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곁가지에 다양한 길이의 알코올 그룹을 지닌 고분자들의 저임계 용액온도 민감성 제어

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Precise Control of Thermoresponsive Properties of Polymers with Hydroxy Groups in the Side Chains

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초록: 하이드록시 그룹을 지닌 온도민감형 고분자들이 원자전이라디칼중합법(ATRP)과 클릭반응(click reaction)에 의해 합성되어졌다. 고분자들의 분자량과 분자량 분포도는 gel permeation chromatography(GPC)에 의하여 얻어졌고, 고분자들의 분자량은 잘 제어되었으며 분자량 분포도도 낮게 유지되었다. 클릭반응의 효율은 ^{1}H NMR spectroscopy에 의해 얻어졌으며, 높은 효율을 나타내었다. 고분자 사슬 곁가지의 아민 그룹의 종류와, 치환된 알코올 그룹의 종류에 따라 저임계 용액 온도(LCST)의 제어가 가능했다.

Abstract: Thermoresponsive polymers 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). Poly(2-hydroxyethyl methacrylate) (PHEMA) was synthesized by ATRP, followed by introduction of alkyne groups using pentynoic acid, leading to HEMA-alkyne. Homopolymers having secondary amine groups, tertiary amines with hydroxyethyl and hydroxypropyl groups were synthesized by adding 2-azido-*N*-ethyl-ethanamine, 2-[(2-azidoethyl)amino]ethanol, and 2-[(2-azidoethyl)amino]propanol, respectively, to the PHEMA-alkyne backbone using click chemistry. Molecular weight (MW), molecular weight distribution (MWD), and click reaction efficiency were determined by gel permeation chromatography (GPC) and ^{1}H NMR spectroscopy. The transmission spectra of the 1.0 wt% aqueous solutions of the resulting polymers at 650 nm were measured as a function of temperature. Results showed that the lower critical solution temperature (LCST) could be easily controlled by the length of the hydroxyalkyl groups.

Keywords: atom transfer radical polymerization, click chemistry, lower critical solution temperature, hydroxyamine.

Introduction

Stimuli-responsive polymers are smart materials that can respond to external stimuli, such as temperature, pH, ionic strength, and light.[1-5] They can exhibit rapid changes in their properties in response to external stimuli.[6,7] Synthetic macromolecules can be used as an ideal substrate for endowing stimuli-responsive molecular elements. Among those external stimuli, thermoresponsive polymers demonstrate thermally induced, reversible phase transitions.[8-10] Such polymers possessing a lower critical solution temperature (LCST) in water are expected to be useful in nanotechnology and biotechnology. These polymers are soluble in water below their LCST by forming hydrogen bonding with water molecules, but become dehydrated and precipitated when heated above the LCST, leading to the fast phase transitions.[11-13]

The synthesis of well-controlled polymers with predetermined molecular weight (MW) and narrow molecular weight distribution (MWD) has been achieved by controlled radical polymerization (CRP). Atom transfer radical polymerization (ATRP),[14,15] stable free radial polymerization (SFRP),[16] and reversible addition fragmentation chain transfer (RAFT)[17] polymerization techniques have been the most successful methods. The 1,3-dipolar azide-alkyne cycloaddition, one of the click reactions,[18] has been employed as a method for chemical transformation. This reaction is combined particularly well with CRP techniques such as ATRP since it can be easily

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employed to prepare functional polymers from ATRP products with high degree of end functionality.

It is well known that LCST values can be governed by many parameters, including MW, MWD, and the structure of the side chains that determines the balance between hydrophilicity and hydrophobicity.[19,20] In order to have different LCST values, one needs to synthesize a series of polymers from different monomers. However, it is often advantageous to prepare several thermoresponsive polymers by simple post modification.

Herein, we report the synthesis of amino group-functionalized polymers by the simple combination of ATRP and click chemistry. ATRP was employed for the polymerization of 2-hydroxyethyl methacrylate (HEMA) to obtain narrow MWD. Secondary amine groups, tertiary amines with hydroxyethyl and hydroxypropyl groups were introduced to the backbone of the polymer to study the response of their aqueous solutions. The cloud points of these polymers were strongly dependent on the length of the hydroxyalkyl groups.

Experimental

Material. 2-Hydroxyethyl methacrylate (HEMA, 95%, Tokyo Chemical Industry; TCI) was purified by passing through a column filled with basic alumina (Acros) to remove inhibitors. Triethylamine (TEA, 99.5%), tetrahydrofuran (THF, 99.9%), 2-bromoethanol (98%), 3-chloropropanol (98%), dichloromethane (DCM, 99.9%), *N,N*-dimethylformamide (DMF, 99.8%), 2-chloroethyl amine (98%), and CuBr (98%) were purchased from Aldrich with the highest purity and were used as received without further purification. *N,N,N',N'',N''*-pentamethyldiethylenetriamine (PMDETA) and anisole (99%) were purchased from TCI and used as received.

