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Novel Thermoresponsive Polymers Tunable by pH

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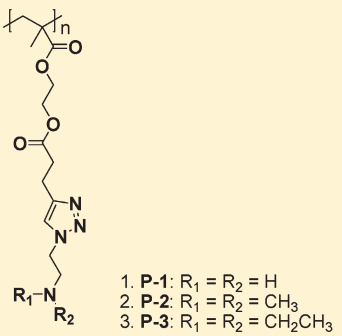
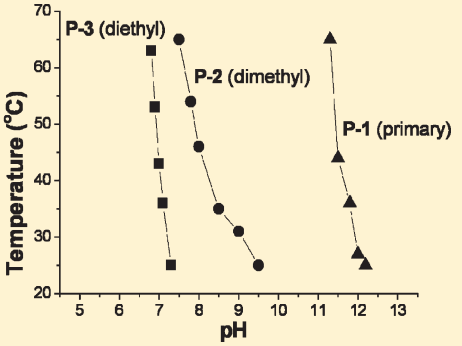
ABSTRACT:





Thermoresponsive polymers that are pH tunable were successfully synthesized by a combination of atom transfer radical polymerization (ATRP) and Cu(I)-catalyzed 1,3-dipolar cycloaddition of azide and alkynes (click chemistry). ATRP was employed to synthesize poly(2-hydroxyethyl methacrylate) (PHEMA), followed by introduction of alkyne groups using pentynoic acid, leading to PHEMA-alkyne. 2-Azidoethylamine, 2-azido-*N*,*N*-dimethylethylamine, and 2-azido-*N*,*N*-diethylethylamine were added to the PHEMA-alkyne backbone via click chemistry. Molecular weight, molecular weight distribution, and click reaction efficiency were determined by gel permeation chromatography (GPC) and ^{1}H NMR spectroscopy. The average molecular weight (M_n) of the resulting polymers ranged from 5.6×10^4 to 7.0×10^4 depending on the molecular architecture. The molecular weight distribution was low ($M_w/M_n = 1.25-1.35$). The transmission spectra of the 0.1 wt % aqueous solutions of the resulting polymers with different pH values at 650 nm were measured as a function of temperature. Results showed that the lower critical solution temperature (LCST) could be dramatically affected by solution pH. To give additional evidence for pH-responsive thermal transition, in-situ temperature-dependent ^{1}H NMR measurements in deuterated water (0.01 wt %) were conducted. The LCST values measured by in-situ ^{1}H NMR correlated well with those determined by turbidimetry.

INTRODUCTION

The conformation and physical properties of macromolecules in nature, including nucleic acids, proteins, and glycoproteins, are influenced by various stimuli such as temperature and pH.[1−6] Driven by the increasing need for mimicking such molecules and providing "smart" macromolecules for biomedical and engineering materials, growing attention has been paid to synthetic polymers that exhibit environmentally responsive behavior.[7−11]

Thermoresponsive polymers, which precipitate in aqueous media upon heating, exhibit a lower critical solution temperature (LCST)[12−15] behavior. Polymers with tunable LCST characteristics have been extensively investigated for biological applications such as cell patterning, smart drug release, and DNA sequencing, to name a few.[16,17] These polymers are soluble in aqueous solution below their LCST through hydrogen bonding with water molecules but become dehydrated and insoluble when heated above the LCST, resulting in fast phase transitions. It has been reported that the LCST is strongly dependent on many parameters, including molecular weight, polydispersity index, and the monomer composition of copolymers that governs the hydrophilicity/hydrophobicity balance.[18−20] Typically, to have different LCST values, a series of polymers must be synthesized.

pH-responsive polymers have functional groups capable of donating or accepting protons upon pH change, which accompanies reversible conformational changes between the extension and collapse state.[21,22] These polymers have attracted a great deal of attention where small variations in pH can induce significant physical and biological changes in macromolecules.[23−25]

Currently, a great deal of effort has been made to prepare polymers with multiple-responsive components.[5,26−28] Block copolymers in which each block has covalently or physically bonded elements responsive to different stimuli are of special interest since they can self-assemble into various supramolecular structures with response to different stimuli.[29−31] It is, however, important to design a simple system which has multiple-responsive behavior with only one responsive component. For example,

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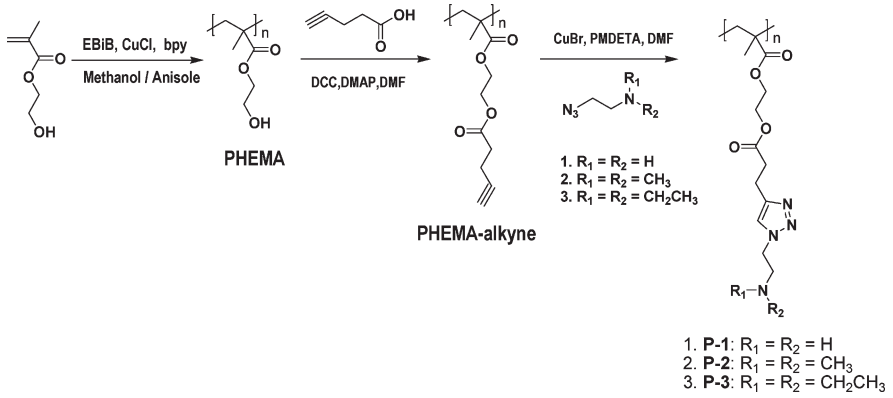
Scheme 1. Synthesis of Amino Group-Functionalized Polymers by Combination of ATRP and Click Chemistry



Muller and co-workers investigated the thermoresponsive properties of poly(*N*,*N*-dimethylaminoethyl methacrylate) (PDMAEMA) upon pH changes.[32,33] They reported that the LCST strongly decreased with increasing pH of the aqueous solution.

