

Responsive Polymers for Detection and Sensing Applications: Current Status and Future Developments

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ABSTRACT: The past two decades have evidenced a tremendous growth in the field of responsive polymers, which can exhibit reversible or irreversible changes in physical properties and/or chemical structures to an external stimulus such as pH, temperature, ionic strength, light irradiation, mechanical forces, electric and magnetic fields, specific analytes, external additives (ions, bioactive molecules, etc.), or a combination of them. Responsive polymers can exist in the form of solutions, gels, self-assembled nanoparticles, (multilayer) films, and bulk solids. The field of responsive polymers has nowadays evolved well beyond the demonstration of novel and interesting properties. Currently, the exploitation of useful and advanced functions, e.g., drug or gene carriers with triggered release properties, catalysis, detection and imaging, environmentally adaptive coatings, and self-healing materials, has emerged to be a more relevant subject. In this Perspective, we focus on recent developments of responsive polymer-based chemo- and biosensors, highlighting this concept with selected literature reports. Such functional polymeric materials show prominent advantages such as tunable detection sensitivity, structural stability, aqueous dispersibility, biocompatibility, processability, and facile integration into detection devices, as compared to their small molecule analogues.

1. Introduction

Representing a main category of soft matter entities, stimuli-responsive polymers are capable of exhibiting reversible or irreversible changes in physical properties and/or chemical structures to small changes in external environment. Various types of stimuli, e.g., pH, temperature, ionic strength, light irradiation, mechanical forces, electric, magnetic, and acoustic fields, specific analytes or external additives (ions, bioactive molecules, etc.), have been employed to induce changes in chain conformation, solubility, and the self-assembly of responsive polymers. Responsive polymers can exist in the form of solutions, gels, self-assembled nanoparticles, (multilayer) films, and bulk solids (Scheme 1).^{1–5} Because of their unique properties, stimuli-responsive polymeric systems enable the fabrication of smart materials with tailorable functions and can be applied in a variety of circumstances, e.g., controlled drug and gene delivery, bioseparation, protein purification, personal care, industrial coatings, oil exploration, biological and membrane science, viscosity modifiers, colloid stabilization, surface modification, and water remediation.^{6–9}

In the past two decades, fundamental research in the field of responsive polymers has mainly focused on the following aspects: (1) designing of novel responsive polymeric systems;¹⁰ (2) investigating the equilibrium transition states and relevant kinetic processes under external stimuli;^{11–17} (3) understanding at the molecular level the effects and interplay of various noncovalent interactions (hydrophobic interactions, hydrogen bonding, electrostatic interactions, host–guest recognition, coordination, π – π stacking), which govern the self-organization and structural adaptivity of responsive polymeric systems;^{18–20} (4) developing

functional systems utilizing responsive polymers based on existing concepts or a combination of them.^{3,21–25}

The chemical and topological structures of responsive polymers are directly related to their responsive properties. The synthesis of responsive polymers with varying chain architectures, e.g., linear, cyclic, graft, (miktoarm) star, and other non-linear polymers, has been facilitated in the past decade by employing group transfer polymerization (GTP), ring-opening polymerization (ROP), click reactions, and various controlled radical polymerization techniques,²⁶ e.g., atom transfer radical polymerization (ATRP),²⁷ reversible addition–fragmentation chain transfer (RAFT) polymerization,^{28–30} and nitroxide-mediated polymerization (NMP).³¹ These new chain topologies can endow responsive polymers with self-assembling nanostructures possessing novel morphologies and functions both in solution and in bulk states.

It should be noted that the field of responsive polymers has nowadays evolved well beyond the demonstration of novel and interesting properties. Currently, the exploitation of useful and advanced functions such as drug or gene carriers with triggered release properties, catalysis, detection and imaging, environmentally adaptive coatings, and self-healing materials has emerged to be a more relevant subject. The capability of facile manipulation of the solubility, hydrodynamic volume, and chain configuration and conformation of responsive polymers by external stimuli has indeed enabled the development of responsive polymeric systems with novel functions. Intuitively, responsive polymers should play an important role in detection and sensing applications. However, stimuli-responsive polymer-based detection systems are still in its infancy stage as compared to the relatively mature field of small molecule probes^{32–34} and conventional polymer-based gas and humidity sensors by exploiting their intrinsic properties.³⁵

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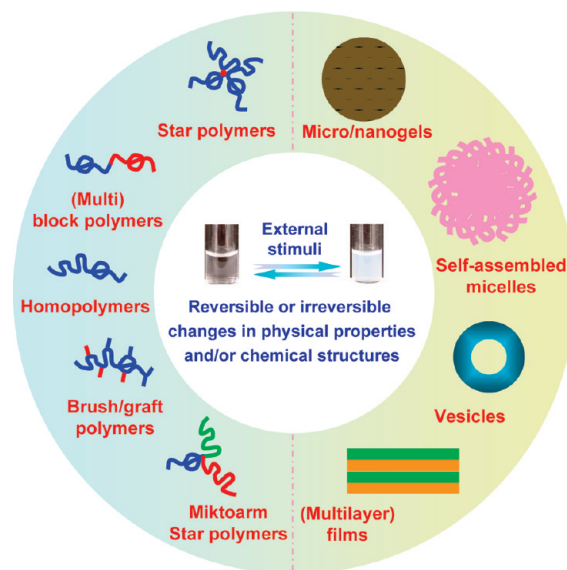
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In the past few decades, thousands of small molecule-based sensing systems have been developed to detect various analytes,³⁶

Scheme 1. Schematic Illustration of Stimuli-Responsive Polymers Existing in a Variety of Forms Including Unimer Chains with Varying Topologies, Self-Assembled Aggregates (Micelles, Vesicles, and Nanoparticles), Microgels/Nanogels, Thin Films, and Multilayer Films

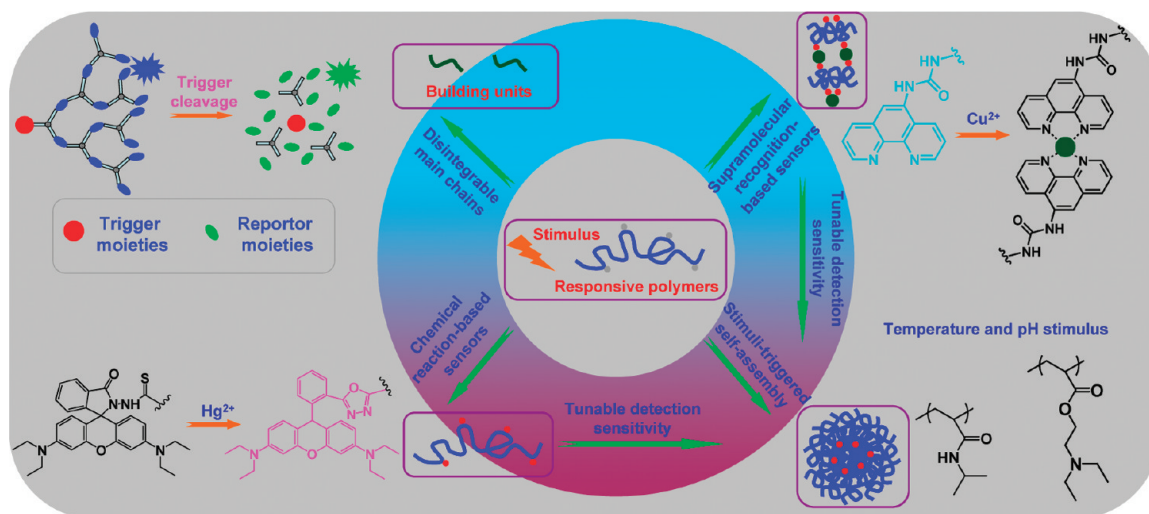


e.g., ions,^{37,38} pH,³⁹ temperature,⁴⁰ biomolecules,³³ explosives,³⁴ and mechanical forces.⁴¹ They can be generally categorized into two main types on the basis of detection principles, namely molecular recognition-based small molecule sensors and chemical reaction-based ones. Based on detection techniques, colorimetric and fluorometric reporting systems have been most often utilized due to their low cost, high sensitivity, and facile operation.^{32,42–44} It is worth noting that small molecule-based chemosensors usually suffer from major limitations such as poor water solubility, low structural stability, and difficulty in further functionalization. In order to overcome these shortcomings, the integration of small molecule probes into other matrices such as natural and synthetic polymers, gels, mesoporous silica, flat substrates, and metal nanoparticles⁴⁵ has been utilized as a novel approach. In addition to the use of polymers as immobilizing matrix for sensing specific analytes by learning from the selectivity and sensitivity of small molecule probes, increasing attention has also been paid to the development of polymer sensors based on their intrinsic properties. This has led to a variety of sensor devices, such as gas sensors, pH sensors, humidity sensors, and ion-selective sensors based on conducting polymers and nonconducting polymers.³⁵

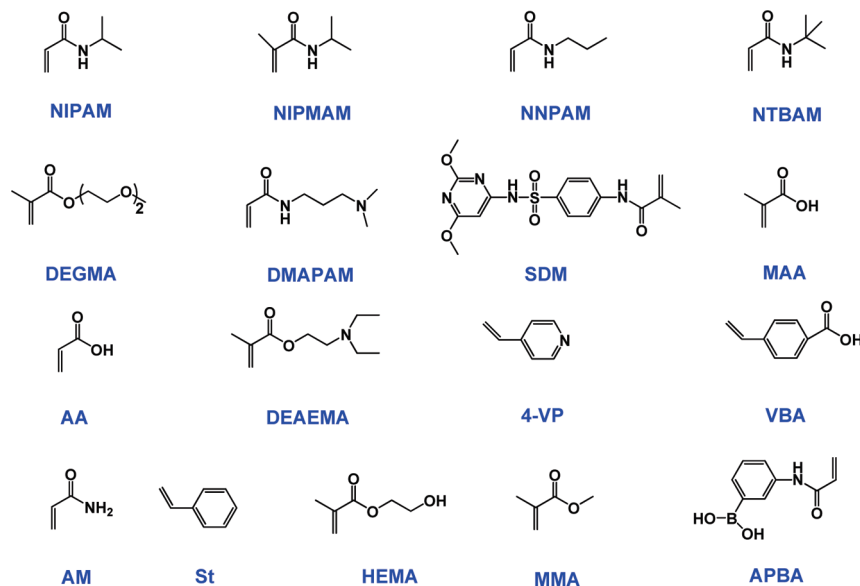
On the other hand, responsive polymer-based detection and sensing systems has been relatively less exploited, as compared to the relatively mature fundamental research in the field of responsive polymers.^{6–9} Based on chemical intuition, the incorporation of responsive polymers into detection and sensing areas can bring extra advantages such as adjustable water dispersibility, multifunctionality, tunable detection sensitivity, and facile integration into sensing devices, as compared to conventional polymer-based sensors and small molecule ones.^{32–35}

