase transitions in VAA-NIPAM copolymeric microgels were shifted to higher temperatures by even small amounts of comonomer, where a relatively low amount of 6.5 mol% VAA increased the VPTT by at least 40 °C. The copolymer containing PNIPAM and polyacrylamide was synthesized and compared with the PNIPAM-PAA system.[69] Acrylamide-containing microgels hydrolyzed below the VPTT, and they possessed (a) broad particle size *versus* temperature profiles, (b) relatively low electrophoretic mobility at basic pH, and (c) time-dependent base titration profiles, suggesting the presence of internal functional groups, where the acid–base neutralization was diffusion-controlled. Methacrylic acid containing microgels exhibited sharper particle size *versus* temperature profiles, higher electrophoretic mobilities at basic pH, and time-independent base titration profiles, suggesting the presence of a "core-shell" structure with primarily surface functionalization. Similar results were obtained when acrylamide-containing microgels were hydrolyzed at temperatures above the VPTT. For the systems with MAA/NIPAM ratios < 10%, Zhou and Chu proposed a "core-shell" microstructure, where the NIPAM-rich core was surrounded by a MAA-rich shell.[70] At AA/NIPAM ratio greater than 30%, the bulk of charges did not reside on the particle surface.[71] Hydrolysis of acrylamide/NIPAM copolymer microgels at temperatures below the VPTT produced microgels with a significant number of carboxylic acid groups (more than 35%) located within the bulk of the microgel. The functional group distribution in hydrolyzed AA-NIPAM copolymer microgels can be influenced by the hydrolysis temperature. Conducting the hydrolysis at temperatures above the VPTT appeared to produce predominantly surface functionalized microgels. However, MAA-NIPAM copolymeric microgels exhibited a core-shell morphology in which most of the carboxylic acid groups resided at or near the microgel surface.[69b] The effect of chain distribution of –COOH groups in five microgels prepared using different –COOH functionalized monomers [AA, MAA, VAA, fumaric acid (FA), and maleic acid (MA)] suggested that the distribution of acidic groups could impact both the pK_a and Gibbs free energy. Phenylboronic acid (PBA)-modified PNIPAM-based microgels exhibited reversible swelling responses to the changes in environmental glucose concentration.[69c] The thermal phase transition can be applied to either amplify or suppress the PBA ionization-driven glucose swelling phase transition, providing highly selective control over the glucose swelling response of a particular PBA-grafted microgel particle. Up to 4-fold

amplifications in volumetric swelling responses can be achieved by tuning the VPTT of microgel conjugates. Both the temperature range and glucose concentration range over which glucose swelling amplification and suppression are achieved can be tuned by changing the underlying composition of the platform microgel and/or the amount of PBA grafted to the microgels. Linear glucose concentration sensors can therefore be designed with specific sensitivities to a targeted glucose concentration range.

The photo-crosslinkable polymer [poly(NIPAM-*co*-CIPAM)-BP] was prepared by condensation reaction between the DCC-activated carboxylic groups on the side chains and amino groups of 4-aminobenzophenone (BP), where CIPAM is 2-carboxyisopropylacrylamide.[72] The photo-crosslinking reaction occurred quickly in spin-coated ultra-thin film, and the prepared film demonstrated excellent stability due to the crosslinking reaction under UV irradiation. Ions could permeate through such photo-crosslinked polymeric film, producing ultra-thin hydrogel films. Furthermore, the permeability of ultra-thin hydrogel films changed as the pH and temperature were varied. A hydrophobically-modified bio-adhesive polyelectrolytic hydrogel was prepared by grafting oligomers of MMA to the backbone of a PAA hydrogel.[73] Slower and lower extent of swelling was observed at higher MMA content, which was probably due to the higher concentration of hydrophobic grafts and their hydrophobic domains within the hydrogel. In the case of hydrophilic drugs, such as theophylline, the drug release rate was enhanced by increasing the MMA content. The formation of hydrophobic domains enlarged the aqueous pore sizes of the hydrogel, thus permitting hydrophilic drugs to diffuse more rapidly. On the contrary, for moderately hydrophobic drugs such as propranolol hydrochloride, the release rate was reduced by MMA content due to the partitioning of hydrophobic groups of the drug to MMA domains. Since the ionic interaction of propranolol hydrochloride and the network was fairly weak, hydrophobic interactions appeared to be the major driving force for loading propranolol hydrochloride to the hydrogel. In the case of a positively charged protein, such as lysozyme, a slower release profile was observed at higher MMA content. In addition to ionic interaction with PAA, lysozyme interacted with hydrophobic domains that may slow or even limit its ionic exchange-driven release characteristics. Such hydrophobically-modified bio-adhesive hydrogel could be successfully applied to sustained release of hydrophobic drugs or oppositely-charged proteins. Thermal responsive PNIPAM copolymer hydrogels have also been used as cell carriers in culture experiments with L929 mouse fibroblast cells to probe cell adhesion, proliferation, and temperature-dependent detachment of cell layers.[74] The fibroblast cells adhered, spread, and proliferated on the hydrogel layers at 37 °C and became completely detached when the temperature was reduced to 34 °C. Such a type of thermo-responsive interfaces could facilitate cell adhesion and proliferation.[75,76]

Random copolymeric hydrogels of MAA and NIPAM were synthesized by free-radical polymerization in the presence of a crosslinking agent, ethylene glycol dimethacrylate (EGDMA).[77] Such hydrogels displayed both temperature- and pH-sensitivity, and the mesh size of the hydrogels changed dramatically between the collapsed and swollen states, which could be beneficial in applications, such as size-selective permeation or controlled drug delivery. Increasing the amount of MAA gave rise to an increase in the VPTT of P(MAA-*co*-NIPAM) microgel. pH-sensitive hydrogels are suitable candidates for oral drug delivery of peptides due to their ability to respond to the external environment. The copolymeric gels containing NIPAM, AA, MAA and 2-acrylamido-2-methyl-1-propanesulfonic acid (AMPS) were synthesized through free radical polymerization in aqueous solution, where their swelling and deswelling behaviors were studied.[68,78] Laser light scattering and NMR analyses revealed that hydrogen bonds were present in the hydrogels based on NIPAM and MAA.[79,80]

3.1.3 Thermo-responsive nanostructured polymeric systems. Nanostructured materials have attracted increasing attention

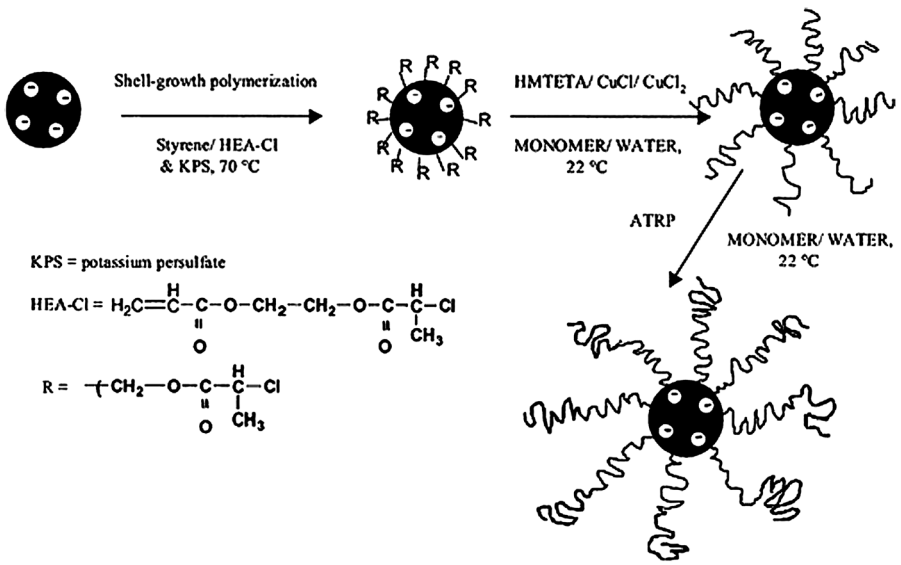


Fig. 3 Representation of the ATRP synthesis of PNIPAM and PDMA block copolymeric brushes on the surface of polystyrene. Reproduced from ref. 81*b* © Elsevier Ltd.