Herein, we report the synthesis of amino group-functionalized polymers by the simple combination of atom transfer radical polymerization (ATRP)[34−37] and click chemistry[38−41] and the response of their aqueous solutions to pH and temperature. pH was employed as the main stimulus, and temperature was used as an additional source of stimulus to further fine-tune the transition of solubility.

EXPERIMENTAL SECTION

Materials. 2-Hydroxyethyl methacrylate (HEMA, 95%, Tokyo Chemical Industry; TCI) was purified by passing through a column filled with basic alumina to remove inhibitors. CuCl (99%, Aldrich), CuBr (98%, Aldrich), ethyl 2-bromoisobutylate (EBiB), 2-chloroethylamine hydrochloride, 2-chloro-*N*,*N*-dimethylethylamine hydrochloride, 2-chloro-*N*,*N*-diethylethylamine hydrochloride, 4-dimethylaminopyridine (DMAP), 4-pentynoic acid, and *N*,*N*′-dicyclohexylcarbondimide (DCC) were purchased from Aldrich with the highest purity and were used as received without further purification. 2,2′-Bipyridyl (bpy), *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA), and sodium azide (NaN_3) were purchased from TCI and used as received.

Instrumentation. ^{1}H NMR spectra were collected in DMF-d_7 and $CDCl_3$ on a Bruker Avance 300 MHz NMR spectrometer. The apparent molecular weights and molecular weight distributions were measured by GPC (Agilent Technologies 1200 series) using a polystyrene standard, with DMF as the eluent at 30 °C and a flow rate of 1.00 mL/min. UV−vis spectra were recorded using an Optizen 3220 UV−vis spectrophotometer equipped with a digital temperature controller. A 650 nm wavelength was used to determine LCST. The temperature range was from 25 to 80 °C with a heating and cooling rate of 1 °C/min.

Syntheses. *2-Azido-1-ethylamine.* NaN_3 (33 g, 0.521 mol) was added to a solution of 2-chloro-1-ethylamine (20 g, 0.174 mol) in water (200 mL), and the reaction mixture was heated to 80 °C for 15 h. The solution was basified with KOH and extracted with diethyl ether. The resulting solution was dried over $MgSO_4$ and concentrated to give a volatile colorless oil (10 g, 0.087 mol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm) was as follows: 3.36−3.29 (2H, t, $N_3CH_2CH_2$); 2.89−2.82 (2H, t, $N_3CH_2CH_2$); 1.42 (2H, s, NH_2).

2-Azido-1-ethyldimethylamine. ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm) was as follows: 3.57−3.52 (2H, t, $N_3CH_2CH_2$); 2.65−2.61 (2H, t, $N_3CH_2CH_2$); 2.27 (6H, s, ($N-CH_3$).

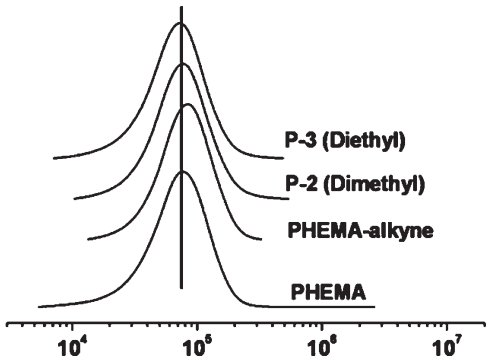


Figure 1. DMF GPC traces of PHEMA, PHEMA-alkyne, **P-2**, and **P-3**.

2-Azido-1-ethyldiethylamine. ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm) was as follows: 3.29−3.25 (2H, t, $N_3CH_2CH_2$); 2.65−2.61 (2H, t, $N_3CH_2CH_2$); 2.58−2.51 (4H, m, $N-CH_2$-CH_3); 1.04−0.99 (6H, t, $N-CH_2-CH_3$).

PHEMA. A clean and dry Schlenk flask was charged with HEMA (19.5 mL, 150 mmol), bpy (28.1 mg, 0.18 mmol), methanol (8 mL), anisole (12 mL), EBiB (44 μL, 0.3 mmol), and $CuCl_2$ (0.9 mg, 0.006 mmol). The flask was deoxygenated by five freeze−pump−thaw cycles. CuCl (8.9 mg, 0.09 mmol) was added to the frozen mixture in the presence of argon. The flask was filled with argon and heated in an oil bath at 50 °C. 4 h later, polymerization was stopped by exposing the solution to air. The resulting solution was passed through neutral alumina to remove the copper complex, and the polymer was precipitated twice in diethyl ether and dried under vacuum at room temperature for 24 h. M_n = 59 300 g/mol, M_w/M_n = 1.34. ^{1}H NMR (300 MHz, DMF-d_7, δ in ppm) was as follows: 5.0 (1H, s, CH_2OH); 4.1 (2H, s, $O-CH_2-CH_2$); 3.7 (2H, s, $O-CH_2-CH_2$); 2.0−1.9 (2H, d, $CH_2-C(CH_3)$); 1.1−0.94 (3H, d, $CH_2-C(CH_3)$).

