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Stereoisomeric Effect on Reverse Thermal Gelation of Poly(ethylene glycol)/Poly(lactide) Multiblock Copolymer

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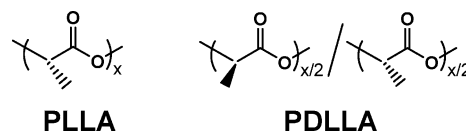
ABSTRACT: Aqueous solutions of both poly(ethylene glycol)/poly(DL-lactic acid) (PEG/PDLLA) and poly(ethylene glycol)/poly(L-lactic acid) (PEG/PLLA) multiblock copolymers underwent “clear sol-to-turbid gel-to-syneresis” transitions as the temperature increased. To investigate the stereoisomeric effect on the phase behavior, PEG/PDLLA and PEG/PLLA multiblock copolymers with a similar block length and total molecular weight were carefully synthesized. Compared with the PEG/PDLLA multiblock copolymer, the PEG/PLLA multiblock copolymer showed a lower critical gel concentration, a lower sol-to-gel transition temperature, and a wider gel window. In addition, the maximal gel modulus of the PEG/PLLA multiblock copolymer (11.0 wt % in water) was 2 times larger than that of the PEG/PDLLA multiblock copolymer. X-ray diffraction spectra, transmission electron microscopic images, and polarizing optical microscopic images suggested the amorphous state for both PEG/PDLLA and PEG/PLLA multiblock copolymer thermogels. ^{13}C NMR spectroscopy, critical micelle concentrations, hydrophobic dye partition, and circular dichroism spectra suggested that the differences in the thermogel properties come from lower dynamic molecular motion and the higher aggregation tendency of the PLLA due to the isotactic localization of the hydrophobic methyl groups rather than crystallization of PLLA.

Introduction

Stereochemistry plays an important role in determining the physicochemical properties of the polymer. The atactic polystyrene that is widely used for general purposes is amorphous and has a low glass transition temperature, whereas syndiotactic polystyrene has a high glass transition temperature.¹ Isotactic poly(acrylic acid) shows antiviral efficacy whereas atactic poly(acrylic acid) does not.² A stereocomplex of the poly(L-lactide) (PLLA) and poly(D-lactide) (PDLA) was reported. The stereocomplex showed higher melting point and stronger mechanical properties than the enantiomeric counterparts. In addition, the ABA-type stereocomplex of PEG–PLLA–PEG/PEG–PDLA–PEG and BAB-type stereocomplex of PLLA–PEG–PLLA/PDLA–PEG–PDLA showed thermoreversible sol–gel transitions, whereas the enantiomeric counterparts were soluble in water in the same temperature range of 0–80 °C.^{3,4}

Recently, DeLong et al. reported that a poly(L-lactide)–poly(ethylene glycol)–poly(L-lactide) (PLLA–PEG–PLLA) triblock copolymer hydrogel exhibited a modulus more than 10 times higher than a poly(DL-lactide)–poly(ethylene glycol)–poly(DL-lactide) (PDLLA–PEG–PDLLA) triblock copolymer hydrogel.⁵ The polymer aqueous solution formed a gel at low temperature, and the gel melted as the temperature increased. On the basis of wide-angle X-ray diffraction, they concluded that that crystallinity of the poly(L-lactide) is responsible for such a high modulus of the hydrogel.

However, the poly(L-lactide) has isotactic methyl groups whereas the poly(DL-lactide) has atactic methyl groups.⁶ When the hydrophobic methyl groups are regularly oriented on the same side along the backbone of the PEG–PLLA, the polymers are expected to have a higher tendency to aggregate in water than the PEG–PDLLA that has randomly oriented hydrophobic methyl groups along the polymer.



To prove the hypothesis and answer the question of what is the reason for the stereoisomeric effect on the gel modulus—that is, crystallinity suggested by DeLong et al.⁵ or higher association tendency of isotactic methyl groups—we investigated the thermogel of multiblock copolymers, consisting of poly(ethylene glycol) and poly(L-lactide) (PEG/PLLA) or poly(DL-lactide) (PEG/PDLLA).

