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Communications

Poly(*N*-isopropylacrylamide-*co*-propylacrylic acid) Copolymers That Respond Sharply to Temperature and pH

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Temperature- and pH-sensitive random copolymers of *N*-isopropylacrylamide (NIPAAm) and propylacrylic acid (PAA) were prepared using the reversible addition fragmentation chain transfer (RAFT) polymerization method. The lower critical solution temperatures (LCSTs) (or phase separation temperatures) of the NIPAAm-*co*-PAA copolymer solutions were measured by the cloud-point method. At slightly acidic conditions, the LCST decreased with increase in PAA content, which suggests that the hydrophobic propyl group of PAA has a greater influence on the LCST than the polar carboxylic acid group at those conditions. An increase of pH led to a significant increase in LCST of the copolymers due to the ionization of the −COOH group. The LCSTs were studied as a function of copolymer composition over the pH range from 5.0 to 7.0. Because the pK_a of the polymers can be tuned to fall close to neutral pH, these polymer compositions can be designed to have phase transitions triggered near physiological pH or at slightly acidic pH values that fall within acidic gradients found in biology. The NIPAAm-*co*-PAA copolymers thus display tunable properties that could make them useful in a variety of molecular switching and drug delivery applications where responses to small pH changes are relevant.

Introduction

Polymer systems that undergo phase transitions in response to environmental stimuli such as temperature and pH have been widely investigated for drug delivery, separations, and diagnostics applications.[1,2] A key temperature-responsive class is based on alkyl acrylamide polymers, especially poly(*N*-isopropylacrylamide) (pNIPAAm), which undergoes a sharp coil−globule transition and phase separation at its lower critical solution temperature (LCST) in water. This spontaneous process is endothermic and is therefore driven by a gain in entropy associated with the release of hydrophobically bound water molecules.[3] The LCST of such thermally sensitive polymers can be tuned to a desired temperature range by copolymerization with a more hydrophilic comonomer (which raises the LCST) or a more hydrophobic comonomer (which lowers the LCST).[4]

pH-sensitive monomers may also be copolymerized with NIPAAm, and then the phase separation can also be triggered by a change in the pH at specific temperatures, such as 37 °C.[5,6] Readily available carboxylic acid monomers, such as acrylic acid (AA) or methacrylic acid (MAA), have been copolymerized with NIPAAm using traditional free radical polymerization techniques, to form random copolymers with both temperature- and pH-responsive properties.[6−9] However, the LCSTs of copolymers increase rapidly with increasing acrylic acid comonomer contents at all pH ranges, because acrylic acid is intrinsically more hydrophilic than NIPAAm in both the protonated and unprotonated states.[6,9] In addition, the critical transitions of pH responsive copolymers of NIPAAm with acrylic acid and methacrylic acid are usually below pH 5.0 due to the low pK_a values of poly(acrylic acid) and poly(methacrylic acid).[6−10] Because of this, it has been a general challenge to design NIPAAm copolymers capable of responding to the physiologically relevant pHs between 5.0 and 7.4.[11]

We have recently described the pH-dependent properties of polymer compositions containing the longer alkyl segment monomers propylacrylic acid and butylacrylic acid.[12,13] These more hydrophobic polymers exhibit higher pK_a values and undergo sharp phase transitions above pH 6.0. We have studied

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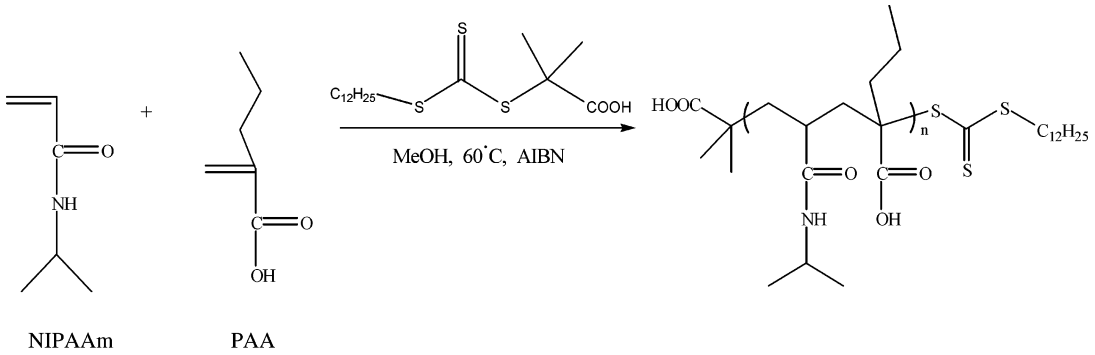
Scheme 1. RAFT Copolymerization of *N*-Isopropylacrylamide (NIPAAm) and Propylacrylic Acid (PAA)