due to their potential for constructing systems using the bottom-up approach. As a result, various well-defined nanostructured particles and surfaces containing thermo-responsive polymers have been developed and fabricated. The core-shell particles consisting of P(NIPAM-*co*-St) cores and PNIPAM shells were synthesized using SFEP process. The feed ratio, stirring speed, and initiator concentration controlled the thermo-responsive behavior, size and polydispersity of core-shell nanoparticles. The NIPAM homopolymers and its copolymers with PDMA and poly(methoxyethylacrylamide) (PMEA) have been grafted onto the surface of negatively charged PS latex through surface initiated ATRP (Fig. 3).[81] Functionalized anionic polystyrene latex particles with ATRP initiators were synthesized by surfactant-free shell-growth emulsion polymerization of styrene and 2-(2′-chloropropionato)ethyl acrylate (HEA-Cl). It has been found that the hydrodynamic thickness decreased with increasing temperature, but the reduction in the hydrodynamic thickness of copolymers was not as significant as homopolymers. The hydrodynamic thickness of grafted PNIPAM layer scaled as $DP^{0.66}$ (where DP is the degree of polymerization) at constant grafting density (chains/nm^2). In order to understand the effect of the microstructure of core-shell responsive particles on the phase behavior, two temperature and pH-responsive core-shell particles comprising of a crosslinked PNIPAM core and P(NIPAM-*co*-AA) shell or P(NIPAM-*co*-AA) core and PNIPAM shell were synthesized *via* free radical precipitation polymerization, where

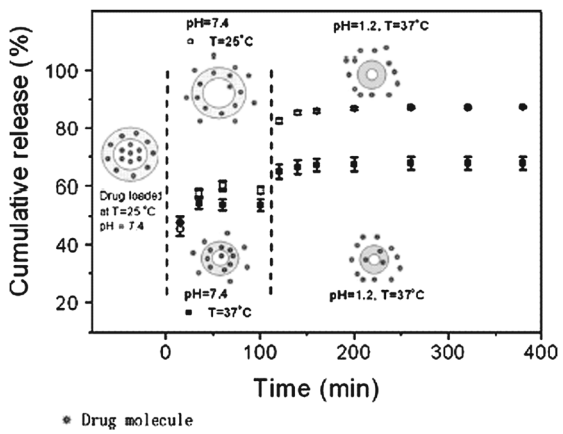


Fig. 4 Structure induced two-step release of INH from PNIPAM/AA cages. Reproduced from ref. 83 © Elsevier Ltd.

the BIS crosslinked cores were first synthesized, and they were then used as seeds for subsequent polymerization of P(NIPAM-*co*-AA) or PNIPAM shell. Both P(NIPAM-*co*-AA) (core)/PNIPAM (shell) and PNIPAM (core)/P(NIPAM-*co*-AA) (shell) particles displayed a significantly more complex pH dependence than homogeneous particles, where the particle swelling behavior was also dominated by temperature. At pH of 6.5, particles comprising of a P(NIPAM-*co*-AA) core and a thin PNIPAM shell displayed two distinct volume phase transitions of between 25 and 40 °C, that corresponded to PNIPAM and PNIPAM/P(NIPAM-*co*-AA) transitions, respectively. However, when the sequence arrangement was reversed, three distinct volume phase transitions were observed at between 25 and 60 °C, reflecting the formation of a more heterogeneous nanostructure in submicron-sized microgels. Small differences from the effect of pH on these two core-shell particles indicated that the influence of PNIPAM was somewhat greater, especially when it was localized within the shell. The core-shell architecture could be a powerful method for constructing multi-responsive or multi-functional particles. The core-shell nanoparticles with gold cores and copolymers of NIPAM and BIS shell were fabricated through surface-initiated ATRP on the surface of gold nanoparticles.[82] Such Au core-shell hybrids possessed distinct thermo-sensitive properties and exhibited an "inspired" and "expired" water behavior in response to temperature changes. The dual responsive hollow cage of P(NIPAM-*co*-AA) with BIS crosslinker was synthesized by hydrolyzing SiO_2-P(NIPAM-*co*-AA) core-shell particles with hydrofluoric acid (HF), where hydrophilic drugs can be encapsulated within the hollow cage.[83] The drug loading and released capacity were influenced by the swelling and mesh size of such hydrogel, where the cavity of hydrogel cages favored drug loading and release compared to solid hydrogel spheres. The hydrophilic drugs can be loaded either by bonding onto the layer of the cage through H-bonding or remained free within the cavity. *In-vitro* drug release studies showed that in a neutral medium (pH = 7.4) and low temperature, most of the drugs were preserved within the shell, while in an acidic medium (pH = 1.2) and high temperature, nearly all the drugs were released due to the dissociation of hydrogen bonds (Fig. 4). Besides, thermo-responsive polymer-encapsulated silica hybrid nanoparticles were also fabricated *via* the self-assembling of RAFT synthesized PNIPAM-*b*-P(methacryloxypropyl-trimethoxysilane) (PNIPAM-*b*-PMPS) block copolymer in aqueous solution into micelles and subsequent sol–gel process in the micellar core.[84]

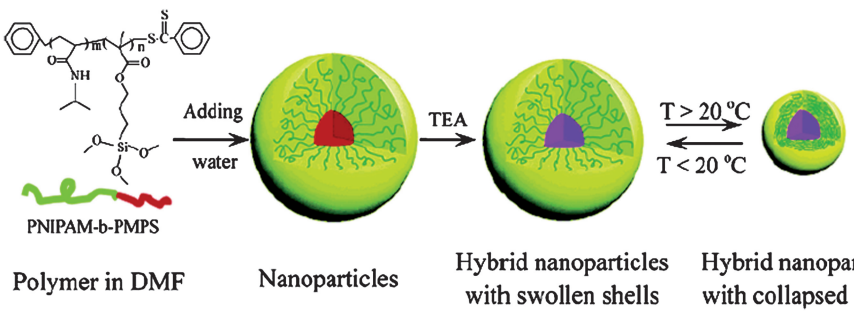


Fig. 5 Schematic illustrating preparation of hybrid nanoparticles and the thermo-responsive nature of the shell. Reproduced from ref. 84 © American Chemical Society.

The monodispersed hybrid nanoparticles with densely grafted PNIPAM brush on the surface of silica core were evident from both TEM and laser light scattering analyses. The core-shell particles were formed by adding water to PNIPAM-*b*-PMPS in DMF solution to induce micellization, followed by hydrolytic polycondensation within the micellar core in the presence of triethylamine. Fig. 5 shows the fabrication process of the core-shell particle and its thermo-responsive behavior.