A thermogel is a free-flowing sol at lower temperature; however, it turns into a gel at high temperature due to the hydrophobic interactions.^{7,8} This differs from the crystallization-induced hydrogel that typically forms a gel at low temperature and flows as the temperature increases.^{5,9,10}

We studied solution and gel behavior of the PEG/PLLA and PEG/PDLLA multiblock copolymers using ^{13}C NMR spectroscopy, X-ray diffraction spectra, transmission electron microscopy, polarizing optical microscopy, UV–vis spectroscopy, circular dichroism, and light scattering.

Experimental Section

Materials. DL-Lactide, L-lactide, stannous octoate, 1,6-dihydroxyhexane, α,ω -dicarboxypoly(ethylene glycol) (MW = 600), dimethylaminopyridine, dicyclohexylcarbodiimide, and 1,6-diphenyl-1,3,5-hexatriene were used as received from Aldrich. Toluene (Aldrich) was dried over sodium before use, and methylene chloride (Dae Jung; Korea) was dried over calcium hydride. *n*-Hexane was used as received from Dae Jung (Korea).

Synthesis. First, the poly(lactide) (PLLA or PDLLA) with hydroxy end groups was prepared by the ring-opening polymerization of lactide. 1,6-Dihydroxyhexane and stannous octoate were used as an initiator and a catalyst, respectively. By controlling the ratio of lactide to 1,6-dihydroxyhexane, the molecular weight of the PLA could be controlled. On the basis of the peaks at 4.1–4.3

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Table 1. List of Polymers

polymer	M_n^a	M_n^b	M_w/M_n^b
PEG	600	1040	1.2
PDLLA	1040	1480	1.2
PLLA	1030	1520	1.2
PEG/PDLLA	600/1000	14400	1.3
PEG/PLLA	600/1000	14300	1.3

^a Determined by ^1H NMR in CDCl_3 based on ethylene glycol (EG) unit (4H, 3.6–3.8 ppm) and lactic acid unit (1H, 5.1–5.3 ppm) of the polymers.

^b Determined by GPC. In the GPC, tetrahydrofuran was used as an eluting solvent, and polystyrenes in a molecular weight range of 1000–20 000 Da were used as the molecular weight standards.

ppm ($-\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}-$) and 5.1–5.3 ppm ($-\text{COOCH}(\text{CH}_3)-$) in the ^1H NMR spectra, PLAs with the number-average molecular weight of 1000, exactly 1040 for PDLLA and 1030 for PLLA, were chosen. PLAs with hydroxyl end groups were coupled with PEG (molecular weight of 600 from Aldrich) with carboxylic acid end groups using dicyclohexylcarbodiimide.¹¹ To synthesize the PEG/PDLLA multiblock copolymer, the dicarboxypoly(ethylene glycol) (8.5 g, 14.1 mmol, MW = 600) was dissolved in anhydrous toluene (200 mL), and the solvent was distilled off to remove the residual water adsorbed to the polymer. The reaction mixture was cooled to 20 °C under dry nitrogen, and anhydrous methylene chloride (200 mL) was added to the flask. Poly(DL-lactide) (10.0 g, 9.61 mmol), dicyclohexylcarbodiimide (4.94 g, 24.0 mmol), and dimethylaminopyridine (0.29 g, 2.4 mmol) were added to the reaction mixture and stirred at 20 °C for 24 h. The product was isolated by precipitation into *n*-hexane. The polymer was dissolved in methylene chloride and fractionally precipitated by slowly adding *n*-hexane. Performing the fractional precipitation twice separated the multiblock copolymer with a final yield of 60–65%. The residual solvent was removed under vacuum. PEG/PLLA multiblock copolymers in Table 1 were similarly synthesized. ^1H NMR (CDCl_3) of PEG/PLA multiblock copolymer: δ 1.2–1.7 ($-\text{COOCH}(\text{CH}_3)-$) and ($-\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}-$), δ 3.6–3.8 ($-\text{OCH}_2\text{CH}_2-$), δ 4.1–4.3 ($-\text{COOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$), and ($-\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}-$), δ 5.1–5.3 ($-\text{COOCH}(\text{CH}_3)-$).