the cell membrane-disruptive properties of pPAA and PAA-*co*-butylacrylate copolymers as a function of pH in order to evaluate their potential for enhancing intracellular drug delivery.[12−14] These compositions at appropriate molecular weights and concentrations display a sharp transition in membrane destabilizing activity as the pH is dropped across the tunable range of 7.4−5.5.[12−16]

These results have led us to characterize the properties of copolymers of NIPAAm and PAA with the goal of defining sharp pH-triggered phase transitions slightly below neutral values at a variety of different temperature conditions. The properties of NIPAAm copolymers with the hydrophobic acidic monomers 4-pentenoic acid,[17] 6-acrylaminohexanoic acid,[18] and *N*-acryloyl-L-phenylalanine[19] have been previously reported. It was found that LCSTs of these copolymers decreased at pH 4.0, whereas they increased at pH 7.4 with increasing the content of comonomer 4-pentenoic acid or 6-acrylaminohexanoic acid.[17,18]

In this study, PAA and NIPAAm copolymer compositions were synthesized using reversible addition fragmentation chain transfer (RAFT) polymerization to give controlled and narrow molecular weight distributions.[20,21] According to a previous report,[22] both the molecular weight and its polydispersity of pNIPAAm influence the LCST. The dual temperature and pH responses have been characterized, and their sharp, tunable phase transitions around neutral pH may be exploitable in drug delivery, molecular switching, and responsive hydrogel applications.

Experimental Section

Materials. All chemicals were purchased from Aldrich and used as received unless otherwise noted. *N*-Isopropylacrylamide (NIPAAm) was recrystallized from hexane prior to use. Propylacrylic acid (PAA) was synthesized according to the protocols published previously.[12] The trithiocarbonate RAFT chain transfer agent (CTA), 2-dodecylsulfanylthiocarbonylsulfanyl-2-methyl propionic acid (DMP), was obtained as a gift from Prof. Charles L McCormick of the University of Southern Mississippi and Dr. John Lai of Noveon Company.

Polymerizations. In a typical procedure, a 10 mL round-bottom flask was charged with NIPAAm (2.36 g, 20.9 mmol), PAA (0.125 g, 1.10 mmol), azobis(isobutyronitrile) (AIBN) (3 mg, 1.83×10^{-5} mol), 2-dodecylsulfanylthiocarbonylsulfanyl-2-methyl propionic acid (DMP) (33.0 mg, 9.15×10^{-5} mol), and methanol (2.50 mL, HPLC grade). The mixture was degassed by purging with nitrogen for 20 min. Polymerization was carried out at 60 °C for 17 h. After polymerization, methanol was evaporated under a stream of air at room temperature, and the polymer was dissolved in THF and precipitated twice into pentane. The final product was dried to constant weight under vacuum to provide 1.97 g of polymer (yield, 79.3%).

Characterizations. Molecular weights of copolymers were determined using a gel permeation chromatograph (Viscotek), using 0.01 mol L^{-1} LiBr DMF solution as eluent at a flow rate of 1 mL min^{-1} and at 60 °C and narrow disperse poly(methyl methacrylate) as calibration standards.

^{1}H NMR spectra of the copolymers were recorded on a Bruker AC 500, using methanol-d_4 as the solvent. Compositions of NIPAAm-*co*-PAA copolymers were determined by comparing the peak areas of NIPAAm unit isopropyl C−H signal at 3.9 ppm, with the total peak area between 0.8 and 1.8 ppm, which includes all other C−H protons. The degree of ionization of the copolymer at deferent pH's was determined from potentiometric titrations curves. Polymer solutions (10 mg/mL) containing 0.15 mol L^{-1} NaCl at pH 12.00 was titrated with 0.1 mol L^{-1} HCl to pH 2.00. The degree of ionization is defined as $\alpha = \alpha_N + [H^+]/C_p$, where α_N is the degree of neutralization, C_p is the equivalent concentration of polymer repeating units, and $[H^+]$ is proton concentration and is deducted from the pH of the solution. The titration was performed at room temperature.

