

1 Responsive Polymers for Analytical Applications:

2 A Review

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7 **Abstract:**

8 Stimuli-responsive polymers are capable of translating changes in their local environment to
9 changes in their chemical and/or physical properties. This ability allows stimuli responsive
10 polymers to be used for a wide range of applications. In this review, we highlight the analytical
11 applications of stimuli responsive polymers that have been published over the past few years
12 with a focus on their applications in sensing/biosensing and separations. From this review, we
13 hope to make clear that while the history of using stimuli responsive polymers for analytical
14 applications is rich, there are still a number of directions to explore and exciting advancements to
15 be made in this flourishing field of research.

16 **Keywords:**

17 Stimuli responsive polymers, Phase transitions, Sensing, Biosensing, Separations, Analytical
18 Applications of stimuli responsive polymers.

20 **1. Introduction:**

21 Polymers, or more colloquially referred to as "plastics", have seemingly found their way into
22 every part of our lives. From the smart phones in our pockets, and the cars we drive, to artificial
23 heart valves that are necessary to keep some alive - polymers are ubiquitous. If that wasn't
24 enough, polymers are also responsible for who we are; DNA, the carrier of all genetic
25 information for individuals, is also a polymer. While polymers seem to be everywhere, they
26 weren't always so openly accepted. Specifically, in the early-to-mid 20th century, there was
27 much debate about the mere existence of such high molecular weight single molecules or
28 "macromolecules". In fact, only after much research and debate, and a Nobel Prize (Staudinger,
29 1953 Nobel Prize in Chemistry) was the idea of the polymer finally accepted. The acceptance of
30 polymers paved the way for the remarkable work of Paul J. Flory (1974 Nobel Prize in
31 Chemistry), Jean-Marie Lehn (1987 Nobel Prize in Chemistry), and Pierre-Gilles de Gennes
32 (1991 Nobel Prize in Physics), which really shaped our understanding of polymers to allow for
33 advances in modern areas such as energy and computing [1-6].

34 While polymers in general are an interesting class of matter, this review will focus on a
35 specific set of polymers termed "stimuli-responsive polymers" or also referred to as smart
36 polymers/materials. These polymers have the ability to respond physically and/or chemically in
37 response to environmental changes [7-13]. As seen schematically in Scheme 1, a polymer chain
38 can undergo a conformational change from extended to collapsed in response to a stimulus.
39 Stimuli responsive polymers can also make up a portion of a block copolymer, and thus, only a
40 portion of the whole polymer will undergo a change in response to a stimulus [14,15]. The
41 environmental changes (or stimulus) can be pH, temperature, ionic strength, light, electric or
42 magnetic field [16-21]. While polymer-based systems can be engineered to respond to a single

43 stimulus, they can also be made to respond to multiple stimuli, e.g., temperature and pH [22-24].
44 That is, by polymerizing multiple monomers together that themselves yield polymers with
45 various responses; one can achieve a system that changes in response to the application of a
46 variety of stimuli. For most applications, the polymer's response to the stimulus should be
47 reversible upon the removal of the stimulus. That is, in the example in Scheme 1, the polymer
48 should re-extend when the stimulus is removed. Furthermore, crosslinked responsive polymer
49 networks have been constructed, as well as responsive gels, self-assembled structures and
50 composites [25-30]. Regardless of the form, these materials have enormous potential in a wide
51 range of modern industries, and have already been used in chromatography [31-38],
52 optoelectronics [39-45], drug delivery and biosensors [46-56].

53
54 While there are a number of polymers that respond to a variety of stimuli [57-77], the
55 thermoresponsive polymer poly (*N*-isopropylacrylamide) (abbreviated as PNIPA, PNIPAAm,
56 PNIPAA, IPAAm or pNIPAm) has received the most attention. PNIPAm was first synthesized in
57 the 1950s [78], but its temperature responsivity, i.e., thermoresponsivity, was discovered later by
58 Heskins and Guillet [79]. They established that the lower critical solution temperature (LCST)
59 for pNIPAm is 32 °C. Contrary to the behavior of most polymers in (aqueous) solutions,
60 polymers that exhibit LCST behavior become less soluble in a given solvent at elevated
61 temperatures. The conformational changes primarily result from dehydration of the isopropyl
62 groups of pNIPAm [80-81]. Crosslinked pNIPAm-based materials, known as hydrogels, can also
63 be synthesized and exhibit LCST behavior. These materials, being chemically crosslinked, are
64 very stable dimensionally and chemically. The behavior of these materials has been extensively
65 studied, and is very well understood, thanks to the pioneering work of T. Tanaka [82-86].

66 Colloidally stable hydrogel particles, known as microgels or nanogels are well known as well.
67 PNIPAm based temperature sensitive microgels were first discovered in 1978 by Robert Pelton
68 and have been studied extensively since [87-93]. Core-shell microgels have also been
69 synthesized [94-98], and have found numerous analytical and biological applications [99-102].
70 Finally, a number of different methods to synthesize responsive polymers and gels with various
71 architectures and functionalities have been introduced [103-112].

72 There are number of reviews [113-121] highlighting the development and success of
73 responsive polymers and responsive polymer-based materials. In this submission, we focus on
74 the *analytical applications* of various responsive polymers and polymer-based materials reported
75 primarily over the last 3 years.

76 **2. Applications of Responsive Polymers**

77 **2.1 Conformationally Responsive Polymers**

78 As mentioned above, conformationally responsive polymers "react" to the application of a
79 stimulus by changing their conformation. The most common conformationally responsive
80 polymers are those that respond to temperature (thermoreponsive), pH and ionic strength [122-
81 144]. Among them, pNIPAm-based polymers, hydrogels, and microgels are the most extensively
82 studied and exploited.

83 PNIPAm-based microgels and their assemblies have found numerous applications in our
84 laboratory over the last few years [122-126]. For example, we demonstrated that pNIPAm-co-
85 acrylic acid (AAc) microgels and their aggregates are capable of removing large amounts of
86 organic molecules from water, which depends on the AAc content of the microgels, as well as
87 their concentration in solution. We also found that the extent of removal depends on temperature,

88 e.g., the extent of removal increases if the temperature of the microgel solution is cycled from
89 low-high-low temperature [122,123,127,128]. Furthermore, we have shown that visually colored
90 materials can be fabricated by depositing, via a “painting protocol”, a layer of pNIPAm-based
91 microgels on a Au coated glass substrate, followed by the deposition of a subsequent Au layer on
92 top [129-132]. A schematic of this device can be seen in Figure 1(a). These devices show visual
93 color and distinct, multiplex reflectance spectra, as seen in Figure 1(b-f). It has also been found
94 that etalons can be fabricated using metal layers other than Au [133]. From Figure 1, it is also
95 apparent that the color of the devices, and the number of peaks in the reflectance spectra (peak
96 order), can be rationally tuned by simply changing the diameter of the microgels between the two
97 Au layers. We have also shown that the color of the devices could be tuned with temperature,
98 pH, and glucose concentration and thus the device can be used for sensing solution temperature,
99 pH [124] and glucose concentration [125]. We also investigated the deswelling kinetics of the
100 devices to understand what controls the deswelling time for the assemblies. We determined that
101 the thickness of the Au layer covering the microgel layer greatly influenced the deswelling and
102 solvent exchange kinetics with thinner layers giving faster responses than etalons coated with
103 thicker Au layers [132, 134]. We recently found that the molecular weight (MW) of
104 polyelectrolyte can be detected by pNIPAm-co-AAc microgel-based etalon by varying the
105 thickness of the Au overlayer [126] as shown in Figure 2. We showed that when the pNIPAm-
106 co-AAc-based etalons are at $\text{pH} > 4.25$ (pK_a for AAc) the microgels become multiply negatively
107 charged. When they are exposed to a solution containing positively charged polymer
108 (polycation) the etalon's microgel layer deswells due to intermolecular crosslinking of the
109 charges in the microgels; they are unresponsive to the presence of the like charged
110 polyelectrolyte. We also found that the etalon's response depended on the thickness of the Au

111 overlayer. Low molecular weight (MW) polyelectrolyte could penetrate the various Au overlayer
112 thicknesses, while high MW polyelectrolytes could only penetrate the etalons fabricated from
113 thin Au overlayers. We hypothesized that this is due to a decrease in the Au pore size with
114 increasing thickness [132, 134], which excludes the high MW polyelectrolytes from penetrating
115 the microgel-based layer. These devices show promise as MW selective sensors and biosensors.

116 Working on the same polymeric system based on pNIPAm, Kumashiro et al. [135]
117 investigated temperature-modulated adsorption of ferritin-modified pNIPAm (pNIPAm-ferritin)
118 on a solid substrate. They found that pNIPAm-ferritin adsorbed onto hydrophobic surfaces with
119 surfactants at 37 °C, while pNIPAm-ferritin did not effectively adsorb onto these hydrophobic
120 surfaces at 25 °C. From these studies, the authors concluded that grafted pNIPAm underwent a
121 phase transition at $T > 32$ °C, subsequently increasing hydrophobicity of the polymer, which in
122 turn promoted polymer binding to the hydrophobic surfaces. Similarly, at $T < 32$ °C, modified
123 pNIPAm becomes more hydrophilic in nature and reduced the efficacy of polymeric binding to
124 hydrophobic surfaces. PNIPAm-ferritin polymers may serve as adaptive biosensors in the
125 detection of disease conditions within biological organs, via thermally induced differential
126 binding of polymers to hydrophobic surfaces.

127 Using 1-alkyl[2-(acryloyloxy)ethyl]dimethylammonium bromides with hexyl or cetyl groups
128 and 2-hydroxyethylacrylate (HEA) or N-isopropylacrylamide (NIPAM), four block copolymers
129 were synthesized by Budgin et al. and employed for functionalization of monodisperse iron
130 oxide nanoparticles (NPs) [136]. The authors claimed that these block copolymer NPs could be
131 used as magnetic stoppers in biorelated membrane separations. They also incorporated Pd
132 species in submicrometer particles making them promising candidates for catalytic applications
133 as magnetically recoverable catalysts with a high magnetic response. In another effort for protein

134 purification, Poly(*N*-isopropylacrylamide-co-*N,N'*-dimethylaminopropylacrylamide-co-*N*-tert-
135 butylacrylamide), P(NIPAm-co-DMAPAAm-co-tBAAm) brush grafted silica beads were
136 prepared through a surface-initiated atom transfer radical polymerization (ATRP). It was
137 reported that the copolymer brush grafted silica beads adsorbed negatively charged proteins both
138 through electrostatic and hydrophobic interactions by the modulation of column temperature
139 [137].