Gel Permeation Chromatography. The gel permeation chromatography system (Waters 515) with a refractive index detector (Waters 410) was used to obtain molecular weight and molecular weight distributions of polymers. Tetrahydrofuran was used as an eluting solvent. The polystyrenes in a molecular weight range of 1000–20 000 Da were used as the molecular weight standards. Styragel HMW 6E and HR 4E columns (Waters) were used in series.

NMR Study. A 500 MHz NMR spectrometer (Varian) was used for ^1H NMR (in CDCl_3) to study composition and number-average molecular weight of the poly(lactide) and ^{13}C NMR (in D_2O) to see the spectral change of the multiblock copolymers as a function of temperature. The solution temperature was equilibrated for 20 min before the measurement.

Phase Diagram. The sol–gel transition was determined by the test tube inverting method and dynamic mechanical analysis. For the test tube inverting method, the 4 mL vials (diameter 1.1 cm) containing 0.5 mL of PEG/PLA multiblock copolymer solutions were immersed in water at 4 °C for 30 min. The transition temperatures were determined by flow (sol)–no flow (gel) criterion when the vial was inverted with a temperature increment of 1 °C per step.^{12,13} For each step, the vials were equilibrated for 5 min. The syneresis temperature was determined by the visual observation of the macroscopic phase separation between the polymer and water.

The sol-to-gel transition of the polymer aqueous solution was also investigated by dynamic rheometry (Thermo Haake, rheometer RS 1).^{14,15} The aqueous polymer solution (11.0 wt %) was placed between parallel plates of 25 mm diameter and a gap of 0.5 mm. The data were collected under a controlled stress (4.0 dyn/cm²) and a frequency of 1.0 rad/s. The heating rate was 0.2 °C/min.

X-ray Diffraction. When the PEG–PDLLA and PEG–PLLA multiblock copolymer aqueous solutions (11.0 wt %) were placed at 20 °C, they formed a gel in 1 min because the sol-to-gel transition

temperature of the solutions was less than 20 °C. The gel was kept at 20 °C for 6 h, which was longer than required to construct the phase diagram or carry out the dynamic mechanical analysis. Such a treatment allows the thermogel to have enough time to crystallize, if any, to induce the difference in the phase diagram and modulus of the multiblock copolymers. Then the X-ray diffraction spectra of the thermogels were recorded with a Rigaku SWXD diffractometer using Cu K α radiation at a scanning rate of 1°/min at 20 °C.

Transmission Electron Microscopy. The microscopic image was obtained after syneresis of the thermogel (11 wt %) at 40 °C for 5 min on the substrate. Phosphotungstic acid was used as a staining agent.

Polarizing Optical Microscopy. The polymer aqueous solution (11.0 wt %) was placed between two slide glasses and a change in morphology was investigated using a polarized optical microscope (Olympus; Bh-753pw). The microscopic images at 3 °C (sol), 20 °C (gel), and 40 °C (syneresis) were photographed.

Critical Micelle Concentration. Critical micelle concentration was determined by the light scattering instrument (Zetasizer Nano ZS; Malvern) at room temperature (20 °C).¹⁶ The PEG/PDLLA, PEG/PLLA, and PEG (MW = 10 000 Da) aqueous solutions were prepared in a polymer concentration range of 5.0×10^{-4} – 3.0×10^{-2} wt %. PEG that does not form a micelle was used for comparison. The scattering intensity of these solutions was recorded as a function of polymer concentration. A He–Ne laser operating at 633 nm was used as a light source. Measurements of scattered light were made at an angle of 90° to the incident beam. The crossing point of the two extrapolated straight lines was defined as the critical micelle concentration of the polymer.