LCST Measurement. The LCSTs of the polymer solutions at 0.2 wt % were measured on a Hewlett-Packard 8480A diode array UV−visible spectrophotometer by monitoring the turbidity of the polymer solutions as a function of temperature at 500 nm and under heating rate of 0.5 °C/min. The temperature at 90% light transmittance of the polymer solution was defined as the LCST. NIPAAm-*co*-PAA copolymer was first dissolved in 0.03 mol L^{-1} PB buffer, and the ionic strength of the buffer was adjusted to 0.15 mol L^{-1} by the addition of NaCl. The pH of the solution was adjusted to the desired values by adding 1 N NaOH or HCl.

Results and Discussion

The preparation of linear, low dispersity pNIPAAm by RAFT polymerization was recently reported by several groups.[23−27] The key to achieving well-controlled RAFT polymerization of NIPAAm is to choose the appropriate CTA. Using a trithiocarbonate, 2-dodecylsulfanylthiocarbonylsulfanyl-2-methyl propionic acid (DMP), as the CTA, McCormick et al. demonstrated a facile and controlled RAFT polymerization of NIPAAm.[27]

Following these reports, we describe herein the RAFT copolymerization of varying ratios NIPAAm and PAA monomers in methanol using AIBN as an initiator and DMP as the CTA (Scheme 1). Five NIPAAm-*co*-PAA copolymers with different PAA contents were prepared, and their characteristics are summarized in Table 1.

The RAFT copolymerization proceeds in a controlled way with a $[CTA]_0/[AIBN]_0$ ratio of 5/1 (Table 1), yielding polymers with low M_w/M_n values (∼1.2) and reasonable agreement between experimental and theoretical molecular weights. Polymers with close molecular weights were targeted in order to eliminate LCST drifts influenced by effects of polymer chain lengths.

As evident from Table 1, the polymer yield decreased with increasing PAA in the feed. With as much as 30 mol % PAA

Table 1. Preparation of *N*-Isopropylacrylamide-*co*-Propylacrylic Acid (NIPAAm-*co*-PAA) Copolymers Using RAFT Copolymerization[a]

	PAA amount (mol %)			[monomer]$_0$				
polymer	in feed	in polymer		[CTA]$_0$+2[AIBN]$_0$	yield (wt %)	M_n[d] (theor)	M_n[e] (expt)	M_w/M_n
NIPAAm				200	86.0	22 900	32 500	1.08
NIPAAm-*co*-PAA3	2.0	2.6[b]	2.3[c]	200	80.5	18 200	27 300	1.16
NIPAAm-*co*-PAA9	5.0	8.8[b]	8.5[c]	200	79.2	17 900	23 400	1.20
NIPAAm-*co*-PAA13	10.0	13.0[b]	12.6[c]	200	68.4	15 500	21 700	1.20
NIPAAm-*co*-PAA28	20.0	27.8[b]	26.2[c]	200	45.4	10 300	15 000	1.18
NIPAAm-*co*-PAA39[f]	30.0	39.2[b]	35.6[c]	400	30.4	13 700	19 200	1.28

[a] Polymerization was carried out at 60 °C for 17h at 50 wt/v % monomer in methanol, 2,2′-azobis(isobutyronitrile) (AIBN) as initiator and 2-dodecylsulfanylthiocarbonylsulfanyl-2-methyl propionic acid as chain transfer agent (CTA). [CTA]$_0$/[AIBN]$_0$ = 5. [b] Estimated from ^{1}H NMR. [c] Estimated from potential titration. [d] Mn (theor) = conversion × $MW_{monomer}$ × [M]$_0$/([CTA] +2[AIBN]). [e] Determined by GPC in DMF containing 0.01 mol L^{-1} LiCl at 60 °C (poly(methyl methacrylate) standard). [f] Polymerization time, 48 h.

