Macromolecules

Volume 27, Number 5 Feburary 28, 1994

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Poly[(amino acid ester)phosphazenes]: Synthesis, Crystallinity, and Hydrolytic Sensitivity in Solution and the Solid State

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Received May 18, 1993; Revised Manuscript Received September 9, 1993[⊕]

ABSTRACT: Fifteen different poly[(amino acid ester)phosphazenes] were synthesized to study their crystalline character and hydrolysis behavior in the solution and solid states. The polyphosphazenes synthesized were poly[bis(methyl glycinat-*N*-yl)phosphazene], poly[bis(ethyl glycinat-*N*-yl)phosphazene], poly[bis(*tert*-butyl glycinat-*N*-yl)phosphazene], poly[bis(benzyl glycinat-*N*-yl)phosphazene], poly[bis(methyl alaninat-*N*-yl)phosphazene], poly[bis(ethyl alaninat-*N*-yl)phosphazene], poly[bis(*tert*-butyl alaninat-*N*-yl)phosphazene], poly[bis(benzyl alaninat-*N*-yl)phosphazene], poly[bis(methyl valinat-*N*-yl)phosphazene], poly[bis(ethyl valinat-*N*-yl)phosphazene], poly[bis(*tert*-butyl valinat-*N*-yl)phosphazene], poly[bis(benzyl valinat-*N*-yl)phosphazene], poly[bis(methyl phenylalaninat-*N*-yl)phosphazene], poly[bis(ethyl phenylalaninat-*N*-yl)phosphazene], and poly[bis(*tert*-butyl phenylalaninat-*N*-yl)phosphazene]. The fully-substituted polymers were obtained by treatment of poly(dichlorophosphazene) with a large excess of the appropriate amino acid ester. Several of these polymers were crystalline as measured by differential scanning calorimetry and by polarized optical microscopy. Hydrolysis studies were performed to estimate the rates of decomposition of the polymers and the duration over which the polymers maintained their structural integrity. The polymers are potential biomedical materials.

Introduction

Hydrolytically-sensitive polymers are used in several areas of medical science.[1-3] Two well-known applications are as absorbable suturing materials and as substrates for the controlled release of drugs.[2,4] The critical requirements for bioerodible polymers are that (1) they should hydrolyze at an appropriate rate to allow wound healing or drug delivery and (2) their degradation products must be nontoxic. At present, poly(lactic acid), poly(glycolic acid), and their copolymers are widely used for this purpose.[2] Polyanhydrides are also used as drug delivery vehicles.[1]

In an attempt to better control the rates of bioerosion and polymer physical properties, we have designed and synthesized several bioerodible systems using a relatively new class of macromolecules, the poly(organophosphazenes). Poly(organophosphazenes) are high molecular weight polymers with a backbone of alternating phosphorus and nitrogen atoms. Each phosphorus atom bears two organic side groups. The use of poly(dichlorophosphazene) (1) as a macromolecular intermediate for nucleophilic substitution reactions allows a broad range of organic side groups to be linked to the polymer chain. By the use of this technique, we have "tailored" polyphosphazenes to possess a wide variety of physical and chemical properties.[5]

Several different poly(organophosphazenes) have been shown to be hydrolytically sensitive.[4,6-9] One of the first hydrolyzable polyphosphazenes discovered in our laboratory was poly[bis(ethyl glycinat-*N*-yl)phosphazene] (**3**).[6] In the present study, the methyl, ethyl, *tert*-butyl, and benzyl ester derivatives of glycine, alanine, valine, and phenylalanine were used as reagents to generate a new series of hydrolytically-sensitive poly(organophosphazenes). These polymers are shown in Scheme 1.

Polymers **2–16** were designed and synthesized with the expectation that they would hydrolyze in contact with water, in a manner similar to poly[bis(ethyl glycinat-*N*-yl)phosphazene] (**3**) but with different hydrolysis rates.[6] The hydrolysis products of polymer **3** are ethanol, glycine, phosphates, and ammonia, which should be nontoxic.[6] Degradation of polymers **2–16** would yield methanol,

⊕ Abstract published in *Advance ACS Abstracts*, January 15, 1994.