Hydrophobic Dye Partition. To study the partitioning of the hydrophobic dye (1,6-diphenyl-1,3,5-hexatriene) between the water phase and the hydrophobic micelle core, a change in the absorbance of the dye in the polymer aqueous solution (0.05 wt %) was monitored while the temperature increases from 3 to 40 °C. The ratio of the absorbance at 356 to 314 nm is a measure of the partitioning of the dye between the water phase and the hydrophobic micelle core. The ratio was investigated as a function of temperature.

Dynamic Light Scattering. The apparent size of polymers or micelles was studied by a dynamic light scattering (DLS) instrument (Zetasizer nano ZS; Malvern) as a function of temperature at a polymer aqueous concentration of 0.05 wt %. A He–Ne laser operating at 633 nm was used as a light source. Measurements of scattered light were made at an angle of 90° to the incident beam. The results of DLS were analyzed by the regularized CONTIN method. The decay rate distributions were transformed to an apparent diffusion coefficient (D). From the diffusion coefficient, the apparent hydrodynamic size of the polymer or micelles can be obtained by the Stokes–Einstein equation.

Circular Dichroism. Molar ellipticity of the PEG/PDLLA and PEG/PLLA multiblock copolymer aqueous solution (0.1 wt %) was determined by the circular dichroism instrument (J-810, JASCO) as a function of temperature in a range of 3–40 °C.

Results and Discussion

The DL- and L-poly(lactide) of molecular weight 1000 were prepared by controlling the ratio of initiator (1,6-dihydroxyhexane) and monomer (lactide). The PEG/PDLLA or PEG/PLLA multiblock copolymer was synthesized by the coupling reaction between hydroxyl groups of PDLA ($M_n \sim 1040$) or PLLA ($M_n \sim 1030$) and carboxylic acid groups of dicarboxy poly(ethylene glycol) using dicyclohexylcarbodiimide as a coupling agent (Scheme 1). Multiblock copolymers with a similar molecular weight (PEG/PDLLA multiblock copolymer: $M_n \sim 14\,400$; PEG/PLLA multiblock copolymer: $M_n \sim 14\,300$ by gel permeation chromatography: Supporting Information, Figure S1) were carefully chosen to study the effect the stereochemistry on the reverse thermal gelation. The polymers studied in this research are listed in Table 1. As the first approximation, PEG/PLLA (or PEG/PDLLA) can be

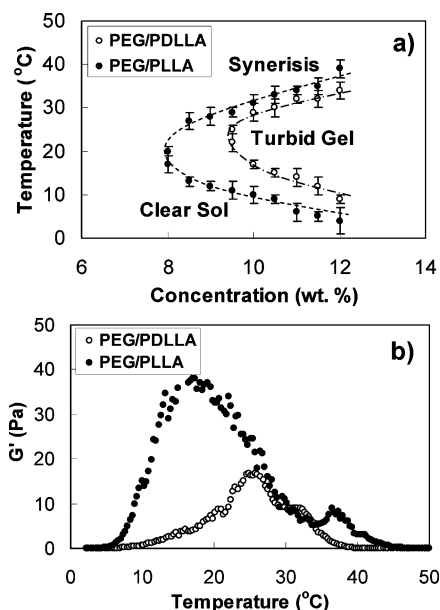
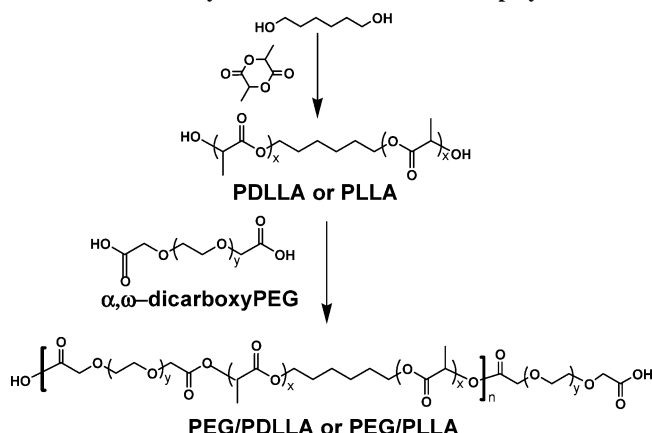


Figure 1. (a) Phase diagram of PEG/PDLLA and PEG/PLLA multiblock copolymer aqueous solutions. The sol-to-gel transition temperatures were determined by the test tube inverting method, and the syneresis temperatures were determined by the visual observation of the macroscopic phase separation between the polymer and water. Each data point is an average of three measurements. (b) The change in storage modulus of multiblock copolymer aqueous solutions (11.0 wt %) as a function of temperature.

