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Synthesis and Characterization of Biodegradable Thermosensitive Poly(organophosphazene) Gels

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ABSTRACT: Thermosensitive poly(organophosphazenes) bearing α-amino-ω-methyl-poly(ethylene glycol) (AMPEG), some hydrophobic amino acid esters, and a depsipeptide ethyl ester (ethyl-2-(*O*-glycyl)glycolate) as a hydrolysis-sensitive moiety have been synthesized. Most of the poly(organophosphazenes) synthesized showed sol−gel transition properties in an aqueous solution. The gelation properties of the polymers were dependent on several factors like the composition of substituents, the chain length of AMPEG, and kinds of amino acid esters. The gelation of the polymers seemed to be imparted by association of hydrophobic groups of amino acid esters. The polymers decomposed under the physiological conditions. The polymer with a small amount of depsipeptide was hydrolyzed more rapidly than that with no depsipeptide. The viscosity of the polymer gels was also affected by their degradation rate.

Introduction

Thermosensitive hydrogels have been extensively studied because of their applications in drug delivery, immobilization matrices for enzymes and cells, and tissue engineering.[1−5] Thermosensitive hydrogels can be formed either by physical gelation owing to the absence of covalent interactions, such as ionic interaction, hydrophobic interaction, and hydrogen bonding between polymer chains in an aqueous solution, or by chemical gelation caused by chemical cross-linkers. The former may go through sol−gel phase transitions in response to changes in temperature, but the latter may undergo swelling−shrinking transitions.

Thermosensitive hydrogels made by physical cross-links between polymer chains are very useful for injectable drug delivery systems because no toxic organic cross-linkers are usually employed. Synthetic polymers such as copolymers of *N*-isopropylacrylamide (NiPAAM),[6] PEO−PPO−PEO block copolymers,[5,7] and PEG−PLGA−PEG triblock copolymers[5,8] are known to form such hydrogels. The aqueous solutions of high molecular weight copolymers of NiPAAM and the commercial polymers of PEO−PPO−PEO exhibited a phase transition of sol to gel as the solution temperature increased. The application of these polymers to injectable drug delivery systems has been extensively studied. However, most of their applications are still not satisfactory because the copolymers of NiPAAM are toxic and nonbiodegradable and also because PEO−PPO−PEO gels dissolved in a few days. Several kinds of partially cross-linked thermosensitive polyphosphazene gels have been reported, but these polymers are also nondegradable.[9] On the other hand, PEG−PLGA−PEG triblock copolymers have been reported to have biodegradable thermogelling properties, and their application studies on the injectable drug delivery systems are known to be under way.[8]

We have studied biodegradable thermosensitive poly(organophosphazenes) and cyclotriphosphazenes[10] and have recently reported that some polyphosphazenes with α-amino-ω-methyl-PEG (AMPEG) and isoleucine ethyl ester (IleOEt) have thermothickening properties.[11]

In this study, we have synthesized thermosensitive poly(organophosphazene) gels bearing AMPEGs, some hydrophobic amino acid esters such as DL-leucine (LeuOEt) ethyl ester, L-isoleucine ethyl ester (IleOEt), and L-valine ethyl ester (ValOEt) along with ethyl-2-(*O*-glycyl)glycolate (GlyGlycOEt) as a hydrolysis-sensitive moiety. Here, we discuss gelation properties and hydrolytic behaviors of these poly(organophosphazenes).

