Polyphosphazenes That Contain Dipeptide Side Groups: Synthesis, Characterization, and Sensitivity to Hydrolysis

Arlin L. Weikel,[†] Nicholas R. Krogman,[†] Nhu Q. Nguyen,[†] Lakshmi S. Nair,[‡] Cato T. Laurencin,[‡,§] and Harry R. Allcock*,[†]

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802, Department of Orthopedic Surgery, University of Connecticut Health Center, Farmington, Connecticut 06030, and Department of Chemical, Materials and Biomolecular Engineering, University of Connecticut, Storrs, Connecticut 06269-3222

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ABSTRACT: The dipeptides alanyl-glycine ethyl ester, valinyl-glycine ethyl ester, and phenylalanyl-glycine ethyl ester were synthesized by mixed anhydride solution-phase peptide reactions. The free N-terminus was used as a reactive site for nucleophilic replacement of the chlorine atoms in poly(dichlorophosphazene). The C-terminus was protected with an ethyl ester to prevent side reactions and cross-linking. The alanyl-glycine ethyl ester replaced all the chlorine atoms in poly(dichlorophosphazene). However, replacement of all the chlorine atoms in poly(dichlorophosphazene) by valinyl-glycine ethyl ester or phenylalanyl-glycine ethyl ester polyphosphazenes was prevented by the insolubility of the partially substituted intermediates. To circumvent this problem, cosubstitution was carried out using the valinyl- or phenylalanyl esters with glycine ethyl ester or alanine ethyl ester in a 1:1 ratio. Cosubstituted polyphosphazenes with alanyl glycine ethyl ester and glycine ethyl ester or alanine ethyl ester were also synthesized with a side group ratio of 1:1. The polymer structures and physical properties were studied using multinuclear NMR, DSC, and GPC techniques. Heterophase hydrolysis experiments in aqueous media at different pH values were carried out to estimate the hydrolytic sensitivity of these polymers. All the polymers were less sensitive to hydrolysis under neutral or basic (pH, 10.0) conditions than at pH 4.0, where rapid hydrolysis occurred.

Introduction

The need for new bioerodible or biostable biomedical materials is a driving force for the development of advanced synthetic macromolecules. Polymeric materials with backbones based on synthetic polypeptides have generated a great deal of interest because new synthetic methods have led to the development of controllable molecular architectures and functionalities that can subsequently be tuned for specific applications.[1−3] These polymers have potential uses as scaffolds for tissue engineering,[4] membranes,[5] surgical adhesives,[6] and antimicrobial materials.[7] However, the insolubility of synthetic polypeptides and their sensitivity to thermal decomposition has limited the usefulness of biomaterials based on these polymers. Thus, the incorporation of peptides into other polymer systems is an alternative approach that might overcome these complications.

Polyphosphazenes are highly tunable via the macromolecular substitution synthetic route that is often employed.[8] This method allows facile changes in the polymer side groups, so that different polyphosphazenes have markedly different properties. Polymers for ionic conduction,[9−11] fire retardance,[12] superhydrophobicity,[13] and various levels of hydrolytic sensitivity[14] have been developed. Hydrolytically sensitive polyphosphazenes have recently received a great deal of attention for applications as biomaterials.[15−18] Hydrolytic sensitivity in a polyphosphazene can be achieved with the use of amino acid ester side groups that are linked to the polymer backbone via the amino terminus. The hydrolytic sensitivity of these polymers is controlled by the molecular structure at the α-carbon of the amino acid[19,20] as well as by cosubstitution with other organic groups along the polyphosphazene backbone.[21] The hydrolytic sensitivity of polyphosphazenes is also pH-dependent. For example, when poly[(ethyl glycinato)$_1$(*p*-methyl phenoxy)$_1$ phosphazene] is blended with poly(lactide-*co*-glycolic acid) (PLGA), the hydrolysis rate of the phosphazene is increased due to the presence of an acid environment created by the hydrolysis of PLGA.[22] The amino terminus of peptides can also be used for chlorine replacement with poly(dichlorophosphazene).

In this study, we have synthesized three dipeptide ethyl esters to give alanyl-glycine ethyl ester, valinyl-glycine ethyl ester, and phenylalanyl-glycine ethyl ester, and these have been linked to the polyphosphazene chain together with glycine or alanine ethyl ester cosubstituents to yield new bioerodible polymers. Heterophase, pH-dependent hydrolysis experiments of these polymer derivatives were carried out with the use of buffered aqueous media at pH 4.0, pH 7.0, and pH 10.0.