Instrumentation. ^{1}H NMR spectra were collected in DMF-d7 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 ºC 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 ºC with a heating and cooling rate of 1 ºC/min. The data were collected dung heating. The cloud point was defined as the middle point of the transmittance change.

Synthesis. 2-Azido-*N*-ethyl-ethanamine (A1): 2-Azidoethyl amine (5 g, 58 mmol), triethyl amine (3.47 mL, 46.5 mmol) were dissolved in 20 mL of dichloromethane. Bromoethane (3.47 mL, 46.5 mmol) was added dropwise to the flask. After 20 h, the solution was filtered and concentrated to give the product. ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 3.38-3.35, 2H, t, NH*C*H$_2$*C*H$_2$N$_3$); 2.65-2.70 (2H, t, NH*C*H$_2$*C*H$_2$N$_3$); 2.58-2.62 (2H, m, *(*NH*C*H$_2$*C*H$_3$); 1.20 (1H, s, N*H*); 1.07-1.03 (3H, t, N-CH$_2$-*C*H$_3$).

2-[(2-azidoethyl)amino]ethanol (A2): 2-Bromoethanol (4.6 g, 37 mmol), **A1** (1.4 g, 12.4 mmol), Na_2CO_3 (5.1 g, 37 mmol) were dissolved in 20 mL of ethanol. The solution mixture was stirred for 2 days at 60 ºC. The resulting solution was filtered and concentrated to give the product. ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 3.58-3.55, 2H, t, OH-*C*H$_2$-CH$_2$); 3.35-3.31 (2H, t, N$_3$-*C*H$_2$-CH$_2$); 2.73-2.59 (6H, m, (CH$_2$)$_3$-N); 1.07-1.03 (3H, t, N-CH$_2$-*C*H$_3$).

2-[(2-azidoethyl)amino]proranol (A3): 3-Chloropropanol (3.5 g, 37 mmol), **A1** (1.4 g, 12.4 mmol), Na_2CO_3 (5.1 g, 37 mmol) were dissolved in 20 mL of ethanol. The solution mixture was stirred for 2 days at 60 ºC. The resulting solution was filtered and concentrated to give the product. ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 3.80-3.76, 2H, t, OH-*C*H$_2$-CH$_2$); 3.41-3.37 (2H, t, N$_3$-*C*H$_2$-CH$_2$); 2.69-2.55 (6H, m, (*C*H$_2$)$_3$-N); 1.72-1.65 (OH-CH$_2$-*C*H$_2$); 1.08-1.03 (3H, t, N-CH$_2$-*C*H$_3$).

PHEMA was Synthesized as Described Previously.[21] M_n = 61000 g/mol, M_w/M_n = 1.22.

PHEMA-alkyne was Synthesized as Described Previously.[21] M_n = 72000 g/mol, M_w/M_n = 1.25.

P1: The ratio of reagent [PHEMA-alkyne]/[**A1**]/[CuBr]/[PMDETA] was 1/2/0.1/0.1. The click reaction between PHEMA-alkyne (91.6 mg, 0.43 mmol) and **A1** (0.1624 g, 0.87 mmol) was conducted in 2 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 2 days. ^{1}H NMR (300 MHz, DMF-d7, δ in ppm): 7.98 (1H, s, triazole); 4.6-4.38 (2H,t, triazole-CH$_2$CH$_2$); 4.38-4.08 (4H, d, -O-C*H*$_2$-C$_{H2}$-O-); 3.37-3.06 (2H, t, triazole-C*H*$_2$-CH$_2$); 3.06-2.98 (2H, t, O-(C=O)-C$_{H2}$-CH$_2$-C-); 2.88-2.77 (2H, d, O-(C=O)-CH$_2$-C*H*$_2$-C-); 2.27-1.72 (4H, s, C*H*$_2$-C(CH$_3$)); 1.26-0.59 (3H, d, CH$_2$-C(C*H*$_3$)). M_n = 119 000 g/mol, M_w/M_n = 1.26.