140 PNIPAm hydrogel-modified silica beads were prepared by a radical polymerization through
141 modified 4,4'-azobis(4-cyanovaleric acid) and *N,N'*-methylenebisacrylamide with
142 chromatography matrices with different architectures and found that prepared beads with a dense
143 polymer brush structure maintained a stable separation efficiency due to strong hydrophobicity
144 arising from dehydrated copolymer at elevated temperature. The retention times of different
145 hydrophobic steroids suggest stronger hydrophobicity of the beads. Thus, precisely modulating
146 graft configuration of thermoresponsive polymers on interfaces provided chromatography
147 matrices with a high separation efficiency and stability for continuous use, resulting in extending
148 the longevity of chromatographic column [138].

149 In a related effort for the separation of biomolecules utilizing pNIPAm and copolymer of *N*-
150 isopropylacrylamide and *N,N'*-dimethylaminopropylacrylamide (DMAPAAm), Nagase et al.
151 performed temperature responsive chromatography with an aqueous mobile phase without using
152 an organic solvent [139]. They prepared thermoresponsive polymer-grafted silica-beads
153 pNIPAm hydrogel-modified beads, pNIPAm brush-grafted surface, and poly(*tert*-
154 butylacrylamide-*b*-*N*-isopropylacrylamide (tBAAm)-*b*-IPAAm) (Figure 3). They used
155 temperature to change surface properties without changing the mobile-phase composition. The
156 separation of the biomolecules, such as nucleotides and proteins were achieved by this dual

157 temperature- and pH-responsive chromatography system with a very high resolution (Figure 4).
158 The same group reported other cationic, bio-responsive and hydrophobic brushes for the
159 separation of biomolecules [140-142].

160 A thin mixed polymer brush has been grafted onto a Si wafer consisting of highly
161 hydrophilic PAA and hydrophobic PS, which were synthesized using a “grafting to” approach. It
162 was found that the wetting properties of the surfaces can be switched between advancing and
163 receding water contact angles [143]. The locking and unlocking of the hydrophobic brush in a
164 specific solvent was demonstrated and proposed that this system could find applications in smart
165 textiles and microfluidic devices [143]. The same group reported that poly (2-vinylpyridine)
166 polymer brushes immobilized on glass substrates exhibited pH responsivity. It was reported that
167 the spacing between two kinds of nanoparticles—gold nanoislands immobilized on a transparent
168 support and gold colloidal particles adsorbed on the brush surface can be tuned by varying the
169 pH of the solution and detected by surface plasmon resonance [144]. The authors claimed that
170 highly sensitive nanosensors could be made out of that system.

171
172
173 Wang et al., synthesized a dual-stimuli responsive Poly (2-(2-methoxyethoxy) ethyl
174 methacrylate-b-oligo (ethylene glycol) methacrylate-b-acrylic acid) (PMOA) hydrogel system
175 through a free-radical polymerization reaction with thermo responsive comonomers, oligo
176 (ethylene glycol) methacrylate (OEGMA) and 2-(2-methoxy-ethoxy)ethyl methacrylate
177 (MEO2MA), and pH responsive acrylic acid (AAc) comonomer. They concluded that
178 temperature and pH induced hydrogel de-swelling is characterized by a first-order kinetics
179 equation, and that de-swelling kinetics is faster from 18 °C to 55 °C [145] which will find
180 application in drug delivery and biosensors.

181 In a recent effort, a novel thermoresponsive statistical block copolymer has been designed
182 from dialkyl vinylphosphonates by rare earth metal-mediated group transfer polymerization
183 using tris-(cyclopentadienyl)ytterbium [146]. The obtained copolymers of diethyl
184 vinylphosphonate (DEVP) and dimethyl or di-n-propyl vinylphosphonate (DPVP),
185 Poly(dimethyl vinylphosphonate-co-diethyl vinylphosphonate) (P(DMVP-co-DEVP) shows
186 thermoresponsive properties with tunable lower critical solution temperature (5 to 92 °C). This
187 copolymer is sensitive to the concentration and to the presence of additives and proposed to be a
188 promising candidate for controlled cell growth and release.

189

190 **2.1.1 pH and Ionic Strength Responsive Polymer**

191 pH responsive polymers contain weak electrolyte groups on the polymer chains, such as a
192 carboxylic acid group, or an amino group, which can accept or donate protons in response to a
193 change in the environmental pH. Around the pK_a of the weak electrolyte groups the degree of
194 ionization is dramatically altered. A change in the net charge of pendant groups causes a change
195 of the hydrodynamic volume of the polymer chains, which ensues from changes in the osmotic
196 pressure exerted by mobile counter ions neutralizing the polymer charges as well as charge-
197 charge (Coulombic) repulsion. Furthermore, pH responsive polymers are also responsive to
198 changes in ionic strength, where screening of repulsive electrostatic interactions increase with
199 increasing ionic strength resulting in polymer chains collapse.

200 Two weak polybases Poly [2-(diethylamino) ethyl methacrylate] (PDEA) and poly[2-
201 (diisopropylamino) ethyl methacrylate] (PDPA) brushes were grown by surface-initiated atom
202 transfer radical polymerization [147]. Using in situ ellipsometry an acid-induced swelling
203 transition was observed at pH 7.4 for PDEA and pH 6.5 for PDPA, similar to the pK_a values

204 reported for the corresponding free polymer chains as shown in Figure 5. On exposure to humid
205 HCl vapor, PDPA brushes become hydrophilic, resulting in water uptake and swelling,
206 producing a visible change in the thin film. This film can be used as chemical sensor.

207 Bousquet et al. reported nanostructured adaptive polymer surfaces by diffusion of
208 amphiphilic polystyrene-block-poly(acrylic acid) (PS-b-PAA) toward the interface[148]. The
209 PAA segments placed at the interface respond to pH and can switch from an extended
210 hydrophilic state at pH values above 6.0 to a collapsed hydrophobic state at pH 3.0. Accordingly,
211 the surface morphology changed from swollen micelles to nanometer size holes. Ampholytic
212 hydrogels through chemical cross-linking were synthesized from two cellulose-based
213 polyelectrolytes quaternized cellulose (QC) and carboxymethyl cellulose (CMC) [149]. The
214 hydrogels exhibited excellent pH sensitivity in the range of pH from 1 to 13 and shrunk
215 significantly at pH 12 on the whole. The hydrogels displayed smart swelling behavior in NaCl,
216 CaCl₂, and FeCl₃ aqueous solutions. The results revealed that CMC mainly contributed to
217 increasing the swelling as a result of strong water adsorption, whereas QC played a role in
218 controlling the charges in the QC/CMC system, leading to the pH sensitivity. An
219 environmentally responsive ultrafiltration membrane was created on a commercial microporous
220 Polyvinylidene fluoride (PVDF) membrane support with a cross-linked poly-N-vinylactam
221 hydrogel [150]. The membrane permeability increased significantly with increase in salt
222 concentration due to the collapse of the hydrogel onto the surface of the supporting PVDF
223 membrane. The transmission behavior of model proteins in response to change in salt
224 concentration was demonstrated by parameter scanning ultrafiltration experiments.

225 pH responsive polymer brushes facilitate efficient transduction mechanisms, which make
226 them suitable for use in sensor applications. For example, Tokareva et al. demonstrated the

227 tuning of the plasmon-resonance coupling between gold nanoparticles and a gold substrate
228 mediated by a 20-nm-thick swellable P2VP brush layer [151]. The film can be used as a highly
229 sensitive pH-responsive nanosensor with short response times by minimizing the diffusion of the
230 analyte to the sensor. The authors demonstrated a large (50 nm) shift in the plasmon-resonance
231 position as a result of changing pH values (within $\text{pH} = 3.8 \pm 0.5$) caused by shrinking of the
232 brush thickness from 22 to 7 nm. Li et al. fabricated 2D inverse opal monolayers out of a
233 swellable P2VP polyelectrolyte gel for pH sensing [152]. The photonic membrane shows a fast
234 response to pH and can be readily read out from either its optical spectra or visible colors (Figure
235 6).

236 Electrostatic layer-by-layer (LbL) assembly has been introduced for the facile fabrication of
237 responsive polyelectrolyte films. The mechanism of response of LbL assemblies was analysed by
238 Rubner and co-workers [153] for poly (allylamine hydrochloride)/ polystyrene sulfonate
239 (PAH/PSS) systems, who attributed the dramatic variation in the degree of swelling (up to 400
240 %) at high pH (pH 9.5) to changes in the degree of ionization of the weak polyelectrolytes. The
241 authors claimed that hydrophobic association can increase the local density of amine groups of
242 the weak polyelectrolyte (PAH) and/or decrease the local dielectric constant experienced by this
243 weak functional group. As a result, weak functional groups become more difficult to ionize. A
244 sharp swelling and deswelling transition detected for LbL films at $\text{pH} > 8.5$ manifested itself in
245 reversible pH-controlled variations of swelling percentage, surface roughness and refractive
246 index. The PAH swelling was associated with the variation in ionization of its free amine groups,
247 and a hysteresis loop was related to the chain dynamics within swollen LbL films.

248 Different LbL films with embedded biomolecules and nanoparticles have been exploited as
249 soft organized matrices for uploading nanoparticles to fabricate pH-responsive and biosensitive

250 polymeric nanomaterials based on the surface plasmon resonance (SPR) phenomena [154].
251 Various metal nanoparticles were embedded within polymeric systems to use them as sensors for
252 various applications [151,155,156]. Specifically, gold nanorods were embedded in crosslinked
253 poly(methacrylic acid)–poly (allylaminehydrochloride) and poly (methacrylic acid)–poly(N-
254 vinylpyrrolidone) LbL films to act as pH-responsive plasmonic sensors. Swelling and de-
255 swelling of these gels at pH 8 and pH 5, respectively, resulted in reversible, large shifts of a
256 strong, easily detectable longitudinal plasmon resonance located in the near-infrared region (\approx
257 700 nm) owing to variable side-by-side nanorod interactions. A novel fiber-optic pH sensor was
258 fabricated by coating LbL films of negatively charged polyelectrolyte complex nanoparticles and
259 positively charged poly(diallyldimethylammonium chloride) (PDDA) on the surface of a thin-
260 core fiber modal interferometer (TCFMI) [157]. The fabricated TCFMI pH sensor has different
261 transmission dip wavelengths under different pH values and shows high sensitivities of 0.6
262 nm/pH unit and -0.85 nm/pH unit for acidic and alkaline solutions, respectively, and short
263 response time of 30-50 s.

264 **2.1.2 Bioresponsive polymers**

265 Recently, thermoresponsive microgels have attracted attention to develop sensors for various
266 biomolecules, such as saccharides, protein, and DNA etc.. Hoare et al. [158] were focused on the
267 use of phenylboronic acid (PBA) functional groups in the design of glucose-sensitive polymers.
268 They synthesized pNIPAm-based PBA-functionalized microgels, which possess well-defined
269 glucose swelling or deswelling responses under a range of environmental conditions. When the
270 microgels are used to detect glucose, the anionic charge density within the gel increases as the
271 glucose concentration is increased, driving a swelling response via both Donnan equilibrium and
272 direct charge-charge repulsion effects. Using the same concept, Sorrell et al. [125] described an

273 APBA- functionalized microgel based etalon device to detect glucose concentration by the shift
274 in the peaks of the device's reflectance spectra. Here APBA functionalized microgels were
275 sandwiched between two gold layers (Figure 7). When glucose interacts with boronic acid
276 modified microgels, they swell, resulting in an increase in the distance between the etalon's Au
277 mirrors, which leads to the red shift of the reflectance peaks.