Experimental Section

Reagents and Equipment. All synthetic reactions were carried out under a dry argon atmosphere using standard Schlenk line techniques. Tetrahydrofuran and triethylamine (EMD) were dried using solvent purification columns.[23] Chloroform (EMD), isobutyl chloroformate (Aldrich), Boc-phenylalanine, Boc-valine, Boc-alanine (Aroz Technologies), alanine ethyl ester hydrochloride (Chem Impex), and glycine ethyl ester hydrochloride (Alfa Aesar) were used as received. Poly(dichlorophosphazene) was prepared by the thermal ring-opening polymerization of recrystallized and sublimed hexachlorocyclotriphosphazene (Fushimi Chemical Co. Japan) in evacuated Pyrex tubes at 250 °C. ^{31}P and ^{1}H NMR spectra were obtained with use of a Bruker 360 WM instrument operated at 145 and 360 MHz, respectively. Glass transition temperatures were measured with a TA Instruments Q10 differential scanning calorimetry apparatus with a heating rate of 10 °C/min and a sample size of ca. 10 mg. Gel permeation chromatograms were obtained using a Hewlett-Packard HP 1100 gel permeation chromatograph equipped with two Phenomenex Phenogel linear 10 columns and a

* Corresponding author. E-mail: hra@chem.psu.edu.
† Department of Chemistry, The Pennsylvania State University.
‡ Department of Orthopedic Surgery, University of Connecticut Health Center.
§ Department of Chemical, Materials and Biomolecular Engineering, University of Connecticut.

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Hewlett-Packard 1047A refractive index detector. The samples were eluted at 1.0 mL/min with a 10 mM solution of tetra-*n*-butylammonium nitrate in THF. The elution times were calibrated with polystyrene standards.

Synthesis of Boc-alanyl-glycine Ethyl Ester. This compound was synthesized by a modification of a published procedure.[24] Specifically, triethylamine was used as a base in place of *N*-methylmorpholine, and the purification procedure was modified. Chloroform (135 mL) was cooled to −15 °C, then Boc-alanine (25.0 g, 132 mmol) and triethylamine (36.8 mL, 264 mmol) were added sequentially. This mixture was stirred at 15 °C for five minutes before the addition of isobutyl chloroformate (IBCF) (17.23 g, 132 mmol). The mixture was then stirred at −15 °C for 2 min, followed by the addition of glycine ethyl ester hydrochloride (18.5 g, 132 mmol). The reaction mixture was stirred for 4 h at −15 °C, and then allowed to warm slowly to room temperature, while stirred overnight. The solvent was removed under reduced pressure and an oily residue remained. The residue was dissolved in ethyl acetate and was washed sequentially with deionized water, 20% citric acid (aq), deionized water, saturated sodium bicarbonate, and deionized water. The organic layer was dried with magnesium sulfate and the solvent was removed under reduced pressure, to yield a viscous oil. The yield was approximately 80%. ^{1}H NMR (D_2O), ppm: δ 1.16 (t, 3H, CH_3), 1.34 (m, 12H, CH_3), 3.80 (m, 4H, CH_2), 4.04 (q, 1H, CH). m/z = 275.

Synthesis of Boc-valinyl-glycine Ethyl Ester. The synthesis of this dipeptide follows the procedure used for Boc-alanyl-glycine ethyl ester dipeptide. ^{1}H NMR (D_2O), ppm: δ 0.87 (d, 3H, CH_3), 0.90 (d, 3H, CH_3), 1.21 (t, 3H, CH_3), 1.38 (s, 9H, CH_3), 2.10 (m, 1H, CH), 3.96 (m, 4H, CH_2), 4.13 (q, 1H, CH). m/z = 292. The yields were typically 82%.

Synthesis of Boc-phenylalanyl-glycine Ethyl Ester. The synthesis of this dipeptide follows the procedure used for Boc-alanyl-glycine ethyl ester dipeptide. ^{1}H NMR (D_2O), ppm: δ 1.20 (t, 3H, CH_3), 1.38 (s, 9H, CH_3), 2.98 (d, 2H, CH_2), 3.82 (m, 4H, CH_2), 4.86 (t, 1H, CH), 7.05 (m, 5H, aromatic). m/z = 350. The yields were typically 85%.

