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Dual stimuli-responsive dendritic-linear block copolymers[†]

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Dendritic-linear block copolymers that have pH responsive poly(benzyl ether) dendrons and temperature responsive PiPrOx chains have been designed by copper-mediated click reactions. These copolymers exhibit sharp thermal transitions with a wide range of pH-dependent thermal transition temperatures.

Dendritic macromolecules are promising nano-objects for use in designing bio-inspired functional materials. Unlike common linear-type polymers, solution properties of dendrimers can be predominantly controlled by the nature of their peripheral functionalities.¹ Dendrimers with an ionic periphery are soluble in aqueous medium, regardless of the hydrophobicity of the dendrimer framework. Poly(benzyl ether) dendrimers, which have a carboxylate periphery, would be one of the typical examples.² Because of the low pK_a of benzoic acid (~4.8), poly(benzyl ether) dendrimers with carboxylate peripheries show appreciable solubility in aqueous medium under neutral conditions. As the pH becomes lower, the peripheral carboxylates are protonated, and the dendrimers eventually precipitate. Using this property, pH responsive materials can easily be designed.³ Recently, great attention has been focused on stimuli-sensitive polymers which changes their propensity response to external physical and chemical stimuli, such as temperature, pH, ionic strength, and light irradiation.⁴ In particular, thermo-responsive polymers have great potential for use as sensors,⁵ catalyst supports,⁶ carriers for bioactive materials delivery,⁷ and in separation processes.⁸ Poly(2-isopropyl-2-oxazoline) (PiPrOx) is a typical thermo-responsive polymer that undergoes a rapid and reversible hydration-dehydration change through the lower critical solution temperature (LCST).^{9,10} The fast responsiveness of PiPrOx is achieved by precise control of well-defined polymeric structures with appreciably narrow molecular weight distributions, which can be achieved by the living cationic polymerization mechanism.¹⁰ Furthermore, PiPrOx is biocompatible, biodegradable, and possesses stealth characteristics in vitro and in vivo comparable to poly(ethylene glycol). Based on the above information, we have designed new type dendritic-linear block copolymers that have pH responsive poly(benzyl ether) dendrons and temperature



Scheme 1 Synthesis of dendritic-linear block copolymers.

responsive P*i*PrOx chains. The dendritic-linear block copolymer exhibits a sharp thermal transition with a wide range of pH-dependent thermal transition temperatures.^{7,11}

Poly(benzyl ether) dendrimers carrying P*i*PrOx were synthesized by copper-mediated click chemistry at 50 °C in DMF for 24 h. Clickable P*i*PrOx with a propargyl end-functional group (Scheme 1; Prop-P*i*PrOx) was synthesized by the cationic ring opening polymerization reaction of *i*PrOx.¹⁰

The reaction was initiated with propargyl tosylate at 40 °C in acetonitrile for 10 days. The products were then characterized with ¹H NMR, GPC, and MALDI-TOF-MS analyses (Fig. S1–S3, ESI†). The estimated number average molecular weight values of Prop-P*i*PrOx ($M_{n,GPC} = 4800$, $M_{n,TOF-MS} = 4900$) were close to the value predicted from the initial

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monomer/initiator ratio $[M_{n,calc.} = 5000]$, and its polydispersity index (PDI = M_w/M_n) was determined to be 1.03. Frechet's type dendritic bromides (GnBr; n = nth generation dendrimer, n = 2, 3)² were reacted with sodium azide to obtain dendritic azides (GnN₃). After conjugating GnN₃ to PiPrOx, Gn-PiPrOxs were obtained and purified using preparative recycled GPC to remove unreacted Prop-PiPrOx and GnN₃. The resulting Gn-PiPrOxs were confirmed by ¹H NMR and MALDI-TOF-MS analyses. Finally, the peripheral methyl ester groups of Gn-PiPrOxs were hydrolyzed using a 3 M NaOH solution, resulting in dual-stimuli-responsive dendritic-linear block copolymers (Scheme 1; 1 and 2).

The thermo-responsibilities of 1, 2, and Prop-PiPrOx were tested in physiological saline (150 mM NaCl) phosphate buffer solution (PBS). Each polymer (0.05 mM) was dissolved in 20 mM PBS, and the pH values were then adjusted from 5.5 to 7.0. Under room temperature conditions, all polymer samples were transparent. However, the transparent solution became turbid when it reached the specific temperature for each polymer solution. For precise determination of the LCST, the change in optical transmittance at 500 nm was measured by a spectrophotometer. The LCST was defined as the temperature corresponding to a 10% decrease in the optical transmittance. All polymer solutions exhibited sharp changes in optical transmittance at specific temperatures. For example, the Prop-PiPrOx solution became turbid around 49 °C, regardless of the solution pH. In sharp contrast, the LCST values of 1 and 2 were greatly dependent on the solution pH (Fig. 1). The LCST of 1 increased from 35 to 65 °C when the pH changed from 5.5 to 6.9. At pH lower than 5.5, the LCST did not decrease further. Therefore, the protonation of carboxylates was determined to be complete at this pH value. Increases in LCST values were also not observed when the pH was greater than 7.0, indicating that carboxylic acid deprotonation was complete under this condition. Compared to 1, 2 exhibited more drastic changes in LCST values. With the pH change from 5.5 to 6.5, the LCST of 2 changed from 35 to 83 °C. In addition, the LCST value of 2 was more pH-dependent than that of 1, possibly because of the large number of carboxylic acid moieties. Due to instrumental limitations, it was

and 2 (d).