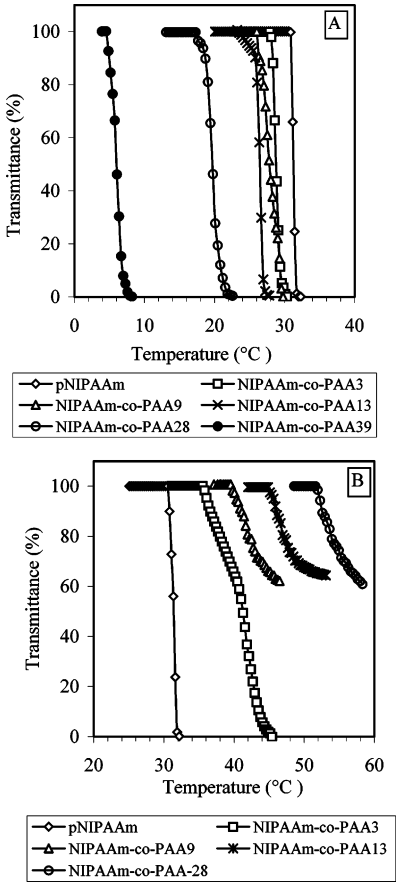


Figure 1. Phase transitions of NIPAAm-*co*-PAA copolymer solutions at (A) pH 5.0, and (B) pH 6.5 as measured by the cloud point method.

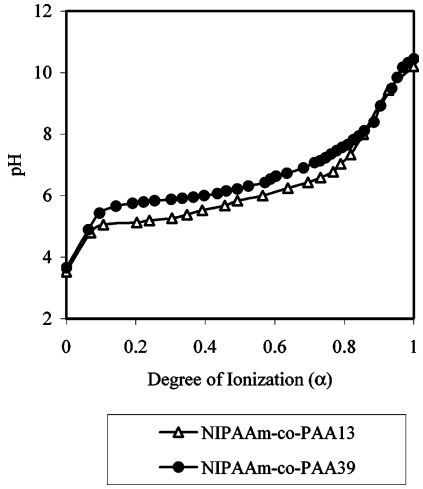


Figure 2. pH vs degree of ionization of NIPAAm-*co*-PAA copolymer solutions (10 mg/mL, 0.15 mol L^{-1} NaCl) at room temperature.

in the monomer feed, the polymerization required higher total monomer concentration in the feed and longer polymerization times to yield polymers with similar chain lengths to those obtained in polymerizations with less that 10 mol % PAA feed. The polymerization reactivity of α-alkylacrylic acid monomers, such as PAA, is relatively low due to the steric hindrance of the growing chain end for chain propagation. In addition, polymers made from such monomers have low ceiling temperatures, where the polymerization equilibrium is reversed, i.e., from growing chain polymer back to monomer. Homopolymerization of ethylacrylic acid or propylacrylic acid worked only under bulk polymerization conditions with low polymer yields.[12,28] Due to the significant potential uses of these hydrophobic poly(carboxylic acids),[29] copolymerizing α-alkylacrylic acid with other monomers such as NIPAAm may offer a facile approach to copolymers with versatile structures and applications.

The LCST behaviors of NIPAAm-*co*-PAA copolymer solutions were characterized by measuring their cloud points. Figure 1 shows typical transmittance vs temperature curves for copolymers with rationally varied compositions at different pH values. The combination of pH-responsive PAA and thermoresponsive NIPAAm in the copolymer leads to a polymer that responds sharply to both pH and temperature.

The LCST of thermoresponsive polymers is attributed to a change in the hydrophilic/hydrophobic balance of the polymers with respect to the hydrophobic and H-bond interactions of water molecules with the polymer chain. At low temperatures, strong H-bonding interactions between polar groups and water lead to good solubility of the polymer, which is opposed by the hydration of apolar groups. The water surrounding the apolar groups is in a low entropy state relative to free water, leading to an entropic penalty. As the apolar surface area of the polymer increases, this entropic penalty will increase and the LCST will decrease.

The LCST values of NIPAAm-*co*-PAA copolymers decrease with increasing PAA contents at pH 5 (Figure 1A). In contrast, they increase with an increase of PAA content at pH 6.5, and NIPAAm-*co*-PAA39 does not exhibit an LCST in the experimental temperature range (0−100 °C) (Figure 1B). Figure 2 shows titration curves of NIPAAm-*co*-PAA13 and NIPAAm-*co*-PAA39 at room temperature. The pK_a values of these copolymers are 5.9 and 6.2, respectively. The copolymers are less than 10% ionized at pH 5.0, whereas about 60% ionized at pH 6.5. PAA is hydrophobic in the acidic form and causes the LCST of PNIPAAm to decrease. It is also possible that the −COOH group of PAA will H-bond with the −CONH− group of NIPAAm at the lower pHs, and that could also contribute to the lowering of its LCST. This effect was seen in graft copolymers of pNIPAAm-*g*-p(acrylic acid),[6] and it might also