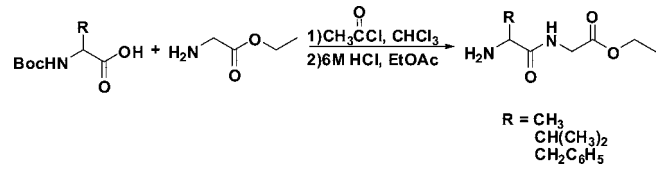
Deprotection of Boc-alanyl-glycine Ethyl Ester.[25] Boc-alanyl glycine ethyl ester (48.0 g, 0.221 mol) was dissolved in 200 mL of ethyl acetate, and 100 mL of 6 M HCl in ethyl acetate were added to this solution. The solution was stirred for 4 h at room temperature. The solvent was removed under reduced pressure and an adhesive oil remained. The oil was triturated with diethyl ether and was dried under reduced pressure. The final product was recovered as a white, crystalline product. The final yield was 87%. ^{1}H NMR (D_2O), ppm: δ 1.02 (d, 3H, CH_3), 1.12 (t, 3H, CH_3), 3.40 (q, 1H, CH), 3.92 (s, 2H, CH_2), 4.03 (q, 2H, CH_2). m/z = 162.

Deprotection of Boc-valinyl-glycine Ethyl Ester. ^{1}H NMR (D_2O), ppm: δ 0.89 (d, 6H, CH_3), 1.10 (t, 3H, CH_3), 2.09 (m, 1H, CH), 3.69 (d, 1H, CH), 4.05 (m, 4H, CH_2). m/z = 190. The yield was 83%.

Deprotection of Boc-phenylalanyl-glycine Ethyl Ester. ^{1}H NMR (D_2O), ppm: δ 1.12 (t, 3H, CH_3), 2.90 (d, 2H, CH_2), 3.80 (m, 1H, CH), 3.90 (m, 4H, CH_2), 7.12 (m, 5H, aromatic). m/z = 238. The yield was 85%.

Synthesis of Cyclic Trimers 2−4. The synthesis of the model compound cyclic trimers **2**−**4** followed similar procedures. The synthesis of **4** is given as a representative example. Hexachlorocyclotriphosphazene (1.00 g, 2.88 mmol) was dissolved in toluene (100 mL). Phenylalanyl glycine ethyl ester hydrochloride (8.25 g, 28.8 mmol) and triethylamine (10.0 mL, 71.9 mmol) were added to the solution. The mixture was stirred at room temperature for 24 h. ^{31}P NMR spectroscopy detected some degree of substitution: however complete chlorine replacement was not achieved. Therefore, the solution was refluxed for 24 h. The absence of a ^{31}P NMR signal indicated that the product had precipitated from solution. The recovered precipitate was insoluble and no further characterization was attempted. The cyclic trimers **2** and **3** also had some degree of substitution after mixing at room temperature, but the products became insoluble after reflux.

Scheme 1. Synthesis of the Boc-Protected Dipeptides Alanyl-glycine Ethyl Ester, Valinyl-glycine Ethyl Ester, and Phenylalanyl-glycine Ethyl Ester[a]



[a] The N-terminus was then deprotected under acidic conditions to yield the free amino dipeptides.

Synthesis of Polymer 6. Poly(dichlorophosphazene) (2.00 g, 17.3 mmol) was dissolved in THF (200 mL). Alanyl-glycine ethyl ester hydrochloride (8.18 g, 36.2 mmol) was suspended in 200 mL of THF, and triethylamine (12.1 mL, 86.5 mmol) was added. This suspension was refluxed for 24 h, and then filtered and added to the polymer solution. The resultant solution was stirred at room temperature for 24 h, and then refluxed for 48 h. The solvent was removed under reduced pressure to yield a yellow solid. This was dialyzed against ethanol for 3 days. The yield was 73% based on the amount of poly(dichlorophosphazene) used.

Synthesis of Polymers 7−12. Polymers **7**−**12** were synthesized using similar procedures. Polymer **7** is described as a representative example. Poly(dichlorophosphazene) (2.00 g, 17.3 mmol) was dissolved in 200 mL of THF. Alanyl-glycine ethyl ester hydrochloride (3.90 g, 17.3 mmol) was suspended in 150 mL of THF, and triethylamine (7.23 mL, 51.9 mmol) was added. This suspension was refluxed for 24 h, then filtered and added to the polymer solution. Glycine ethyl ester hydrochloride (7.25 g, 51.9 mmol) was suspended in 150 mL of THF and triethylamine (24.1 mL, 173 mmol) was added. This suspension was refluxed for 24 h, then filtered and added dropwise to the polymer solution, which was then stirred at room temperature for 24 h, and refluxed for a further 48 h. The solvent was removed under reduced pressure to yield a yellow solid. The polymer was purified by dialysis versus methanol for 3 days. Yields were in the range of 70−80%.