In the past 5 years, the development of responsive polymer-based sensors has been an emerging research field, which mainly include three research directions: (1) development of sensors by exploiting intrinsic properties of responsive polymers; (2) the incorporation of small molecular detecting components into responsive polymers, enabling improved sensing performance; (3) the introduction of novel detecting mechanisms and concepts into responsive polymer-based sensors to achieve high selectivity and sensitivity, such as self-immolative polymers and mechano-responsive polymers (Scheme 2). In this Perspective, we focus

Scheme 2. Schematic Summary of Responsive Polymer-Based Sensors, Which Can Be Categorized into Sensors by Exploiting the Intrinsic Responsive Properties, Supramolecular Recognition-Based Sensors, Chemical Reaction-Based Sensors, Self-Immolative Polymer-Based Sensors, and Mechano-responsive Polymer-Based Sensors



Scheme 3. Chemical Structures of Polymerizable Monomers Employed for the Synthesis of Responsive Polymers Described in This Perspective



on recent developments of responsive polymer-based chemo- and biosensors, highlighting this concept with selected literature reports. Such functional polymeric materials show prominent advantages such as tunable detection sensitivity, structural stability, solvent dispersibility, biocompatibility, processability, and facile integration into detection devices, as compared to their small molecule analogues. An outlook on future developments in the field of responsive polymer-based sensors is also presented.

2. Sensors by Exploiting Intrinsic Properties of Responsive Polymers

pH- and thermo-responsive polymers can molecularly dissolve in aqueous solution under certain conditions; however, they undergo chain collapse and aggregation in aqueous solution above or below a critical pH (pK_a) or temperature, accompanied by changes in chain conformations and the formation of hydrophobic domains (Scheme 1).^{1–5} By covalently incorporating environmentally sensitive fluorescent reporters (Schemes 3 and 4) into responsive polymers, pH and temperature variations can be transformed into significant changes in fluorescence signal

intensities owing to changes in microenvironmental hydrophilicity/hydrophobicity. Thus, small variations in pH and temperatures can be monitored by exploiting the intrinsic responsive properties of the polymer matrix (Scheme 2). Some typical examples of responsive polymer-based pH and thermal sensors are highlighted below.

2.1. Responsive Polymer-Based Temperature Sensors. Original examples of thermo-responsive polymer-based fluorescent thermometers were reported in 2003 by Uchiyama and Iwai et al.,⁴⁶ taking advantage of the combination of polarity-sensitive fluorescent dyes and aggregation properties of responsive polymers. The screening of suitable fluorescent reporter sensitive to microenvironmental changes is quite critical in the sensor design. Thermo-responsive polymers in aqueous solution typically form aggregates with decreased polarity above their lower critical solution temperatures (LCSTs). A variety of thermo-responsive polymers with varying LCSTs have been employed for the construction of polymer-based thermometers, such as homopolymers or copolymers of *N*-isopropylacrylamide (NIPAM), *N*-isopropylmethacrylamide

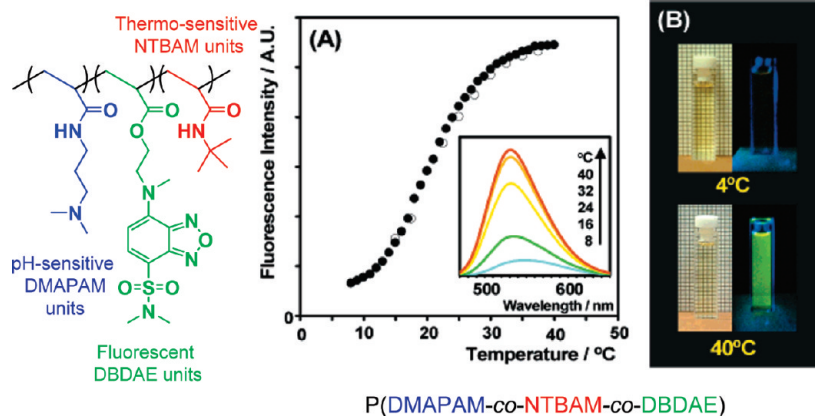
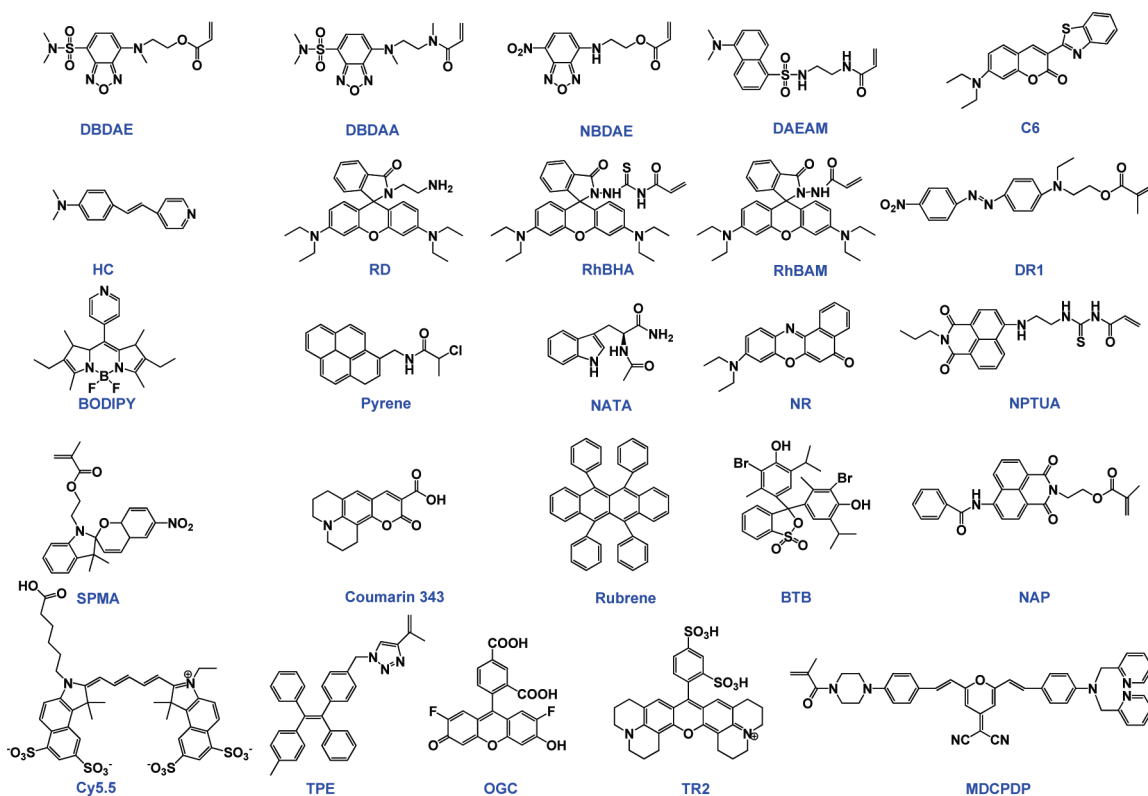


Figure 1. Thermoresponsive P(DMAPAM-co-NTBAM-co-DBDAE) copolymer in aqueous solution serves as a fluorescent molecular thermometer. (A) Fluorescence intensity changes upon heating and cooling cycles. Inset: fluorescence spectra. (B) Visual and fluorescent images at temperatures below and above the LCST. Reproduced with permission from ref 47.

Scheme 4. Chemical Structures of Polymerizable and Functionalized Fluorescent Dyes Involved in This Paper



(NIPMAM), *N*-*n*-propylacrylamide (NNPAM), and *N*-*tert*-butylacrylamide (NTBAM). Typical polymerizable fluorescent reporters employed by Uchiyama et al.^{46–53} contain benzoxadiazole motifs, such as 4-*N*-(2-acryloyloxyethyl)-*N*-methylamino-7-(*N,N*-dimethylamino)sulfonyl-2,1,3-benzoxadiazole (DBDAE) and 4-(2-acryloyloxyethylamino)-7-nitro-2,1,3-benzoxadiazole (NBDAE). They share common characteristics in aqueous dispersion, i.e., weakly fluorescent in the hydrophilic microenvironment and strongly fluorescent in hydrophobic domains.

In a typical example, DBDAE monomer was copolymerized into a thermoresponsive polymer; in aqueous solution, the obtained P(DMAPAM-co-NTBAM-co-DBDAE) exhibits dramatic increase in fluorescence emission intensity at temperatures above the LCST. Thermal phase transition leads to the collapse and aggregation of polymer chains,

and this renders the microenvironment of DBD dyes to transform from being hydrophilic to hydrophobic, accompanied by the considerable increase in quantum yields of covalently embedded DBDAE dyes. Because of the presence of pH-sensitive DMAPAM moieties ($pK_a \sim 9.8$), P(DMAPAM-co-NTBAM-co-DBDAE) copolymer in aqueous solution can also serve as a sensitive pH probe (Figure 1).⁴⁷ By copolymerizing DBDAA dyes into thermoresponsive PNIPAM microgels, they also obtained nanoparticle-based thermometers which exhibit enhanced fluorescence intensity above the LCST. More interestingly, the presence of increasing amounts of KCl (0–100 mM) can enable more accurate temperature detection capability (up to ~ 0.5 °C resolution). They also successfully demonstrated that this novel type of microgel-based thermometer can be employed for intracellular thermometry.⁵⁰

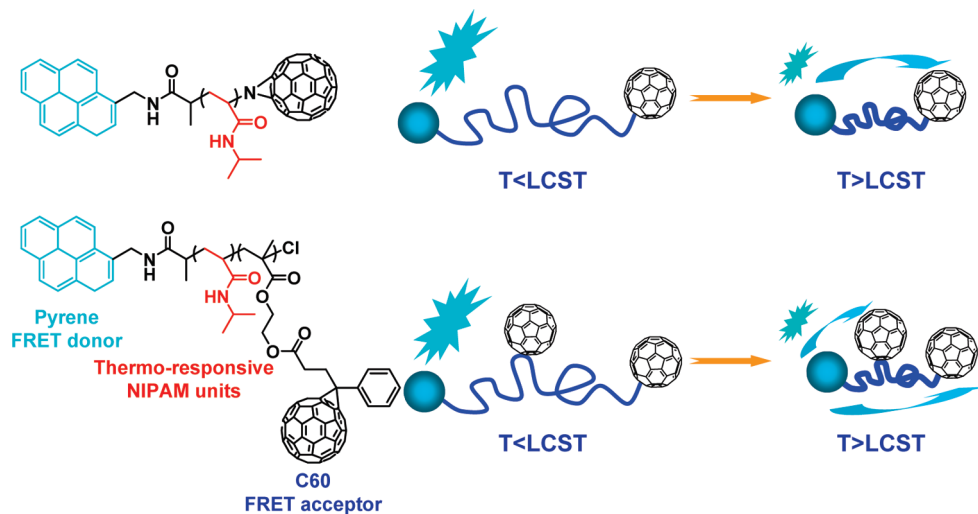


Figure 2. Thermoresponsive *Py*-PNIPAM-C60 in extremely dilute aqueous solution (10^{-7} M) serves as a fluorescent molecular thermometer. Reproduced with permission from ref 64.