PNIPAM has also been grafted onto the backbone of carboxylmethylcellulose (CMC) through the interaction of amino-terminated PNIPAM with CMC using water-soluble 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide (EDC) as the coupling agent.[85] The phase separation was reduced due to the introduction of hydrophilic segments as evident from the increase in the VPTT for large amounts of NIPAM grafting. Although the hydrophobic domains were formed in solution, as evident from steady-state fluorescence spectra, phase separation was not observed in small amounts of NIPAM grafting beyond the LCST of NIPAM due to the amphiphilic character of the grafted polymer. However, such a system underwent a thermal-responsive sol–gel transition in semi-dilute solutions. In addition, thermo-responsive PNIPAM and dextrin hybrid particles were produced by surface initiated aqueous ATRP *via* the attachment of an initiator onto dextrin microspheres followed by the polymerization of NIPAM.[86]

It has also been reported that PNIPAM could be grafted from electrodeposited Laponite RD particles using surface-initiated ATRP to yield a temperature-responsive surface.[87] Due to the diverse biological applications, research on different temperature-responsive functional surfaces have attracted increasing attention. Grafting polymer brushes on a solid substrate is an effective method to modify the surface properties of substrates.[88] Generally, two fabrication methods, "grafting to" or "grafting from" are used for the synthesis of polymeric brushes on surfaces. In the former method, end-functionalized polymeric chains are grafted to the surface by chemical methods to form a polymer layer, and producing a very dense monolayer is difficult due to the self-exclusion of polymeric chains as surface polymer concentration increases. In the "grafting from" technique, polymer chains are grown from functionalized surfaces by surface initiated polymerization, allowing the generation of high density brushes. Of all the methods available for surface initiated polymerization, ATRP and RAFT are the most versatile techniques for the controlled synthesis of polymers with different monomers and reaction media (aqueous or organic). Another advantage of "living" radical polymerization methods is that the end of the polymer chains is capped with an active functional group that can be reinitiated to form block copolymer brushes by the addition of fresh catalyst and monomer. PNIPAM segment was successfully grafted on the surface of gold and silicon-oxide through ATRP.[89] The temperature-dependent conformational change of PNIPAM chains was examined by neutron reflectivity over a range of surface density and molecular weight. The greatest conformational change was observed for intermediate grafting densities and high molecular weights, which is attributed to the competition between chain stretching effect of laterally interacting tethered chains and the phenomenological Flory interaction parameter χ determined empirically for free PNIPAM chains in water. The applications of polymer modified solid surfaces depend primarily on the changes in short-ranged interactions, such as controlling the adsorption of bacteria and tissue cells *via* changes in hydrophobicity.[90] However, some

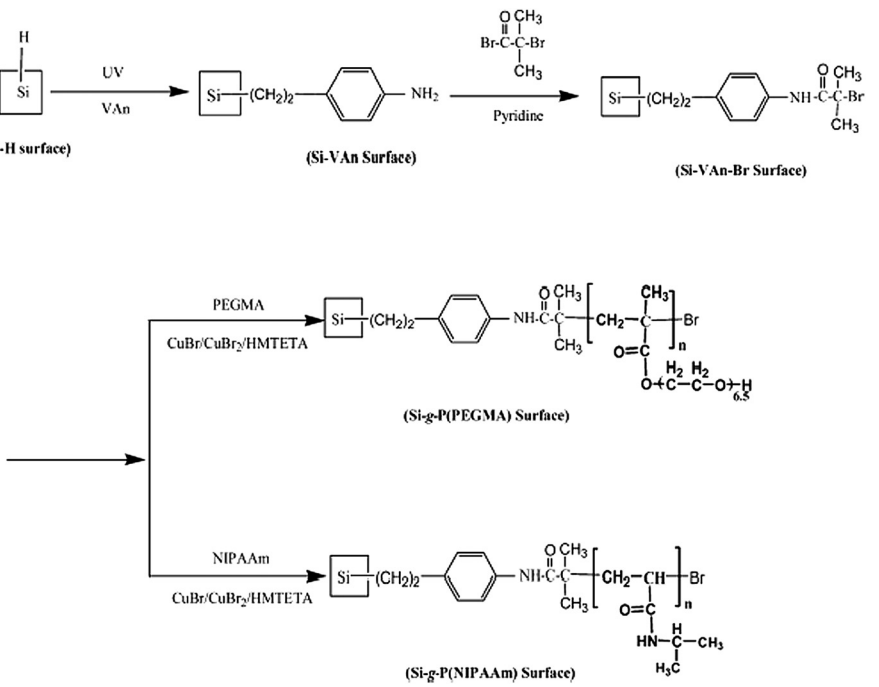


Fig. 6 Schematic diagram illustrating the processes of UV-induced coupling of VAn (4-vinylaniline) on the Si-H surface to give rise to the Si-VAn surface, reaction of the Si-VAn surface with 2-bromoisobutyrate bromide to give the Si-VAn-Br surface, and surface-initiated ATRP on the Si-VAn-Br surface. Reproduced from ref. 92 © American Chemical Society.

applications depend critically on the magnitude of conformational changes that result from the shift in fundamental interactions, such as separating molecules on the basis of size and controlling ligand binding to receptors.[91] For example, well-defined functional polymer-Si hybrids, consisting of covalently tethered brushes of poly(ethylene glycol monomethacrylate) (PEGMA), PNIPAM, and NIPAM-PEGMA block copolymers were prepared *via* surface-initiated ATRP (Fig. 6).[92] Surface cultures of 3T3-Swiss albino cell line on the hybrids were evaluated, where the cell adhesion and detachment characteristics of functionalized silicon surfaces were assessed by optical microscopy. The PEGMA graft-polymerized silicon [Si-*g*-PEGMA] surface was effective in preventing cell attachment and growth. Above the LCST of PNIPAM, the seeded cells adhered, spread, and proliferated on the NIPAM graft polymerized silicon [Si-*g*-PNIPAM] surface. Below the LCST, the cells spontaneously detached from the Si-*g*-PNIPAM surface. The copolymer resulted in more rapid cell detachment at the transition temperature. In addition, the preparation of NIPAM containing magnetic particles have been reported, where the 10 nm magnetic particles were treated with sodium citrate to produce negatively charged magnetic particles.[93] After being coated with a thin layer of silica, and by hydrolysis of tetraethylorthosilicate (TEOS) in methanol/water mixture, templated cores were produced. The silane coupling agent, 3-(trimethoxysily)propyl methacrylate (MPS) was then used to modify the surface of the silica coated magnetic particles to obtain a vinyl bond on the surface, and NIPAM and BIS were introduced by seeded precipitation polymerization. A reversible color change from dark yellow to transparent was observed in the presence of an external magnetic field or temperature change, making such materials suitable for targeted drug delivery and biomacromolecular separations (Fig. 7). The PNIPAM brush nano-patterns could be prepared on gold-coated silicon substrates in a "grafting-from" approach that combined "nano-shaving", a scanning probe lithography method, with surface-initiated polymerization using ATRP. The reversible, stimuli-responsive conformational height change of these nano-patterned polymer brushes was demonstrated by inverse transition cycling in water, and water-methanol mixtures (1 : 1 by volume). Such nanofabrication approach is generic and can likely be extended to a wide range of vinyl monomers.[94] The nano- and micro-patterned polymer brush arrays composed of pH- and salt-sensitive polyelectrolyte copolymers of 3 : 1 P(NIPAM-*co*-MAA) on a gold surface was fabricated using the "lift-off" electron-beam lithography. A silicon surface was first pre-patterned with gold, and the resulting pattern was then amplified by surface-initiated photo-polymerization by conventional UV induced reaction through surface radical polymerization, which displayed externally triggered conformational changes of the micro- and nano-patterned polymer brushes on the basis of ionic strength and pH (Fig. 8).[94] The height of nano-patterned ionized polymer brushes increased with increasing feature size of the pattern, where the height increased with pattern diameter at high pH and low salt concentration, but was independent of diameter at low pH and high salt concentration. With increasing amount of PAA, the VPTT might exceed that of the homopolymer. The brush and crosslinked gold and NIPAM hybrids were synthesized through ATRP and their

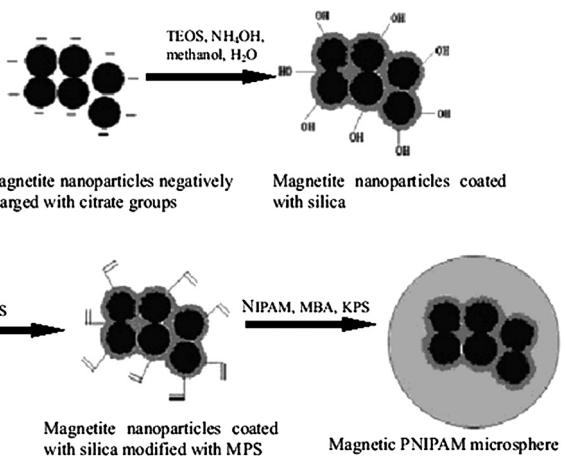


Fig. 7 Schematic illustrating the preparation of magnetic PNIPAM microspheres. Reproduced from ref. 93 © Wiley-VCH Verlag GmbH & Co.