278 Using pNIPAm-co-AAc microgel-based etalons, Islam et al. recently reported a method to
279 detect the concentration of streptavidin in solution [159]. In this method the authors exploited the
280 phenomenon of penetration of positively charged polyelectrolyte PAH and biotinylated-PAH
281 through the etalon's Au overlayer to interact with the microgel in the etalon, which were at a pH
282 that rendered them negatively charged. The PAH and PAH-biotin is capable of crosslinking the
283 microgels, causing them to collapse, resulting in a blue shift in the peaks in the etalon's
284 reflectance spectrum. The extent of the shift in the reflectance peaks is related to the
285 concentration of PAH-biotin and hence was used to determine the concentration of streptavidin
286 in solution as shown in Figure 8.

287
288 Lyon et al. developed a new approach to biosensing using microlenses derived from dual
289 thermo- and pH responsive NIPAm and acrylic acid (AAc) microgels [160-162]. They designed
290 microlenses that would display a change in refractive index and particle diameter upon binding
291 with protein for use in sensing applications [162-166]. They designed microlenses for two
292 different sensing pathways: a direct binding-induced response and a displacement-induced
293 response. To illustrate each method; a small vitamin biotin was conjugated to the acrylic acid
294 groups on the microgels. For the binding induced method, avidin or anti-biotin (antibody) was
295 added to the solution around the microlens, resulting in binding of the protein to the microlens

296 surface. Since both avidin (four binding sites) and anti-biotin (two binding sites) are able to bind
297 multiple equivalents of biotin, the protein-binding events increase the surface cross-linking of the
298 microlens and hence changes the refractive index. A displacement- induced method can be
299 achieved by designing a reversible antibody--- antigen cross-linking construct. In this case, a
300 photoaffinity approach is used to couple a bound antibody to the antigen-laden microlens. When
301 the free biotin disrupts the cross-links via displacement, the microlens swells and the focal length
302 increases accordingly. A biotin-free buffer wash removes the free biotin, allowing for re-cross-
303 linking of the gel and regeneration of the sensor. Using microgels as microlenses is attractive
304 because of the ability to use many different solution-based bioconjugation methods and the ease
305 of assembly with simple electrostatic adsorption [167,168].

306

307 Miyata et al. [169,170] have reported antigen-responsive hydrogels using antigen-antibody
308 binding. They synthesized acrylamide-based hydrogels using a co-monomer ((N,N-succinimidyl
309 acrylate, NSA) which is covalently attached with antigen and antibody. When free antigens are
310 present in the analyte solution, the hydrogel swells due to the disruption of crosslinks between
311 the polymerized antigen and antibody. Another example of biomolecule recognition in a
312 hydrogel is the lectin-glycoprotein interaction. Maeda et al. [171] detected saccharide-protein
313 interaction capitalizing on the gel-modified field effect. This lectin-sensitive polymer gel
314 changes volume in response to the formation of molecular interactions between carbohydrate and
315 the lectin concanavalin A and this polymer gel has the ability to transduce volume changes into
316 electrical signals for the field effect transistor. Kuroki et al. [172] presented for the first time that
317 a biomolecule-recognition gating system responding to small signals of biomolecules by the
318 cooperation of biorecognition cross-linking and polymer phase transition in nanosized pores

319 (Figure 9). They used pNIPAm as the stimuli-responsive polymer and biotin as a biomolecule-
320 specific receptor for avidin. The pore states can be distinguished by a volume phase change of
321 biotin grafted polymers.

322 Feng et al. [173] synthesized a new fluorescent polyelectrolyte microgel for detecting DNA
323 and enzymes. The covalent linking of a conjugated polyelectrolyte moiety into the microgel
324 prevents leakage of fluorophore and retains its fluorescent property. The microgel can be used to
325 detect DNA and enzyme in homogeneous solution and in gel phase the microgel is reusable after
326 washing with high ionic strength aqueous solution. Zhao et al. [174] made a novel hydrogel
327 suspension array, which is capable of label-free, multiplex detection of DNA. To accomplish this
328 they designed acrylamide based hydrogel beads with 5'-and 3'-acryoyl-modified ssDNA as
329 crosslinkers. In the presence of complementary ssDNA, these hydrogel beads swell due to the
330 coiling of the dsDNA. This can be detected as a corresponding blue shift in the Bragg diffraction
331 peak position of the beads that can be used for quantitatively estimating the amount of target
332 DNA. Kivlehan et al. [175] have prepared and fabricated surface-attached PEG-diacrylate
333 hydrogel, by a photopolymerization process. Control of gel growth to micrometer size was
334 achieved by controlling the light source. This hydrogel was used as a sensing platform in DNA
335 hybridization assays with a detection limit of 3.9 nM. They allow for the diffusion of
336 fluorescently labeled target sequences into the hydrogel matrix to hybridize to probe oligos,
337 which are attached to the polymer backbones.

338 **2.1.3 Electric Responsive Polymer**

339 Polymers that change conformation in response to the application of an electrical stimulus
340 have also been synthesized and used for analytical applications. Ouyang et al. [176] investigated
341 that polyelectrolyte brushes can be grafted on a nanofluidic channel to control flow. Under

342 external electric fields, polyelectrolytes brushes undergo extension/collapse transition, which can
343 be used to regulate the opening and thus the flow rate of the channel. With molecular dynamics
344 simulation, they showed that the polymer brush modified nanochannel can be closed and opened
345 by switching on and off external electric fields (Figure 10), and the flow rate can also be
346 adjusted. Moreover, as a nanoscale valve the dynamic response time is at the sub-microsecond
347 level.

348 **2.1.4 Pressure Response**

349 There are various pressure responsive polymers such as N-isopropylacrylamide (NIPAm),
350 polydimethylsiloxane (PDMS), polyethylmethacrylate (PEMA) reported so far which respond to
351 a specific pressure stimulus by changing their conformation. In 2010, Lietor-Santos et al. [177]
352 found that the particle size of pNIPAm decreases with hydrostatic pressure by small angle
353 neutron scattering and Puhse et al. [178] confirmed the result by FTIR-spectroscopy. Lietor-
354 Santos et al. [179] published a study about the effect of hydrostatic pressure on the polymer
355 solubility. In 2012, Chen et al. [180] demonstrated Belousov Zhabotinsky (BZ) oscillations in the
356 matrix containing pNIPAm-co-Ru(bpy)₃ gels. Under the influence of a critical pressure, the BZ
357 oscillations are initiated and the whole polymer system is developed into a medium with periodic
358 color changes in the solution. Fan et al. [181] designed a self-powered pressure sensor device
359 based on PDMS gel where a pyramid patterned arrays polydimethylsiloxane film was
360 sandwiched between two ITO-coated PET membranes for measuring the amplitude of the
361 pressure on the device by voltage. Hoe et al. [182] embedded the vertical-cavity surface-emitting
362 laser (VCSEL) into the PDMS gel and then added a reflective phase on the top of gel to measure
363 the pressure by self-mixing interferometry of the emitting light.

364 A polymer has been prepared by photopolymerization of a mixture of cholesterylacrylate and
365 the eutectic mixture of cholesteryloleylcarbonate, cholesterylchloride and cholesterylnonanate
366 with polyethyleneglycol diacrylate and Genocure LTM (photo initiator) at room temperature by
367 Seeboth et al. [183], which exhibits a pressure dependent reversible shift of the selective
368 reflection wavelength over the entire visible range. The change of the selective reflection has its
369 origin in a compressible helix structure. Thus, the pitch length is switched by pressure changes.
370 The pressure controlled color changes can be detectable by the naked eye.

371 **2.1.5 Magnetic Responsive Polymer**

372 Magnetic responsive polymers have been widely investigated due to the unique properties of
373 the magnetic responsive particles (MRPs). As such, the properties of the magnetic responsive
374 polymers can be triggered by external magnetic field. These MRPs include iron [184-186] (e.g.,
375 Fe_2O_3 , Fe_3O_4), nickel [187] as well as cobalt [188]. One of the most common approaches of
376 making magnetic responsive polymers is cross-linking monomers in the presence of an aqueous
377 solution of MNPs via a physical encapsulation [185, 186, 189-191]. The most common
378 monomers are NIPAm and Oleic acid [189-191]. Covalently bound magnetic nanoparticles with
379 polymers have been prepared [188, 192-196]. Magnetic responsive gels have found various
380 applications in drug delivery,[189, 190] soft actuators, and separations[196]. There have been
381 reports on sensing applications, e.g., detection of DNA [197], bovine serum albumin [198], as
382 well as small molecules [191, 199]. There has been some research on cellular tracking by
383 magnetic responsive particle. Lee et al. [200] synthesized microgels doped with MNPs, which
384 served to enhance contrast by magnetic resonance imaging. More importantly, these MNPs did
385 not affect cellular function and phenotype.

386 **2.1.6 Explosives and Gas Responsive Polymer**

387 Detection of explosive chemicals and gases is very important due to the threat to human
388 health and security. It is very important to sense and monitor the presence of minute amounts of
389 explosive chemicals and gases accurately and quickly. Among all of the high energy explosives,
390 trinitrotoluene (TNT) is a widely used explosive that brings devastation to human lives and
391 contaminates soil and water. Even though a large number of reports are available, a simple and
392 quick approach to the detection of explosives at extremely low concentration still remains a
393 challenge. Swager et al. reported conjugated organic polymer based molecular wires for sensing
394 chemicals. This strategy of molecular wires are capable of enhancing the chemosensory
395 responses over many orders of magnitude and based on that principle a number of advanced
396 sensors have been developed. Based on the chemoresistivity of molecular wires, Nomadics Inc.
397 markets the Fido, which is able to detect very low levels of explosives [201-205]. The challenge
398 can be overcome by translating molecular events to a detectable signal. Fluorescence-quenching
399 based sensing has gained increasing interest in detection of explosives because of
400 reproducibility, stability, high sensitivity, low cost, ease of use, and quick signal transmission
401 and we will mention some recent works based on fluorescent quenching.

402 A coil-shaped twisted plastic optical fibre (POF) of different diameters coated with
403 conjugated polymer poly (2-methoxy- (2-ethylhexyloxy)-p-phenylene-vinylene) (MEH-PPV) was
404 employed as sensor head to detect nitro aromatic explosives by Chu et al. [206]. The most
405 sensitive sensor head was the coil with diameter of 4 mm with sensitivity 5 ng/mL. By
406 incorporating 2,2-isopropylene spacer to introduce a bend in the structure of a conjugated
407 polymer composed of p-quaterphenylene segments tethered by their meta positions along the
408 polymer main, an improved method of the sensing power of fluorescent polymer thin films has
409 been reported [207].