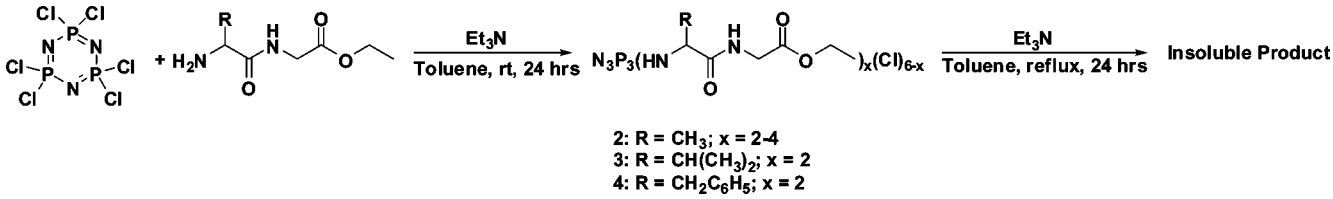
Controlled pH Hydrolysis Studies. Polymers **6**−**12** were dissolved in chloroform (100 mg/1 mL) and were solution cast into films. These were air-dried for 24 h and then vacuum-dried for another seven days. The dried films were cut into squares (10 mm × 10 mm) and placed in specific pH buffered aqueous media. Aqueous media with pH 4.0, 7.0, and 10.0 were used. Three samples were removed from each medium after 1, 2, 3, and 4 weeks to measure weight loss. The pH of each hydrolysis medium was monitored throughout the study. GPC analysis of the polymers during the hydrolysis was precluded by the insolubility of the polymers in THF after hydrolysis was initiated.

Results and Discussion

Synthesis of Alanyl-glycine Ethyl Ester, Valinyl-glycine Ethyl Ester, and Phenylalanyl-glycine Ethyl Ester. The mixed anhydride solution-phase synthetic route was utilized for the synthesis of alanyl glycine ethyl ester, valinyl glycine ethyl ester, and phenylalanyl glycine ethyl ester.[24,25] Isobutyl chloroformate was chosen to synthesize the mixed anhydride. The appropriate Boc-protected amino acid and glycine ethyl ester were added in stoichiometric amounts to form the protected N-terminus dipeptide. Deprotection of the N-terminus yielded the desired dipeptide ethyl ester. The complete synthesis of the dipeptides is outlined in Scheme 1. Proton NMR techniques confirmed the removal of the Boc-protection group by the disappearance of the proton shift at approximately 1.3 ppm for all dipeptides. Mass spectrometry characterization confirmed the final mass of the dipeptides with free amino termini.

Synthesis of Model Cyclic Trimers 2−4. Small molecule model reactions were attempted with the use of hexachlorocy-