Experimental Section

Materials. Hexachlorocyclotriphosphazene (Aldrich) was purified by sublimation at 55 °C under vacuum (about 0.1 mmHg). The ethyl esters of amino acids were prepared according to the literature.[12] Ethyl-2-(*O*-glycyl)glycolate (GlyGlycOEt) was prepared as described by Crommen et al.[13] Tetrahydrofuran (THF) was dried by reflux over sodium metal and distilled, and triethylamine was distilled over BaO under dry nitrogen. α-Amino-ω-methoxypoly(ethylene glycols) (AMPEGs) with molecular weights of 350, 550, and 750 were prepared by a published method.[14]

Synthesis of Poly(organophosphazenes). Poly(organophosphazenes) (**1**, **2**, **3**, and **6**) were synthesized similarly by the procedure stated in the previous report.[11]

$[NP(AMPEG350)_{1.06}(IleOEt)_{0.94}]_n$ (1).[11] IleOEt (19.0 mmol) and AMPEG 350 (31.0 mmol).Yield: 56%. ^{31}P NMR ($CDCl_3$), δ (ppm): 19.1. Elemental analysis (%) calcd: C, 50.01; H, 8.77; N, 7.47. Found: C, 49.8; H, 8.80; N, 7.67.

$[NP(AMPEG350)_{0.99}(LeuOEt)_{1.01}]_n$ (2). LeuOEt (19.03 mmol) and AMPEG 350 (34.6 mmol). Yield: 60%. ^{31}P NMR ($CDCl_3$), δ (ppm): 18.7. Elemental analysis (%) calcd: C, 50.14; H, 8.78; N, 7.65. Found: C, 50.00; H, 8.79; N, 7.69.

$[NP(AMPEG350)_{1.00}(ValOEt)_{1.00}]_n$ (3). ValOEt (17.0 mmol) and AMPEG 350 (34.6 mmol). Yield: 65%. ^{31}P NMR ($CDCl_3$), δ (ppm): 19.5. Elemental analysis (%) calcd: C, 49.17; H, 8.63; N, 7.47. Found: C, 48.90; H, 8.69; N, 7.55.

Synthesis of $[NP(AMPEG350)_{0.92}(IleOEt)_{0.92}(GlyGlycOEt)_{0.07}]_n$ (4). Poly(dichlorophosphazene) was prepared as described previously.[15] L-Isoleucine ethyl ester hydrochloride (3.0 g, 15.5 mmol) suspended in dry THF (100 mL) containing triethylamine (6.3 g, 62.0 mmol) was added slowly to poly(dichlorophosphazene) (2.0 g, 17.3 mmol) dissolved in dry THF (100 mL). The reaction mixture was stirred for 4 h at 4 °C and then for 20 h at room temperature. To this mixture, triethylamine (0.3 g, 3.2 mmol) and ethyl-2(*O*-glycyl)glycolate oxalic salt (0.3 g, 0.8 mmol) dissolved in acetonitrile (50 mL) were added, and the reaction mixture was stirred for 19 h in an ice−water bath. After AMPEG350 (12.1 g, 34.5 mmol) dissolved in dry THF (100 mL) containing triethylamine (7.0 g, 69.0 mmol) was added to the polymer solution, the reaction

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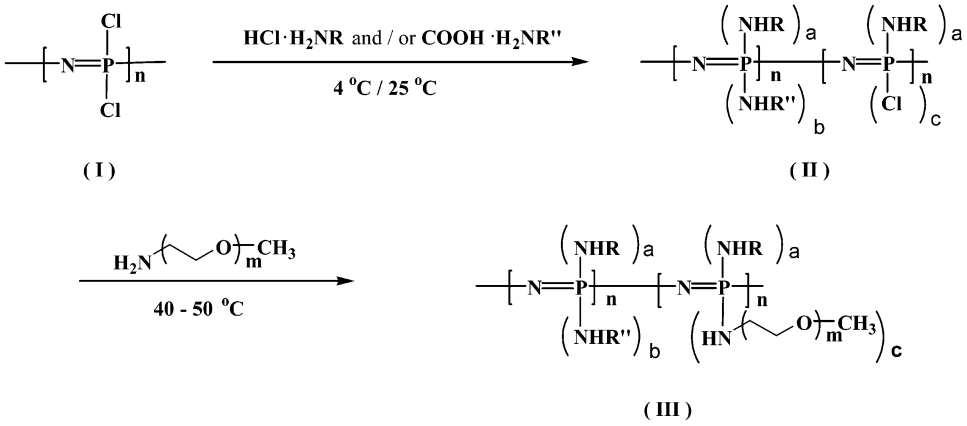
Scheme 1