PHEMA-Alkyne. PHEMA (2.5 g, 0.019 mol, per HEMA repeating unit), DCC (5.97 g, 0.029 mol), and pentynoic acid (2.84 g, 0.029 mol) were added sequentially into a 50 mL round-bottomed flask containing 50 mL of DMF. The flask was immersed into an ice−water bath. DMAP (0.22 g) in 5 mL of DMF was added into the mixture within 5 min. The reaction mixture was allowed to stir for 40 h at room temperature, allowing insoluble DCC urea to precipitate out of solution. After filteration, the polymer product was precipitated in water to remove excess pentynoic aid. After redissolving the product in dichloromethane, polymers were precipitated again in hexane to remove excess DCC and DCC urea. After redissolving in dichloromethane, the polymers were precipitated in methanol and dried under vacuum at room temperature

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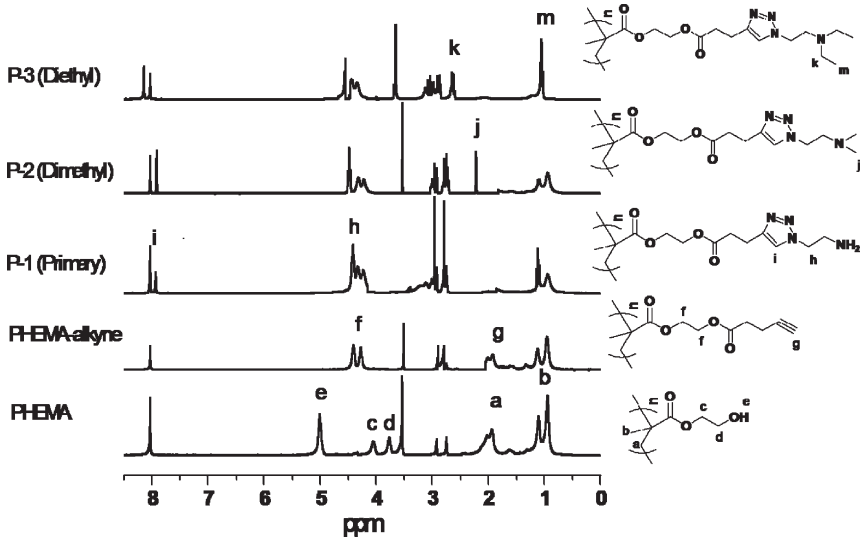

Figure 2. ^{1}H NMR spectra of PHEMA, PHEMA-alkyne, **P-1**, **P-2**, and **P-3**.

Table 1. Summary of DMF GPC Results and Efficiency of Click Reactions Determined by ^{1}H NMR

	$M_{n\text{theory}}$ (g/mol)	$M_{n\text{app}}$ [b] (g/mol)	PDI[b]	y_{graft} [c] (%)
PHEMA	26 000[a]	59 300	1.34	
PHEMA-alkyne	31 500	69 500	1.26	
P-1 (primary amine)	44 400	N/A	N/A	100
P-2 (dimethylamine)	48 600	63 000	1.32	100
P-3 (diethylamine)	52 800	55 900	1.36	100

[a] Theoretical molecular weight determined from monomer conversions. [b] Apparent number-average molecular weight and PDI determined by DMF GPC with PS calibration. [c] Determined by ^{1}H NMR spectroscopy.

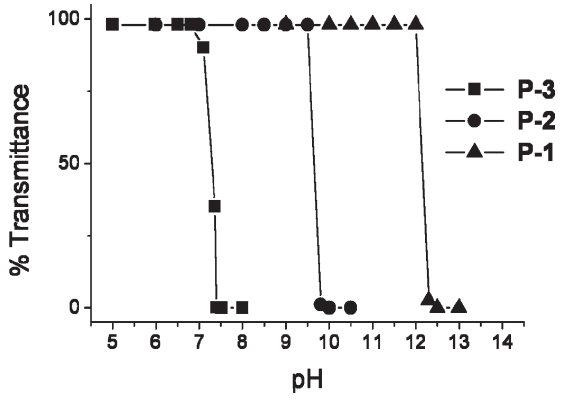

Figure 3. Percent transmission vs pH plots at 650 nm for 0.1 wt % aqueous solutions of **P-1**, **P-2**, and **P-3**.

for 48 h (yield: 88%). M_n = 69 500 g/mol, M_w/M_n = 1.26. ^{1}H NMR (300 MHz, DMF-d_7, δ in ppm) was as follows: 4.4−4.27 (4H, d, −O−CH_2−CH_2−O−), 2.69−2.68 (2H, d, O−(C═O)−CH_2−CH_2−), 2.58−2.56 (2H, s, d, O−(C═O)−CH_2−CH_2−C−), 2.18−1.74 (3H, d, CH_2−C(CH_3)), CH_2−C−CH), 1.2−0.8 (3H, d, CH_2−C(CH_3)).