Other fluorescent dyes such as hemicyanine (HC),⁵⁴ rhodamine (RD),^{55,56} and BODIPY⁵⁷ were also covalently attached to thermoresponsive PNIPAM chains to construct polymer-based thermometers, which were reported by Shiraishi's research group. Different mechanisms, i.e., decreased microenvironmental polarity^{54–56} and increased local viscosity,⁵⁷ were ascribed to the fluorescence enhancement above the LCSTs of P(NIPAM-*co*-HC), P(NIPAM-*co*-RD), and P(NIPAM-*co*-BODIPY) systems. However, the incorporation of fluorescent dyes into thermoresponsive polymers does not always lead to enhanced fluorescence emission above the thermal phase transition. PNIPAM incorporated with pyrene and carbazole moieties were known to exhibit decreased fluorescence emission above the LCST.^{17,58,59} Taking RD as an example, it is quite tricky to judge the trends of fluorescence intensity changes under different circumstances. PNIPAM functionalized with RD derivatives, which were synthesized from rhodamine B (RhB) and 1,2-ethylenediamine or hydrazine, in acidic aqueous media exhibits enhanced fluorescence upon thermal phase transition,^{55,56} whereas films of RhB-functionalized PMMA exhibit decreased fluorescence upon heating.⁶⁰

Near-infrared (NIR) fluorescent dyes can also be incorporated into thermoresponsive polymers for temperature sensing. Because of improved penetration depth and less interference from tissue autofluorescence, NIR dye-labeled responsive polymers are suitable for tissue thermal imaging. In a typical example, NIR dyes (Cy5.5) were covalently attached to chain terminals of pluronic triblock copolymers, poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide) (PEO-*b*-PPO-*b*-PEO). In this case, fluorescence intensity decreases monotonically with temperature in the broad range of temperatures (1–80 °C) though it is known that this triblock copolymer exhibits thermoinduced aggregation behavior above ~20 °C. As Cy5.5 was attached to hydrophilic PEO block, it seems that in aqueous solution the formation of PPO-core micelles does not affect the trend of decreasing fluorescence quantum yield with increasing temperatures.⁶¹ Another interesting thermosensitive fluorescent dye in the UV region is *N*-acetyl-L-tryptophanamide (NATA), which was employed for temperature calibration (up to 0.1 °C accuracy) in the stopped-flow T-jump experiments.⁴⁰

Under extremely dilute conditions, thermoresponsive polymers typically exhibit single chain collapse upon heating.¹⁷ If both chain ends were labeled with fluorescent donor and acceptor, the principle of Förster resonance energy transfer

(FRET) can be employed for thermal sensing. It should be noted that the same strategy has been conventionally employed in protein and DNA folding studies.^{62,63} In a recent example, the chain ends of PNIPAM were labeled with pyrene and C60. Thermoinduced collapse of *Py*-PNIPAM-C60 chain leads to decreased spatial distance between fluorescent pyrene dyes and the C60 quencher; i.e., enhanced FRET process can be achieved above the LCST. Thus, temperature changes can be transformed into fluorescence intensity changes due to enhanced or weakened fluorescence quenching efficiency at temperatures above or below the LCST, respectively (Figure 2).⁶⁴ Just recently, Zentel et al.⁶⁵ reported another example based on α,ω -heterodifunctionalized thermoresponsive polymers of diethylene glycol methacrylate (DEGMA) via the RAFT technique. Fluorescence donor, Oregon Green cadaverine (OGC), and acceptor, Texas Red-2-sulfonamidoethyl methanethiosulfonate (TR2), were chosen as labeling dyes. This example allows the ratiometric fluorescent temperature sensing by comparing the relative intensities of donor and acceptor emissions due to that the FRET efficiency is closely correlated to the thermal phase transition of dye-labeled PDEGMA.

Tang et al.^{66,67} recently employed the concept of aggregation-induced emission (AIE) effects to construct PNIPAM-based thermal sensors. The monomer derived from tetraphenylethene (TPE), which exhibits an AIE emission feature, was copolymerized with NIPAM. In THF, P(NIPAM-*co*-TPE) is nonemissive and increasing water contents leads to enhanced fluorescence emission due to the formation of solvophobic domains. Interestingly, heating the aqueous solution of P(NIPAM-*co*-TPE) above its LCST further leads to ~2 times increase in fluorescence intensity. This has been ascribed to the fact that the more prominent aggregation of PNIPAM chains at elevated temperatures can further depress the intramolecular rotation of TPE moieties.

It is well-known that spiropyran (SP) is nonfluorescent under visible light and transforms to the ring-opened merocyanine (MC) form possessing red fluorescence emission under UV irradiation.^{68,69} Recently, Wu et al.⁷⁰ reported the construction of a colorimetric and fluorometric temperature sensor based on organic/inorganic hybrid PNIPAM brushes (Figure 3). Consecutive ATRP copolymerization of NIPAM with specific fluorescent dyes from the surface of silica nanoparticles leads to hybrid nanoparticles coated with PNIPAM brushes of two layers, with the inner

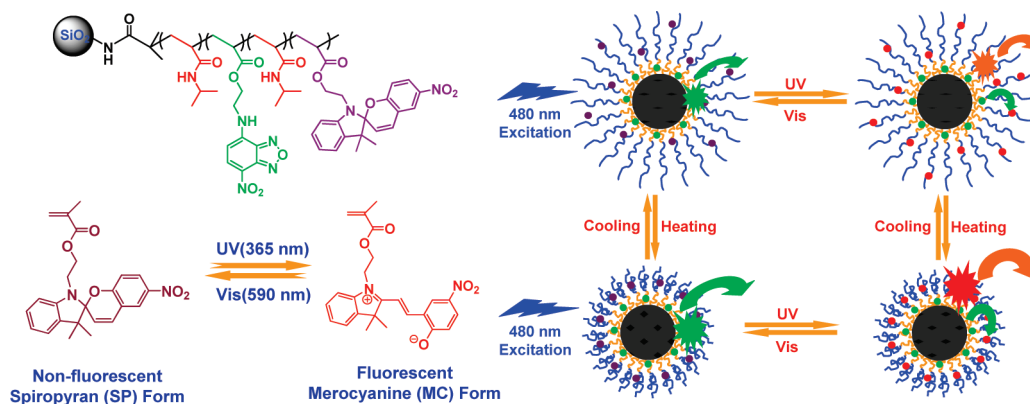


Figure 3. Schematic illustration for the reversible modulation of multicolor fluorescent system fabricated from hybrid silica nanoparticles coated with thermoresponsive P(NIPAM-*co*-NBDAE)-*b*-P(NIPAM-*co*-SPMA) brushes, which can serve as a ratiometric temperature sensor. Reproduced with permission from ref 70.

and outer layer covalently labeled with NBDAE and SP moieties. Under visible light, the outer layer is nonemissive. Heating the aqueous dispersion of hybrid nanoparticles leads to the collapse of PNIPAM brushes, accompanied by enhanced fluorescence emission from NBDAE moieties. Under UV irradiation, a ratiometric thermal sensor can be constructed based on the FRET process between NBDAE (fluorescence donor) in the inner layer and ring-opened MC form of SP (fluorescence acceptor) in the outer layer. Upon heating, the collapse of PNIPAM brush leads to decreased spatial distances between fluorescent donors and acceptors, i.e., enhanced FRET efficiency. In the temperature range of 20–40 °C upon UV irradiation, a colorimetric yellow-to-red transition can also be discerned by the naked eye.

Because of their unique photoluminescence behavior of quantum dots (QDs),⁷¹ i.e., size-tunable emission color, narrow and symmetric emission profile, and high emission stability against bleaching, they have also been integrated into thermoresponsive PNIPAM microgels to construct thermal sensors. In a typical example, two types of CdTe QDs with emissions at 520 and 610 nm were embedded into PNIPAM microgels via hydrogen-bonding interactions. Thermoinduced collapse and swelling of microgels leads to tunable spatial distance between two types of QDs; thus, temperature variations can be transformed into ratiometric fluorescence intensity changes.⁷²

2.2. Responsive Polymer-Based pH Sensors. In living organisms, intracellular pH plays key roles in enzyme, cell, and tissue activities. Monitoring pH changes and gradients is vital to diagnose certain cancer diseases and investigate cellular internalization pathways.³⁹ pH sensors based on synthetic responsive polymers have been constructed according to similar design principles employed for temperature sensors. Typical pH-responsive polymers include poly(4-vinylpyridine) (P4VP), poly(2,2-diethylaminoethyl methacrylate) (PDEAEMA), and poly(4-vinylbenzoic acid) (PVBA). pH variations above or below their pK_a lead to either protonation or deprotonation of polymer chains, which are accompanied by dramatic changes in aqueous solubility. Jo et al.^{73–75} labeled pH-responsive poly(sulfadimethoxine) (PSDM, $pK_a \sim 7$) with pyrene and coumarin 343 at both chain terminals. pH changes below or above 7 lead to chain collapse/aggregation or swelling, respectively, resulting in enhanced or decreased FRET efficiency. Ratiometric pH sensors can thus be constructed. To avoid uncontrolled aggregation of PSDM at low pH, they further introduced hydrophilic segment onto PSDM and labeled coumarin (fluorescent donor) and coumarin 343 (fluorescent acceptor) at the diblock junction

point and the PSDM chain end of PEO-*b*-PSDM block copolymers, respectively. By decreasing the pH from 7.6 to 6.8, a blue-to-green emission transition can be observed under UV irradiation.⁷⁴