Scheme 1. Synthesis of the Multiblock Copolymer



considered as an alternating multiblock copolymer consisting of 9.4 PEGs ($M_n \sim 600$) and 8.4 PLLAs (or PDLLA) ($M_n \sim 1000$).

Both PEG/PDLLA and PEG/PLLA multiblock copolymer aqueous solutions underwent sol (clear)-to-gel (turbid)-to-syneresis transitions as the temperature increased. For example, the aqueous solution (11.0 wt %) of the PEG/PDLLA multiblock copolymer underwent sol-to-gel transition at 14 °C and gel-to-syneresis transition at 32 °C, whereas that of PEG/PLLA multiblock copolymer underwent sol-to-gel transition at 6 °C and gel-to-syneresis transition at 34 °C. When the PEG/PDLLA and PEG/PLLA multiblock copolymer thermogels were cooled to a low temperature (4 °C), they turned into clear solutions again, and the same transition temperatures were observed as the temperature increased, suggesting the reversibility of the phase transition. The phase diagrams of PEG/PDLLA and PEG/PLLA multiblock copolymer aqueous solutions were compared (Figure 1a). The PEG/PLLA multiblock copolymer system showed a lower critical gel concentration above which the gel

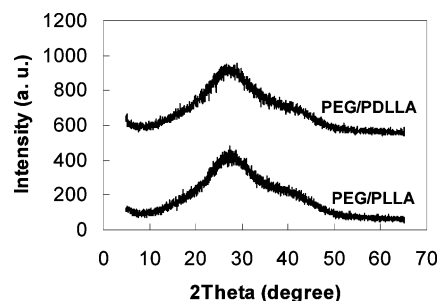


Figure 2. Wide-angle X-ray diffraction spectra of PEG/PDLLA and PEG/PLLA multiblock copolymer thermogels (11.0 wt %) formed at 20 °C.

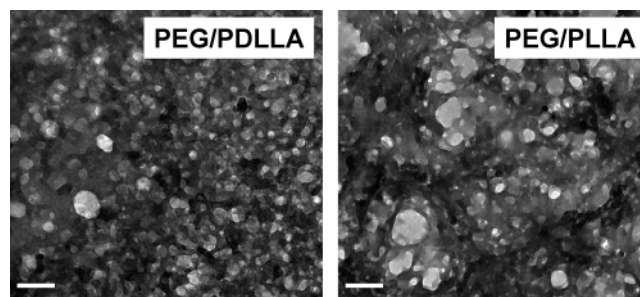


Figure 3. Transmission electron microscopic images of PEG/PDLLA and PEG/PLLA multiblock copolymer thermogels. The scale bar is 100 nm.

phase exists and a wider gel window than the PEG/PDLLA multiblock copolymer system.

During the sol-to-gel transition of the polymer aqueous solution (11.0 wt %), an increase in the modulus was observed (Figure 1b).^{14,15} The modulus is negligible in the sol state, and the first maximal modulus appears at the mid-temperature of the gel which is 24–26 °C for PEG/PDLLA and 16–21 °C for PEG/PLLA. The maximal modulus of the PEG/PLLA multiblock copolymer thermogel (37 Pa) was 2.3 times stronger than the PEG/PDLLA multiblock copolymer thermogel (16 Pa). Further aggregation of the polymers in a dehydrated or syneresized state led to the second maximal gel modulus at 31–33 °C for PEG/PDLLA and 36–38 °C for PEG/PLLA.

The crystalline domain formation of PLLA or the cooperative aggregation tendency of the isotactically distributed methyl groups might contribute to such differences.