P-1 (Primary Amine). The ratio of reagent [PHEMA-alkyne]$_0$/[azido-ethylamine]$_0$/[CuBr]$_0$/[PMDETA]$_0$ was 1/2/0.1/0.1. The click reaction between PHEMA-alkyne (0.2 g, 0.95 mmol) and azidoethylamine (163 μL, 1.9 mmol) was conducted in 3 mL of DMF using CuBr/PMDETA as a catalyst. After 10 h, the polymer solution was exposed to air, diluted with DMF, and passed through neutral alumina to remove the copper catalyst. The resulting polymer was precipitated in diethyl ether and dried in a vacuum oven for 24 h. ^{1}H NMR (300 MHz, DMF-d_7, δ in ppm) was as follows: 7.98 (1H, s, triazole); 4.6−4.38 (2H, t, triazole−CH_2CH_2); 4.38−4.08 (4H, d, −O−CH_2−CH_2−O−); 3.37−3.06 (2H, t, triazole−CH_2−CH_2); 3.06−2.98 (2H, t, O−(C═O)−CH_2−CH_2−C−); 2.88−2.77 (2H, d, O−(C═O)−CH_2−CH_2−C−); 2.27−1.72 (4H, s, CH_2−C(CH_3)); 1.26−0.59 (3H, d, CH_2−C(CH_3)).

P-2 (Dimethylamine). M_n = 63 000 g/mol, M_w/M_n = 1.32. ^{1}H NMR (300 MHz, DMF-d_7, δ in ppm) was as follows: 7.97 (1H, s, triazole); 4.86−4.54 (2H, t, triazole−CH_2CH_2); 4.54−4.10 (4H, d, −O−CH_2−CH_2−O−); 3.23−3.06 (4H,t, triazole−CH_2−CH_2, O−(C═O)−CH_2−CH_2−C−); 2.98−2.88 (2H, s, O−(C═O)−CH_2−CH_2−C−); 2.53−2.23 (2H, s, N(CH_3)$_2$); 2.25−1.82 (2H, s, CH_2−C(CH_3)); 1.37−0.79 (3H, d, CH_2−C(CH_3)).

P-3 (Diethylamine). M_n = 55 900 g/mol, M_w/M_n = 1.36. ^{1}H NMR (300 MHz, DMF-d_7, δ in ppm) was as follows: 8.00 (1H, s, triazole); 4.68−4.54 (2H, t, triazole−CH_2CH_2); 4.5−4.19 (4H, d, −O−CH_2−CH_2−O−); 3.22−3.09 (2H, t, triazole−CH_2−CH_2); 3.02−2.94 (2H, t, O−(C═O)−CH_2−CH_2−C−); 2.94−2.89 (2H, d, O−(C═O)−CH_2−CH_2−C−); 2.61−2.47(4H, m, N−(CH_2−CH_3)$_2$); 2.39−1.87 (2H, d, CH_2−C(CH_3)); 1.56−0.86 (9H, m, CH_2−C(CH_3); N−(CH_2−CH_3)$_2$).

RESULTS AND DISCUSSION

Synthesis and Characterization. The synthesis of 2-azidoethylamine (**1**) involved the reaction of NaN_3 with 2-chloroethylamine hydrochloride in water. Compounds **2** and **3** were synthesized in a similar manner. ^{1}H NMR spectra confirmed the successful synthesis of **1**−**3**.

The strategy employed in this study is schematically illustrated in Scheme 1. ATRP was used to directly prepare PHEMA with a controlled molecular weight and low polydispersity. A CuCl/bpy catalyst system was used for the ATRP of HEMA using ethyl 2-bromoisobutyrate (EBiB) as an initiator. Since PHEMA is soluble only in polar solvents, a mixed solvent system of anisole/methanol (3/2 by volume ratio) was employed to ensure a