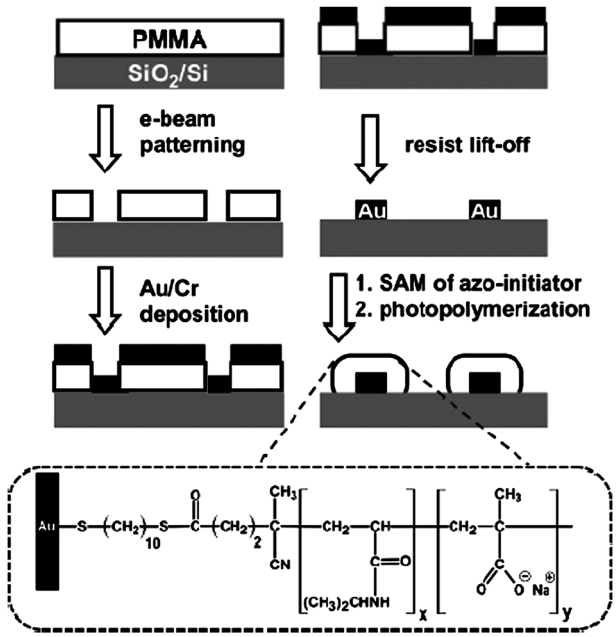


Fig. 8 Preparation of P(NIPAM-*co*-NaMA) copolymer brush patterns by combining lift-off electron beam lithography (EBL) and photo-initiated polymerization, using a surface-tethered azo initiator immobilized on gold templates. Reproduced from ref. 94*b* © American Chemical Society.

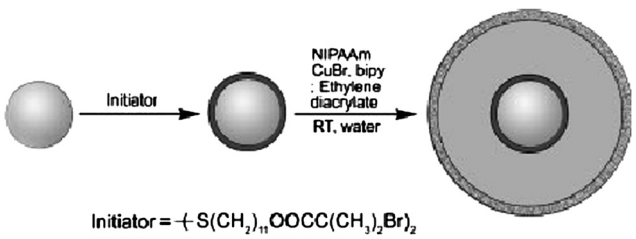


Fig. 9 Schematic illustrating the preparation of AuNP/PNIPAM core-shell hybrid structures by surface-initiated ATRP in aqueous media. Reproduced from ref. 95 © WILEY-VCH Verlag GmbH & Co.

thermo-responsive behaviors were compared (Fig. 9).[95] The diameter decreased with increasing temperature, where the change in hydrodynamic diameter was fully reversible. The phase transition temperatures of all the hybrids was about 32 °C, regardless of the presence of crosslinker, indicating that crosslinkers did not affect the VPTT of PNIPAM in microgels, and only the diameters and the shrinkage of microgels were affected. The results indicated that the thermal-tunability of diameters could be achieved by crosslinking without changing the VPTT since the shrinkage factor decreased with increasing crosslinker concentration. The copolymers of NIPAM and three different succinimide-bearing comonomers were used to synthesize semi-telechelic cotelomers through free radical polymerization.[96] All these polymers underwent phase behavior beyond the VPTT, but the VPTTs were different from the PNIPAM copolymer. An analogous polymer route exploiting the *N*-hydroxysuccinimide groups of cotelomers was then used to introduce light-responsive azobenzene groups into the molecules. The observed shifts of the critical solution temperature were determined not only by the hydrophobic/hydrophilic balance and the chemical microstructure of cotelomers, but also by their conformation in solution. In addition, peptide-polymer hybrid nanotubes (PPNT) were prepared by a combination of self-assembling functional cyclic peptides and *in-situ* surface-initiated ATRP using Me_6TREN as a ligand.[97] This allows the tailoring of the outer diameter of self-assembled peptide nanotubes in a precise manner without changing the primary sequence of the peptide rings (Fig. 10).

In contrast to PNIPAM, aqueous solutions of more polar homopolymers, such as poly(*N*,*N*-dimethylacrylamide (PDMA) do not exhibit a LCST at low pH. However, with the introduction of hydrophobic comonomers that enhanced polymer–polymer interactions, modified PDMA copolymers displayed thermally responsive characteristics. However, these PDMA copolymers undergo liquid–liquid phase transitions, whose phase transition is temperature dependent on the amount of hydrophobic comonomers.[98] Thermo-responsive poly(DMA-*co*-*N*-phenylacrylamide) P(DMA-*co*-PhAm) copolymers were prepared by ATRP in methanol/water mixture at room temperature using the methyl 2-chloropropionate initiator and CuCl/Me_6TREN catalyst, where PhAm was used to enhance the hydrophobicity of the copolymer.[99] It was found that the LCST of the copolymer was dependent on the chemical composition, molecular weight, polymer and salt concentration.

3.1.4 Natural and synthetic thermo-responsive hydrogels. Besides synthetic polymers, some chemically modified natural macromolecules also possess thermo-responsive characteristics. The thermal gelation behavior of methylcellulose (MC) was extensively studied using rheological techniques, where the thermo-reversibility was dependent on the heating and cooling rates.[100a] The thermal recovery exhibited a hysteresis, where the cooling did not follow the same pathway as the heating process. The reason for such observed phenomenon is that the hydrophobic association and dissociation are kinetic processes that

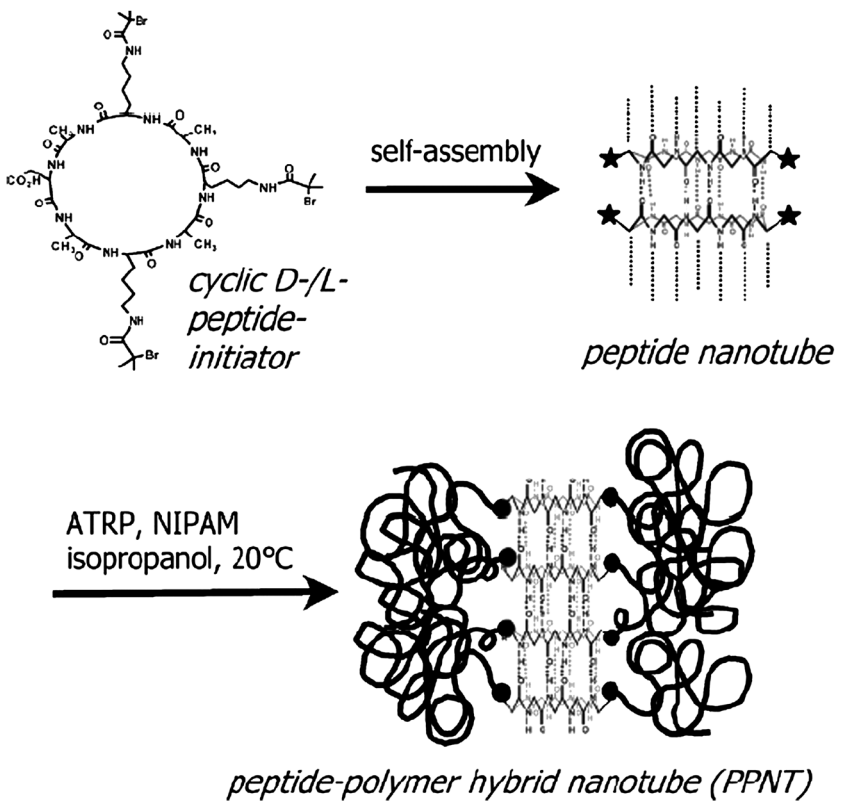


Fig. 10 Schematic description of the initiator-modified cyclic D-/L-peptide (upper left), the self-assembly of the peptide into peptide nanotubes, where the initiation moieties are located on the outer surface (upper right), and the surface-initiated ATRP reaction that wraps the peptide nanotube *in-situ* in a soft polymeric shell, thereby forming a so-called peptide-polymer nanotube (PPNT, bottom). Reproduced from ref. 97 © American Chemical Society.