To investigate the origin of the difference in phase behavior between PEG/PDLLA and PEG/PLLA multiblock copolymers, the X-ray diffraction spectra of the thermogel were compared. PLLA is reported to exhibit sharp peaks at 2θ angles of 15°, 17°, 19°, and 23°, which are characteristics of an orthorhombic crystal.¹⁸ PEG–PLLA–PEG (2000–2000–2000) and PLLA–PEG–PLLA (1400–4600–1400 or 3300–8900–3300) hydrogels were reported to show crystalline peaks at 2θ angles of 17° and 19° and assigned to be a hexagonal crystal.^{3–5} However, any significant peaks corresponding to these positions were observed in the XRD pattern of PEG/PLLA. Instead, a typical amorphous scattering pattern similar to PEG/PDLLA was observed (Figure 2).^{19,20} The fact that the XRD pattern did not show any sharp diffraction peaks suggests that both PEG/PLLA and PEG/PDLLA thermogel are amorphous or ultrasmall crystalline materials where diffraction peaks cannot be resolved.^{21,22} The transmission electron microscopic images of both PEG–PDLLA and PEG–PLLA thermogels showed significant networks of the polymers (Figure 3). However, any indication of a crystalline domain was not observed by the transmission electron microscope (TEM). In addition, a differ-

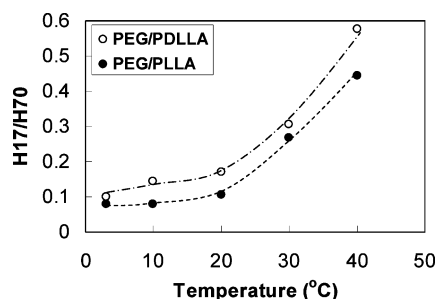


Figure 4. Peak height ratio of methyl (PLA) at 17 ppm to ethylene (PEG) at 70 ppm in the ^{13}C NMR spectra of the PEG/PDLLA and PEG/PLLA multiblock copolymers (11.0 wt % in D_2O) as a function of temperature. The ratio is a measure of relative mobility of the PLA to PEG in the multiblock copolymers.

ence in the characteristic microscopic image was not observed between PEG/PDLLA and PEG/PLLA multiblock copolymer thermogels in the polarized optical microscope (Supporting Information, Figure S3). On the basis of the XRD pattern, TEM images, and polarizing optical microscopic images, the PEG/PLLA thermogel is considered to be amorphous. Therefore, the crystalline domain formation as reported in the PLLA-PEG-PLLA (MW = 3300–8900–3300) triblock copolymer hydrogel could not be claimed as an origin of the high gel modulus and wide gel window of the current PEG/PLLA multiblock copolymer thermogel in comparison with the PEG/PDLLA multiblock copolymer thermogel.⁵

The ^{13}C NMR spectra were compared between PEG/PDLLA and PEG/PLLA multiblock copolymer aqueous solutions (11.0 wt % in D_2O) as a function of temperature. As the temperature increased, the PEG peak at 70 ppm broadened and downfield shifted whereas the PLA peak at 17 ppm sharpened (Supporting Information, Figure S4). When the ratio of the peak at 17 ppm (methyl group of poly(lactide)) to 70 ppm (ethylene group of poly(ethylene glycol)) was compared, the PEG/PDLLA multiblock copolymer showed a larger value than PEG/PLLA multiblock copolymer, suggesting the higher molecular motion of the PDLLA than PLLA in sol (3 °C), gel (20 °C), and even syneresis (40 °C) states (Figure 4). From this observation, we can conclude that the methyl group of the PEG/PDLLA multiblock copolymer intrinsically has a higher molecular motion than that of the PEG/PLLA multiblock copolymer. The higher molecular motion suggests that the randomly oriented methyl groups along the atactic PDLLA have a larger free volume than isotactically arranged methyl groups of the PLLA.²⁰ Therefore, the maximal modulus of PEG/PDLLA multiblock copolymer thermogel with a higher mobility of methyl groups is smaller than the maximal modulus of the PEG/PLLA multiblock copolymer thermogel.