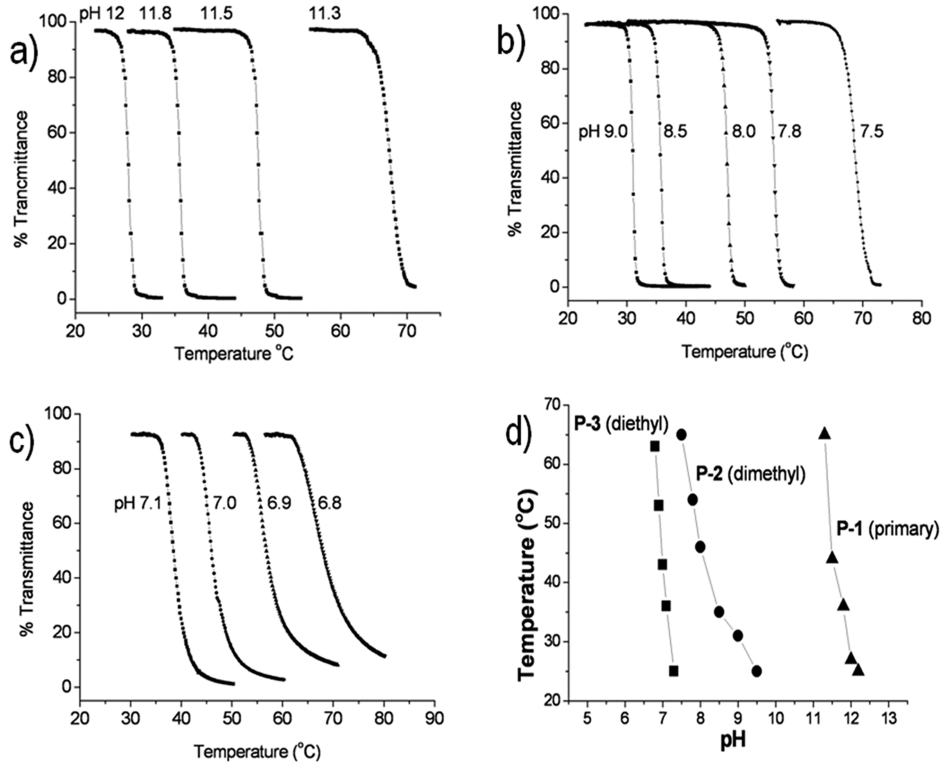

Figure 4. Thermoresponsiveness of 0.1% aqueous solutions of (a) **P-1**, (b) **P-2**, and (c) **P-3** at different pH levels measured by percent transmission at 650 nm. (d) The pH ranges for the thermal transitions of three polymers as a function of temperature.

homogeneous reaction mixture throughout the HEMA polymerization. The polymerization was stopped at 40% monomer conversion, and the molecular weight and molecular weight distribution of the resulting PHEMA were obtained using a GPC DMF line with polystyrene (PS) standards (M_n = 59 300 g/mol, M_w/M_n = 1.34) (Figure 1). The apparent molecular weight obtained by GPC was higher than the theoretical molecular weight ($M_{n,theory}$=26 000 g/mol) calculated from the HEMA conversion ($M_{n,\ theory}$ = conversion × MW_{HEMA} × $[HEMA]_0/[EBiB]_0$) due to the differences in hydrodynamic volumes of PHEMA and PS standards.[42]

In the next step, PHEMA was reacted with pentynoic acid to yield PHEMA-alkyne in the presence of DCC. The resulting PHEMA-alkyne was analyzed by GPC and ^{1}H NMR spectroscopy using DMF-d_7 as the solvent. Figure 2 shows the successful transformation of PHEMA into PHEMA-alkyne by monitoring the disappearance of a hydroxyl peak (e) of PHEMA at 5.0 ppm after esterification. The GPC traces in Figure 1 show that the apparent molecular weight of the PHEMA-alkyne backbone did not increase after transformation, suggesting that the hydrodynamic volumes of PHEMA and PHEMA-alkyne were almost the same in DMF.

Compounds **1**, **2**, and **3** were successfully added to the PHEMA-alkyne backbone in DMF with a CuBr/PMDETA complex at room temperature using click chemistry. To ensure 100% conversion, the molar ratio between 2-azidoethylamines and the PEMA-alkyne backbone remained constant at 2 to 1. After 10 h, quantitative conversions were observed for the reactions with all 2-azidoethylamines (**1**, **2**, and **3**). The ^{1}H NMR spectra provided evidence of the successful synthesis of amine-functionalized polymers by click reactions. For amine-functionalized polymers (**P-1**, **P-2**, and **P-3**), a new peak (i) representing the proton on the 1,2,3-triazole rings appeared at 7.9 ppm while an alkyne peak (g) disappeared completely. The GPC traces in Figure 1 also show that there was no significant change in the apparent molecular weight for tertiary amine-functionalized polymers (**P-2** and **P-3**) compared with PHEMA and PHEMA-alkyne (Table 1). However, no detection signal was identified via GPC for the primary amine-functionalized polymer (**P-1**), which was presumably due to strong interactions between the primary amine and the GPC column.

pH-Tunable Thermal Transition: Percent Transmittance by UV−vis Studies. The reversible solubility of **P-1**, **P-2**, and **P-3** was achieved by changing the pH of the aqueous solution. The pH-induced transition in solubility was studied by observing changes in percent transmission with a fixed wavelength (650 nm) from UV−vis spectroscopy. The initial pH of the aqueous solutions for the three polymers (0.1 wt %) was calibrated to be 5.0 at 25 °C. The pH was then increased by the slow addition of 0.1 M NaOH solution until the polymers precipitated. The most hydrophobic **P-3** molecule showed a sharp transition at pH 7.4 while the most hydrophilic **P-1** molecule precipitated at pH 12.3. As expected, the transition pH of **P-2** was 9.7, which was in between those of **P-1** and **P-3**. This pH-induced transition was stable and reversible with the alternating addition of an acid and base.