mixture was stirred for 2 days at 40−50 °C. The reaction mixture was filtered. After the filtrate was concentrated, it was poured into *n*-hexane to obtain a precipitate, which was reprecipitated twice in the same solvent system. The polymer product was further purified by dialysis in methanol for 2 days and then in distilled water for 2 days at 4 °C. The final dialyzed solution was freeze-dried to obtain polymer **1**. Yield: 68%. ^{31}P NMR ($CDCl_3$), δ (ppm): 19.7. ^{1}H NMR ($CDCl_3$), δ (ppm): 0.8−1.0 (s, 6H), 1.1−1.3 (b, 3H), 1.3−1.6 (b, 2H), 1.6−1.9 (b, 1H), 2.8−3.1 (b, 2H), 3.4 (s, 3H), 3.5−3.9 (b, 26H), 3.9−4.1(b, 1H), 4.1−4.3 (b, 2H). Elemental analysis (%) calcd: C, 49.79; H, 8.69; N, 7.69. Found: C, 48.23; H, 8.61; N, 8.11.

The other polymers (**5** and **7**) were prepared analogously using different mole ratios and molecular weights of AMPEG.

$[NP(AMPEG550)_{0.74}(IleOEt)_{1.24}(GlyGlycOEt)_{0.02}]_n$ (5). IleOEt (10.4 mmol), GlyGlycOEt (0.4 mmol), and AMPEG 550 (48.3 mmol). Yield: 70%. ^{31}P NMR ($CDCl_3$), δ (ppm): 19.7. Elemental analysis (%) calcd: C, 49.95; H, 8.61; N, 6.46. Found: C, 49.57; H, 8.60; N, 6.99.

$[NP(AMPEG750)_{0.65}(IleOEt)_{1.35}]_n$ (6). IleOEt (24.2 mmol) and AMPEG 750 (24.2 mmol). Yield: 65%. ^{31}P NMR ($CDCl_3$), δ (ppm): 19.0. Elemental analysis (%) calcd: C, 52.01; H, 8.91; N, 5.64. Found: C, 51.32; H, 8.96; N, 6.21.

$[NP(AMPEG750)_{0.64}(IleOEt)_{1.23}(GlyGlycOEt)_{0.13}]_n$ (7). IleOEt (22.5 mmol), GlyGlycOEt (2.6 mmol), and AMPEG 750 (24.2 mmol). Yield: 70%. ^{31}P NMR ($CDCl_3$), δ (ppm): 19.7. Elemental analysis (%) calcd: C, 50.34; H, 8.44; N, 6.77. Found: C, 51.00; H, 8.52; N, 6.90.

$[NP(AMPEG750)_{0.43}(IleOEt)_{1.30}(GlyGlycOEt)_{0.27}]_n$ (8). IleOEt (22.6 mmol), GlyGlycOEt (5.19 mmol), and AMPEG 750 (13.8 mmol). Yield: 65%. ^{31}P NMR ($CDCl_3$), δ (ppm): 19.5.