To compare the aggregation tendency between PEG/PDLLA and PEG/PLLA multiblock copolymers, the critical micelle concentration in water was studied. The scattering intensity of light was investigated as a function of polymer concentration. An abrupt increase in the scattering intensity was observed when the polymer concentration was above a certain value, which was used as a critical micelle concentration (Figure 5).¹⁶ On the other hand, PEG (MW = 10 000 Da) aqueous solutions did not show an abrupt increase in scattering in the same concentration range. The cmc values of the PEG-PLLA and PEG-PDLLA were estimated to be 4.0×10^{-3} and 7.0×10^{-3} wt %, respectively. The lower cmc of PEG-PLLA than PEG-PDLLA suggests a higher aggregation tendency of the PEG-PLLA than PEG-PDLLA in water.

The partitioning of the hydrophobic dye (1,6-diphenyl-1,3,5-hexatriene) between the water and micelle core was studied as

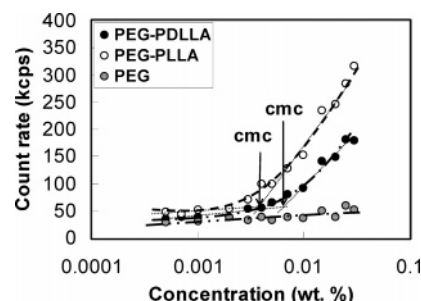


Figure 5. Comparison of the critical micelle concentration of the PEG/PDLLA and PEG/PLLA multiblock copolymers in water.

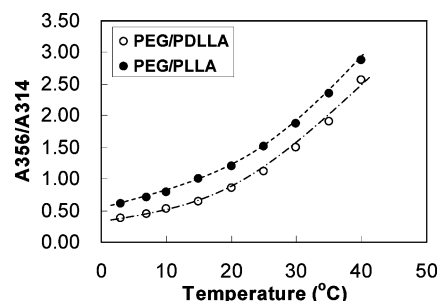


Figure 6. Change in the ratio of the band at 356 nm to the band at 314 nm as a function of temperature. The ratio is a measure of the dye partitioned in the hydrophobic core of the polymer relative to water.

a function of temperature. The polymer and dye concentration were fixed at 0.05 wt % and $4.0 \mu\text{M}$. When the temperature increased from 3 to 40 °C, the absorbance at 314 nm (dye in water) decreased whereas the absorbance at 339, 356, and 378 nm increased, indicating the partitioning of the dye into a micellar hydrophobic environment (Supporting Information, Figure S6).¹⁷ The ratio of absorbance at 356 to 314 nm can be a measure of the partitioning of the hydrophobic dye into the micelle core. The ratio was significantly increased above 15 °C. In addition, the ratio of the PEG/PLLA multiblock copolymer was 12%–50% larger than PEG/PDLLA multiblock copolymer in a temperature range of 3–40 °C (Figure 6).

The lower critical micelle concentration and the higher partition ratio of the hydrophobic dye suggest that the PEG/PLLA multiblock copolymer intrinsically has a higher aggregation tendency than PEG/PDLLA multiblock copolymer in water. The isotactic distribution of the methyl groups in the PLLA block might drive cooperative association of the PEG/PLLA multiblock copolymer.

The micelle formation of the multiblock copolymer in water (0.05 wt %) was also studied by dynamic light scattering as a function of temperature. The bands at 6–7 nm and 95–140 nm can be considered as unimers and micelles, respectively (Figure 7a,b). As the temperature increased from 3 to 40 °C, the micelle/or polymer size of both PEG/PLLA and PEG/PDLLA decreased at 10–15 °C, suggesting that dehydration of the polymer occurred at sol-to-gel transition temperature. The variation of the micelle/or polymer size was larger for PEG/PDLLA than PEG/PLLA as can be seen from the deviation from the reference size at 3 °C (dotted lines).