Having demonstrated the pH-induced transition of these three polymers, we attempted pH-tunable thermal transitions with different temperature ranges. Note that the pH-induced transitions occurred at room temperature, meaning that the LCST of these polymers is 25 °C at the transition pH values. If the solution pH is slowly decreased to make the polymers more hydrophilic by quarternization, one can expect that the LCST would increase. The percent transmission at 650 nm of the aqueous solution of

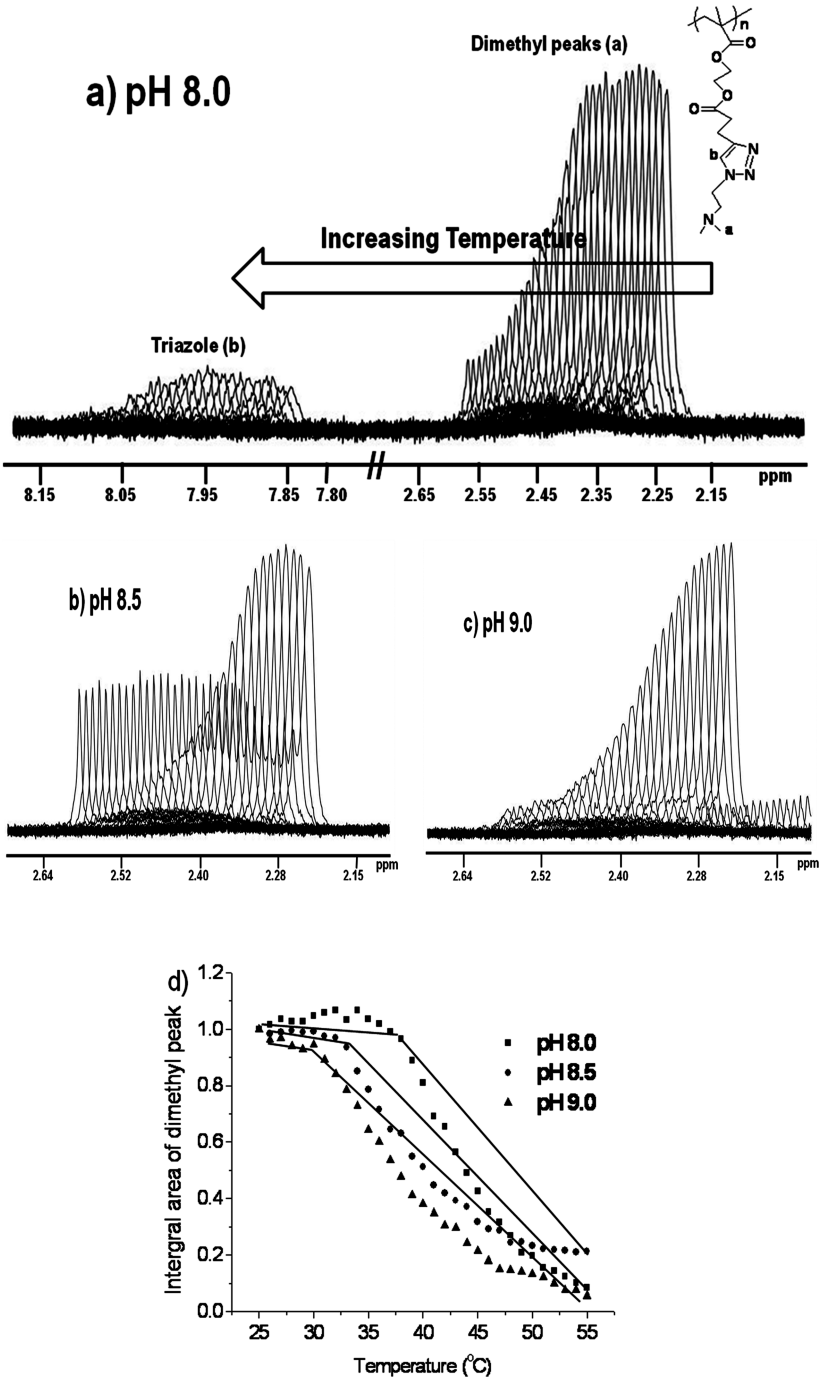

Figure 5. In-situ temperature-dependent ^{1}H NMR measurements of **P-2** at (a) pH 8.0, (b) pH 8.5, and (c) pH 9.0 in deuterated water (0.01 wt %): changes of positions and areas of a dimethyl peak. (d) The integral area of the dimethyl peak vs temperature plots with different pH values.

P-1 at pH 12.0 started to decrease at 28 °C (Figure 4a), indicating a LCST. As expected, LCST values increased as solution pH decreased. Visually, it was easy to observe the sharp transition between a transparent and cloudy solution with increasing temperature. The pH range for the thermal transition of **P-1** was very narrow, from pH 12.0 to 11.3. In this system, the principal stimulus was pH, which governs the primary transition. Temperature was used as a secondary stimulus that additionally tuned the transition deliberately. For the most hydrophobic **P-3**, the LCST of the initial solution at pH 7.4 appeared at 25 °C. The pH range for the thermal transition of **P-3** was also very narrow, from pH 7.1 to 6.8 (Figure 4c). A further decrease in pH below 6.8 did not induce thermal transitions. Contrary to **P-1** and **P-3**, which are too hydrophilic and too hydrophobic, respectively, the pH range for the thermal transition of **P-2** was relatively broad, from pH 9.0 to 7.5 (Figure 4b). Figure 4d shows the pH ranges for the thermal transitions of three polymers as a function of temperature. The pH values of the three polymer solutions that showed transition at room temperature were also added to the plot (Figure 4d). The temperature ranges examined in this study for the thermal transitions ranged from 25 to 65 °C. It should be noted that each polymer solution had a different and distinct

range of pH values that induced the thermal transition within the given temperature ranges.