possess different rate constants. It was found that a critical temperature of 42.5 °C differentiated the weak from strong gels. The thermal analysis results showed that the association of methylcellulose molecules in water was thermo-reversible but the dissociation temperatures were much lower than the association temperatures.[100b] At a high concentration of methylcellulose, the gel elasticity varied with temperature, and it did not obey a single scaling law. For weak gels (c < 1 wt%), the elasticity modulus G_e at 70 °C scaled with polymer concentration c as $G_e \sim c^{1.34}$, while G_e scaled with c as $G_e \sim c^{3.03}$ for strong gels (c > 1 wt%). The gelation of methylcellulose was an entropic-driven process as observed from MicroDSC scans.[100c] At the same time, electrolytes could affect the intermolecular interaction of MC in aqueous media. The effects of various salts on the sol–gel transition of aqueous MC solutions were studied, where the addition of salts did not change the gelation and degelation characteristics of MC.[100d] However, salts could shift the sol–gel transition to lower or higher temperatures in a pure MC solution, depending on salt types. Cations exhibited weaker effects than anions. Some salts (*e.g.*, NaCl, Na_2SO_4) enhanced the sol–gel transition, while others (*e.g.*, KI, NaSCN) suppressed the formation of gels. The reason is attributed to the fact that salts may either enhance or reduce the hydrophobicity of a solute in water. The so-called "Hofmeister series" represents the order of ions ranked in terms of how strongly they affect the hydrophobicity of the system.[101] Accordingly, ions can be classified as either kosmotropes (structure makers) or chaotropes (structure breakers). The structure makers or breakers refer to the ability of an ion to stabilize or weaken (or destroy) the structure of water, respectively. A typical Hofmeister order for anions was reported as $SO_4^{2-} > F^- > Cl^- > Br^- > NO_3^- > ClO_4^- > I^- > SCN^-$. Ions on the left hand, called kosmotropes, can be strongly hydrated, exhibiting strong interactions with water molecules. As a result, they tend to induce "salt-out" or enhance hydrophobicity of a solute in water. In contrast, ions on the right hand (called chaotropes) can be weakly hydrated, tending to induce "salt-in", which increases the solubility of a nonpolar solute.[102] The salt mixture was found to have a combined effect from the salt-out (NaCl) and salt-in (NaI) compounds, and the salt effect was dependent on the water hydration abilities of component ions and ionic concentration. The effect of mixed salt obeyed the simple linear mixing rule.[103] Besides MC, such thermo-responsive gelation behaviors have also been observed for other cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC).[104] It has been found that H-bond and hydrophobic interactions are dominant driving forces controlling the thermo-responsive gelation behaviors. Considering the biocompatible and biodegradable characteristics of such cellulose derivatives, they could be used as carriers for hydrophilic drugs.[105]

Beside hydrogels from chemically modified natural polymers and synthetic PNIPAM or PPG/PEG, thermo-responsive biodegradable hydrogels are another important class of materials. Copolymer of PEG and polyester is of interest due to its biodegradable and biocompatible characters.[106] The combination of low molecular weight PEG and high molecular weight of poly(D,L-lactic acid-co-glycolic acid) (PLGA) produces polymers that display amphiphilic characteristics and thermo-responsive sol–gel transitions similar to those of Pluronic or Pluronic-R copolymers. The PEG-*b*-PLGA-*b*-PEG has been explored for the delivery of hydrophobic drugs.[107] PLGA-PEG-PLGA has been applied in controlled release of water-insoluble testosterone.[108] For such system, a slow release was observed, which might be related to the biodegradation of PLGA. A novel class of dextran–maleic anhydride (Dex–MA)/PNIPAM hybrid hydrogels was prepared by UV photo-crosslinking technique, where the Dex–MA precursor was photo-crosslinked with a temperature responsive NIPAM precursor to form hybrid hydrogels.[109] Such hydrogel is biodegradable, exhibits thermo/pH responsive behaviors, and the phase transition temperature of such intelligent hydrogels can be controlled to occur close to the body temperature needed for biomedical applications. In addition, SFEP polymerization has been applied to prepare microgels of NIPAM and dextran-lactate-2-hydroxyethyl methacrylate (DEXlactateHEMA).[110] Other hydrogels comprising of NIPAM (thermo-responsive), poly(L-lactic acid) (PLLA, hydrolytically degradable and hydrophobic), and dextran (enzymatically degradable and hydrophilic) have been reported.[111] The VPTT was found to be ~32 °C. FTIR study revealed the degradation of hydrogels caused by hydrolytic cleavage of ester bonds was faster at a temperature below the VPTT than above the VPTT. Such DEX/NIPAM hydrogels have been explored for applications in antibody purification through the thermo-responsive phase behavior and centrifugation.[112]

3.1.5 Applications of various thermo-responsive polymeric systems. NIPAM containing thermo-responsive polymeric systems have found wide applications in drug delivery and related fields.[2,113,114] Besides those discussed previously, some interesting applications that were reported recently are described below. A molecular recognition ion-gating membrane was developed by a peroxide plasma graft copolymerization process.[115] The membrane composed of a porous polyethylene

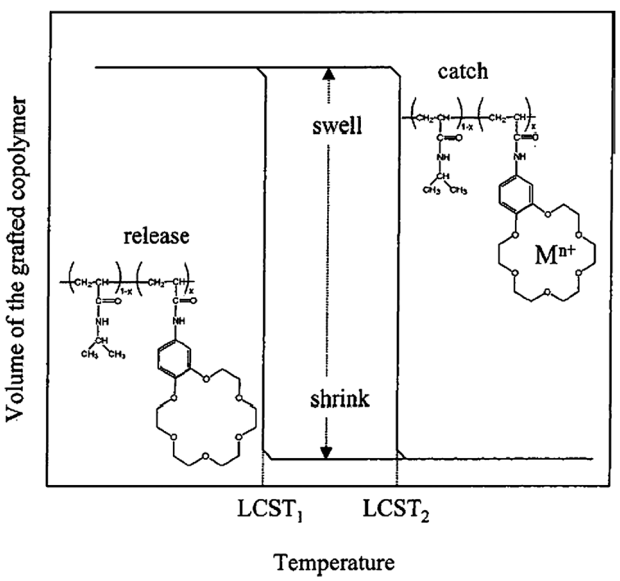


Fig. 11 Schematic illustration for the volume change of the grafted NIPAM/BCAm copolymer. On capturing a specific ion, this copolymer changes its LCST from LCST1 to LCST2; thus, the copolymer swells and shrinks in response to M^{n+} at a temperature between LCST1 and LCST2. Reproduced from ref. 115*a* © American Chemical Society.

film with a copolymer of NIPAM and benzo[18]crown-6-acrylamide (BCAm) grafted within the pores, where PNIPAM and BCAm were used to trap specific ions. The trapping of ions shifted the LCST of PNIPAM, which induced the synthetic membrane pores to spontaneously open and close in response to specific solvated ions (Fig. 11). A molecular recognition function was investigated using various aqueous ionic solutions, where the order of the width of LCST was observed to be $Ba^{2+} > Sr^{2+} > K^{+} > Li^{+} \sim Na^{+} \sim Ca^{2+}$. This order showed a good correlation with the complexation constant of crown ether receptors. In addition, the membrane altered its pore size of between 5 and 27 nm in response to changes in Ba^{2+}, but not for Ca^{2+}. Therefore, such a membrane can be used in various applications, for instance, artificial internal organs, drug delivery systems, and treatment of wastewater.