Table 1 Result of DLS and ζ -potential measurement of 1 and 2

Polymer	pН	Temperature/ $^{\circ}C$	Size/nm (PDI)	ζ -Potential/mV
1	5.1	30	51.9 (0.332)	-5.97
		60	Precipitation	N.A. ^a
	6.8	30	N.A.	-9.94
		60	587.3 (0.245)	-22.4
2	5.1	30	81.4 (0.540)	-9.45
		60	Precipitation	N.A.
	6.2	30	N.A.	-13.7
		60	796.1 (0.459)	-27.97
^{<i>a</i>} Not ava	ilable.			

impossible to determine reliable LCST values for **2** when the pH was greater than 6.3.

Because solubility was greatly altered by pH and temperature variation in the solutions, we hypothesize that the dendriticlinear block copolymers exhibit pH- and temperaturedependent morphology changes.^{11,12} For example, both P*i*PrOx and the dendritic block become hydrophilic under conditions of high pH with low temperature. Conversely, both P*i*PrOx and the dendritic block become hydrophobic under conditions of low pH with high temperature. The ζ potential and dynamic light scattering (DLS) of each polymer solution under several selected conditions were measured (Table 1). Due to instrumental limitations, the upper limit of the ζ potential measurement was 60 °C.

As shown in Table 1, both 1 and 2 exhibited very low light scattering intensity and *ca*. -10 mV of ζ potential when the temperature was lower than the LCST at high pH. This indicates that the polymers are highly soluble in their monomeric state because both PiPrOx and the dendritic block are hydrophilic. In contrast, both 1 and 2 demonstrated obvious precipitation when the temperature was higher than the LCST. The polymers are expected to adopt self-assembled supramolecular architectures under conditions of low temperature with high pH and high temperature with low pH because both 1 and 2 become amphiphilic under these conditions.¹³ If the temperature is lower than the LCST under low pH, the hydrophilic PiPrOx block should be predominantly located at the surface area, while the hydrophobic dendritic block should be located interior to the supramolecular architectures. This is supported by the relatively small ζ potential values of **1** and 2 under those conditions. The DLS results at 30 °C and pH 5.1 show a relatively broad distribution with average sizes of 52.9 and 81.4 nm for 1 and 2, respectively. TEM was used to confirm the polymer morphology under these conditions. As expected, both 1 and 2 showed the formation of a fibrous assembly through hydrophobic interactions of the dendritic wedges (Fig. 2). Alternatively, the charged dendritic block should be predominantly located at the surface under conditions of high pH and high temperature. In fact, the ζ potential values of 1 and 2 ($\zeta < -22$ mV) under these conditions were much greater than those under conditions of high pH and low temperature. This indicates that the charged dendritic wedges were predominantly located in the surface area of this formulation. Therefore, we have tried to obtain information about the morphology of self-assembled structures under these conditions. The DLS results indicate that 1 and 2 form very large particles



variation for 1 (a) and 2 (b), and pH-dependent LCST changes of 1 (c)



Fig. 2 TEM images of 1 and 2. Samples were prepared from PBS solution of pH 5.1 at 30 $^{\circ}$ C for 1 (a) and 2 (b), and pH 6.2 at 80 $^{\circ}$ C for 2 (c).



Fig. 3 Proposed temperature- and pH-dependent morphology changes of dendritic-linear block copolymers.

that cannot be explained by the formation of a simple micellar structure. Notably, we did not observe any precipitation under these conditions, even though the particle size was very large. When considering the hydrophobic nature of the dendritic framework except carboxylate periphery, the hydrophobic portion of the dendritic-linear block copolymers was much greater than the hydrophilic portions under these conditions. Therefore, the dendritic-linear block copolymers possibly form a lamellar structure. To confirm the morphology, a hot solution of the dendritic-linear block copolymers was freeze-dried and subjected to TEM measurement. A sheet-like structure was observed for **2**. Dendritic-linear block copolymers successfully change their morphologies depending on the pH and temperature of solution (Fig. 3).

In conclusion, new pH- and temperature-responsive dendriticlinear block copolymers were designed by copper-mediated click reactions between *Pi*PrOx and poly(benzyl ether) dendrimers. The dendritic-linear block copolymers exhibited a very wide range of LCST variations with changes in solution pH. Dendritic-linear block copolymers successfully changed their morphologies with variations in pH and temperature. This concept may contribute to the design of functional materials.

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