pH-Tunable Thermal Transition: In-Situ ^{1}H NMR Studies. pH-dependent thermal transition behaviors of **P-2** observed by UV−vis studies correlated with in-situ temperature-dependent ^{1}H NMR measurements in deuterated water. **P-2** was chosen since it showed thermal transitions over a broad range of pH values. Contrary to the percent transmission studies by UV−vis, which determined the macroscopic, intermolecular aggregation trend, ^{1}H NMR spectroscopy can provide information on microscopic, intramolecular transitions. Figure 5a shows the ^{1}H NMR spectra of 0.01 wt % aqueous solution of **P-2** at pH 8.0 measured at different temperatures. The signals at 7.97 and 2.25 ppm are characteristic of a triazole ring and dimethyl group, respectively (see peak assignment in Figure 2) at 25 °C. Upon increasing the temperature to 55 °C, all proton signals shifted to higher ppm values, and the peak intensities of both signals gradually decreased due to phase separation. Specifically, it is important to monitor the dimethyl peak since it generates hydrogen bonding with water molecules below the LCST but become dehydrated and insoluble when heated above the LCST. Similar trends were observed for pH 8.5 and 9.0, except the dimethyl group peak intensities started to decrease at a relatively low temperature (Figure 5b,c). As shown in Figure 5d, the integral area of the dimethyl peak was plotted as a function of temperature for the three solutions with different pH values. It should be noted that there was a distinct temperature point (39 °C) for pH 8.0 where the integral area dropped abruptly. This onset temperature where peak intensities started to decrease significantly can be assigned as the LCST. The LCST values of aqueous solutions at pH 8.5 and 9.0 were 32 and 30 °C, respectively. The reason that the LCST decreased as solution pH increased could be explained as the increasing pH of the solution enhanced hydrophobicity by deprotonation, resulting in slow decrease of the number of quarternary ammonium cation groups. The LCST values of the three different **P-2** pH solutions determined by in-situ temperature-dependent ^{1}H NMR almost matched with those values determined beforehand by percent transmission obtained from UV−vis spectroscopy.

■ CONCLUSIONS

Well-defined dual responsive polymers were successfully synthesized using ATRP and click reactions. The transmission spectra of an aqueous solution of these polymers at different pH values as a function of temperature showed that the LCST of the molecule was significantly affected by variation of the solution pH. Contrary to turbidimetry, which determined the trend of temperature-induced intermolecular aggregation, in-situ temperature-dependent ^{1}H NMR measurements in deuterated water with a relatively low concentration gave insight into intramolecular aggregation behavior. The LCST values measured by both methods corresponded well with each other. In conclusion, we designed a very simple system where one functional group was responsive to two different stimuli. The LCST of these polymers were fine-tuned by changing solution pH, indicating that dual responsive polymers were prepared.