Scheme 2. Synthesis of Dipeptide Substituted Cyclic Trimers 2−4



Scheme 3. Synthesis of Dipeptide Substituted Polyphosphazenes 6−12

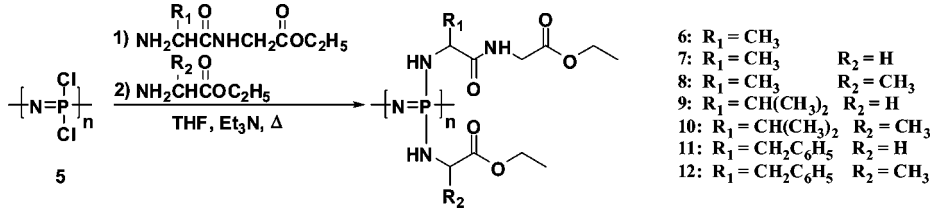


Table 1. Structural and Physical Properties of Polymers 6−12

polymer	^{31}P NMR (ppm)	^{1}H NMR (ppm)	T_g (°C)	M_w (g/mol)
6	−0.8	0.8 (6H), 1.2 (6H), 3.0 (2H), 4.1 (8H)	28.2	198 000
7	−3.8	1.2 (9H), 3.7 (1H), 4.1 (8H)	23.4	165 000
8	−2.8	1.4 (12H), 3.2 (2H), 4.7 (6H)	25.2	178 000
9	−1.2	1.2 (6H), 1.3 (6H), 1.8 (1H), 3.1 (1H), 3.6 (2H), 3.8 (2H), 4.1 (4H)	29.8	231 000
10	−2.2	1.2 (6H), 1.4 (9H), 1.8 (1H), 3.1 (1H), 3.6 (1H), 3.9 (2H), 4.1 (4H)	36.9	220 000
11	−3.1	1.2 (6H), 3.2 (2H), 4.1 (1H), 4.2 (4H), 4.4 (4H), 7.3 (5H)	31.5	242 000
12	−1.1	1.3 (9H), 3.3 (1H), 4.0 (2H), 4. two (4H), 4.3 (3H), 7.1 (5H)	43.7	261 000

clotriphosphazene (**1**). A stoichiometric excess of each dipeptide ethyl ester was added to a solution of (**1**) in toluene or THF in the presence of excess triethylamine, as described in Scheme 2. The reaction mixture was stirred at room temperature for 24 h. The ^{31}P NMR spectra revealed that the unexpected geminal disubstituted cyclic trimer was formed with valinyl glycine ethyl ester (**3**) or phenylalanyl glycine ethyl (**4**) substituents. The cyclic trimeric species partially substituted with the alanyl glycine ethyl ester (**2**) reacted with (**1**) to form a mixture of products including those formed by geminal disubstitution to tetra-substitution. However, by the time the reaction mixtures had been heated at reflux for 24 h, the products had precipitated from solution as incompletely substituted species. These experiments revealed that some chlorine replacement did occur at the small molecule model level, but that the degree of substitution depended on the dipeptide ethyl ester that was used. This information was used as a basis to plan the substitution reactions of poly(dichlorophosphazene) with the dipeptide ethyl esters.

Synthesis of Polymers 6−12. Initial attempts to synthesize polyphosphazenes that contained only valinyl-glycine ethyl ester or phenylalanyl-glycine ethyl ester as side groups were unsuccessful. Approximately 50% of the chlorine atoms were replaced after 24 h at room temperature, as indicated by ^{31}P NMR spectra. These partly substituted polymers precipitated from a refluxing solution in THF. Subsequent syntheses of polymers with valinyl-glycine ethyl ester or phenylalanyl-glycine ethyl ester side groups were therefore carried out after half the chlorine atoms in poly(dichlorophosphazene) had been replaced by the dipeptide, followed by the replacement of the remaining chlorine atoms by glycine ethyl ester or alanine ethyl ester to yield polymers **9**−**12**. The synthesis of polymers **9**−**12** is described in Scheme 3. Polymers **9**−**12** were yellow, brittle solids that were soluble in THF, chloroform, and methanol.

Alanyl-glycine ethyl ester was the only dipeptide ethyl ester able to replace 100% of the chlorine atoms in poly(dichlorophosphazene) while remaining soluble in THF during the synthesis process (polymer **6**). Two polyphosphazenes were also cosubstituted with both alanyl-glycine ethyl ester and glycine ethyl ester or alanine ethyl ester in a 1:1 ratio (polymers **7** and **8**). Polymers **6**−**8** were isolated as yellow, brittle solids that were soluble in the same solvents as polymers **9**−**12**.

Molecular characterization of all the polymers was by multinuclear NMR and IR spectroscopy, as shown in Table 1. ^{31}P NMR experiments suggested that complete replacement of all the chlorine atoms had occurred. It is known that polyphosphazenes that have 100% dipeptide and/or amino acid ester side groups give a broad ^{31}P NMR signal at approximately 0 ppm. ^{1}H NMR shifts were used to determine the percentages of substitution for each side group. For polymers **6**−**12**, a 1:1 ratio was attempted and each polymer was within 3% of the target ratio. The infrared spectra of polymers **6**−**12** were used to confirm the side group and polymer backbone structural characteristics. The P−N bonds were evident from absorbances at 1214 cm^{-1}, C═O bonds were obvious at 1738 cm^{-1}, and N−H bonds showed stretching modes at 3200 cm^{-1}.