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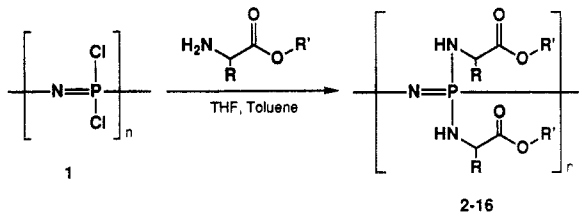
Scheme 1



2. R= H R'= Me
3. R= H R'= Et
4. R= H R'= ^{t}Bu
5. R= H R'= Bz
6. R= Me R'= Me
7. R= Me R'= Et
8. R= Me R'= ^{t}Bu
9. R= Me R'= Bz
10. R= ^{i}Pr R'= Me
11. R= ^{i}Pr R'= Et
12. R= ^{i}Pr R'= ^{t}Bu
13. R= ^{i}Pr R'= Bz
14. R= Bz R'= Me
15. R= Bz R'= Et
16. R= Bz R'= ^{t}Bu

ethanol, *tert*-butyl alcohol, or benzyl alcohol; glycine, alanine, valine, or phenylalanine; phosphates; and ammonia. With the exception of methanol and *tert*-butyl alcohol, these products are also nontoxic. Hydrolysis products that would be toxic at high concentrations (such as ammonia) should be released in such low concentrations that harmful side effects would be negligible.

During this investigation, we have attempted to answer the following questions: (1) Can fully organo-substituted phosphazene polymers of structures **2–16** be obtained? (2) Are any of these solid polymeric materials strengthened by microcrystallinity? (3) By what reaction routes do the polymers hydrolyze? (4) What are the relative rates of hydrolytic degradation for polymers **2–16**? (5) Can the hydrolysis behavior be controlled by rational changes in macromolecular or materials structure?

Results and Discussion

Synthesis of Polymers 2–16. In each of these syntheses, poly(dichlorophosphazene) (1) was allowed to react with a large excess of the appropriate amino acid ester. A general synthetic route to the polymers is shown in Scheme 1.

Precautions were taken during isolation and purification of these products to avoid exposure of the polymers to water to prevent hydrolysis before characterization. The solid polymers were stored under vacuum. In solution, they were maintained under a stream of dry nitrogen. Characterization data are shown in Tables 1 and 2. The physical character of the polymers varied from flexible solids (**2–4**) through tough, leathery materials (**5–9**) to brittle glasses (**10–16**). All the polymers formed good films when solvent cast from tetrahydrofuran (THF).

Crystallinity in Polymers 2–16. Microcrystallinity and the resultant materials strength are useful properties for polymers designed for structural medical applications such as in sutures. Crystallinity in polymers **2–16** was studied by differential scanning calorimetry (DSC) and hot stage polarized optical microscopy.

By DSC analyses, it was found that polymers **5**, **6**, **8**, **9**, and **15** possessed a melting transition. This transition was represented by a peak at a considerably higher temperature than the glass trasition temperature (T_g) for each of the polymers (see Table 1). However, when the temperature was increased by an additional 10–20 °C above the melting point, each of these polymers showed evidence of decomposition as seen by the extremely complex thermogram at temperatures above the melting transition. Polymers **5**, **6**, **8**, **9**, **14**, and **15** showed optical birefringence when observed by cross-polarized optical microscopy. The other polymers showed no optical birefringence. Finally, hot stage microscopy was used to follow the physical changes of polymers **2–16** during heating. Polymers **5**, **6**, **8**, **9**, and **15** were the only materials which appeared to possess distinct melting transitions. The other polymers softened above their glass transition temperatures and showed evidence of decomposition at temperatures in the range of 120–197 °C. Those polymers that underwent a clean melting phase transition did so at temperatures that corresponded well to those measured from the DSC plots (see Table 1). The hot stage microscopy data are shown in Table 3. The indications of instability of these polymers at temperatures above their melting points suggested that solution fabrication rather than melt fabrication techniques would probably be appropriate.