A novel separation system using porous thermo-sensitive membranes has been proposed for macromolecule separation.[115b] NIPAM was grafted on the pores of porous polypropylene (PP), which enabled the hydrophobicity of the pore surface to be varied by a slight temperature change. A solution containing hydrophobic and hydrophilic solutes was continuously supplied to the feed stream, and the membrane temperature was changed stepwise to below and above the LCST. Above the LCST, only hydrophilic solutes permeated through the pores of the thermo-sensitive membrane, and hydrophobic solutes adsorbed on the pore surface of the membrane induced by hydrophobic interaction. Lowering the temperature to below the LCST made the pore surface hydrophilic, and adsorbed hydrophobic solutes desorbed and concentrated on the permeate. By cycling the temperature at below and above the LCST, specific solutes can be concentrated and purified (Fig. 12). The adsorption selectivity used in such a system is unlike ultra-filtration, hence mixtures of solute with identical molecular sizes can be separated. The system can operate by manipulating the external stimuli, and in contrast to chromatographic separation, it does not require an elution liquid.

Fluorescent molecular thermometers have recently been developed based on the temperature responsive PNIPAM and fluorescence-sensitive benzofurazans.[116] By changing temperatures, the copolymers displayed a temperature-induced phase transition of ~32 °C, resulting in the reversible increase in fluorescence intensities. The sensitive range of temperature of these fluorescent molecular thermometers could be tailored by replacing NIPAM (29–37 °C) with *N*-isopropylmethacrylamide (45–54 °C) or *N*-*n*-propylacrylamide (18–24 °C).

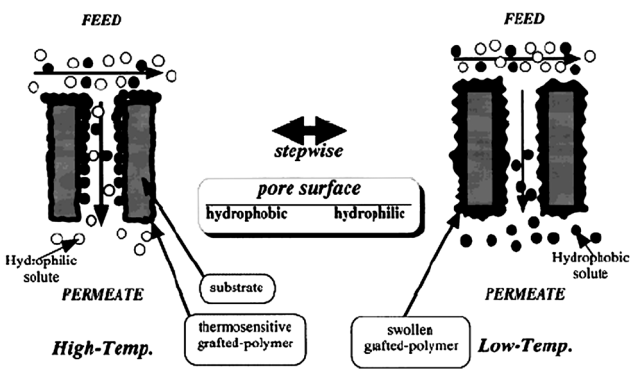


Fig. 12 Description on separation systems using a thermo-sensitive gel membrane. Reproduced from ref. 115*b* © American Chemical Society.

Using PNIPAM nanogels that self-organized into crystalline colloidal arrays (CCA), robust nanosecond photonic crystal switching material was developed.[117] These nanosecond phenomena may be useful in the design of fast photonic crystal switches and optical limiting materials, where smaller nanogels will exhibit even faster volume phase transitions. In addition, the P(NIPAM-*co*-MAA) nanoparticles based glucose-sensitive polymeric composite membrane was developed.[118] The rate of insulin permeation through the membrane was modulated by glucose concentration that was regulated by shrinkage or swelling of embedded pH-sensitive nanoparticles. Protein-polymer conjugates are widely used in biotechnology and medicine, and new methods for preparing bioconjugates would be advantageous for these applications. The bioactive "smart" polymer conjugates can be synthesized by polymerizing from defined initiation sites on proteins, thus preparing polymer conjugates *in-situ*. In particular, free cysteines, Cys-34 of bovine serum albumin (BSA) and Cys-131 of T4 lysozyme V131 C, were modified with initiators for ATRP either through a reversible disulfide linkage or irreversible bond by reaction with pyridyl disulfide- and maleimide-functionalized initiators. The protein macroinitiators were synthesized and used for the ATRP of NIPAM to produce thermal-sensitive BSA-PNIPAM and lysozyme-PNIPAM, where the lytic activities of lysozyme conjugates were compared.[119] The hydrogel layer consisting of a mixture of NIPAM and AA was introduced onto the surface of gold nanoparticles through surfactant-free emulsion polymerization.[120] When the temperature was raised above the LCST, the hydrogel polymer shrank dramatically. These hybrid nanoparticles were designed for an optically modulated drug delivery system that responds to ambient changes in temperature. Specifically, drug-impregnated hydrogel coatings can be photothermally activated by exposure to light that can be absorbed by plasmon resonance of gold nanoparticle cores.

3.2 Photo-responsive polymeric systems

Photo-responsive polymers are another category of stimuli-responsive systems that have attracted much attention due to their fully reversible responses when irradiated by a light source. Since light is non-destructive, and can be localized (in time and space), remote activation and delivery of energy to a system resulting in the photo triggering sensing, actuation, and transport, makes photo-functional material an interesting system. Within these polymeric systems, azobenzene containing polymers are the most widely studied systems, where the polymers undergo significant changes in geometry or polarity owing to the *cis*- to *trans*- isomerization.[121] For azobenzene modified derivatives, the inter-conversion between low energy *trans*- and higher energy *cis*- isomeric states can be achieved by either a photochemical or thermal approach with a high degree of efficiency without any competing side reactions. The *trans*- form can be converted to the *cis*- form using an appropriate wavelength of light. A different wavelength of light can be used to convert the molecule back to the *trans*- form. Alternately, the *cis*- molecule can thermally relax to the stable *trans*- form. Polymers containing azobenzene moieties often displayed remarkable photo- and

thermo-regulated behavior when subjected to changes in incident light or heat.[122] The switching of chiroptical properties of polymers upon external stimuli are of great interest because of potential applications in data storage, optical devices, and liquid crystalline displays.[123,124] Many new phenomena, related to this photo-isomerization, have been discovered, including photo-orientation of materials, photo-switching of material properties, and even an all-optical surface patterning phenomenon. These effects have been suggested for a wide variety of applications, from lithographic patterning, to optical switches, photo-actuation, and many others.[125]

The azobenzene segments could be located on either the backbone or the side-chain of the polymers. Several photo-responsive chiral polymers containing azobenzene on the main chain or side chain have been reported. For polymers with azobenzene located on the main chain, the photo induced isomerization had a profound impact on the polymer conformation and physical properties. These changes were dependent on the percentage of azobenzene segments and the rigidity of polymer backbone. Azobenzene modified poly(aryl ether ketone amide)s have been synthesized through low temperature polycondensation polymerization, where these materials were amorphous and possessed mixed physical properties.[126] They were photo-responsive and thermally stable up to 400 °C. Photo-induced *trans*- to *cis*- isomerization was observed under UV irradiation as evident from optical absorption spectroscopy, NMR and SEC. The reverse *cis*- to *trans*- isomerization could be triggered by either photochemical or thermal means. The *trans*- to *cis*- transition was found to be ~70% of the higher energy *cis*-isomer under UV irradiation. The calculated activation energy associated with *cis*- to *trans*- thermal isomerization was found to be ~21–23 kCal/mol, which was independent of molecular weight and backbone structure. Conformational restriction gave rise to a reduction in the impact of UV on the hydrodynamic volume. Circular dichroism (CD) spectra confirmed the presence of one-sided helical conformation in the *trans*-azobenzene modified polymers that were severely disrupted following the *trans*- to *cis*- isomerization reaction, which gave rise to a fully reversible thermal- and photo-responsive chiroptical behavior (Fig. 13).[126] These conformationally restricted copolyaramides underwent periodic and wavelength-dependent inversions, which might constitute a new class of solution-based, photo-modulated chiroptical switches suitable for applications in a number of emerging technological areas.