Instruments and Measurements. All reactions were carried out under an atmosphere of dry nitrogen by using standard Schlenk-line techniques. Elemental analysis was carried out with a Fisons 1108 CHNS Microanalizer and Polyscan 61E ICP. ^{1}H NMR measurements were made with a Varian Gemini-300 spectrometer operating at 300 MHz in the Fourier transform mode. Proton-decoupled ^{31}P NMR spectra were measured with the same spectrometer operating at 121.4 MHz using triphenyl phosphate as an external standard. A higher resolution NMR spectrometer (Varian UI-500) was used for ^{1}H NMR studies on the phase transition behaviors in the range 5−60 °C. Thermal analysis of the polymers was carried out using Dupont DSC 2100 TA Instruments. The sample was heated at a rate of 5 °C/min in the range −100 to 100 °C. Gel permeation chromatography was carried out using a GPC system (Waters 1515) with a refractive index detector (Waters 2410) and two styragel columns (Waters styragel HR 5E) connected in line at a flow rate of 0.8 mL/min at 35 °C. THF containing 0.1 wt % of tetrabutylammonium bromide was used as the solvent. Polystyrenes (M_w: 1140, 3570, 14 100, 28 700, 65 300, 181 000, 613 000, 1 010 000, 2 660 000) were used as standards to calibrate the column. The viscosity of the aqueous solutions of polymers was measured as a function of temperature: Viscosity measurements on polymer solutions were carried out on a Brookfield RVDV-III+ viscometer between 5 and 80 °C with a heating rate of 0.25 °C/min and under a shear rate of 0.07−1.7 s^{-1}.

Results and Discussion

All the polymers were prepared by the synthetic Scheme 1. Poly(dichlorophosphazene) (**I**) dissolved in THF reacted with amino acid ethyl ester and/or GlyGlycOEt to yield the partially substituted polymer (**II**), which then reacted with α-amino-ω-methyl-PEG to give the final polymer products (**III**). Different copolymers were obtained by varying the kinds of amino acid esters, the length of α-amino-ω-methyl-PEG, and the mole ratio of the substituents. The polymer products obtained were characterized by means of multinuclear NMR spectroscopy, GPC, and elemental analysis.

The polymers synthesized are listed in Table 1. These are soluble in cold water as well as in polar organic solvents such as chloroform and THF. The polymers were found to have weight-average molecular weights in the range (2.1−8.6) × 10^4.

The gelation properties of polymers **1**, **2**, and **3** in aqueous solutions (10 wt %) are presented in Table 1. The gelation property of the polymers with a similar mole ratio of amino acid ester was dependent on the structure and hydrophobicity of the amino acids. The more hydrophobic the amino acid esters side groups, the stronger the gelation properties exhibited by the poly-

Table 1. Characteristics of Poly(organophosphazenes)

polymer	structure	T_{ass} (°C)[a]	T_{max} (°C)[b]	T_{lcst} (°C)[c]	V_{max} (Pa·s)[d]	MW[e]
1	$[NP(AMPEG350)_{1.06}(IleOEt)_{0.94}]_n$[f]	11	38	55	28.6	2.1×10^4
2	$[NP(AMPEG350)_{0.99}(LeuOEt)_{1.01}]_n$	10	34	40	26.7	4.2×10^4
3	$[NP(AMPEG350)_{1.00}(ValOEt)_{1.00}]_n$			57		8.6×10^4
4	$[NP(AMPEG350)_{0.92}(IleOEt)_{0.92}(GlyGlycOEt)_{0.07}]_n$	14	39	54	6.7	5.6×10^4
5	$[NP(AMPEG550)_{0.74}(IleOEt)_{1.24}(GlyGlycOEt)_{0.02}]_n$	23	48	75	121.3	2.6×10^4
6	$[NP(AMPEG750)_{0.65}(IleOEt)_{1.35}]_n$	18	56	84	497.5	2.2×10^4
7	$[NP(AMPEG750)_{0.64}(IleOEt)_{1.23}(GlyGlycOEt)_{0.13}]_n$	33	62	87	325.0	2.5×10^4
8	$[NP(AMPEG750)_{0.43}(IleOEt)_{1.30}(GlyGlycOEt)_{0.27}]_n$	8	28	51	747.5	4.2×10^4

[a] The association temperature at which the viscosity of the polymer solutions (10 wt %) begins to increase sharply. [b] The temperature at which the polymer solutions (10 wt %) reach their maximum viscosity. [c] The LCST was identified as the temperature at which the polymer solutions (10 wt %) became turbid. [d] The viscosity of the polymer solutions at T_{max}. [e] The molecular weight of the polymers was measured by GPC using THF solutions containing 0.1% (w/v) TBAB (tetrabutylammonium bromide). [f] Reference 14.