Table 1. Characterization Data for Polymers 2–16

polymer	^{31}P NMR (ppm)	^{1}H NMR (ppm)	^{13}C NMR (ppm)	M_2	T_g (T_m) (°C)
2	0.8	4.4 (2H) 3.6 (3H)	175, 69, 49	1.9×10^5	−24
3	1.5	4.3 (2H) 3.7 (2H) 1.4 (3H)	176, 65, 60, 26	1.8×10^5	−40
4	0.9	4.2 (2H) 1.4 (9H)	178, 91, 48, 33	3.2×10^5	−5
5	2.1	7.6 (5H) 5.3 (2H) 4.2 (2H)	177, 156, 139, 138, 137, 77, 60	9.0×10^5	53 (234)
6	0.5	4.1 (1H) 3.7 (3H) 1.4 (3H)	171, 80, 67, 18	3.3×10^5	33 (248)
7	−1.1	4.4 (1H) 4.1 (2H) 1.6 (3H) 1.3 (3H)	177, 81, 59, 28, 26	1.7×10^5	19
8	−1.5	4.1 (1H) 1.5 (12H)	179, 94, 58, 38, 26	2.6×10^5	36 (154)
9	−1.4	7.3 (5H) 5.2 (2H) 4.6 (1H) 1.4 (3H)	177, 145, 137, 136, 135, 76, 69, 27	3.1×10^5	58 (207)
10	2.0	4.0 (1H) 3.8 (3H) 2.3 (1H) 1.2 (6H)	171, 77, 63, 30, 19, 17	2.7×10^5	87
11	2.1	4.3 (3H) 2.6 (1H) 1.1 (9H)	180, 77, 68, 40, 29, 22	0.8×10^5	56
12	−1.8	4.0 (1H) 2.3 (1H) 1.6 (15H)	175, 88, 68, 41, 37, 27	1.7×10^6	115
13	−1.3	7.7 (5H) 5.4 (2H) 4.6 (1H) 2.6 (1H) 1.1 (6H)	176, 145, 137, 133, 80, 68, 40, 27	5.9×10^5	124
14	−0.2	7.4 (5H) 4.8 (1H) 4.3 (2H) 3.6 (3H)	172, 135, 130, 128, 127, 61, 52, 35	3.1×10^5	98
15	0.0	7.6 (5H) 4.7 (1H) 4.4. (2H) 4.1 (2H) 1.2 (3H)	178, 144, 140, 139, 138, 136, 72, 68, 45, 23	2.2×10^5	68 (158)
16	−0.8	7.3 (5H) 3.6 (2H) 1.5 (9H)	117, 146, 140, 140, 138, 96, 63, 47, 37	2.1×10^5	115

Table 2. Elemental Microanalytical Data for Polymers 2–16

polymer		% C	% H	% N	% Cl[a]
2	calcd	32.58	5.43	19.00	
	found	32.86	5.38	18.72	0.05
3	calcd	38.55	6.43	16.87	
	found	38.43	6.56	16.90	0.12
4	calcd	47.21	7.21	13.77	
	found	47.18	7.25	13.85	0.08
5	calcd	57.91	5.36	11.26	
	found	58.02	5.32	11.22	0.15
6	calcd	38.55	6.43	16.87	
	found	38.62	6.48	16.77	0.11
7	calcd	43.32	7.21	15.16	
	found	43.41	7.30	15.26	0.28
8	calcd	50.45	7.80	12.61	
	found	50.39	7.68	12.68	0.30
9	calcd	59.85	5.99	10.47	
	found	60.03	5.93	10.53	0.26
10	calcd	47.21	7.87	13.77	
	found	47.12	7.93	13.88	0.34
11	calcd	49.56	8.26	12.39	
	found	49.66	8.18	12.44	0.36
12	calcd	55.53	9.77	10.80	
	found	55.65	9.85	11.02	0.42
13	calcd	63.02	7.00	9.19	
	found	62.89	6.87	9.43	0.40
14	calcd	59.85	5.99	10.47	
	found	59.79	6.09	10.60	0.51
15	calcd	61.54	6.06	9.79	
	found	61.62	5.97	9.85	0.42
16	calcd	64.32	7.01	8.66	
	found	64.50	6.88	8.79	0.56

[a] The residual chlorine was attributed to small amounts of hydrogen chloride on the polymer backbone, a common problem with aminophosphazene synthesis.