410 The same group demonstrated that amorphous segmented conjugated polymers bearing
411 relatively compact shape chromophores such as 2,7-diphenylfluorene chromophores tethered by
412 isopropylidene connectors can be used as sensing materials with performances comparable to
413 those presented by conjugated polymers with more elaborate structural design [208]. It has been
414 reported that isopropylene increases the porosity and hence enhances the sensitivity (Figure 11).
415 Poly[2-methoxy-5-(30,70- dimethyloctyloxy)-1,4-phenylenevinylene(MDMO-PPV) solution has
416 been reported to show very fast response for detecting nitrated explosives such as 2,4,6-
417 trinitrotoluene (TNT) by changing color from orange to brownish black [209].

418 In another report, the fluorescence quenching properties of thin film of poly(phenylene
419 ethynylene) containing the rigid pentyptycene and large cholesteryl ester pendent groups in
420 response to vapour of 2,4-dinitrotulene (DNT) have been investigated by varying the film
421 thickness and by applying an undercoating and blending with another polar polymer [210]. A
422 widely available polymer, polyfluorene has been reported as an excellent sensor for low vapour
423 pressure explosive detection of DNB at 9.8 ppb [211]. Conjugated microporous polymers
424 (CMPs) achieved by condensation of a carbazole derivative has been shown to exhibit enhanced
425 detection sensitivity of arenes upon exposure to their vapors [212]. There are several recent
426 reports where conjugated polymer and silica hybrid materials were used to detect TNT in
427 solution through electron transfer [213-215].

428 Dudhe et al. [216] reported that a combination of poly 3-hexylthiophene (P3HT), Cu(II)
429 tetraphenylporphyrin) and a copolymer of diethynyl-pentyptycene and dibenzyl-ProDOT
430 (substituted decyloxythiophene) is a good sensor for nitro based explosives. It was found that
431 graphene oxide-methyl cellulose composite is capable of detecting picric acid [217]. An
432 optimized and highly sensitive piezoresistive SU-8 polymer nanocomposite microcantilever

433 sensor has been reported [218] with dispersed carbon black for application in detection of
434 explosives in the vapor phase at ppb levels. A nano-aggregate formed from addition of water into
435 THF solution of a high molecule weight hyperbranched polysilole reported to be used as the
436 fluorescent sensor [219] for nitro based gas sensors.

437 Guan et al. [220] reported a facile and general methodology for the synthesis of various
438 molecularly imprinted shells at the surface of polystyrene (PS) colloidal spheres to recognize
439 nitro-based explosive compounds (Figure 12). Molecularly imprinted microparticles (MIP)
440 prepared using methacrylic acid as the functional monomer to detect high explosive compounds
441 such as TNT has been reported as well [221]. Lee et al. [222] have demonstrated the first
442 example of a selective chemosensor for the detection of chloride by conversion of a coordination
443 gel.

444 The attachment of the sensing polymers onto a chromatographic support also allows for
445 simultaneous separation of an explosive mixture, and component identification through the use
446 of multiple sensing polymers. In this regard, Martinez et al. [223] reported that the luminescent
447 organosilicon copolymers poly(silafluorenyldiethynylspirobifluorene) and poly
448 (tetrasilolethynylspirobifluorene) can be covalently linked to a silica gel thin layer
449 chromatography (TLC) support through the use of a trimethoxysilyl end group. Surface
450 functionalization of silica with the fluorescent sensing polymer allows enhanced detection
451 sensitivity. A terthiophene (3T) derivative of 5-(1-pyrenyl)-2,2': 5',2''-terthiophene (Py-3T) was
452 chemically immobilized onto a glass wafer surface via a flexible spacer by employing a single-
453 layer chemistry technique, which displays unprecedented photochemical stability at ambient
454 conditions [224]. Fluorescence studies confirmed that the emission of the film as fabricated is
455 significantly and selectively quenched by the presence of nitroaromatic compounds (NACs),

456 both in the vapor phase and in aqueous solution. Thin films of thiophene-based polymers
457 containing 1,2,3-triazole with appropriate alkyl side chains show enhanced fluorescence
458 quenching in the presence of nitroaromatic vapors [225]. A new nanoscale sensing concept was
459 developed by Wyatt E. Tenhaeff et al. [226] which consists of poly(4-vinylpyridine)
460 (P4VP)layers deposited inside microfabricated trenches which on contact with nitro aromatic
461 swell and close the electric circuit making it possible to detect ppb level explosive.

462

463 **2.2 Chemically Responsive Polymers**

464 Chemically responsive polymers respond to various stimuli by chemical bond formation or
465 dissociation. Various degradable crosslinkers are used to make the polymeric systems chemically
466 responsive. Winnik and co-workers reported a thermal and/or redox sensitive nanogel prepared
467 via RAFT polymerization of NIPAM mediated by a polysaccharide (pullulan)-based chain
468 transfer agent [227]. In the presence of an oxidant, pNIPAm-graft- polysaccharide with thiol end
469 groups readily formed disulfides, which produced chemically cross-linked nanogels able to
470 withstand changes in temperature (Figure 13). Vancso et al. grafted individual PFS polymer
471 molecules to gold surfaces for force spectroscopy experiments on the single molecule level [228,
472 229]. Shi et al. have shown in single-molecule force spectroscopy studies that ex situ redox
473 chemistry using FeCl_3 can be used to change the elastic properties of
474 poly(ferrocenyldimethylsilane) (PFS) macromolecules[230]. Recently, significant efforts have
475 been directed at redox-labeled nucleotides, especially ferrocene, towards the development of
476 DNA biosensors, which are able to detect single nucleotide mismatches under real-to-life
477 conditions ideally without the need for PCR amplification of the analyte [231-233].

478 Recent interest in developing molecularly imprinted polymers (MIP) as biomimetic materials
479 has been extended to realize a wide variety of applications due to the fact that MIPs can be
480 synthesized to identify specific molecules and molecular events. Molecular imprinting is a
481 process by which a specific functional monomer is allowed to self-assemble around a template
482 molecule and is subsequently polymerized in the presence of a crosslinker. After the extraction
483 of the template molecule, a cavity is left, which is capable of rebinding the template molecule
484 [234]. MIP could selectively perform molecular recognition and hence it can be applied for the
485 determination of several analytes represented by small molecules such as pharmaceuticals,
486 pesticides, amino acids, sugars, and so forth. Herein, the most recent applications of preparing
487 electrodes modified with MIPs are introduced for capacitive biosensing [235], potentiometric
488 sensing [236-238] and other electrochemical sensing approaches [239]. Aghaei et al. [235]
489 developed a capacitive biosensor by electropolymerization of 2-mercaptobenzimidazole (2-MBI)
490 on a gold electrode in the presence of cholesterol as a template. The sensor's linear response
491 range was between 5 and 30 μM , with a detection limit of 0.42 μM . The proposed molecularly
492 imprinted polymer capacitive (MIPC) sensor exhibited good selectivity for cholesterol. Alizadeh
493 et al. [239] prepared an Hg^{2+} imprinted polymer based on cross-linked vinyl pyridine for a novel
494 highly selective and sensitive electrochemical sensor. Compared to previously developed
495 mercury selective sensors, the proposed electrochemical sensor was more selective, regarding the
496 common potential interference. This sensor showed a linear response range of 2.5×10^{-9} - $5.0 \times$
497 10^{-7} M and lower detection limit of 5.2×10^{-10} M (S/N). Moreover, the sensor was successfully
498 applied to the determination of mercury in real samples. Liang et al. [236] described a
499 potentiometric sensor based on a polymeric membrane ion-selective electrode for determination
500 of melamine. The membrane electrode shows near-Nernstian response (54 mV/decade) to the

501 protonated melamine over the concentration range of 5.0×10^{-6} to 1.0×10^{-2} mol L⁻¹. A
502 potentiometric sensor is also fabricated for determination of 2-aminopyridine (2-AP) [237]. The
503 membrane potential, increases with 2-AP concentration over a wide range of concentration (5
504 μ M to 100 mM) with a near Nernstian response of 54.1 mV/decade and detection limit of 2.0
505 μ M. The utility of the sensor was successfully tested by examining of 2-AP in piroxicam (PX) as
506 a potential impurity.

507 Electrodes have also been modified with polymers other than MIP for voltammetric and
508 amperometric sensing. Based on polyaniline composite with graphene, a voltammetric sensor of
509 4-aminophenol (4-AP) has been designed [240]. This sensor 4-AP exhibits enhanced
510 voltammetric response at GR-PANI modified GCE. This electrochemical sensor shows a
511 favorable analytical performance for 4-AP detection with a detection limit of 6.5×10^{-8} M and
512 high sensitivity of $604.2 \mu\text{A mM}^{-1}$. Moreover, 4-AP and paracetamol can be detected
513 simultaneously without interference of each other in a large dynamic range. A polymer
514 electrogenerated from Fe(III)-5-amino-1,10-phenantroline solution at a carbon nanotubes paste
515 electrode (CNTPE) is investigated in amperometric response of hydrogen peroxide. The
516 analytical application of the resulting electrode is demonstrated in connection with the design of
517 a glucose biosensor based on the deposition of GO_x and diluted Nafion on the top of the
518 polymer-modified CNTPE. The quantification of glucose in human serum samples showed a
519 good correlation with the values obtained by the spectrophotometric technique.

520 Conductive electroactive polymers have been blended or cross-linked to form highly
521 hydrated hydrogels, which is named electroconductive hydrogels (ECHs). An electroconductive
522 hydrogel describes a polymer that combines the properties of hydrogels and conductive systems
523 and appears to have first originated with Gong et al. [241] who described a conductive charge

524 transfer salt complex of 7,7,8,8-tet-racyanoquinodimethane (TCNQ)-loaded hydrogel. In
525 analytical fields, electroconductive hydrogels can be applied as a biorecognition membrane layer
526 in a biosensor. Enzymes entrapped within polypyrrole (PPy) films and other electroconductive
527 hydrogels have been commonly used to prepare electrodes. Kotanen et al. [242] reported a
528 glucose responsive biotransducer which was prepared by potentiostatic electropolymerization of
529 pyrrole at Poly(hydroxyethyl methacrylate)-based hydrogel-coated Pt micro-electrodes from
530 aqueous solutions. A glucose bioelectrode [243] was coated with carboxylated carbon nanotubes,
531 a biocatalytic hydrogel composed of a conductive redox polymer, glucose oxidase, and a
532 crosslinker. The current density on oxidation of glucose is 16.6 mA cm^{-2} at 0.5 V (vs. Ag/AgCl)
533 in oxygen-free glucose solution. Moreover, Guiseppi-Elie et al. [244] developed a temporary,
534 implantable, integrated glucose and lactate biosensor and communications biochip. The dual
535 responsive, amperometric biotransducer was fabricated on a microdisc electrode array format
536 upon which were separately immobilized glucose oxidase and lactate oxidase within
537 biorecognition layers of 3 mol % tetraethyleneglycol diacrylate cross-linked p(HEMA-co-
538 PEGMA-co-HMMA-co-SPA)-p(Py-co-PyBA) electroconductive hydrogels. The device was then
539 coated with a bioactive hydrogel layer containing phosphoryl choline and polyethylene glycol
540 pendant moieties [p(HEMA-co-PEGMA-co-HMMA-co-MPC)] for indwelling biocompatibility.
541 The glucose and lactate biotransducers exhibited linear dynamic ranges of 0.10-13.0 mM glucose
542 and 1.0-7.0 mM and response times of 50 and 35-40 s, respectively. Operational stability gave 80
543 % of the initial biosensor response after 5 days of continuous operation at 37 °C. The author
544 reported that in vivo studies in a Sprague–Dawley hemorrhage model showed tissue lactate
545 levels rise more rapidly than systematic lactate. The study shows the potential of an implantable

546 biochip that supports telemetric reporting of intramuscular lactate and glucose levels allows the
547 refinement of resuscitation approaches for civilian and combat trauma victims.