Another strategy for the construction of pH sensors employs inert or responsive polymers functionalized with pH-sensitive dyes. Fluorescein is one of the most well-known pH sensitive dyes. It possesses a pK_a of ~ 5.6 and exhibits pH-switchable transformation between mono- and dianionic states.⁷⁶ By covalently attaching fluorescein onto inert polymer matrices, such as poly(acrylamide) (PAM) microgel,⁷⁷ poly(styrene) nanoparticles,⁷⁸ and biocompatible dextran nanoparticles,⁷⁹ ratiometric pH probes can be constructed via the extra introduction of reference dyes. Hoogenboom et al.⁸⁰ recently copolymerized DEGMA with dispersed red 1 (DR1)-based azo monomer; the obtained thermoresponsive polymer can act as dual sensors for pH and temperature by taking advantage of the solvatochromic behavior of DR1. Another polarity-sensitive dyes such as calcon was also covalently incorporated into P(NIPAM-*co*-AA-*co*-AM) microgels to fabricate nanoparticle-based pH sensors.⁸¹

Very recently, Peng and Wolfbeis et al.⁸² synthesized fluorescent polyurethane nanogels physically embedded with three types of dyes for intracellular pH sensing. Coumarin 6 (C6) and Nile Red (NR) were chosen as fluorescent donor and acceptor, respectively, and the pH-sensitive moieties, bromothymol blue (BTB), were entrapped into the nanogel. BTB in aqueous solution is yellow at pH < 6 with an absorption peak at around 435 nm. At pH > 8, however, it turns blue with an absorption band at 628 nm. Upon excitation of C6 at 440 nm, green fluorescence at 520 nm is observed, accompanied by partial energy transfer to NR via the FRET mechanism, resulting in an emission at 620 nm. Because of the overlap of C6 emission or NR emission with the absorption of BTB at low and high pH conditions, respectively, pH changes, especially in the range of pH 6–8, can be monitored via changes in relative fluorescence intensity ratios of C6 and NR emissions. A main limitation of this report is that all dyes were physically embedded into the nanogel matrix; thus, the long-term stability of this pH-sensing system is partially problematic due to the uncontrolled diffusion of dyes out of nanogels.

Another notable example of ratiometric fluorescent pH sensors was constructed from amphiphilic diblock copolymers, P(St-*co*-NBDAE-*co*-SPMA)-*b*-P(NIPAM-*co*-RhBAM). The fluorescent donor (NBDAE), and two types of acceptors, photoresponsive SPMA and pH-sensitive RhBAM, were all covalently attached to diblock copolymer chains (Figure 4).

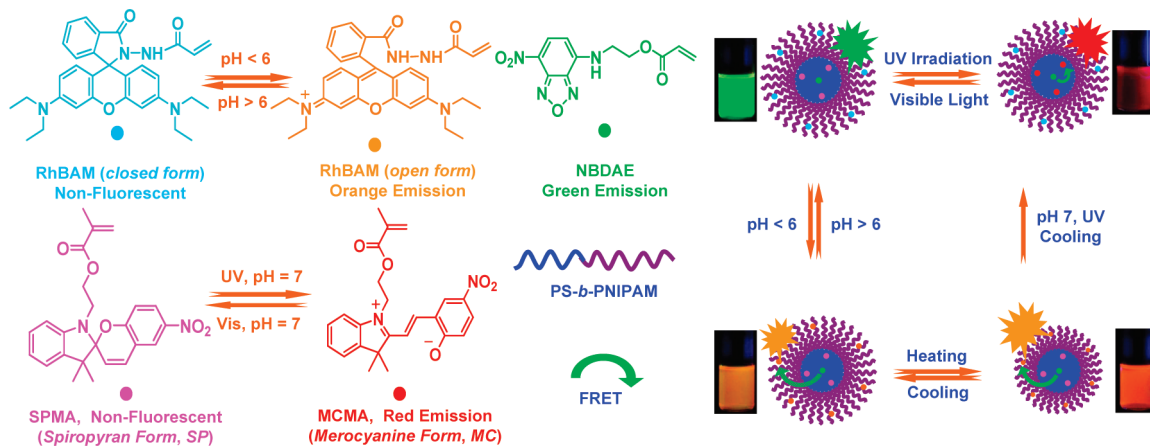


Figure 4. Schematic illustration for the construction of polymeric micelles-based reversible three-state switchable multicolor luminescent system fabricated from amphiphilic and thermoresponsive diblock copolymer, $P(\text{St-co-NBD-DAE-co-SPMA})-b-P(\text{NIPAM-co-RhBAM})$, bearing NBD-DAE and photoswitchable SPMA fluorophores in the hydrophobic PS block and pH-switchable RhBAM dyes in the thermoresponsive PNIPAM block. Also shown are macroscopic images recorded under UV light. Reproduced with permission from ref 83. Copyright 2010 Wiley-VCH.

RhBAM moieties are nonfluorescent at $\text{pH} > 6$ and highly emissive at $\text{pH} < 6$. Thus, self-assembled micelles fabricated from the amphiphilic diblock copolymer exhibit on/off pH-switchable FRET process for the NBD-DAE/RhBAM pair. Moreover, the pH-detection sensitivity can be further tuned by temperatures via thermoinduced collapse of PNIPAM coronas, which will decrease the relative spatial distance between the FRET pair. Small variation in pH around 6 leads to apparent changes in fluorescence emissions which can be easily discerned by the naked eye. Because of the presence of photoresponsive SPMA, the micelle-based detection system also possesses extra feature of photoswitchable on/off control of the FRET process between NBD-DAE and SPMA moieties (Figure 4).⁸³

In the above examples relevant to responsive polymer-based pH and temperature sensors, either polarity-sensitive dyes or thermo- and pH-sensitive dyes were physically embedded or covalently attached to the responsive polymer matrix. It is quite expected that the “covalent” approach will be more promising as it provides long-term structural integrity and stability, whereas physically embedded dyes are subjected to uncontrolled diffusion out of the polymer matrix and seriously affect reliability and repeatability of the detection system. Moreover, for the approach of physical embedding of fluorescent dyes within responsive polymer matrix, typically via hydrophobic associations, it is difficult to precisely control the locations and spatial distributions of fluorescent reporter moieties. It is worth noting that currently chain topologies of responsive polymers employed for temperature and pH sensing reported in the literature reports are mainly concerned with homopolymers and random copolymers. For the construction of efficient responsive polymer-based FRET systems, other chain topologies such as star (block) copolymers, (multi)block copolymers, dendrimers, and hyperbranched polymers can be further employed to accurately control the distribution and location of functional moieties along the polymer chains. Finally, supramolecular assemblies of responsive polymers such as micelles, vesicles, and other aggregates with well-defined microstructures should be further exploited to enhance the detection efficiency and sensitivity and achieve functional integration and cooperativity.

3. Responsive Polymer-Based Sensors via Supramolecular Recognition

The design of intrinsic sensors based on responsive polymers mainly takes advantage of polarity or microenvironment-

sensitive dyes covalently incorporated into responsive polymers, which exhibit reversible chain conformational changes and controlled aggregations upon pH or temperature variations. Thus, sensing functions mainly focused on pH and temperature detections. The design of supramolecular recognition-based small molecular probes typically relies on the covalent linkage between molecular recognition and fluorescence reporter units, which requires tedious and multistep synthetic procedures. In the new concept of self-assembled sensors, molecular recognition and reporter units can be embedded into surfactant micelles or covalently attached to the surface of silica nanoparticles, mesoporous silica, and glass substrates.⁴² Previously, the combination of specific supramolecular recognition processes with fluorescent systems has allowed the construction of on/off switchable molecular logic gates.^{84,85}

Polymers can act as the immobilizing matrices for anchoring supramolecular recognition-based small molecule probes. In a notable example, the covalent linkage of photoinduced electron transfer (PET)-based small molecule ion-sensing motif via the K^+ -crown ether recognition mechanism to natural polymers such as hydroxypropyl cellulose (HPC) enabled the construction of a portable blood/serum K^+ analyzer in Roche OPTI CCA.⁸⁶ In this example, HPC was only utilized as a hydrophilic detecting matrix for the covalent embedment of small molecule probes, and this concept is quite typical in polymer-derived sensors.³⁵ On the other hand, the introduction of responsive polymers into sensor design is expected to enable the fine-tuning of spatial distributions between molecular recognition units and fluorescence reporter units, which can enhance the detection sensitivity, as compared to supramolecular recognition-based small molecule probes.^{32–34} It should be noted that there exist only a few relevant literature reports in this aspect.

In a recent example of responsive polymer-based self-assembled Cu^{2+} sensors, thermoresponsive collapse/swelling of microgels has been utilized to construct detection systems with tunable sensitivity. Metal-chelating monomer, N -(2-(2-oxo-2-(pyridine-2-ylmethylamino)ethylamino)ethyl)acrylamide (PyAM), and fluorescence reporter, dansyl-based monomer (DAEAM), were copolymerized into PNIPAM microgels. The binding of Cu^{2+} ions by PyAM units leads to the fluorescence quenching of DAEAM. However, the quenching efficiency greatly depends on the relative distance between neighboring PyAM units (for the effective binding of Cu^{2+} ions) and that between bound Cu^{2+} ions and DAEAM (for effective quenching). Below and above the volume phase transition (VPT) temperature ($\sim 32^\circ\text{C}$), the synthesized microgels exhibit a hydrodynamic volume change of ~ 30 times.