Table 3. Thermal Transitions of Polymers 2–16[a] (in °C)

polymer	T_m[b]	T_d[c]
2		120
3		131
4		157
5	230	243
6	239	255
7		136
8	167	178
9	205	211
10		150
11		167
12		173
13		186
14		197
15	173	185
16		182

[a] All measurements were obtained with a Fisher-Johns melting point apparatus with a heating stage and magnifying lens. [b] T_m = melting temperature, the temperature at which the polymer first became fluid. [c] T_d = decomposition temperature, the temperature at which the polymer first darkened in color.

No predictable trends were discerned in the crystalline or noncrystalline character of these polymers. Only the valinato series of polyphosphazenes (**10–13**) contained no examples that were crystalline. This could be due to the presence of the isopropyl substituent on the α-carbon of the amino acid ester. Although the valinato side group probably restricts polymer backbone motion (all the glass transition temperatures within this series are high), the isopropyl group may still be sufficiently disordered to prevent alignment of the side groups. Polymers **6**, **8**, and **9** all possess the alaninato amino acid ester as the main side group structure. The methyl group on the α-carbon of these species may be sufficiently compact to allow ordering of the ester groups of the side units. Polymer **7**, which also possesses the alaninato amino acid unit, showed no crystallinity, possibly due to the presence of the ethyl ester group, which would provide more side group flexibility than the methyl, *tert*-butyl, or benzyl groups.

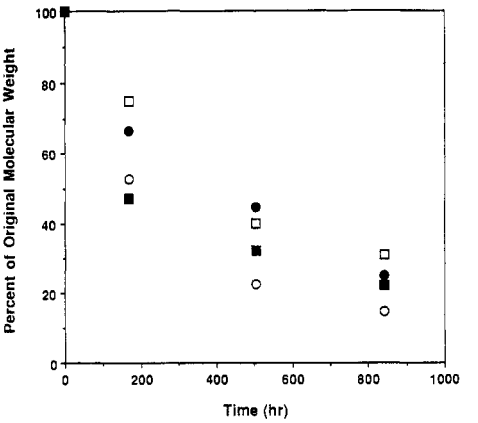


Figure 1. Percentage molecular weight decline during solution-state hydrolysis of poly[(glycinato ester)phosphazenes] (**2–5**): (○) poly[bis(methyl glycinat-*N*-yl)phosphazene] (**2**); (●) poly[bis(ethyl glycinat-*N*-yl)phosphazene] (**3**); (□) poly[bis(*tert*-butyl glycinat-*N*-yl)phosphazene (**4**); (■) poly[bis(benzyl glycinat-*N*-yl)phosphazene] (**5**).

Hydrolysis Studies of Polymers 2–16. The hydrolytic decomposition of the polymers was studied by two independent methods. The first procedure involved solution reactions, in which a dilute solution of the polymer in THF was treated with a small amount of water (3.9% v/v). Gel permeation (size exclusion) chromatograms of the solutions were then obtained at intervals over a period of 5 weeks. The second method involved immersion of solid polymer samples in deionized water during a 7-week period. The polymers were then dissolved in THF and monitored for molecular weight decline by GPC analysis.

In the solution hydrolysis studies, all the polymers underwent molecular weight declines. The polydispersities broadened during hydrolysis and changed from 1.8–2.5 to 3.7–5.0. Hydrolysis in solution generated a broader molecular weight distribution than did the corresponding solid-state reaction. However, no trends could be detected in the rates of solution decomposition of (a) polymers with the same amino acid residue or (b) those with the same ester end unit. For example, the hydrolysis rate of poly[bis(benzyl glycinat-*N*-yl)phosphazene] (**5**) did not differ significantly from that of poly[bis(ethyl glycinat-*N*-yl)phosphazene] (**3**); nor did the rates of decomposition of poly[bis(methyl glycinat-*N*-yl)phosphazene] (**2**) or poly[bis(methyl alaninat-*N*-yl)phosphazene] (**6**) differ appreciably from one another. The graphs in Figures 1 and 2 illustrate these data. No gelled products were detected during the solution hydrolysis studies.