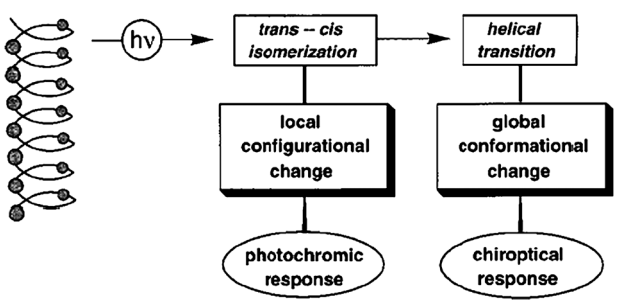


Fig. 13 Coupled photochromic and chiroptical responses in azobenzene modified helical polymers. Reproduced from ref. 126*c* © American Chemical Society.

For polymers with azobenzene on the branch chains, the isomerization behavior was different from that located on the backbone. The most common monomer was *trans*-4-methacryloyloxyazobenzene, which could be synthesized through the reaction of 4-hydroxyazobenzene and methacryloyl chloride in the presence of 2,6-di-*tert*-butyl-*p*-cresol and triethylamine.[127,128] The random copolymer of 4-methacryloyloxyazobenzene and MMA was synthesized, where the kinetics of photo-isomerization reaction of the monomer species under UV irradiation could be described by a simple first order exchange between the *trans*- and *cis*- forms of the monomer. However, the solution behavior was different from the bulk, and could be described by the sum of two equilibria, one was the first order exchange kinetics from *trans*- to *cis*- isomer similar to that of the monomer and the other was from the same *trans*- to *cis*- isomer with a much faster *cis*-/*trans*- exchange rate. The glutamic acid and azobenzene containing novel *N*-propargylamide was synthesized and polymerized using (nbd)RhC[h6–$C_6H_5BK(C_6H_5)_3$] catalyst.[129] This polymer possessed a helical structure in different solvents, and is dependent on UV irradiation. The *cis*- azobenzene moiety re-isomerized into *trans*- upon visible light irradiation, but the polymer could not recover the original helicity. It seemed that the driving force for helix deformation was induced by the increase in steric repulsion between side chains resulting from the isomerization of azobenzene moieties. Zentel and co-workers investigated a series of chiral polyisocyanates, which served as optical switches triggered by a small amount of azobenzene moieties.[130] Ueno and Ciardelli reported the helix transition of azobenzene-containing polypeptides.[131,132] The new liquid crystalline polymer poly[(4-{40-[(*S*)-2-methyl-1-butyloxycarbonyl]phenylazo}phenoxyl)x-methylene methacrylate] was synthesized and the chiroptical properties of the polymers were investigated by CD.[133] The length of spacer chains between the azobenzene segments and methacrylate backbone played important roles on both the transfer of chirality and photoinduced chirality in the polymeric films. The geometric change induced by the isomerization of azobenzene chromophore produced conformational changes in the polymer backbone. The well-defined water-soluble azobenzene containing block copolymers of DMAEMA and azobenzene (azo) methacrylates have recently been reported.[25,134] It was found that the ATRP of azo-methacrylates were achieved up to 50% conversion, after which deviation occurred. Such block copolymer self-assembled into micelles, but the *trans*–*cis*- isomerization had only a small effect on the critical micelle concentration of such azo methacrylate block copolymers due to the formation of a compact core in the micelles. Polymers of cyano- and butoxy-substituted azobenzenes exhibited liquid crystalline textures. The rates of *trans*- to *cis*- photoisomerization were almost identical to the DMAEMA copolymers of 6-[4-phenylazo]phenoxy]hexyl methacrylate (PPHM), P($DMAEMA_{172}$-*b*-$PPHM_9$), and 6-[4-(4-cyanophenylazo)phenoxy]hexyl methacrylate (CPHM), P($DMAEMA_{172}$-*b*-$CPHM_7$), where slightly slower rates have been observed for the copolymer of 6-[4-(4-butoxyphenylazo)phenoxy]hexyl methacrylate (BPHM), P($DMAEMA_{172}$-*b*-$BPHM_7$), due to steric hindrance presented by the bulky butoxy group. The rates in aqueous micellar solutions were only marginally faster than those in films for all the three di-block copolymers. In contrast, significant rate differences for the thermal *cis*–*trans*- isomerization of

P(DMAEMA$_{172}$-*b*-CPHM$_7$) were observed in film and in solution due to the donor–acceptor effect of CPHM. Recently, the azobenzene terminated PNIPAM has been synthesized using ATRP.[135] The azobenzene derivative substituted with a 2-chloropropionyl group was used as the initiator and thus azobenzene moiety was located at one end of resulting azo-PNIPAM polymers. Such polymer in solution revealed both temperature and photo responsive characters. The difference between the LCST after exposure to UV and visible irradiation increased linearly up to a value of 10 °C upon decreasing polymer molecular weight.

Azobenzene containing polymers can also be conjugated onto solid surfaces to impart photo-responsive characteristics to the surface. A dual-responsive silicon surface was fabricated by conjugating it with a DMA copolymer containing azobenzene moiety (Fig. 14).[136] The surface contact angles could be tailored by temperature or UV irradiation. The azobenzene groups in the polymer switched from normal *trans*- to a more polar *cis*-configuration, where potential applications in microfluidic devices and process separation were proposed. The azobenzene modified cyclodextrins have been used as the stationary phase in micro-HPLC for separating perylene and pentacene.[137] The temperature and light responsive stationary phase could provide selective retention control in the micro-HPLC system. Upon photo-radiation, not only the conformation but also the physicochemical properties were altered. The interactions between these azobenzene containing polymers and amphiphilic organic systems have been investigated. For azobenzene modified PAAs in aqueous solution, the highest degree of binding was achieved by using either a spacer chain between the backbone and azobenzene segments or by increasing the content of azobenzene.[138] Interaction between such azobenzene-modified PAAs and non-ionic surfactant indicated that the exposure to UV light rapidly converted the azobenzene to their more polar *cis*- isomer, which weakened the association with surfactant as illustrated in Fig. 15. The reversible light-triggered control of emulsion has been demonstrated by exposing a solution containing non-ionic surfactant $C_{12}E_m$, poly(sodium acrylate) grafted with azobenzene chromophore groups, *n*-dodecane, and a sodium nitrate aqueous phase to visible or UV light. The emulsion can be reversibly switched from an oil-in-water (dispersion of oil droplets into the water phase) to a water-in-oil (dispersion of water droplets into the oil phase) system since the high conductivity is related to the oil-in-water phase and zero conductivity indicates water-in-oil phase (Fig. 16).[138b]

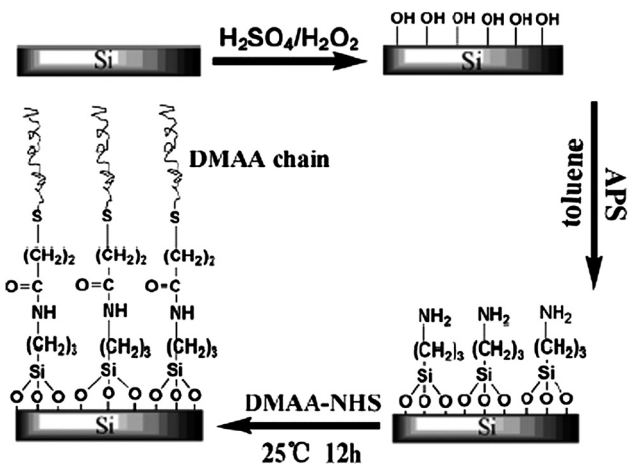


Fig. 14 Preparation process of the DMA-grafted silicon surface. Reproduced from ref. 136 © American Chemical Society.