Thermal Characterization of Polymers 6−12. The glass transition temperatures (T_g) for polymers **6**−**12** are shown in Table 1. Polymer **12** has the highest T_g at 43.7 °C. For comparison, poly[bis(ethyl phenylalanato)phosphazene] has a T_g of 68 °C.[19] The presence of glycine ethyl ester as the cosubstituent together with phenylalanyl-glycine ethyl ester (polymer **11**) causes a small T_g decrease, presumably because of the lower steric hindrance characteristics of the glycine unit. A similar trend exists for polymers **7** and **8**, and polymers **9** and **10**. The T_g decreased as the size of the α-carbon substituent decreased from an isopropyl function to the methyl group of the dipeptide ethyl ester. Polymer **6** is unique because this polymer contains 100% of the dipeptide ethyl ester and the T_g of 28.2 °C is higher than for polymers **7** and **8**. This could be a consequence of stronger hydrogen bonding within the amide linkage of the dipeptide, which would cause additional restriction of the polymer backbone tensional mobility.

Heterophase Hydrolysis of Polymers 6−12 under Different pH Conditions. The weight loss of films immersed in pH 4, 7, and 10 aqueous media was used as a preliminary

criterion of hydrolytic stability, and this was followed by an analysis of molecular weight changes. At pH 4, the molecular weight of polymers **6**−**8** declined drastically within one week due to the high acidity and lack of steric bulk at the α-carbon that helps to retard hydrolysis. The introduction of steric hindrance via the isopropyl and phenyl group in polymers **9**−**12** retarded the hydrolysis in this acidic environment, resulting in weight losses of 67% for polymer **9**, 55% for polymer **10**, 35% for polymer **11**, and 32% for polymer **12** during the 4 weeks of hydrolysis.

The pH 7 data provide a preliminary estimate of the hydrolysis behavior of these polymers if implanted in mammals. At pH 7, the heterophase hydrolysis rates were slower than the rates at pH 4. Polymers **6**−**8** had 90% weight loss during the 4 weeks of hydrolysis. Polymers **9**, **10**, **11**, and **12** lost 67%, 50%, 20%, and 5% weight respectively during the same period of hydrolysis. At pH 10, polymers **6**−**8** lost 75% of their weight during the 4 weeks of hydrolysis. Once again, the steric bulk in the valine- and phenylalanine ethyl ester side groups retards the hydrolysis of polymers **9**, **10**, **11**, and **12** resulting in weight losses of 40%, 20%, 19%, and 14% respectively. Overall, the rates of hydrolysis for polymers **6**−**12** decrease as the pH increases from 4 to 10. This reduction in the rate of hydrolysis as the pH increases is due to the loss of protons that help to increase the rate of hydrolysis. All of the dipeptide polymers hydrolyzed slower than their amino acid counterparts at neutral pH 7.

The differences in hydrolytic stability reflect the influence of several different factors associated with the dipeptide and amino acid side groups. The presence of the phenyl- and isopropyl groups on the α-carbon in the phenylalanine and valine dipeptide residues provide steric hinderence that blocks hydrolytic access to the polymer backbone and results in retardation of the rate of hydrolysis compared to the alanine dipeptide. Furthermore, for polymers **7**−**12** the steric hindrance of the cosubstituent glycine- or alanine ethyl ester helps to control the rate of hydrolysis associated with the alanine cosubstituent, and provides a 5−20% retardation in hydrolysis compared to when glycine is the cosubstituent. One conclusion is clear, fine-tuning of the substituent ratios has the potential to allow control of the hydrolysis behavior to satisfy the diverse properties needed for different biomedical applications such as in tissue engineering and controlled drug release. Moreover, the potential exists for further control of both physical properties and hydrolysis behavior through the formation of composites of these polymers with other biomedical polymers such as poly(lactic-*co*-glycolic acid) or polycaprolactone.

Conclusions

Polyphosphazenes that contain the side groups alanyl-glycine ethyl ester, valinyl-glycine ethyl ester, and phenylalanyl-glycine ethyl ester with the cosubstituents glycine ethyl ester or alanine ethyl ester were synthesized. After deprotection of the N-terminus, the dipeptides were used for nucleophilic replacement of the chlorine atoms in poly(dichlorophosphazene). The final polymeric products were characterized structurally by multinuclear NMR techniques, and by GPC. Glass transitions were identified by DSC. The pH-dependent heterophase hydrolyses of polymers **6**−**12** were analyzed and showed that aqueous acidic pH media cause rapid hydrolysis. As the medium becomes more alkaline, the polymers are more stable. The weight loss and hydrolysis behavior of the polymers reflect both the hydrophobicity and the steric protection provided by the group on the α-carbon atom of the amino acid esters. Thus, alanine-linked units hydrolyzed more rapidly than the valine-based species, which degraded faster than the phenylalanine-substituted polyphosphazenes.

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