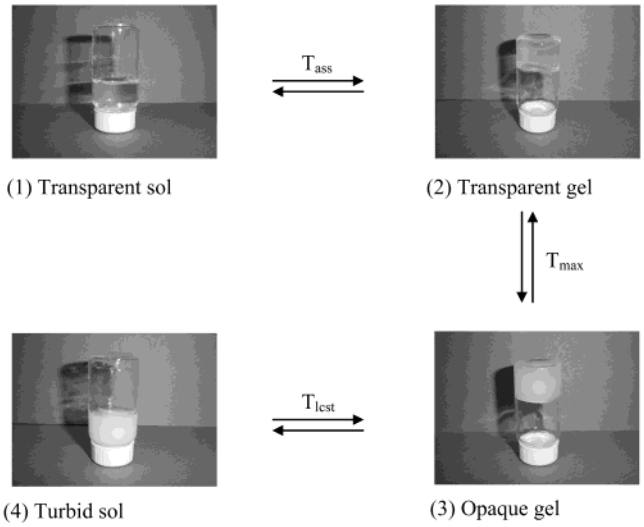


Figure 1. Demonstration photograph of the sol−gel transition of polymer **6** in aqueous solution observed as temperature gradually increased.

mer. For example, polymers **1** with IleOEt (0.94 mol) and **2** with LeuOEt (1.00 mol) increased rapidly in viscosity as the temperature was raised to T_{max}, while polymer **5** with ValOEt (1.00 mol) had no thermothickening property. As shown in Table 1, the T_{ass} and T_{max} values of polymer **1** are 11 and 38 °C, respectively, and those of polymer **2** are 10 and 34 °C, respectively, while the T_{ass} and T_{max} values of polymer **3** were not detected for this composition. The V_{max} values of polymers **1** and **2** are similar at 28.6 and 26.7 Pa·s, respectively. Such results may be related to the fact that Ile and Leu have the same hydrophobicity (0.943) since they bear isomeric leucine groups and that they are more hydrophobic than Val (0.825).[16] On the whole, the higher content of IleOEt and the longer chain length of AMPEG cause the higher viscosity of the polymer gels to rise up: The V_{max} values for polymers **4** (AMPEG350), **5** (AMPEG550), and **7** (AMPEG750) were 6.7, 121.3, and 325.0 Pa·s, respectively. For polymers **7** ($[NP(AMPEG750)_{0.64}(IleOEt)_{1.23}(GlyGlycOEt)_{0.13}]_n$) and **8** ($[NP(AMPEG750)_{0.43}(IleOEt)_{1.30}(GlyGlycOEt)_{0.27}]_n$) with the same side chains but different mole ratios, the higher content of IleOEt and the lower content of AMPEG gave rise to the lower T_{max} and the higher V_{max} value owing to the increase in hydrophobicity. The T_{max} and V_{max} values for polymers **7** and **8** were 62 and 28 °C and 325.0 and 747.5 Pa·s, respectively.

Figure 1 photographically demonstrates the sol−gel transition of the present polymers. Polymer **6** was dissolved in distilled water. Just as it was taken out of the cold chamber at 4 °C, the polymer solution was in a transparent sol state as (1) shows in Figure 1. In contrast to this, 30 min after the temperature jumped from 4 to 56 °C, the polymer solution became a transparent gel state like (2). As the temperature was raised above 56 °C, it became an opaque gel such as (3), and finally a turbid solution like (4) was obtained at 87 °C.