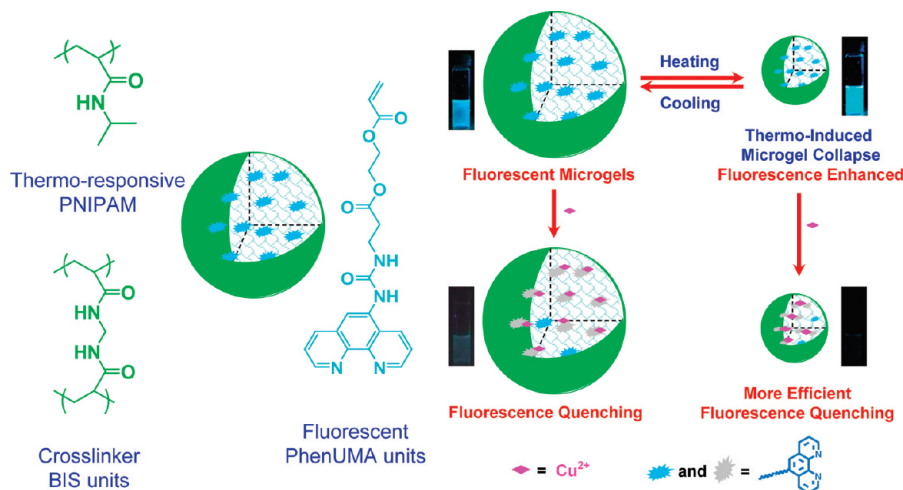


Figure 5. Schematic illustration of the strategy employed for enhancing the detection sensitivity of microgel-based Cu^{2+} sensors via thermoinduced microgel collapse. Reproduced with permission from ref 88.

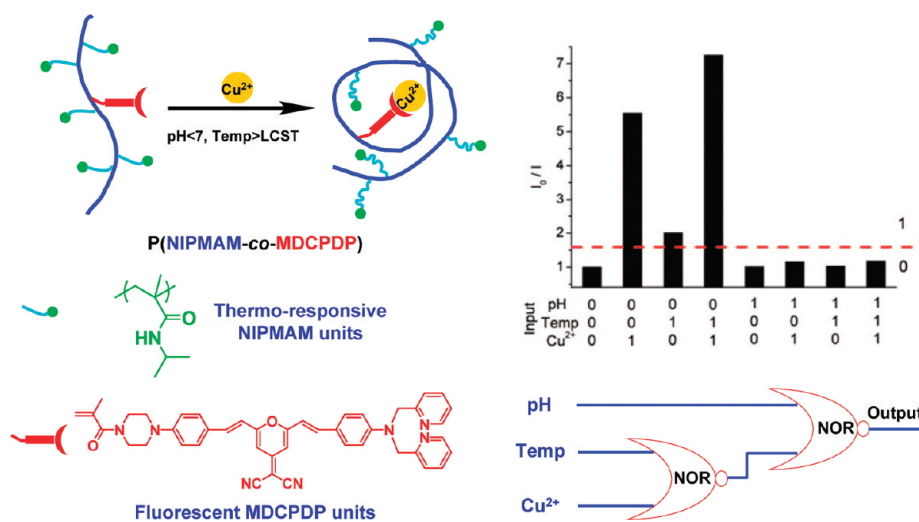


Figure 6. Schematic illustration of the strategy employed for the construction of fluorescent multiple logic gates capable of sensing Cu^{2+} , pH, and temperature. Reproduced with permission from ref 89.

The dramatic microgel shrinkage upon heating can decrease the average distance between neighboring PyAM and DAEAM moieties from ~ 8.5 nm at 20°C to ~ 2.7 nm at 45°C . Accordingly, the Cu^{2+} detection limit drastically improved from ~ 46 nM at 20°C to ~ 8 nM at 45°C . Within collapsed microgels at elevated temperatures, the more effective binding with Cu^{2+} and decreased spatial distance between DAEAM and Cu^{2+} both contributed to the enhanced detection sensitivity. The use of responsive microgel matrix thus leads to the cooperativity of sensing sequences.⁸⁷

PNIPAM microgels imbedded with fluorescent blue-emission phenanthroline units (PhenUMA), which possesses dual capabilities of Cu^{2+} recognition and fluorescence signal reporting, also exhibit thermotunable detection sensitivity to Cu^{2+} (Figure 5).⁸⁸ Tian et al.^{89,90} reported another example of thermoresponsive polymer-based Cu^{2+} sensors, utilizing the supramolecular recognition of Cu^{2+} by dicyanomethylene-4*H*-pyran units (MDCPDP). The fluorescence emission of MDCPDP-labeled PNIPAM exhibits sensitive responses to multiple stimuli, e.g., pH, temperature, and Cu^{2+} (Figure 6).

Yin et al.⁹¹ recently reported on the fabrication of ratiometric fluorescent K^+ sensors based on thermoresponsive PNIPAM microgels covalently incorporated with K^+ -recognizing 4-acrylamidobenzo-18-crown-6 residues (B18C6Am), fluorescence resonance energy transfer (FRET) donor dye, NBD-DAE, and

rhodamine B-based FRET acceptor (RhBEA) by utilizing K^+ -induced changes in microgel VPT temperatures. The spatial distance between fluorescent donors and acceptors (NBD-DAE and RhBEA) within microgels can be tuned via thermoinduced collapse and swelling of thermoresponsive microgels above and below VPT temperatures, leading to the facile modulation of FRET efficiencies (Figure 7).

Ohawada et al.⁹² synthesized stimuli-responsive polymers consisting of NIPAM, fluorescence reporter (DBDAE), and ion-recognizing units, e.g., crown ether-based monomer for K^+ and tris(3-aminopropyl)amine-based monomer for SO_4^{2-} . They successfully achieved multiple detections of pH, temperature, and specific ions. However, they have not investigated the correlation between pH- and thermoresponsiveness of the polymer matrix and the enhancement of detection sensitivity, and this aspect is worthy of further investigation. Recently, Tian et al.⁹³ reported a polymer-based fluoride (F^-) sensor, which were prepared via the RAFT polymerization of naphthalimide-containing monomer. The selective recognition of F^- by amide groups leads to the dramatic shift of absorption and fluorescence emission spectra. Thus, the presence of F^- can be even checked by the naked eye. Singaram et al.⁹⁴ constructed glucose sensors based on poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogels, which were covalently labeled with anionic dyes and boronic

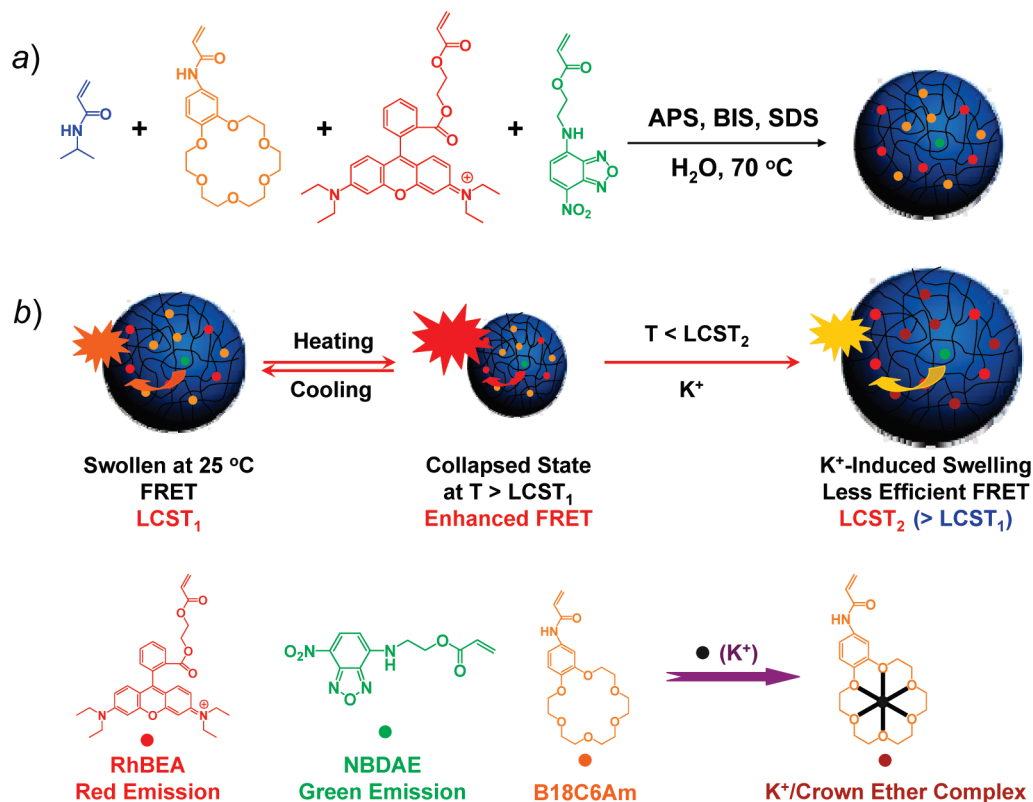


Figure 7. (a) Synthetic scheme employed for the preparation of thermo- and K^+ -responsive P(NIPAM-B18C6Am-NBDAE-RhBEA) microgels via emulsion polymerization. (b) Schematic illustration for tuning the FRET efficiency within P(NIPAM-B18C6Am-NBDAE-RhBEA) microgels by temperature, K^+ ions and a combination of them. Reproduced with permission from ref 91.

acid-functionalized positively charged quencher. At pH 7.4, boronic acid moieties are neutral, and electrostatic interactions between anionic dyes and positively charged quencher leads to effective fluorescence quenching. In the presence of glucose, its supramolecular recognition with boronic acid led to charge neutralization of the quencher, accompanied by the recovery of fluorescence emission intensity.⁹⁵ This approach also enables the continuous detection of glucose in the range of 2.5–20 mM under physiological conditions. Thermoresponsive P(NIPAM-*co*-acrylamide-*co*-phenylboronic acid) microgels embedded with CdS quantum dots can be also employed as optical glucose sensors. The presence of glucose led to microgel swelling via supramolecular recognition with phenylboronic acid moieties, and the fluorescence emission of CdS QDs was considerably quenched due to the more hydrophilic microenvironment in the presence of glucose.⁹⁶

In designing responsive polymer-based sensors via the supramolecular recognition mechanism, the following issues need to be noted. First, the introduction of responsive polymers into the detection system should endow it with extra properties and functions, such as biocompatibility, water dispersibility, targeting, and sensing capabilities. Most importantly, the intrinsically responsive properties of the matrices should allow functional cooperation and enhance the detection performance such as selectivity and sensitivity. Second, the supramolecular recognition-based detection motif typically consists of analyte-recognizing moieties and signal reporting moieties, which can be covalently linked to each other or spatially separated within the responsive polymer matrices. In the former case, upon properly choosing the anchoring sites within responsive polymers, external stimuli-triggered changes in hydrophilicity/hydrophobicity can be utilized to enhance the fluorescence quantum yield in order to increase the detection sensitivity. If the analyte-recognizing and signal reporter moieties are spatially separated to each other, it is

crucial to control their spatial locations and distributions. Finally, the responsiveness of the polymer matrix, typically associated with reversible chain collapse and aggregation, can be utilized to tune the spatial distances between recognizing and reporter functionalities. This can be achieved through the design of responsive polymers of specific chain topologies with sensing moieties locating at well-defined positions and the control of the morphology and microstructures of self-assembled nanostructures.