P2: ^{1}H NMR (300 MHz, DMF-d7, δ in ppm): 7.97 (1H, s, triazole); 4.86-4.54 (2H, t, triazole-C*H*$_2$CH$_2$); 4.54-4.10 (4H, d,-O-C*H*$_2$-C*H*$_2$-O-); 3.23-3.06 (4H, t, triazole-CH$_2$-C*H*$_2$, O-(C=O)-CH$_2$-CH$_2$-C-); 2.98-2.88 (2H, s, O-(C=O)-C*H*$_2$-CH$_2$-C-);

2.53-2.23 (3H, s, N(C*H*3)$_2$); 2.25-1.82 (2H, s, CH_2-C(CH$_3$)); 1.37-0.79 (3H, d, CH$_2$-C(CH_3)). M_n = 129000 g/mol, M_w/M_n = 1.28.

P3: ^{1}H NMR (300 MHz, DMF-d7, δ in ppm): 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$_2$-); 2.94-2.89 (2H, d, O-(C=O)-CH$_2$-CH_2-); 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, CH2-C(CH_3); N-(CH$_2$-CH_3)$_2$). M_n = 116000 g/mol, M_w/M_n = 1.35.

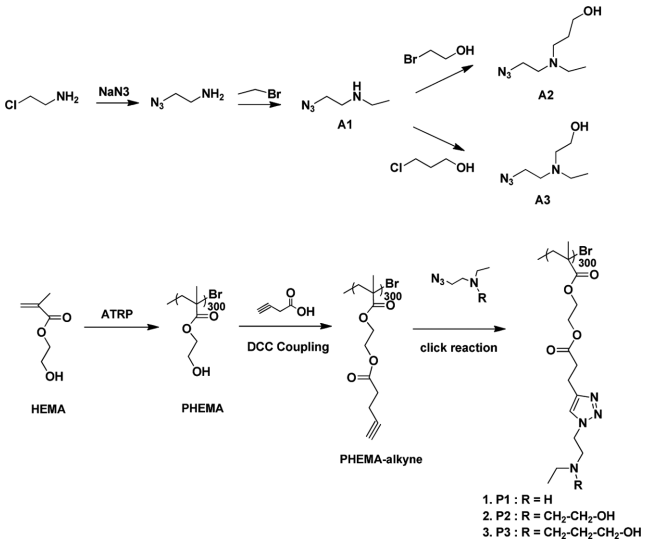
Results and Discussion

2-Azidoethylamine was synthesized through the reaction of NaN_3 with 2-chloroethylamine hydrochloride in water. 2-Azidoethylamine was reacted with bromoethane to produce compound **A1. A2** and **A3** were synthesized through the reaction of **A1** with 2-bromoethanol and 3-chloropropanol, respectively. ^{1}H NMR spectra confirmed the successful synthesis of **A1**, **A2**, and **A3** (Figure 1).

PHEMA and PHEMA-alkyne was prepared as described previously.[21] Briefly, atom transfer radical polymerization (ATRP) was directly employed to prepare PHEMA using a CuCl/bpy catalyst system with 2-bromoisobutyrate (EBiB) as an initiator. The resulting PHEMA was reacted with pentynoic acid to yield PHEMA-alkyne in the presence of DCC. The molecular weight (MW) and molecular weight distribution (MWD) of the resulting PHEMA (M_n = 61000 g/mol, M_w/M_n = 1.22) and PHEMA-alkyne (M_n = 72000 g/mol, M_w/M_n = 1.25) were obtained using a GPC DMF line with polystyrene (PS) standards.

The strategy employed in this study is schematically illustrated in Scheme 1. Homopolymers having secondary amine groups (**P1**), tertiary amines with hydroxyethyl and hydroxypropyl groups (**P2** and **P3**, respectively) were synthesized by adding **A1**, **A2**, and **A3** with excess amounts with respect to the PHEMA-alkyne backbone using click chemistry. The reaction was carried out in DMF with a CuBr/PMDETA complex at room temperature. MW and MWD data of all polymers are summarized in Table 1.

The ^{1}H NMR spectra provided additional evidence of the successful synthesis of hydroxy-functionalized polymers by click reactions. 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



Scheme 1. Synthesis of hydroxy group-functionalized polymers by combination of ATRP and click chemistry.

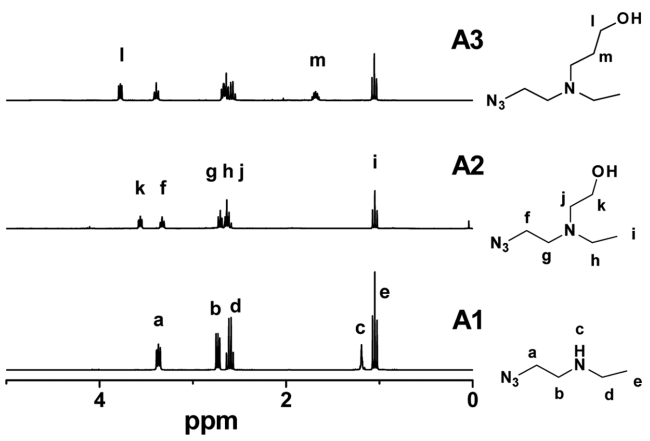


Figure 1. ^{1}H NMR spectra of **A1**, **A2**, and **A3**.