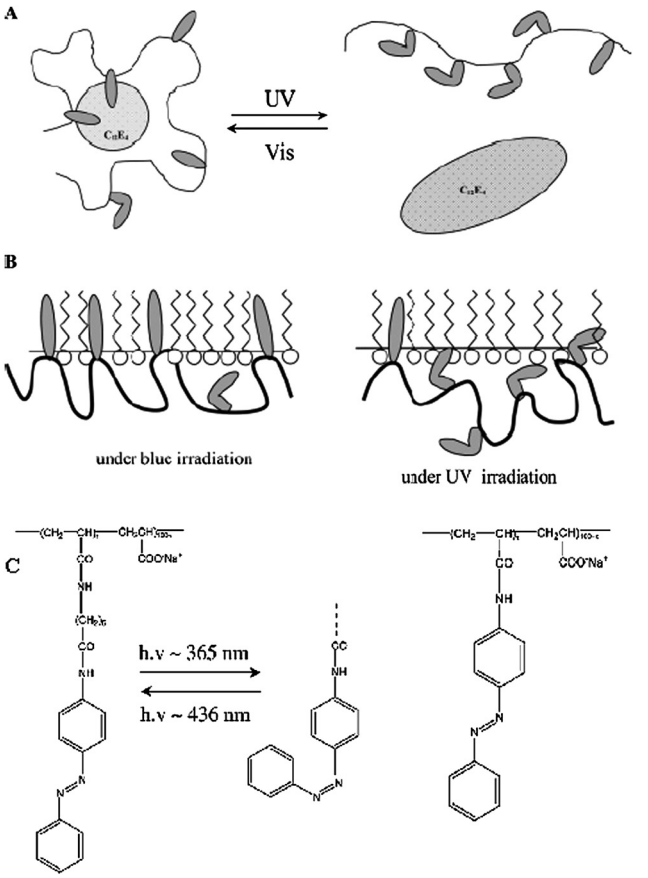


Fig. 15 Illustration of the mechanisms of azobenzene-modified polymer (AMP) binding onto a micelle of $C_{12}E_4$ (A) or at the air–water interface with $C_{18}E_4$ (B), the apolar isomer (*trans*-) of AMP reversibly converted into the polar *cis*- isomer by exposure to UV light (C). Reproduced from ref. 138*a* © American Chemical Society.

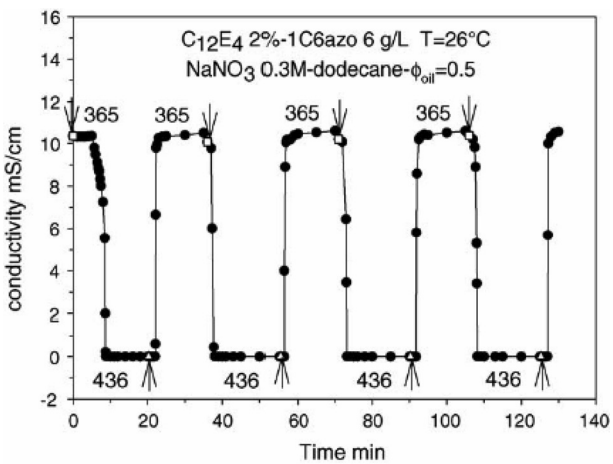


Fig. 16 Time dependence of the conductivity at constant temperature showing the reversible light-induced sweep of the Direct–Unstable–Inverse sequence of emulsions submitted to alternating UV (365 nm) and blue (436 nm) exposure. Reproduced from ref. 138*b* © Elsevier Ltd.

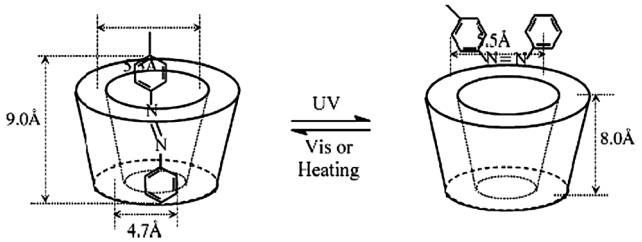


Fig. 17 The formation of inclusion complex between *trans*- and *cis*-azobenzene groups and cyclodextrins. Reproduced from ref. 140*c* © American Chemical Society.

The formation of an inclusion complex between cyclodextrins or cyclodextrin containing polymers and azobenzene modified PAAs indicated that the light-triggered *trans*- to *cis*- conformation of azobenzene moieties of azobenzene-modified polyacrylate (AMP) led to a marked increase in the viscosity of semi-dilute solutions.[139] The published data provided guidelines for the formulation of cyclodextrin/polymer systems, specifically, as viscosity enhancers that could be applied to pharmaceuticals or cosmetics formulations. Novel azobenzene functionalized hydroxypropyl methylcellulose (HPMC) was prepared and their interactions with different cyclodextrins were examined.[140] It was found that α-cyclodextrin could improve the water solubility of azo-HPMC by forming inclusion complexes with azobenzene side groups. The effect of photo-irradiation on the rheological behavior revealed that the gelation temperature of azo-HPMC increased after UV irradiation, while the gelation temperature of azo-HPMC/α-cyclodextrin complex decreased after UV irradiation. Isothermal titration calorimetry (ITC) indicated that α-cyclodextrin formed stable 1 : 1 stoichiometric inclusion complexes with *trans*- azo-HPMC, and not with *cis*- azobenzene groups (Fig. 17).[140c] Azo-HPMC with higher azobenzene content was less favored to form inclusion complexes. Recently, Lam and co-workers synthesized a water-soluble azobenzene containing functional monomer 4-[(4-methacryloyloxy)phenylazo] benzenesulfonic acid (MAPASA) that was used for the fabrication of a photo-responsive molecularly imprinted hydrogel material.[141] The affinity of the hydrogel for paracetamol can be photo-regulated, and upon irradiation at 353 nm, 83.6% of receptor-bound paracetamol was released from the imprinted hydrogel. Subsequent irradiation at 440 nm caused 94.1% of the released paracetamol to be re-bound by the hydrogel.

4. Conclusions and perspectives

Stimuli-responsive polymeric systems can be synthesized through conventional free radical, ring opening and controlled polymerization techniques from lab to industrial scale. The "living" radical polymerization provides an easy approach to synthesize well-defined block copolymers, and such polymers form nanostructured particles in solution or polymer brushes on solid surfaces. Besides pH, external stimuli, such as temperature, ionic strength, and light can be applied to manipulate their physicochemical properties. In aqueous microgel system, external stimuli produce phase separation and swelling/deswelling of the particles, respectively. For block copolymers, the stimuli-responsive polymers self-assembled into different types of aggregates on application of an external stimulus. Azobenzene containing photo-responsive polymers alter their configurations and hydrophobicity on the application of an external light source. Such polymeric materials have found wide applications in controlled release drugs, DNA or gene delivery, protein separation, coating thickeners and applications where triggering by external stimuli is necessary.

Response to an external stimulus is a common characteristic of many biological systems. The stimuli-responses of most living systems is usually very complex, thus the creation of model systems with well-defined properties will advance our understanding on their applications in living systems. The reported increased interest by the scientific community on the research and development of stimuli-responsive polymeric systems is a positive trend that should be encouraged. Funding agencies should invest and support these activities, as such collaboration will lead to innovative solutions for various chemical and biomedical applications. Novel materials and new synthetic techniques (*e.g.* controlled/living emulsion polymerization) are being developed, such as the use of novel and non-toxic catalysts as recently reported by Matyjaszewski and co-workers.[142] Using ATRP and click chemistry in conjugating various types of polymeric segments, ligands, receptors or peptides offer a simple and robust method to produce functional stimuli-responsive polymers for many new emerging applications.[143,144] We should see an increasing range of novel systems with attractive properties that will be developed for many different applications. The development of rapid response hydrogels and nanogels that are biocompatible and biodegradable would be essential for the successful applications in biological systems. In addition, the application of biomolecular responsive polymeric systems in novel biosensor devices would be an exciting field for future activity. For application in many biological systems, the interactions of stimuli-responsive systems and biological substrate or interfaces (*e.g.* cell membrane) needs to be addressed, and greater insight should be developed. The thermodynamics and kinetics of such interactions in combination with a detailed understanding on the transport characteristics of the drug or biomolecules to the target site should be addressed.

5. Acknowledgement

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