4. Chemical Reaction-Based Polymeric Chemosensors and Biosensors

Over the past few years, more attention has been paid to chemical reaction-based small molecule probes due to their high selectivity and detection efficiency.³² However, there exist only a few examples of polymer-based sensors by employing this designing principle. In a notable example, nonfluorescent poly[3',6'-bis(1,3,2-dioxaborinane)fluoran] (PolyF-1) was synthesized via double transesterification reaction of 3',6'-bis(pinacolatoboron)-fluoran with pentaerythritol. The presence of trace amount of H_2O_2 vapor can lead to the oxidative deprotection of boronate functionalities, accompanied by the appearance of green fluorescence emission due to newly generated fluorescein. A detection limit of ~ 3 ppb can be achieved via the surface detection method (Figure 8).⁹⁷ Very recently, Chujo et al.⁹⁸ reported the synthesis of biodegradable polymers consisted of tandemly linked phosphate-caged fluorescein within the main chains, which were prepared via the polycondensation reaction between phosphoramidite-difunctionalized fluorescein and diol derivatives. The presence of oxidation and alkaline condition allows the cleavage of main chains, accompanied by the release of highly emissive fluorescein. They successfully demonstrated that the enzymatic activity of cell lysate can be quantified via the fluorometric technique.

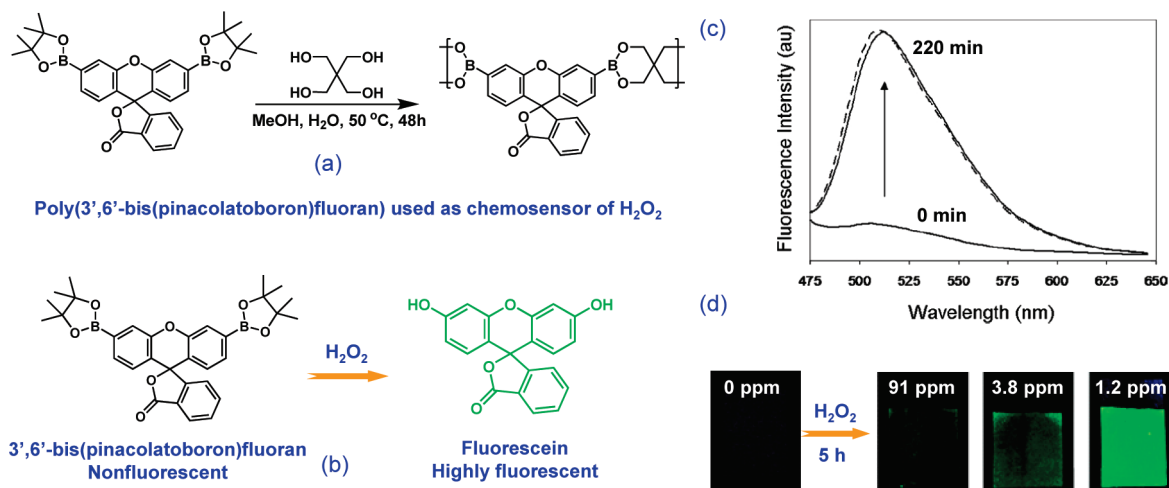


Figure 8. (a) Synthesis of Poly-F-1 via the formation of six-membered boronic ester rings by double transesterification. (b) Selective oxidation of 3',6'-bis(pinacolatoboron)fluoran in the presence of H₂O₂ to produce highly fluorescent fluorescein. (c) Fluorescence emission spectra (solid line) recorded for PF film in the absence and presence of 2.9 ppm of H₂O₂ vapor, respectively; the dashed line represents the reference fluorescence spectrum recorded for fluorescein. (d) Macroscopic fluorescent images of PF films in the presence of various concentrations of H₂O₂ vapor. Reproduced with permission from ref 97. Copyright 2008 The Royal Society of Chemistry.

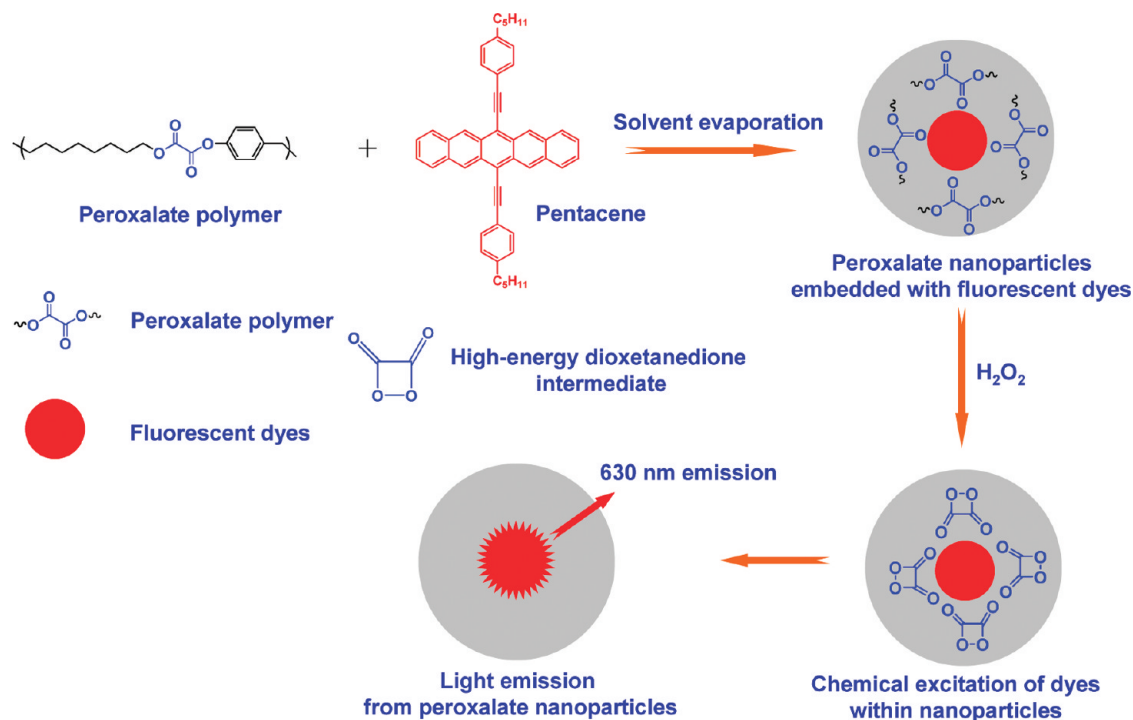


Figure 9. Peroxalate nanoparticles embedded with fluorescent dyes (pentacene) employed for the in vivo imaging of hydrogen peroxide via the chemiluminescence of peroxalate ester moieties. Reproduced with permission from ref 100. Copyright 2007 Nature Publishing Group.

Peroxalate ester moieties are known to generate a high-energy intermediate (dioxetanedione) in the presence of H₂O₂, which can then excite fluorescent dyes, i.e., chemiluminescence. Murthy et al.⁹⁹ synthesized amphiphilic block copolymers containing peroxalate ester group within the hydrophobic segments. After self-assembling into micelle nanoparticles and encapsulating hydrophobic dyes (rubrene) within micellar cores, the presence of H₂O₂ led to prominent chemiluminescence emission. Lee and Khaja et al.¹⁰⁰ recently reported the synthesis of polymers incorporated with peroxalate ester linkage within backbone chains. The self-assembled nanoparticles embedded with suitable organic dyes have been successfully utilized for the in vivo imaging of H₂O₂, accompanied by the disintegration of main chains (Figure 9).

The strategy employed for designing chemical reaction-based small molecule probes can be also combined with conventional stimuli-responsive polymers. In a recent example, Hu et al.¹⁰¹ synthesized double hydrophilic block copolymers (DHBCs), PEO-*b*-P(NIPAM-*co*-RhBHA), in which RhBHA is a reaction-based Hg²⁺ detection motif. In the absence of Hg²⁺, RhBHA is nonfluorescent in the spirolactam form, whereas the presence of Hg²⁺ can trigger the chemical transformation of RhBHA into the highly fluorescent acyclic form. Moreover, the thermoresponsive property of PNIPAM block and the pH-dependent fluorescence emission of RhBHA enable PEO-*b*-P(NIPAM-*co*-RhBHA) di-block copolymer to behave as multifunctional probes to pH, temperature, and Hg²⁺ ions.

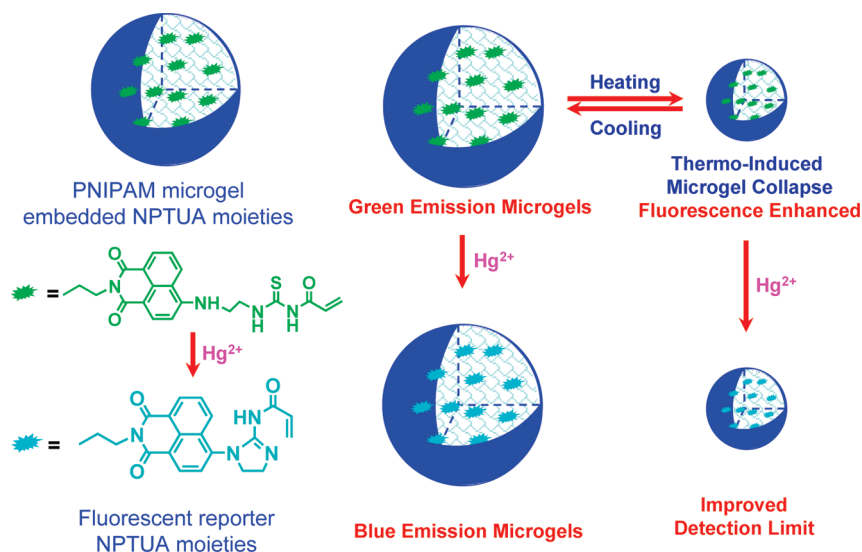


Figure 10. NPTUA moieties bearing PNIPAM nanogel employed as a ratiometric fluorescent sensor of Hg^{2+} ions with enhanced detection sensitivity due to thermoinduced collapse of the thermoresponsive nanogel. Reproduced with permission from ref 102. Copyright 2010 The Royal Society of Chemistry.