Polymers **2–16** also underwent molecular weight decline during the solid-state hydrolysis studies. After 5 weeks of reaction, the extent of degradation of each polymer in both the solution- and solid-state experiments was approximately the same. However, differences between and within different series of poly(amino acid ester)phosphazenes were detected in the solid-state hydrolysis reactions. The bulkier the ester end group, the less hydrolytically sensitive was the polymer (the benzyl esters being less sensitive than the *tert*-butyl esters which were less sensitive than ethyl esters, and with the methyl esters being the most sensitive to hydrolysis) for the same amino acid. This is shown in Figure 3. Moreover, the larger the group linked to the α-carbon atom of the amino acid residue, the more stable was the polymer to hydrolysis (phenylalaninato units were more stable than the valinato units which were more stable than the alaninato groups, and with the glycinato side groups being the least stable

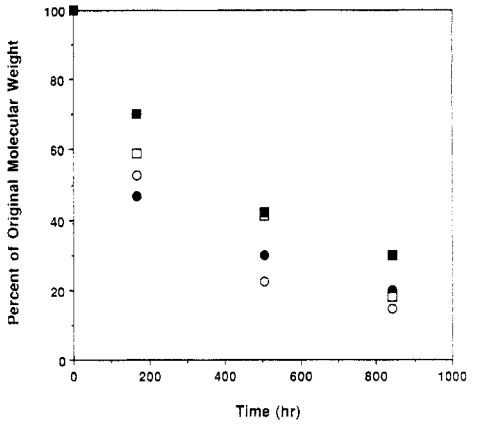


Figure 2. Percentage molecular weight decline during solution-state hydrolysis of poly[(amino acid methyl ester)phosphazenes] (2, 6, 10, 14): (○) poly[bis(methyl glycinat-*N*-yl)phosphazene] (2); (●) poly[bis(methyl alaninat-*N*-yl)phosphazene] (6); (□) poly[bis(methyl valinat-*N*-yl)phosphazene] (10); (■) poly[bis(methyl phenylalaninat-*N*-yl)phosphazene] (14).

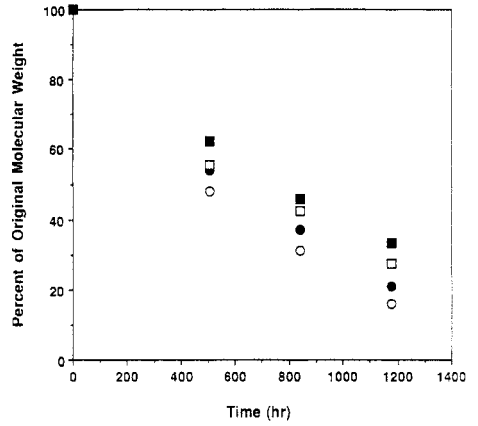


Figure 3. Percentage molecular weight decline during solid-state hydrolysis of poly[(glycinato ester)phosphazenes] (2–5): (○) poly[bis(methyl glycinat-*N*-yl)phosphazene] (2); (●) poly[bis(ethyl glycinat-*N*-yl)phosphazene] (3); (□) poly[bis(*tert*-butyl glycinat-*N*-yl)phosphazene (4); (■) poly[bis(benzyl glycinato-*N*-yl)phosphazene] (5).