548 **3. Conclusion**

549 Researchers around the globe are constantly pursuing highly efficient responsive polymer-
550 based materials and systems to translate the application of a stimulus (e.g., an analyte) into a
551 response. A majority of the reports published to date describe temperature, pH, and ionic
552 strength responsivity, although emerging systems are able to respond to mechanical forces,
553 electrical and magnetic field, light, redox potential, and molecules/biomolecules etc. Along these
554 lines, responsive polymers and systems have been developed that are capable of responding to
555 the application of multiple stimuli. In this review, we pointed out representative examples of
556 each, and more. We would like to point out that while responsive polymers show great promise
557 in the field of analytical chemistry, they have found many applications associated with health,
558 energy and the environment. With so much chemical versatility, and a wide reaching array of
559 applications, the future is bright for stimuli responsive polymers.

560

561 **References:**

562

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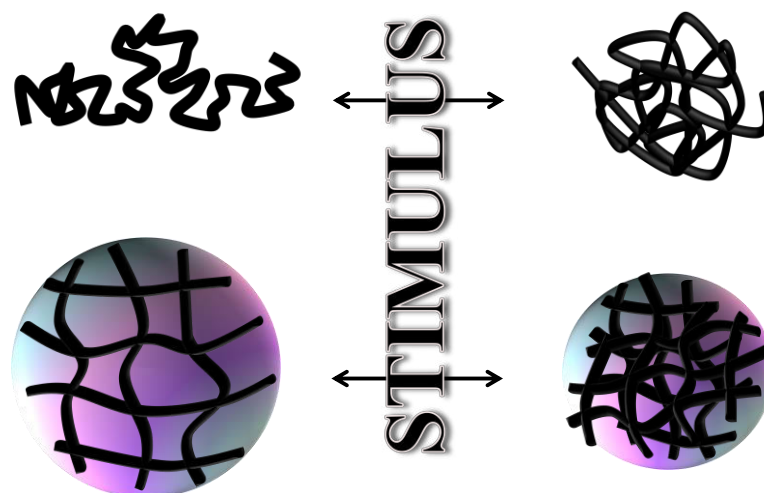
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909 **Scheme 1.** (top), A stimuli responsive polymer showing a conformational change in response
910 to a stimulus and (bottom), a crosslinked stimuli responsive polymer-based material showing
911 reversible swelling and deswelling due to the application of a stimulus.

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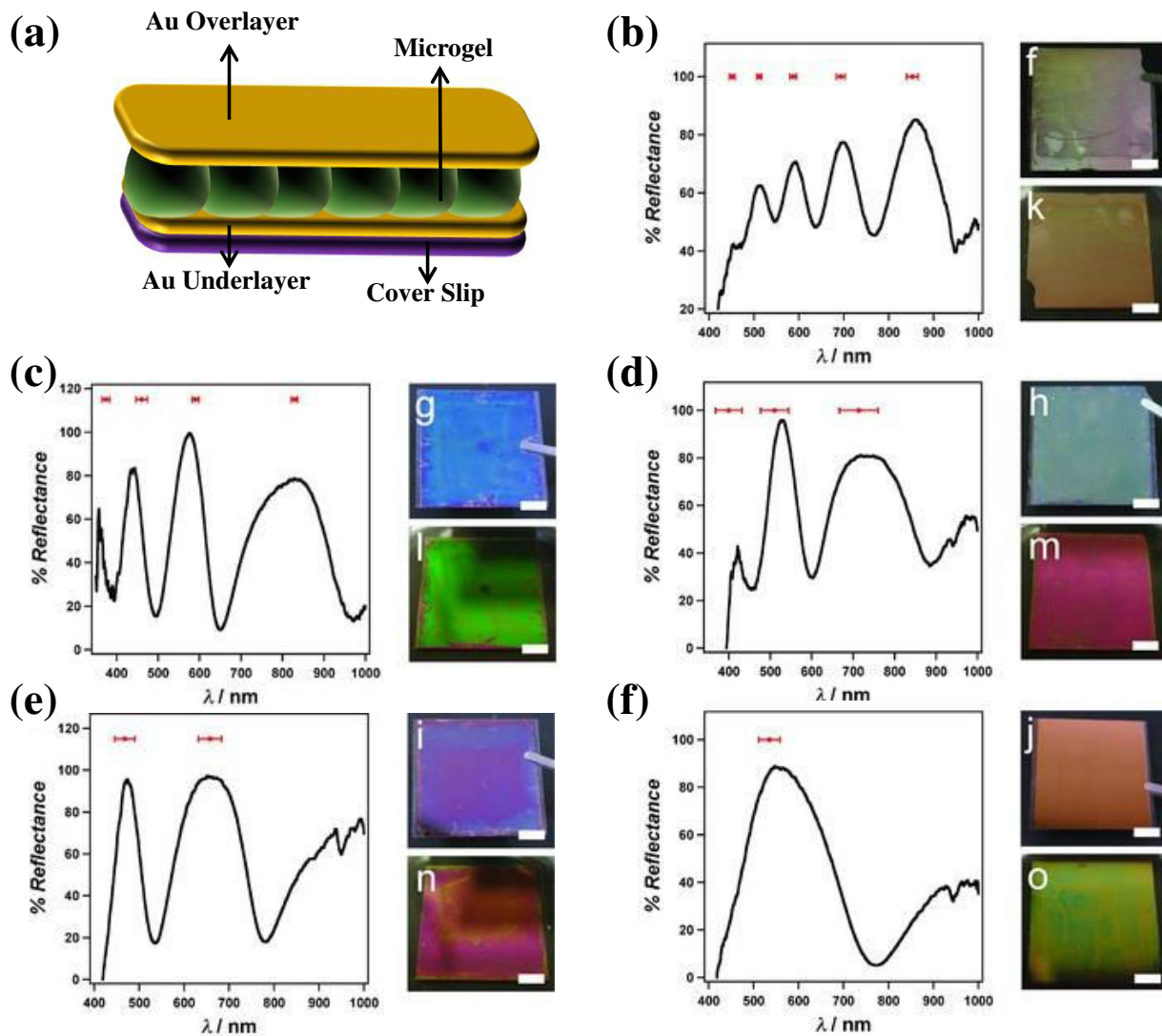
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Figure 1: (a) Schematic illustrating the structure of a poly (*N*-isopropylacrylamide)

microgel-based etalon (b-f) Representative spectra for etalons composed of a) large diameter

poly (*N*-isopropylacrylamide)-co-acrylic acid (pNIPAm-co-AAc) microgels (hydrodynamic

diameter (D_H) = 1548 ± 69 nm) b) poly (*N*-isopropylacrylamide)-co-acrylamide (pNIPAm-co-

AAm) (D_H = 653 ± 10 nm) c) medium diameter poly (*N*-isopropylacrylamide)-co-acrylic acid

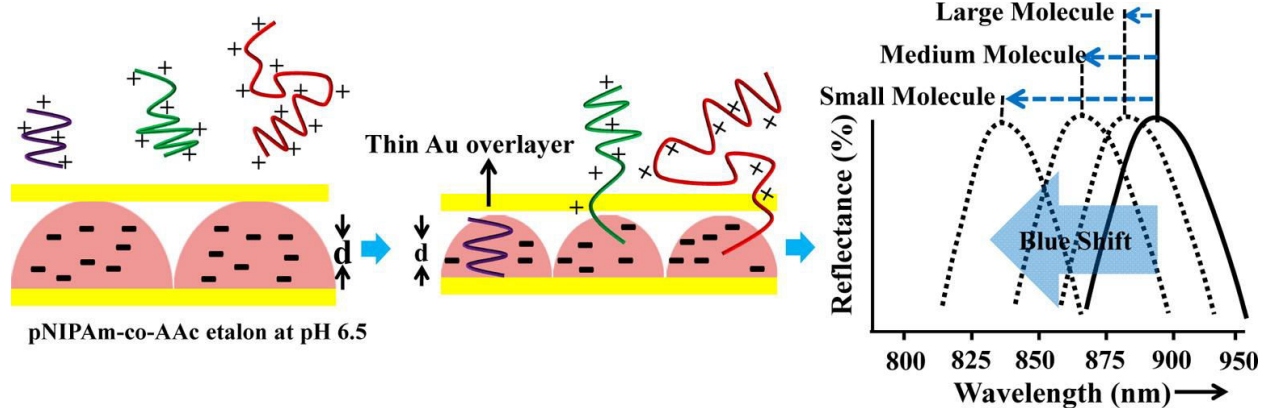
(pNIPAm-co-AAc) microgels (D_H = 653 ± 10 nm) d) poly (*N*-isopropylacrylamide)-co- vinyl

acrylic acid (pNIPAm-co-VAA) (D_H = 603 ± 17 nm), and e) small diameter poly (*N*-

isopropylacrylamide)-co-acrylic acid (pNIPAm-co-AAc) microgels (D_H = 229 ± 10 nm), all

935 obtained in pH 3 formate buffer. The average peak position (\pm one standard deviation) from six
936 spectra is shown in red above each spectrum. f–j) Photographs for the etalons (a–e) in the dry
937 state, respectively. k–o) Photographs of the etalons (a–e) hydrated in pH 3 formate buffer. Scale
938 bars in the photographs are 5 mm. Figure b–f are reproduced with permission from reference 131.