Very recently, Li et al.¹⁰² reported the fabrication of near-monodisperse thermoresponsive nanogels prepared via emulsion polymerization of NIPAM and a novel 1,8-naphthalimide-based polarity-sensitive and Hg^{2+} -reactive fluorescent monomer (NPTUA) for the sensing of temperature and Hg^{2+} (Figure 10). At room temperature, PNIPAM nanogels labeled with a single type of naphthalimide-based dye (NPTUA) can act as ratiometric Hg^{2+} probes at the nanomolar level. Upon heating above the VPT temperature, the fluorescence intensity of NPTUA-labeled nanogels in the absence of Hg^{2+} exhibit ~ 3.4 -fold increase due to that NPTUA moieties are now located in a more hydrophobic microenvironment. Moreover, it was observed that the detection sensitivity to Hg^{2+} can be further improved above the nanogel phase transition temperature. Because of the high selectivity of reaction-based detection method, it is quite expected that the same design principles can be applied to a variety of matrices, such as responsive polymers with varying topologies, gels, microgels, and (multilayer) films to achieve multifunctional integration and enhance detection efficiency.

Though chemical reaction-based chemosensors typically possess high selectivity and sensitivity for the sensing of cations and bioactive molecules, an inherent drawback is that they are only suitable for one-time used due to the irreversible nature of chemical reactions during sensing. Using responsive polymers as the matrices, future research in this direction might consider the reversible linkage, such as dynamic combinatorial chemistry, of chemical sensing ensembles to the polymer matrices. Thus, reuse and recycle of the detection system can be rendered possible. Moreover, the integration of sensing functions with other useful functions, such as accumulation and separation, should also be advantageous in certain application circumstances such as contaminant heavy metal ions.^{103,104} Finally, considering the rich variety of chemical reaction-based small molecule probes, currently existing examples of integrating them into responsive polymers are quite rare, and much more endeavor should be paid to this research area.

5. Self-Immolative Polymers for High Sensitivity Detection

In 2003, Shabat et al.,¹⁰⁵ de Groot et al.,¹⁰⁶ and McGrath et al.¹⁰⁷ independently reported the synthesis of self-immolative dendrimers. The concept of self-immolative polymers represents a special type of responsive polymers. They typically possess a specific trigger, the reaction of which can initiate segment

fragmentation of dendrimer and linear polymers in a domino-like manner, accompanied by the release of multiple building units. This concept has been successfully utilized in drug delivery and diagnostic applications by taking advantage of the nonlinear amplification ability. Very recently, the subject of self-immolative dendrimers and their applications was reviewed by Shabat et al. (Figure 11).¹⁰⁸

During the past few years, Shabat et al. have made significant strides in this field by attaching different triggers such as aryl borate ester,¹⁰⁹ *tert*-butyl chloroformate,¹¹⁰ and phenylacetamide¹¹¹ onto self-immolative polymers. By utilizing rationally designed segment fragmentation mechanisms, such as 1,6-elimination and decarboxylation reactions, and taking advantage of the dramatic differences in colorimetric and fluorometric properties of signal reporting units before and after segment disintegration, a variety of functional systems for the sensing of H_2O_2 , organic acids, and penicillin-G-amidase (PGA) enzyme were constructed. Alexander et al.¹¹² recently reported another example of protein detection based on self-immolative polymers embedded with the 4-hydroxy-2-butanone group; the domino-type β -elimination reaction in the presence of proteins such as bovine serum albumin (BSA) led to the green-to-blue fluorescence emission transition.

Just recently, a new mechanism for signal amplification has been developed.^{113,114} The disintegration of newly designed H_2O_2 -responsive self-immolative dendron can release multiple small molecules (choline); in the presence of choline oxidase, the newly generated H_2O_2 can further trigger the disintegration of dendrons and result in the release of more choline molecules. Thus, the exponential signal amplification can be achieved via the circular amplification strategy. Currently, this new field deserves further exploitation in several aspects such as developing new principles in designing the disintegrable segments by employing new chemical reactions and utilizing new chain topologies such as hyperbranched polymers, which are more synthetically accessible.

Self-immolative polymers have emerged to be a novel strategy in design sensing and detection systems with signal amplification capabilities to considerably enhance the detection sensitivity and selectivity. In terms of their applications in biosensing, it is imperative to determine the biotoxicity of released building units upon triggered disassembly of self-immolative polymers and further explore their applications in clinical diagnoses and detections. New designing principles in aspects such as new trigger

motifs and sequential disintegrable building scaffolds need to be further explored and expanded.

6. Mechanoresponsive Polymers

Similar to self-immolative polymers, mechanoresponsive polymers also represent a novel type of responsive polymers. The photoluminescent colors of mechanoresponsive polymers can be modulated by various types of mechanical forces such as shearing, grinding, and elongation. Recently, various responsive systems exhibiting changes in colors and/or fluorescence emission

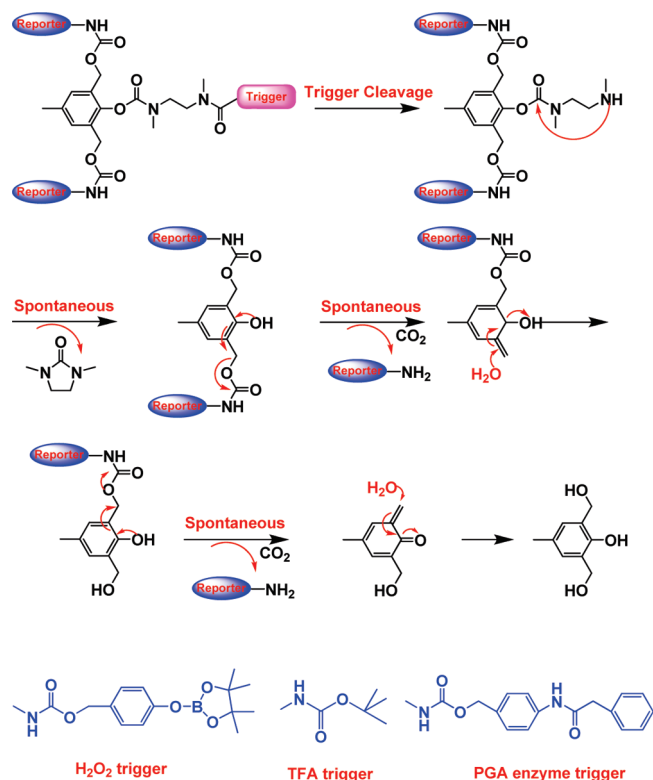


Figure 11. Disassembly mechanism of a self-immolative dendron through spontaneous domino-like segment disintegration upon suitable triggering reaction. Reproduced with permission from ref 108. Copyright 2010 The Royal Society of Chemistry.

properties upon mechanical stimuli were reviewed by Kato et al.⁴¹ In a notable example, mechanoresponsive polymeric systems were reported by Sottos and co-workers,¹¹⁵ who synthesized poly(methyl acrylate) (PMA) with the SP motif covalently incorporated at the middle of the chain (Figure 12). Upon mechanical deformation of the polymer film (elastomers), SP transforms from closed state to the open state (MC), accompanied by macroscopic color changes and the appearance of red fluorescence emission, which is ascribed to the unstable carbon–oxygen (C–O) bond as illustrated in Figure 12a. It should be noted that currently it is difficult to in situ determine the percentage of SP actually undergoing the isomerization reaction at a given stress. This novel type of responsive polymers provides great advantages in the detection of stress-induced deformation and failure. This smart design concept augurs well for their practical applications and can be generalized in circumstances where the transformation of mechanical stress into useful chemical reactions is required. They might also be applied to monitor polymerization or cross-linking reactions (network formation) or phase transitions (sol–gel transitions and gel swelling/collapse), which are typically associated with release or generation of internal stresses.¹¹⁶

In addition to covalently attaching mechanophores to the polymer matrices to produce mechanoresponsive materials, polymer materials physically embedded with suitable dyes can also work.^{117–119} In an earlier example, oligo(*p*-phenylenevinylene) dyes with varying chemical structures and unique fluorescence emissions in solution and crystallization states (Figure 13) were blended with linear low-density polyethylene polymeric materials by melt-processing, exhibiting luminescent colors tunable by the extent of tensile deformation.¹¹⁹ Before deformation, embedded dyes aggregate in the stacked form within the host polymer matrix, leading to emission from excimers; however, these dye aggregates were dissociated under tensile deformation, and the molecularly dispersed form of dyes can produce significantly different luminescent emissions (Figure 13). It is worthy of noting that remarkable emission changes strongly depend on the deformation-induced π – π interactions within the crystalline lattice aligned in a planar fashion. Intriguingly, other stimuli such as temperature, pH, and phase transition in the responsive polymer-based systems with mechanophores can also achieve changes in emission intensities and colors.

Representing a new research direction, the field of mechano-responsive polymer-based sensors needs to be further exploited.

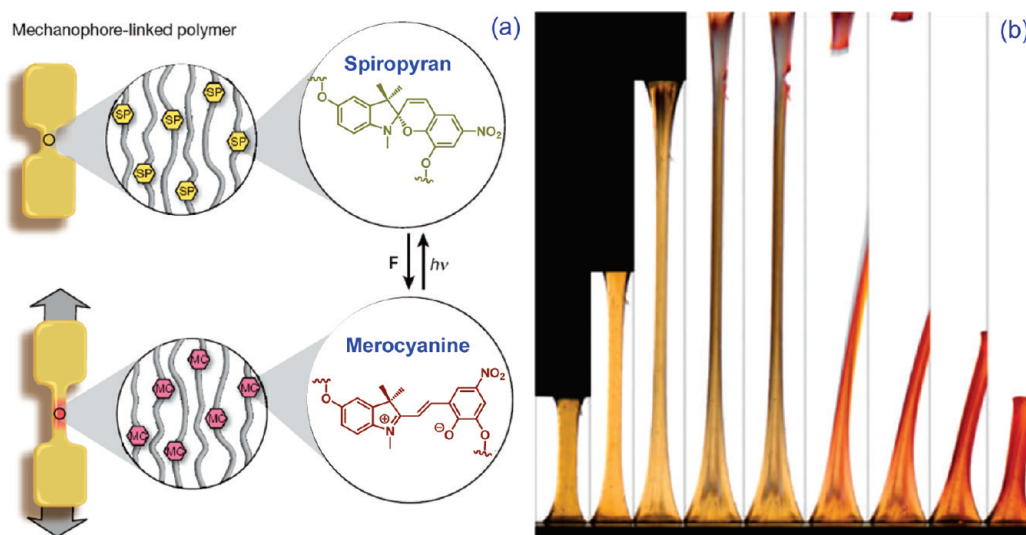


Figure 12. (a) Mechanochromic responses of mechanophore-linked PMA elastomers under tensile loading. (b) The mechanochromic polymer materials turn red under mechanical stress (tearing). Reproduced with permission from ref 115. Copyright 2009 Nature Publishing Group.