On the basis of the above-mentioned data, we propose a gelation mechanism for the polymer solution. The polymer aqueous solution containing more than the critical concentration may have four distinct phases depending on its temperature. The polymer solution at lower than T_{ass} is clear, and it has a fully expanded coil state in water (phase I). As temperature is raised, the polymer solution becomes more and more viscous and reaches the maximum viscosity at T_{max}, and a transparent gel (phase II) is formed owing to the physical association of the hydrophobic groups of amino acid esters like isoleucine ethyl ester and leucine ethyl ester in pendant groups on the polymer backbone. We presume that the hydrophobic interaction between the side-chain fragments of amino acid esters acts as a physical junction in the aqueous polymer solution, resulting in the formation of hydrogel. The transparent gel becomes an opaque gel (phase III) as temperature is further raised from T_{max}, leading to a subsequently shrunken gel by expelling water, but at higher temperature the gel is broken to become a turbid sol (phase IV).

To study hydrolytic properties of the present thermosensitive polymer gels, polymers **6** and **7** were dissolved in the buffer solutions (10 wt %) of pH 7.4 (10 mM phosphate buffered saline), and they were incubated at 4, 37, and 50 °C for 30 days. Samples were taken every other day and lyophilized. The samples obtained were dissolved in THF, and the molecular weights of the polymer residues were determined by GPC. Figure 2 shows the profiles of the time-dependent molecular weight decrease for polymer **7** in the pH 7.4 buffer solutions at 4, 37, and 50 °C. The rate of hydrolysis of the polymer solution greatly depended on the temperature of the polymer solution. The rate of degradation at different incubation temperature increased in the order of 4 °C < 37 °C ≪ 50 °C. According to the observation, around 9% and 55% of molecular weight losses for polymer **7** have been observed at 37 and at 50 °C, respectively, during the 30 days, while the polymer showed almost no degradation at 4 °C during the same period.

The rates of hydrolytic degradation of the present polymers were affected by the content of the depsipeptide (GlyGlycOEt). Polymer **6** bearing AMPEG750 and IleOEt degraded more slowly than polymers **7** and **8** with AMPEG750, IleOEt, and GlyGlycOEt substituents, as shown in Figure 3. About 9% and 30% molecular

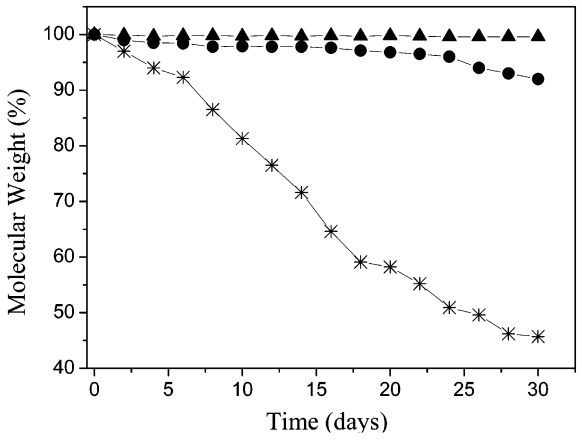


Figure 2. Time-dependent hydrolytic degradation of polymer **7** in 10 mM phosphate buffered saline solution at pH 7.4: 4 °C (▲), 37 °C (●), and 50 °C (*).

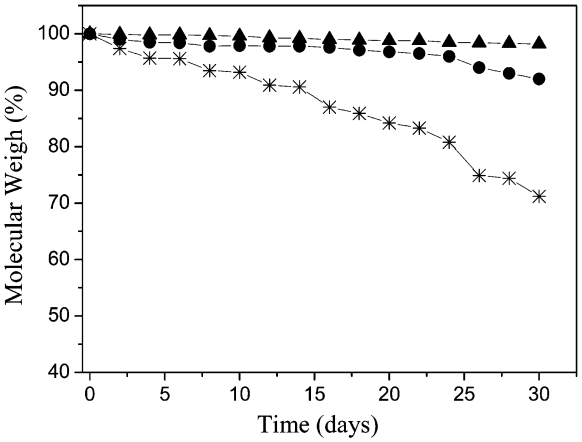


Figure 3. Time-dependent hydrolytic degradation of polymers **6, 7,** and **8** in 10 mM phosphate buffered saline solution at pH 7.4 and 37 °C: polymer **6** (▲), polymer **7** (●), and polymer **8** (*).