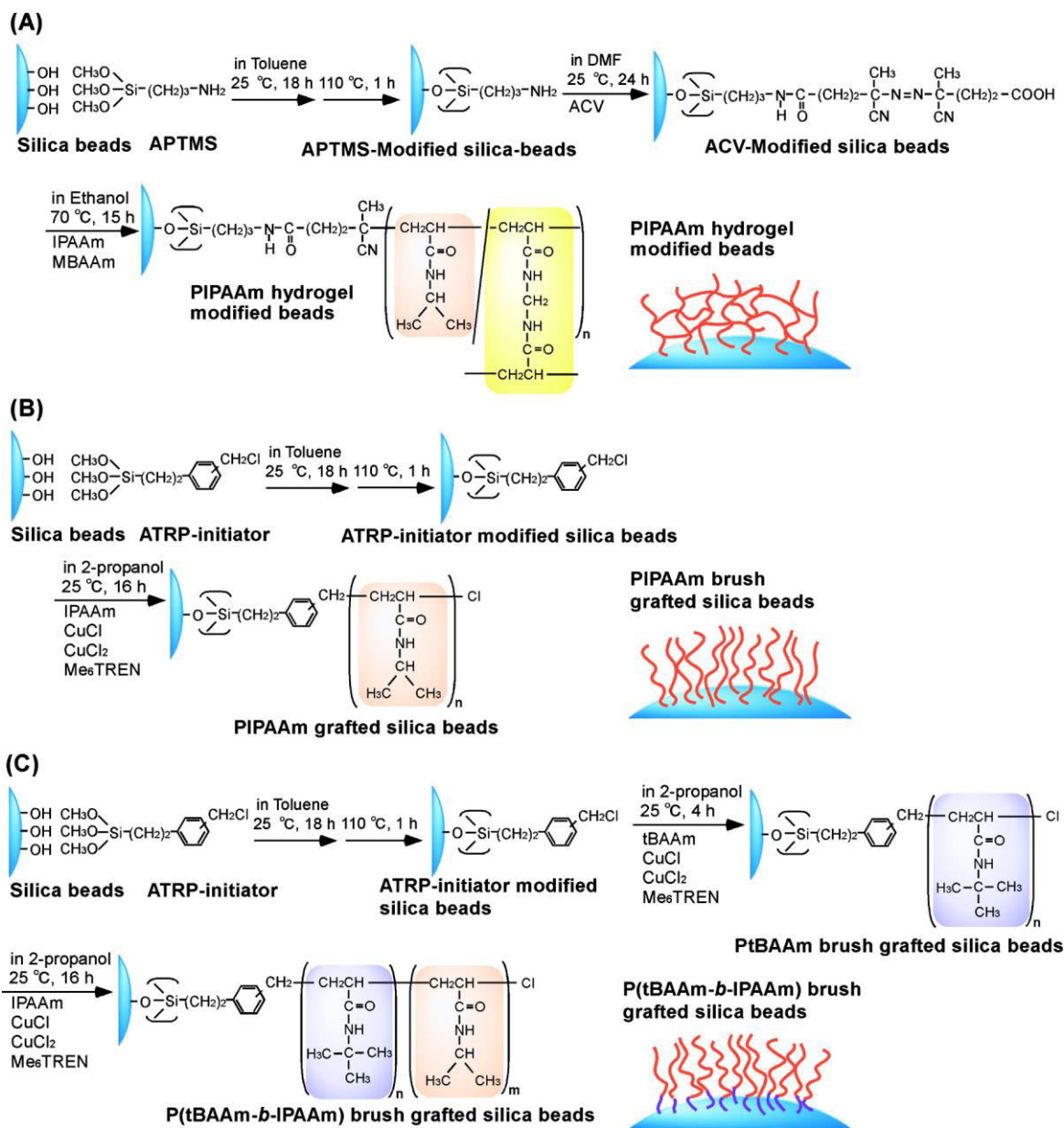
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946 **Figure 2:** Polyelectrolyte penetration through the porous Au overlayer of an etalon.

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955 **Figure 3.** Schematic showing the preparation of thermoresponsive polymer-grafted silica-

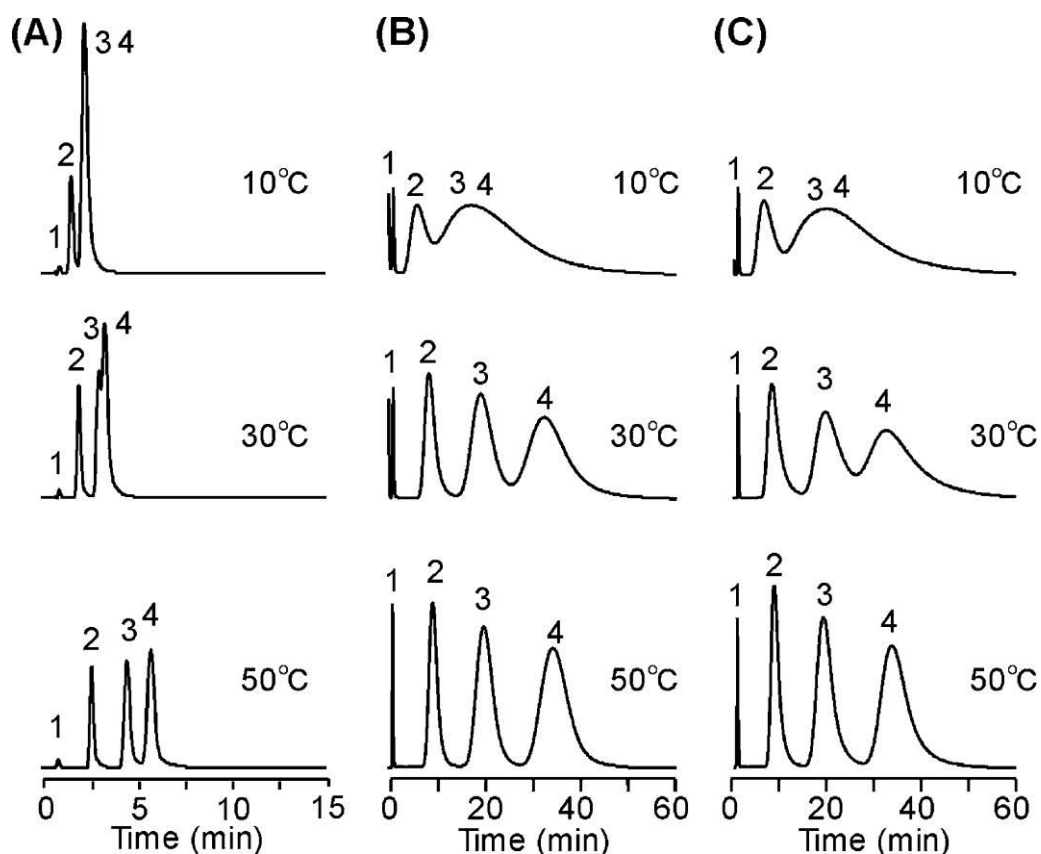
956 beads using a surface-initiated atom transfer radical polymerization (ATRP); (A) pNIPAM

957 hydrogel-modified beads and (B) pNIPAM brush-grafted surface, and (C) poly(*tert*-

958 butylacrylamide-*b*-N-isopropylacrylamide (tBAAm)-*b*-IPAAm). Reproduced with permission

959 from reference 139.

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962

963 **Figure 4.** HPLC chromatograms of steroids separated using pNIPAm-grafted silica beads as

964 the packing materials at various temperatures: (A) PIPAAm hydrogel-modified silica-bead-

965 packed column, (B) PIPAAm-brush-grafted silica-bead column (IP-B), and (C) poly(*tert*-

966 butylacrylamide(*t*BAAm)-*b*-IPAAm) brush-grafted silica-bead column (*t*BIP-B). Mobile phase

967 was Milli-Q water. The peak 1 represents adenosine; peak 2, hydrocortisone; peak 3,

968 dexamethasone; peak 4, hydrocortisone acetate. Reproduced with permission from reference 139.

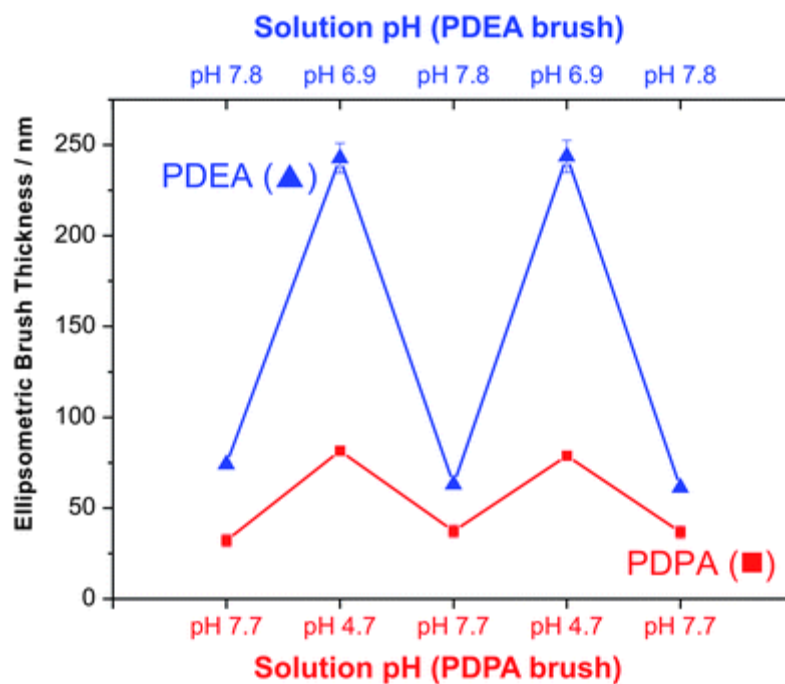
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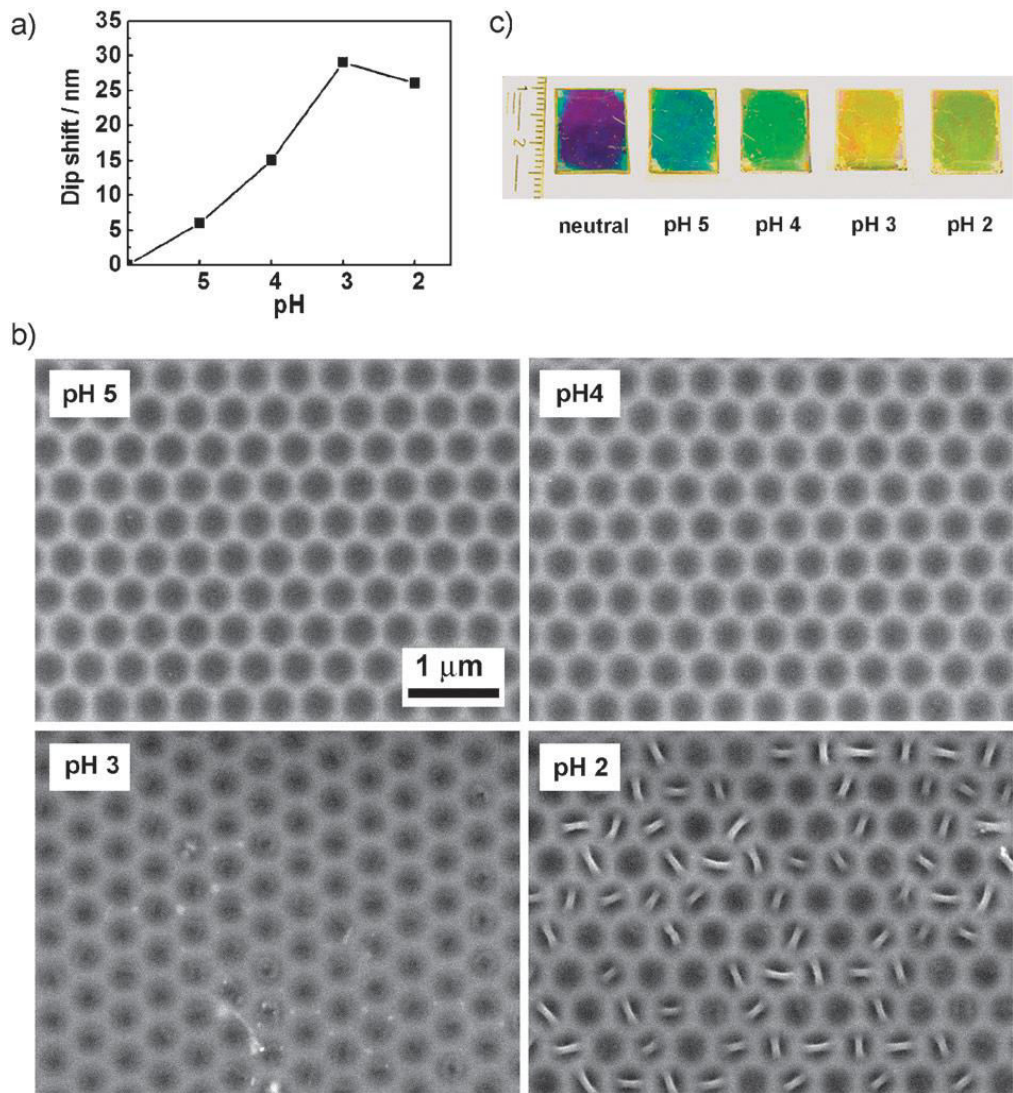
975 **Figure 5.** Aqueous in situ ellipsometric thickness against pH for a PDPA (■) and a PDEA (▲)