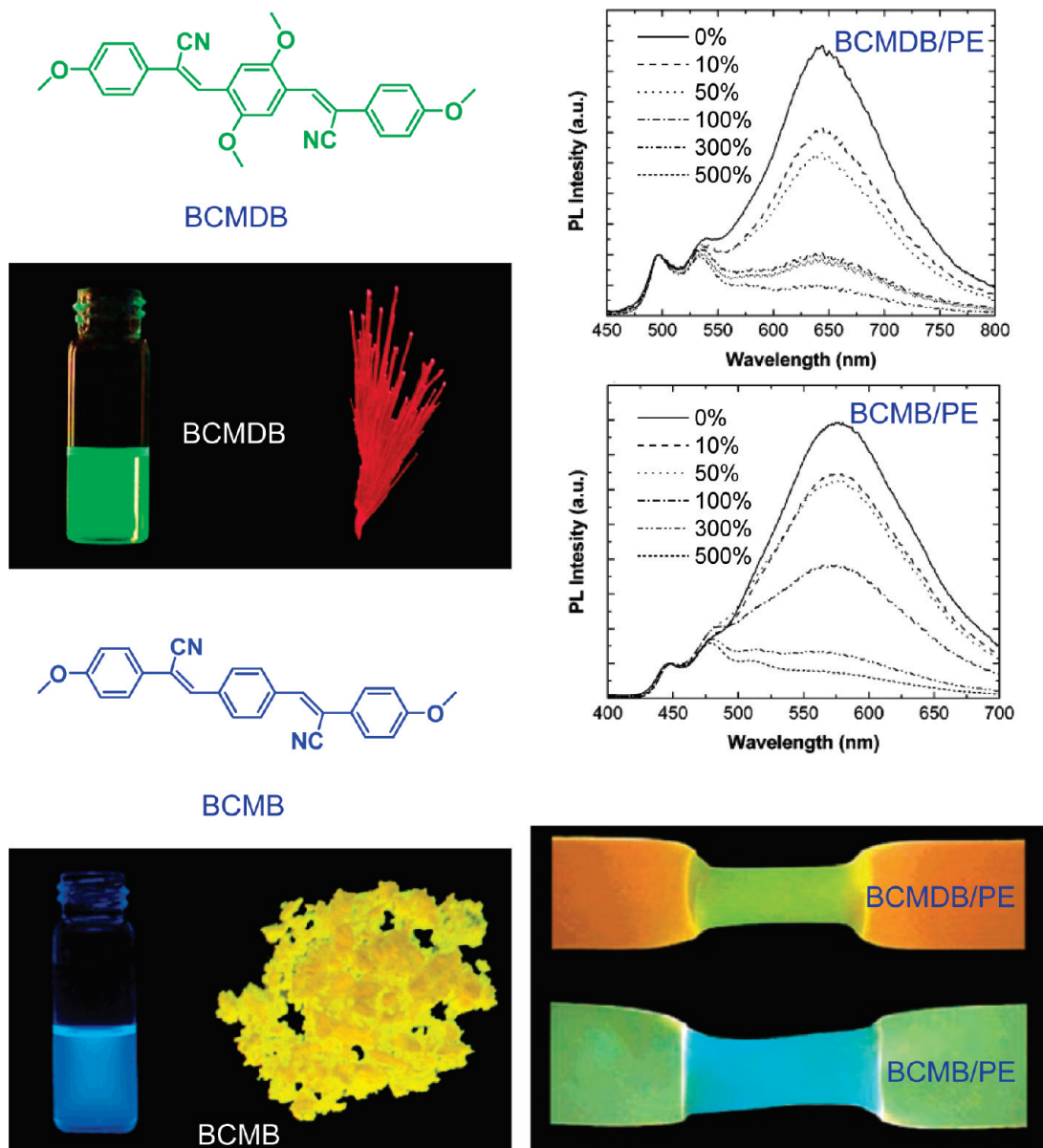


Figure 13. Chemical structures of oligo(*p*-phenylenevinylene)-based piezochromic dyes, BCMDB and BCMB, and macroscopic fluorescent images recorded under UV 365 nm irradiation for BCMDB and BCMB crystals and chloroform solutions, respectively. Also shown are fluorescence emission spectra recorded for blend films of linear low-density polyethylene (PE) with BCMDB or BCMB upon stretching to varying draw ratios and macroscopic fluorescent images upon stretching to a draw ratio of 500%. Reproduced with permission from ref 119.

Future developments might consider the introduction of reference dyes to allow the ratiometric determination of mechanical deformation, and this can effectively avoid the background fluorescence interferences. Novel mechanophores capable of sensitively and selectively respond to mechanical stresses need to be further invented to enrich the choices in designing new systems. The integration of mechanophores into conventional responsive polymer matrix might also allow multipurpose sensing with functional cooperativity. Finally, the applications of mechanoresponsive polymers systems in the control or monitoring polymerization or cross-linking reactions and phase transitions can be further exploited.

7. Summary and Outlook

This Perspective focuses on recent developments of the applications of responsive polymers in sensing and detection applications. We have termed “responsive polymers” in a broader extent by including those systems containing building motifs capable of

triggering molecular recognition events and analyte-specific chemical reactions. From these selected examples, we can see a fast-growing trend in the exploitation of responsive polymers for the design of novel detection and sensing systems. Challenges and future developments in the five research directions of responsive polymer-based sensing and detection systems, i.e., sensors by exploiting the intrinsic properties of responsive polymers, supramolecular recognition and chemical reaction-based responsive polymer sensors, and self-immolative polymer and mechano-responsive polymer-based detection systems, have already been described at the end of each section. In general, the field of responsive polymer-based sensors can be further developed and exploited as described below.

First, the spatial location and distribution of fluorescent dyes within responsive polymer matrix and their supramolecular assemblies are directly related to the detection performance such as sensitivity and selectivity. In a recent review article by Beija, Charreyre, and co-workers,¹²⁰ they summarized the synthesis and

properties of dye-labeled polymers at well-defined positions such as chain terminals or diblock junctions, which can dramatically affect the photophysical processes such as FRET and signal amplification. Current investigations concerning responsive polymer-based sensing systems mainly focus on linear homopolymers, random copolymers, diblock copolymers, and micro/nanogels. Theoretically, other chain topologies, such as star (block) copolymers, (multi)block copolymers, dendrimers, and hyperbranched polymers, should provide additional advantages if FRET processes are involved or the locations analyte-recognizing and signal reporter moieties need to be accurately controlled. The FRET pair or supramolecular recognition/signal reporting functionalities can be precisely anchored to the core and shell regions and peripheries of these nonlinear polymers. Thus, enhanced detection sensitivities can be achieved through cooperative recognition and more effective energy transfer processes. The morphologies, microstructures, and structural stability of supramolecular assemblies are also closely related to the chain topologies of responsive polymers. Overall, from the point of view of synthetic polymer chemistry aspects, the design of new generations of responsive polymer-based sensors should pay more attention to chain topologies of responsive polymer matrices, especially nonlinear chain architectures, and the fabrication and tuning of the microstructures of supramolecular assemblies of responsive polymers.

Second, considering their bioapplications, the covalent stabilization of supramolecular assemblies of responsive polymers (e.g., shell or core cross-linking strategies) can be utilized to achieve long-term structural stability.^{121–124} Cell or tissue-targeting moieties can be introduced to the chemical design for specific in vitro and in vivo applications. Moreover, detection motifs exhibiting more sensitive and selective responses should be further developed and incorporated into responsive polymer matrices, aiming at sensing and discriminating subtle changes in the gradients and concentrations of pH, temperature, glucose, bioactive small molecules, and other biorelevant macromolecular species. Biodetections are typically associated with low concentrations of analytes (down to the nanomolar concentration range) and complex detection media (salts, various bioactive molecules, etc.). Thus, the development of responsive polymer-based systems capable of selectively detecting multiple analytes simultaneously is quite imperative.¹²⁵

Finally, the field of responsive polymer-based chemo- and biosensors calls for new designing principles and concepts and creative detection strategies. Self-immolative polymers and mechanoresponsive polymers represent two new directions that have considerably advanced this research field. Self-immolative polymers can achieve the nonlinear chemical amplification of detection signal via triggered chain segment disintegration. Under certain circumstances, the circular amplification effect can be also achieved if proper biochemical process (e.g., choline/choline oxidase) is involved for the sensing of H₂O₂ traces. Recently, the embedment of fluorescent dyes into mesoporous silica nanoparticles (MSN) followed by the capping of nanopore entrances with analyte-cleavable large organic molecules leads to preparation of detection systems with physical amplification characteristics.¹²⁶ New concepts in responsive polymers such as charge-reversal polymers^{127–129} and charge-generating polymers^{130,131} can also be introduced to design novel sensing systems. On the other hand, responsive polymer-based sensors possessing multiple photophysical processes such as fluorescence, phosphorescence, and chemiluminescence can further increase the design multiplicity and adaptivity.^{100,132} Finally, the integration of responsive polymers with inorganic nanoparticles, e.g., fluorescent quantum dots,^{71,133} noble metal nanoparticles,¹³⁴ or nanoclusters,¹³⁵ also represent a future direction in designing responsive polymer-based detection systems. Overall, the new

research field described in this Perspective deserves systematic and in-depth investigations in the future, aiming at exploring novel responsive polymer-based functional materials and devices.

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