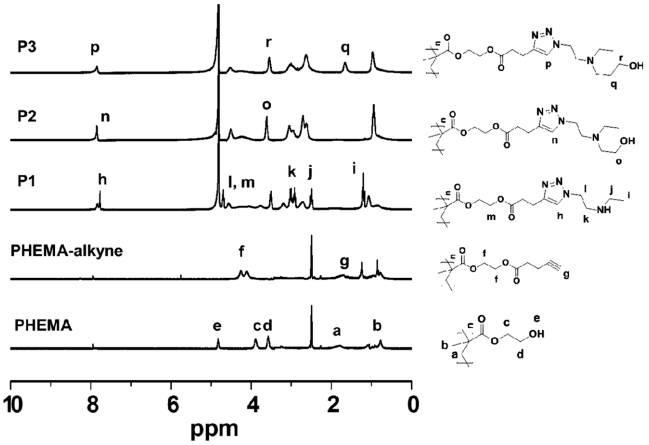


Figure 2. ^{1}H NMR spectra of PHEMA, PHEMA-alkyne, **P1**, **P2**, and **P3**.

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

Polymers	$M_{n,\ theory}$ (g/mol)	$M_{n,\ app}$[b] (g/mol)	PDI[b]	LCST[c] (°C)
PHEMA	39000[a]	61000	1.22	
PHEMA-alkyne	63000	72000	1.25	
P1	93000	119000	1.26	18
P2	106000	129000	1.28	40
P3	110000	116000	1.35	60

[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 turbidimetry.

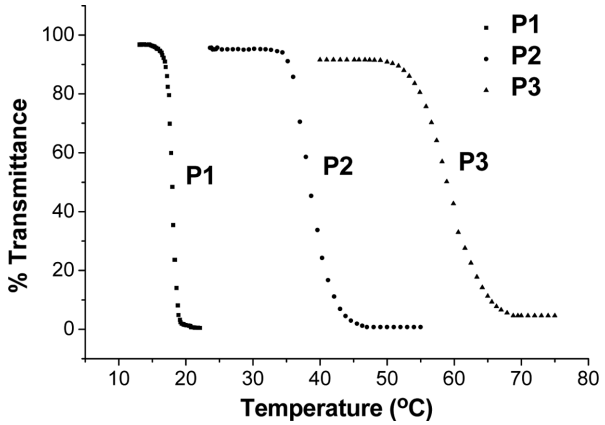


Figure 3. Thermoresponsiveness of 1.0 wt% aqueous solutions of **P1**, **P2**, and **P3** measured by percent transmission at 650 nm.

esterification. For amine-functionalized polymer (**P1**), a new peak (h) representing the proton on the 1,2,3-triazole rings appeared at 7.90 ppm while an alkyne peak (g) disappeared completely. **P2** and **P3** were characterized similarly.

Figure 3 shows the values of LCST measured for aqueous solutions of the polymers with secondary amine groups (**P1**), hydroxyethyl (**P2**), and hydroxypropyl groups (**P3**) (studied reference concentration was 1.0 wt%). A cloud point of **P1** homopolymer with secondary amine groups was 18 °C. For a series of hydroxyl-functionalized polymers (**P2** and **P3**), measured LCST values increased. More interestingly, A cloud point of **P3** (60 °C) was higher than that of **P2** (40 °C) since hydroxypropyl group is more hydrophobic than hydroxyethyl group. Therefore, the LCST of a series of hydroxyl-functionalized polymers can be precisely controlled from the number of methylene units of hydroxyalkyl groups.

Conclusions

Thermoresponsive polymers were successfully synthesized using ATRP and click chemistry. Well-defined polymers with predictable molecular weights and low molecular weight distribution were formed. The thermal properties of aqueous solutions of the polymers were studied by turbidimetry. The transmission spectra of an aqueous solution of these polymers as a function of temperature showed that the LCST of these polymers was significantly affected by the number of methylene units of hydroxyalkyl groups. In conclusion, we designed a very simple system where the LCST values can be easily controlled by small change in the length of hydroxyalkyl groups.

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