976 brush grown from anionic macro-initiator on aminated silicon wafers. The samples were

977 immersed in buffer solutions with alternating pH and allowed to reach equilibrium. Dilute

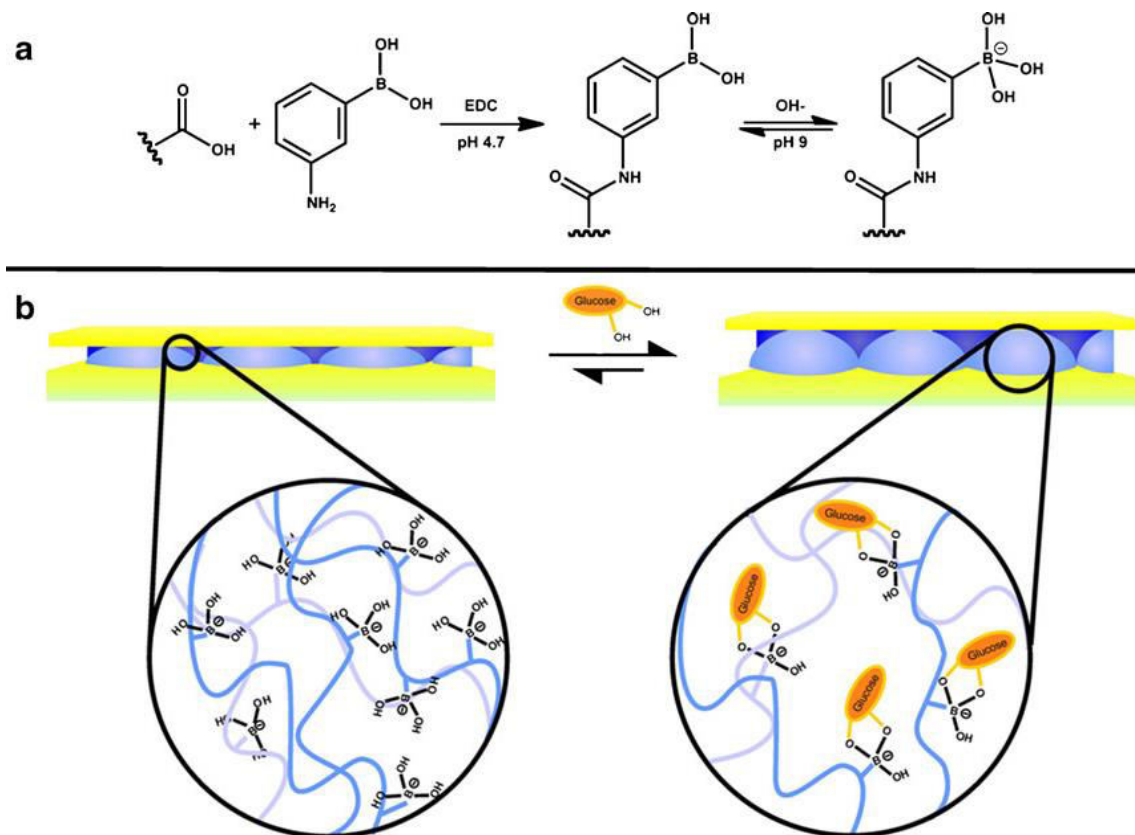
978 phosphate buffer solutions (0.01 M) were used to perform the experiment. Reproduced with

979 permission from reference 147.



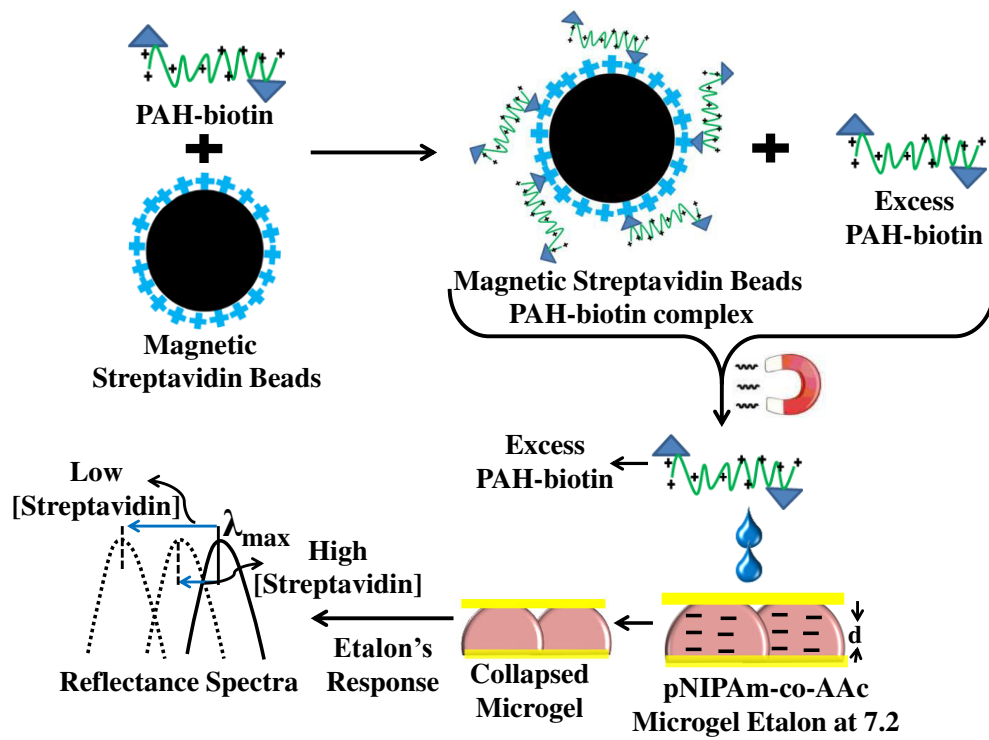
980

981 **Figure 6.** Transmission dip shift (a), morphological changes (b) and interference colors (c) of
 982 2DPC-PGs in response to different pH conditions. The 2DPC-PGs were prepared with 470 nm
 983 opal monolayers and a spin-coating speed of 2000 rpm on glass (a) and silicon wafer (b, c),
 984 respectively. Reproduced with permission from reference 152.



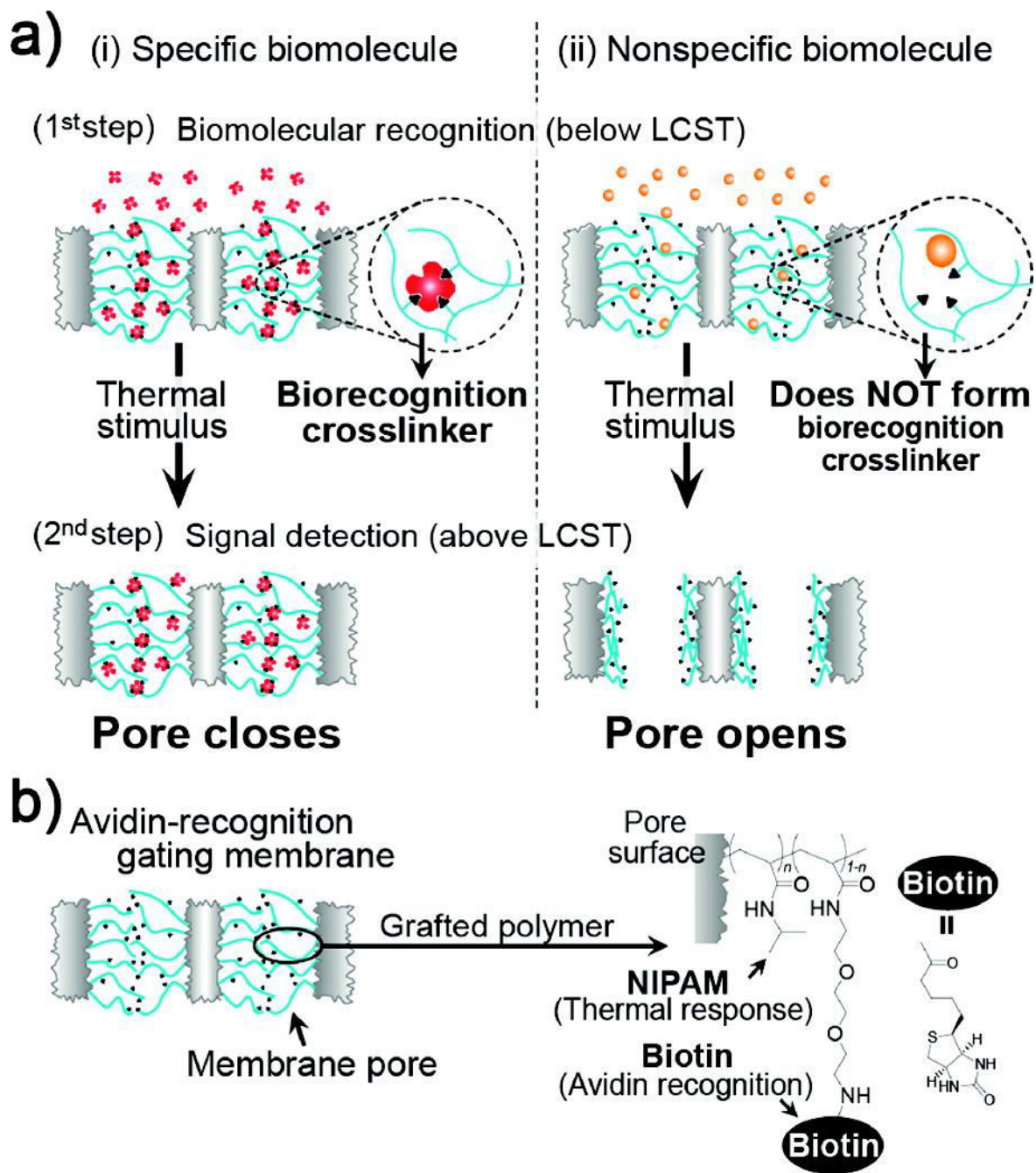
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986 **Figure 7.** Reaction scheme for (a) the functionalization of the acrylic acid moieties on the
 987 microgel with 3-aminophenylboronic acid (APBA) followed by the activation of the boronic acid
 988 with base and (b) a cartoon depiction of the glucose responsivity of an APBA-functionalized
 989 microgel etalon at pH 9. Reproduced with permission from reference 125.