Table 2. LCSTs of *N*-Isopropylacrylamide-*co*-Acrylic Acid (NIPAAm-*co*-AA), *N*-Isopropylacrylamide-*co*-Methacrylic Acid (NIPAAm-*co*-MAA), and *N*-Isopropylacrylamide-*co*-Propylacrylic Acid (NIPAAm-*co*-PAA) Copolymers with Similar NIPAAm Contents at Different pHs[a]

pH	NIPAAm-*co*-AA	NIPAAm-*co*-MAA	NIPAAm-*co*-PAA13
4.0	34.3 °C	29.0 °C	not soluble above 0 °C
5.0		36.7 °C	23.0 °C
5.5		63.8 °C	27.1 °C
6.0		no LCST	34.2 °C
6.5		no LCST	46.0 °C

[a] NIPAAm-*co*-AA has 10 mol % AA and the LCST was extracted from Ref. [6]. NIPAAm-*co*-MAA with 11.5 mol % MAA was prepared by RAFT polymerization, and its M_n and PDI were 28,100 and 1.21, respectively. The composition of NIPAAm-*co*-PAA13 was shown in Table 1.

occur to some extent in the random copolymers studied here. At higher pH values, the copolymer clearly becomes much more ionized, leading to the increase in LCST. Upon ionization at higher pH values, the copolymer chains will also expand due to the electrostatic repulsion between charged sites along the backbone and thus lower the polymer−polymer interactions.

It can also be seen in Figure 1, panels A and B, that the phase transition curves of NIPAAm-*co*-PAA copolymer solutions are sharp at pH 5.0 (Figure 1A), whereas the transmittance decreases much more gradually at pH 6.5 (Figure 1B) and does not reach 0% over a wide temperature range, especially for polymers with high PAA contents, due to the ionization of PAA units. As more of the PAA monomer units of the copolymer chains are ionized, their hydrophilicity will interfere with the thermally induced phase separation tendencies of the NIPAAm chain sequences and subsequently weaken the aggregation of pNIPAAm chain segments. In addition, the aggregation of polymer chains into large aggregates may also be decreased due to the ionic stabilization by ionized PAA units of smaller aggregates in the solution.

Table 2 shows the comparison of LCSTs of *N*-isopropylacrylamide-*co*-acrylic acid (NIPAAm-*co*-AA), *N*-isopropylacrylamide-*co*-methacrylic acid (NIPAAm-*co*-MAA), and *N*-isopropylacrylamide-*co*-propylacrylic acid (NIPAAm-*co*-PAA) copolymers with similar NIPAAm contents at different pHs. NIPAAm-*co*-AA with 10 mol % AA has higher LCST than homoNIPAAm even at pH 4.0 due to the intrinsically hydrophilic AA units and its low pK_a value. PolyMAA has a relatively higher pK_a value, and it is hydrophobic at acidic conditions.[10] The LCST of NIPAAm-*co*-MAA with 11.5 mol % MAA is lower than that of homoNIPAAm at pH 4.0 but higher at pH 5.0. No LCST was detected at pH ≥ 6.0. In contrast, the hydrophobic PAA causes the LCST of polyNIPAAm to decrease at pH up to 5.5. At pH 6.0, this copolymer still exhibits LCST behavior at temperatures below physiological temperature (37 °C).

The influence of pH on the LCSTs of varying NIPAAm-*co*-PAA copolymer compositions was systematically studied from pH 5.0 to 7.0 (shown in Figures 3 and 4). The phase transition curves of the copolymers with ca. 3 mol % PAA are shown in Figure 3A. At pH 5.0, the LCST is about 28 °C, which is lower than that of homopolymer pNIPAAm (31 °C) in the same solution. The LCST increases to ca. 45 °C at pH 7.0 due to the ionization of PAA units. For copolymers with 39 mol % PAA, the LCST is influenced by pH more dramatically: for example, LCSTs are 4.8 °C at pH 5.0, 26.2 °C at pH 5.5, and 48 °C at pH 6.0. The LCST disappears at and above pH 6.5, indicating that the ionized PAA units significantly reduce the effect of any hydrophobically bound water and convey sufficient solubility to offset the temperature-sensitivity of NIPAAm components.