weight loss for polymers **7** and **8** were attained at 37 °C, while for polymer **6** (with no depsipeptide) a molecular weight loss of around 2% was observed under the same conditions. It has been reported that depsipeptide ethyl ester is more hydrolytically labile than amino acid esters.[17] The hydrolytic degradation of polyphosphazenes substituted with amino acid esters as side groups can be explained in terms of carboxylic acid-catalyzed degradation.[18]

The degradation rate of the polymer solution was also estimated from the intensity of a sharp resonance appearing in the ^{31}P NMR spectrum at approximately 20 ppm (degradation products: phosphates). As shown in Figure 4, after a 30 day incubation, the ^{31}P NMR spectra of polymer **7** at 4 °C seemed to remain unchanged and somewhat broad while a sharp peak near 20 ppm was observed at both 37 and 50 °C, which seemed to be attributable to degradation products. It was also found that there was significant difference in intensity of the sharp peak in different incubation temperatures of the polymer solutions and that the rate of degradation in polymer solutions increased in the order of 4 ≪ 37 ≪ 50 °C. This result is consistent with the GPC data.

Figure 5 shows the results of viscosity changes in the polymer solutions. Polymers **6** and **7** were dissolved in the buffer solutions (10 wt %) of pH 7.4 (10 mM phosphate buffer). Then they were incubated at 37 °C for 3 days. The viscosity of the polymer was measured over 3 days. The viscosity change of the polymer with GlyGlycOEt was much higher than that of the polymer with no GlyGlyOEt. The orginal viscosity is reduced by 10% for polymer **6** while over a 90% reduction in viscosity was observed for polymer **7.** The viscosity change in the polymer solution in the buffer solution seems to be affected by the rate of polymer degradation. Generally, the polymer with GlyGlycOEt has a more rapid degradation rate; hydrolysis of the polymers generates free carboxylic acid groups and causes the polymers to be more hydrophilic, resulting in the decrease in viscosity. For polyacrylamides, the viscosity loss was attributed to a conformational change of the macromolecules by a cooperative effect of breaking and forming of hydrogen bonds rather than chain degradation as reported in the literature.[19] In the present polyphosphazene gels, it is presumed that this phenomenon may be caused by a hydrophilic−hydrophobic balance change by a cooperative effect of the polymer degradation as well as the hydrogen bonds since they are biodegradable in an aqueous solution. The faster degradation of depsipeptide moieties of the polymers gives rise to free carboxylic acid, resulting in the faster polymer degradation. Thus, the hydrolysis of the polymers generates free carboxylic acid groups, and it seems to cause the viscosity of polymer gels to decrease.

We have examined the pH dependence of the gelation property in acetate buffer solutions of different pHs 3.9, 4.7, 5.4, and 7.4. The results are shown in Figure 6. The gelation property of the present polymer depends greatly on pH. As the pH was decreased, the V_{max} of the polymer greatly decreased and the T_{max} of the polymer increased. The gelation property of the polymer was not detectable at about pH < 4. This phenomenon also seems to be due to a change in hydrophilic−hydrophobic balance

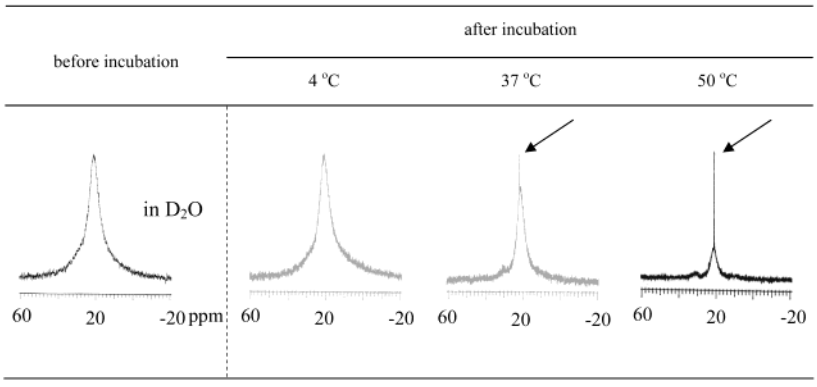


Figure 4. ^{31}P NMR spectra of polymer **7** before and after a 30 day incubation in D_2O (10 wt %).