990

991 **Figure 8.** The proposed mechanism of sensing highlighting the interaction of PAH-biotin with
 992 the streptavidin modified magnetic beads and the effect of addition of free PAH-biotin to the
 993 pNIPAm-co-AAc microgel-based etalon on its reflectance spectrum. Reproduced with
 994 permission from reference 159.

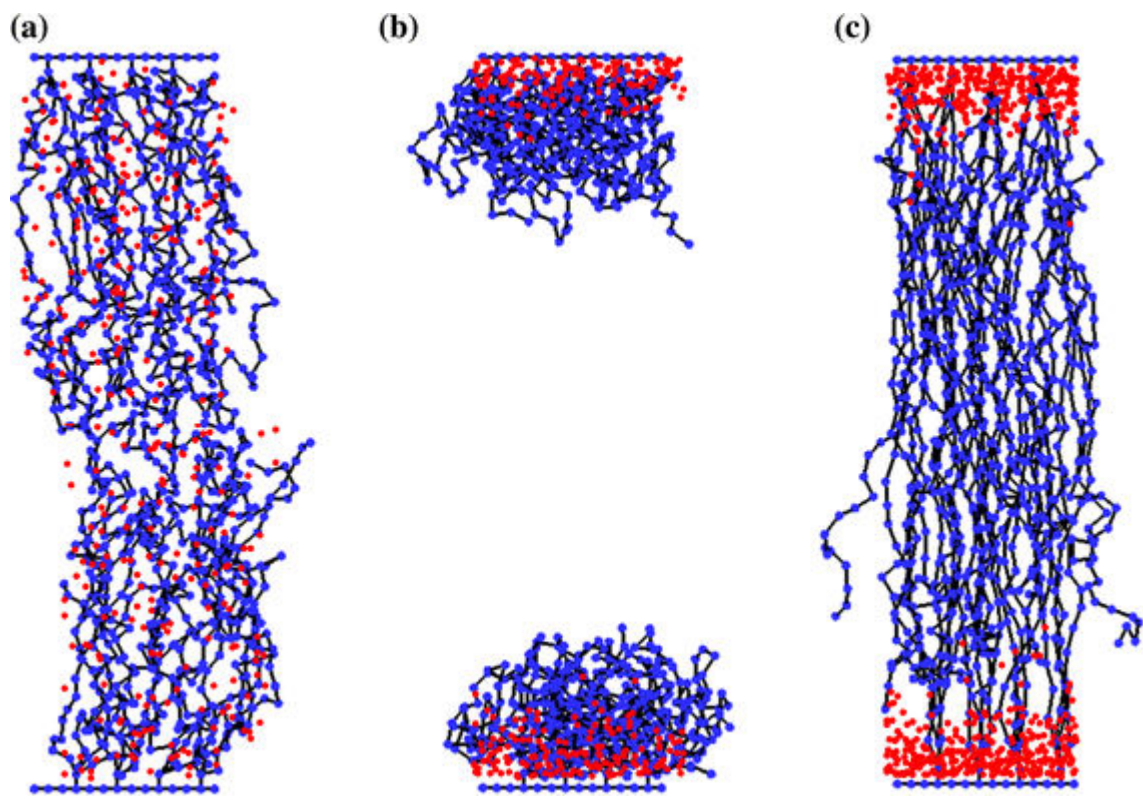


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996 **Figure 9.** (a) Schematic describing this study: (i) specific biomolecule and (ii) nonspecific

997 biomolecule. (b) Illustration of an avidin-recognition gating membrane. Reproduced with

998 permission from reference 172.



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Figure 10. Snapshots of hydrophilic polyelectrolyte brushes for zero pressure gradient ($F_x =$

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0) at a) equilibrium state, $E = 0$; b) open state, $E = -3$; c) close state, $E = 3$. Here “E” stands for

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electric field strength. Blue beads on black curves represent polyelectrolyte monomers; blue

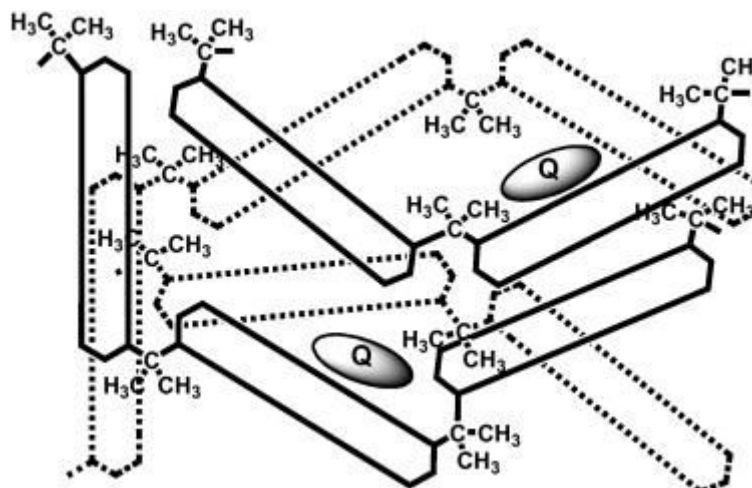
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beads on straight lines represent wall beads; red beads represent counterions. Water beads are not

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shown for simplicity. Reproduced with permission from reference 176.

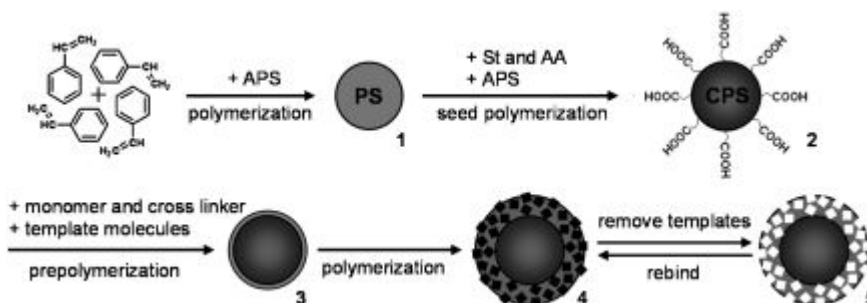
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1007 **Figure 11.** Schematic illustration of how isopropylene spacers induce porosity in films.

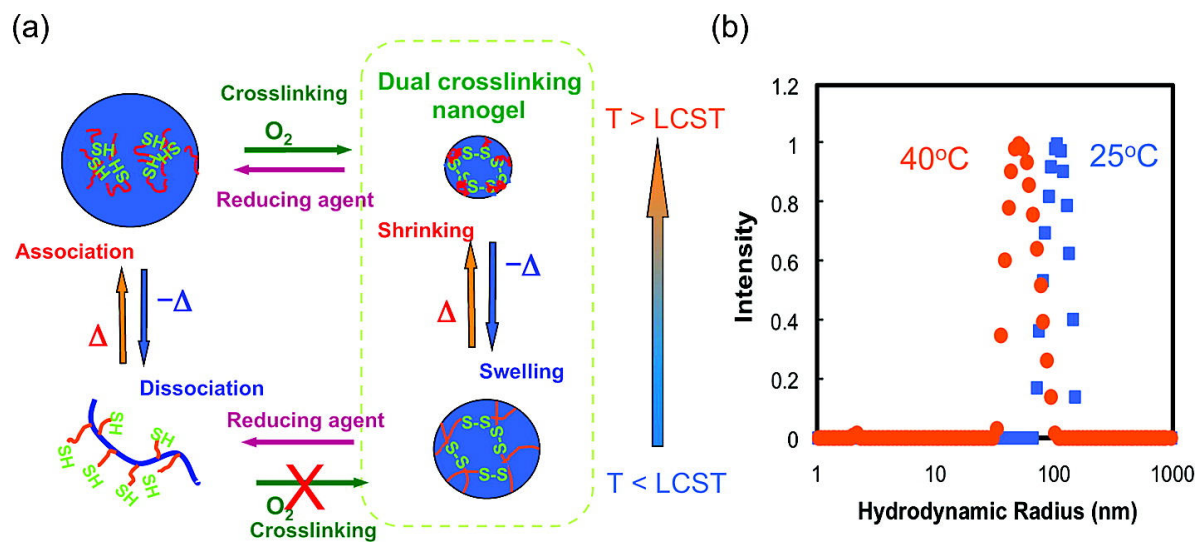
1008 Reproduced with permission from reference 208.



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1010 **Figure 12.** Preparation of molecularly imprinted core-shell microspheres. PS seeds (1) were
 1011 first prepared by polymerization of styrene (St), and then transferred to carboxyl-capped PS
 1012 (CPS) spheres (2) through the copolymerization of St and acrylic acid (AA) on PS seeds. When
 1013 CPS spheres were suspended in the reaction solution, the imprinting precursors assembled on the
 1014 surface of PS cores and pre-polymerized to form oligomer coated PS spheres (3). Subsequently,
 1015 the oligomer layers directed the selective imprinting polymerization, leading to the core-shell
 1016 microspheres (4). After removal of templates, molecularly imprinted core-shell microspheres (5)
 1017 were obtained. Reproduced with permission from reference 220.

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1020 **Figure 13.** (a) Schematic representation of temperature and redox responsive SS-N26gPul
 1021 nanogels constructed by RAFT polymerization of NIPAm onto PulSTS. (b) Hydrodynamic
 1022 radius of the dual responsive SS-N26gPul nanogels in water below and above LCST.
 1023 Reproduced with permission from reference 227.

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