To confirm the chiroptical properties in a temperature range of 3–40 °C, the circular dichroism spectra were compared between PEG/PDLLA and PEG/PLLA multiblock copolymers in water (0.1 wt %). The molar ellipticity of PEG/PDLLA multiblock copolymer is zero due to the achiral, racemic nature of the polymer. However, the molar ellipticity of PEG/PLLA multiblock copolymer was around 60 000 deg cm^2/dmol and slightly decreased as the temperature increased, suggesting that

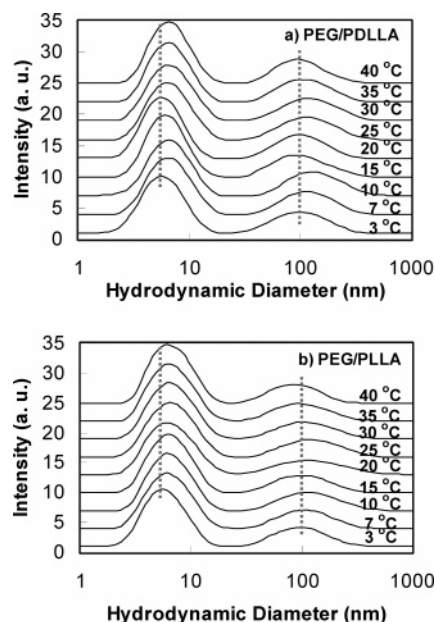


Figure 7. Dynamic light scattering study of the PEG/PDLLA (a) and PEG/PLLA (b) multiblock copolymer aqueous solutions (0.05 wt %). The size variations of the micelle and polymer can be seen from the reference (dotted lines) at 3 °C.

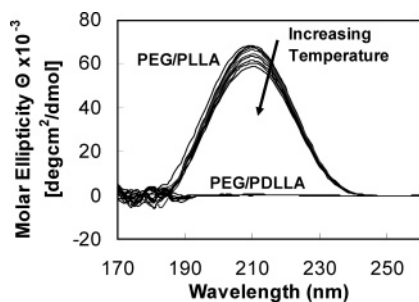


Figure 8. Circular dichroism of PEG/PDLLA and PEG/PLLA multiblock copolymer aqueous solution (0.1 wt %) as a function of temperature. The temperature was varied through 3, 7, 10, 15, 20, 25, 30, 35, and 40 °C.

the polymer keeps its isotactic characteristics in a temperature range of 3–40 °C (Figure 8).

Conclusions

PEG/PDLLA and PEG/PLLA multiblock copolymers with a similar block length and total molecular weight were carefully synthesized, and their solution behavior was compared. The PEG/PLLA multiblock copolymer showed a wider gel window and a larger maximal gel modulus than the PEG/PDLLA multiblock copolymer. On the basis of the X-ray diffraction spectra, transmission electron microscopic images, and polarizing optical microscopic study, the difference in phase diagram and gel modulus between PEG/PDLLA and PEG/PLLA multiblock copolymer thermogelling system is not caused by crystallinity of the PEG/PLLA multiblock copolymer. ^{13}C NMR, UV–vis spectra, dynamic light scattering analysis, and circular dichroism spectra suggest that the isotactic attachment of the hydrophobic methyl groups gives the PEG/PLLA multiblock copolymer a strong tendency to aggregate in water due to the cooperative hydrophobic interactions. In addition, the methyl

groups of the PEG/PDLLA multiblock copolymer showed higher molecular motion than PEG/PLLA and might reduce the modulus of the thermogel.

This study suggests that the stereoisomeric variation of a thermogel modulus is induced by intrinsically higher aggregation tendency of the isotactic polymer.

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Supporting Information Available: Gel permeation chromatograms and ^1H NMR spectra (in CDCl_3) of the PEG/PDLLA and PEG/PLLA multiblock copolymers; polarized optical microscopic images and ^{13}C NMR spectra of the PEG/PDLLA and PEG/PLLA multiblock copolymers in water (11.0 wt % in D_2O) as a function of temperature; UV–vis spectra of a hydrophobic dye (1,6-diphenyl-1,3,5-hexatriene) in the PEG/PDLLA and PEG/PLLA multiblock copolymers in water as a function of temperature. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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