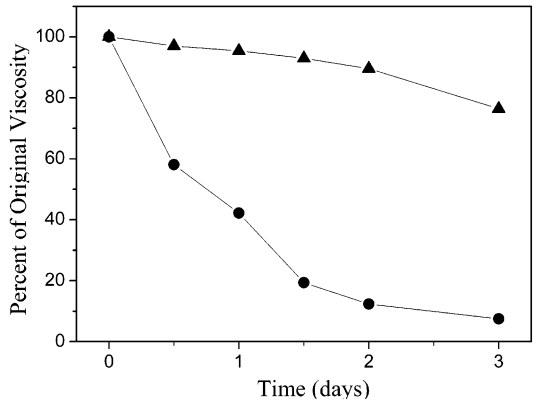


Figure 5. Time-dependent viscosity variation of polymers **6** and **7** in 10 mM phosphate buffered saline solution at pH 7.4 and 37 °C: polymer **6** (▲) and polymer **7** (●).

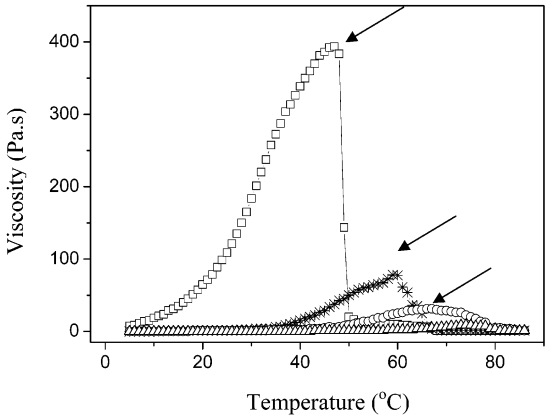


Figure 6. pH-dependent viscosity variation of polymer **6** in acetate buffer solutions of different pHs: 3.9 (△), 4.7 (○), 5.4 (*), and 7.4 (□).

caused by the protonation of the skeletal nitrogen, the amino group of AMPEG, and the amino acid esters linked to the backbone. The degree of ionization of the amino groups in the present polymer is presumed to increase in the acidic buffer solution, which makes the polymer hydrophilic and decreases the intensity of the polymer gel.

In conclusion, the thermosensitive poly(organophosphazenes) bearing AMPEG and some hydrophobic amino acid esters like isoleucine ethyl ester, leucine ethyl ester, and valine ethyl ester and a depsipeptide as side groups have been synthesized and compared in terms of the gelation property. The gelation properties of the polymers depend on several factors such as the composition of substituents, the chain length of AMPEG, type of amino acid esters, and pHs.[11] The present poly(organophosphazenes) showed four-phase transitions such as a transparent sol, a transparent gel, an opaque gel, and a turbid sol, as the temperature increased. The gelation of the polymers seemed to be imparted by the physical cross-linking between the side-chain fragments of amino acid esters in aqueous solutions. The polymers degraded under the physiological condition and their rates of hydrolytic degradation were largely affected by their solution temperature. The polymer with a small amount of glycylglycolate was hydrolyzed faster than that without glycylglycolate. The viscosity changes in the polymer gels are also dependent on their rate of hydrolysis. The present biodegradable thermosensitive poly(organophosphazene) gels showing the sol−gel transition are expected to be useful for applications as injectable drug delivery systems.

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