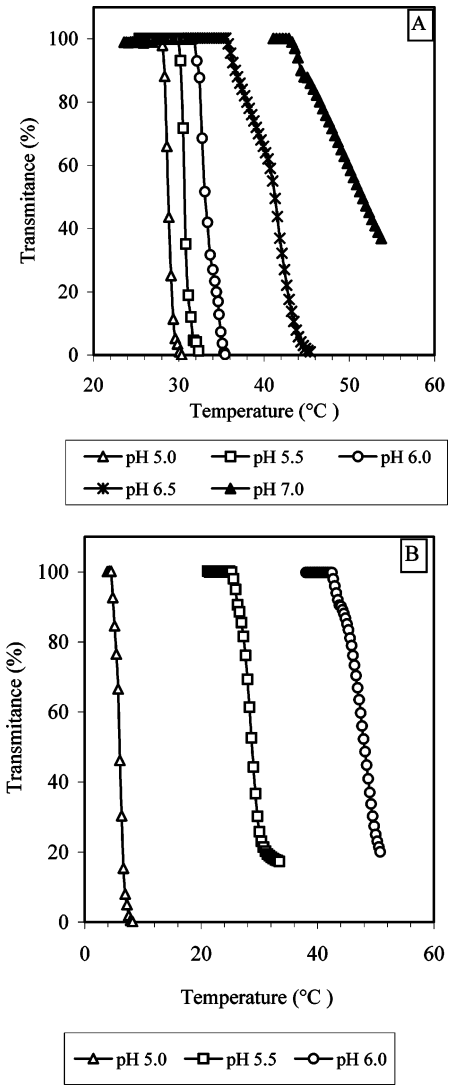


Figure 3. Phase transitions of NIPAAm-*co*-PAA copolymer solutions at different pHs. (A) NIPAAm-*co*-PAA-3 and (B) NIPAAm-*co*-PAA-39.

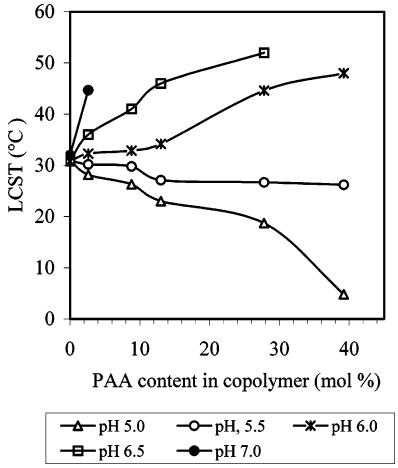


Figure 4. LCSTs of 0.2 wt % poly(*N*-isopropylacrylamide-*co*-propylacrylic acid) (NIPAAm-*co*-PAA) solutions with different PAA contents at different pHs as measured by the cloud point method.

It can also be seen in Figure 4 that both the percentage of PAA and the pH are important to the shift in LCST. At both

low and high PAA contents, a small increase in pH can cause dramatic increases in the LCST. Thus, the LCST can be adjusted to any desired range at a particular pH value (such as endosomal pH) by changing the PAA content of the copolymer. The temperature-responsive NIPAAm-*co*-PAA copolymer is triggered under a small pH change window as sufficient PAA units switch from a hydrophobic state to an ionized state at defined regions between pH 5.0−7.0. This remarkable pH/temperature responsiveness could be useful in a variety of biomedical applications. In molecular switching applications,[30] the expansion and collapse of these chains could be controlled to occur more sharply over a small pH range nearer to neutral pH, which is important to protect protein stability. The combined pH/temperature responsiveness could also be used to enhance drug delivery where acidic pH gradients are encountered in the body.

Conclusions

N-Isopropylacrylamide-*co*-propylacrylic acid random copolymers with narrow polydispersities have been synthesized by RAFT copolymerization. These copolymers exhibit temperature-induced phase transition behavior over small pH ranges. The polar character of the PAA units changes from strongly hydrophobic when it is protonated at slightly acidic conditions to highly hydrophilic upon ionization, leading to copolymers whose polarity and solubility is very sensitive to small environmental pH changes. With increasing PAA content in the copolymers, their LCSTs decrease between pH 5.0−5.5 and increase between pH 6.0−7.0. In addition, the phase transition curves become less sharp at pH 7.0. The high sensitivity of these NIPAAm-*co*-PAA copolymers to small changes in pH and temperature suggest that they could be useful in biotechnology and drug delivery applications where small changes in pH or temperature may exist or may be imposed.

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