■ AUTHOR INFORMATION

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■ REFERENCES

(1) Bajpai, A. K.; Shukla, S. K.; Bhanu, S.; Kankane, S. *Prog. Polym. Sci.* **2008**, *33* (11), 1088–1118.
(2) Rapoport, N. *Prog. Polym. Sci.* **2007**, *32* (8−9), 962–990.
(3) Wu, D. Y.; Meure, S.; Solomon, D. *Prog. Polym. Sci.* **2008**, *33* (5), 479–522.
(4) Yamato, M.; Akiyama, Y.; Kobayashi, J.; Yang, J.; Kikuchi, A.; Okano, T. *Prog. Polym. Sci.* **2007**, *32* (8−9), 1123–1133.
(5) Dimitrov, I.; Trzebicka, B.; Mueller, A. H. E.; Dworak, A.; Tsvetanov, C. B. *Prog. Polym. Sci.* **2007**, *32* (11), 1275–1343.
(6) Lee, H.-i.; Pietrasik, J.; Sheiko, S. S.; Matyjaszewski, K. *Prog. Polym. Sci.* **2010**, *35* (1−2), 24−44.
(7) Roy, D.; Cambre, J. N.; Sumerlin, B. S. *Prog. Polym. Sci.* **2010**, *35* (1−2), 278–301.
(8) Lee, H.-i.; Pietrasik, J.; Matyjaszewski, K. *Macromolecules* **2006**, *39* (11), 3914–3920.
(9) Lee, H.-i.; Wu, W.; Oh, J. K.; Mueller, L.; Sherwood, G.; Peteanu, L.; Kowalewski, T.; Matyjaszewski, K. *Angew. Chem., Int. Ed.* **2007**, *46* (14), 2453–2457.
(10) Oh, J. K.; Drumright, R.; Siegwart, D. J.; Matyjaszewski, K. *Prog. Polym. Sci.* **2008**, *33* (4), 448–477.
(11) Oh, J. K.; Siegwart, D. J.; Lee, H.-i.; Sherwood, G.; Peteanu, L.; Hollinger, J. O.; Kataoka, K.; Matyjaszewski, K. *J. Am. Chem. Soc.* **2007**, *129* (18), 5939–5945.
(12) Aoshima, S.; Kanaoka, S. *Adv. Polym. Sci.* **2008**, *210*, 169–208.
(13) De, P.; Gondi, S. R.; Sumerlin, B. S. *Biomacromolecules* **2008**, *9* (3), 1064–1070.
(14) McCormick, C. L.; Sumerlin, B. S.; Lokitz, B. S.; Stempka, J. E. *Soft Matter* **2008**, *4* (9), 1760–1773.
(15) Vogt, A. P.; Sumerlin, B. S. *Macromolecules* **2008**, *41* (20), 7368–7373.
(16) Pelah, A.; Bharde, A.; Jovin, T. M. *Soft Matter* **2009**, *5* (5), 1006–1010.
(17) Gil, E. S.; Hudson, S. M. *Prog. Polym. Sci.* **2004**, *29* (12), 1173–1222.
(18) Lutz, J.-F.; Akdemir, O.; Hoth, A. *J. Am. Chem. Soc.* **2006**, *128* (40), 13046–13047.
(19) Lutz, J.-F.; Hoth, A. *Macromolecules* **2006**, *39* (2), 893–896.
(20) Lutz, J.-F.; Weichenhan, K.; Akdemir, O.; Hoth, A. *Macromolecules* **2007**, *40* (7), 2503–2508.
(21) Dai, S.; Ravi, P.; Tam, K. C. *Soft Matter* **2008**, *4* (3), 435–449.
(22) Lee, H.-i.; Boyce, J. R.; Nese, A.; Sheiko, S. S.; Matyjaszewski, K. *Polymer* **2008**, *49* (25), 5490–5496.
(23) Lynn, D. M.; Amiji, M. M.; Langer, R. *Angew. Chem., Int. Ed.* **2001**, *40* (9), 1707–1710.
(24) Murthy, N.; Campbell, J.; Fausto, N.; Hoffman, A. S.; Stayton, P. S. *J. Controlled Release* **2003**, *89* (3), 365–374.
(25) Murthy, N.; Campbell, J.; Fausto, N.; Hoffman, A. S.; Stayton, P. S. *Bioconjugate Chem.* **2003**, *14* (2), 412–419.
(26) Fournier, D.; Hoogenboom, R.; Thijs, H. M. L.; Paulus, R. M.; Schubert, U. S. *Macromolecules* **2007**, *40* (4), 915–920.
(27) Schmaljohann, D. *Adv. Drug Delivery Rev.* **2006**, *58* (15), 1655–1670.
(28) Roy, D.; Cambre, J. N.; Sumerlin, B. S. *Chem. Commun.* **2009**, No. 16, 2106–2108.
(29) Yamamoto, S.-i.; Pietrasik, J.; Matyjaszewski, K. *Macromolecules* **2008**, *41* (19), 7013–7020.

(30) Xu, Y.; Bolisetty, S.; Drechsler, M.; Fang, B.; Yuan, J.; Ballauff, M.; Mueller, A. H. E. *Polymer* **2008**, *49* (18), 3957–3964.
(31) Klaikherd, A.; Nagamani, C.; Thayumanavan, S. *J. Am. Chem. Soc.* **2009**, *131* (13), 4830–4838.
(32) Plamper, F. A.; Ruppel, M.; Schmalz, A.; Borisov, O.; Ballauff, M.; Mueller, A. H. E. *Macromolecules* **2007**, *40* (23), 8361–8366.
(33) Plamper, F. A.; Schmalz, A.; Ballauff, M.; Mueller, A. H. E. *J. Am. Chem. Soc.* **2007**, *129* (47), 14538–14539.
(34) Matyjaszewski, K.; Xia, J. *Chem. Rev.* **2001**, *101* (9), 2921–2990.
(35) Patten, T. E.; Xia, J.; Abernathy, T.; Matyjaszewski, K. *Science* **1996**, *272* (5263), 866–868.
(36) Wang, J.-S.; Matyjaszewski, K. *J. Am. Chem. Soc.* **1995**, *117* (20), 5614–15.
(37) Matyjaszewski, K.; Tsarevsky, N. V. *Nature Chem.* **2009**, *1* (4), 276–288.
(38) Sumerlin, B. S.; Vogt, A. P. *Macromolecules* **2010**, *43* (1), 1–13.
(39) Sumerlin, B. S.; Tsarevsky, N. V.; Louche, G.; Lee, R. Y.; Matyjaszewski, K. *Macromolecules* **2005**, *38* (18), 7540–7545.
(40) Fournier, D.; Hoogenboom, R.; Schubert, U. S. *Chem. Soc. Rev.* **2007**, *36* (8), 1369–1380.
(41) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46* (7), 1018–1025.
(42) Oh, J. K.; Matyjaszewski, K. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44* (12), 3787–3796.