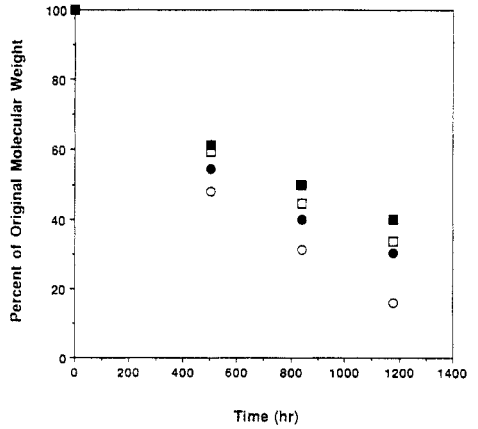
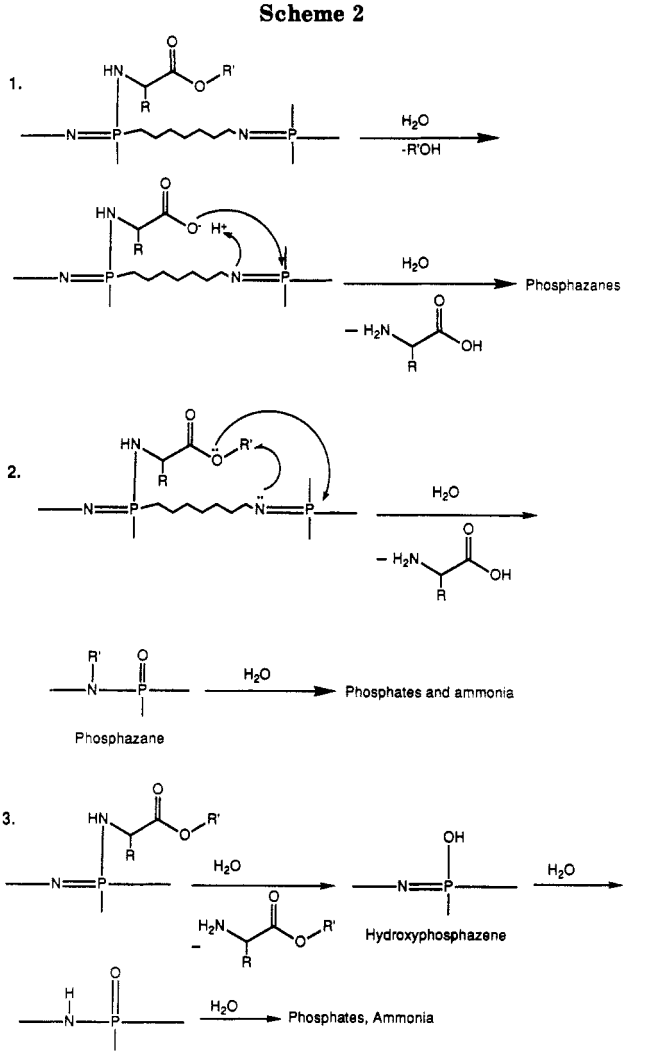


Figure 4. Percentage molecular weight decline during solid-state hydrolysis of poly[(amino acid methyl ester)phosphazenes] (2, 6, 10, 14): (○) poly[bis(methyl glycinat-*N*-yl)phosphazene] (2); (●) poly[bis(methyl alaninat-*N*-yl)phosphazene] (6); (□) poly[bis(methyl valinat-*N*-yl)phosphazene] (10); (■) poly[bis(methyl phenylalaninat-*N*-yl)phosphazene] (14).

to solid-state hydrolysis). This point is illustrated in Figure 4. The products of hydrolysis were identified as phosphates, the amino acid, the alcohol derived from the ester group, and ammonia (see Experimental Section).

Scheme 2



Several routes exist by which poly(amino acid ester)-phosphazenes might hydrolyze.[11] These are shown in Scheme 2.

The ester functionality may be involved in the breakdown of the polyphosphazene skeleton via three different mechanisms. In the first, water would hydrolyze the ester unit to form the corresponding polymer-bound amino acid. The carboxylic acid unit could then attack a nearby phosphorus atom in the polymer chain. This species would then react further with water to release the amino acid and to form a hydrolytically-unstable phosphaz*ane*, which would ultimately break down to phosphates and ammonia.[12] In a second mechanism, the presence of water would facilitate an attack on the polymer backbone by the ester functionality itself. Water molecules could then react with the unstable phosphorus–ester bond. As a result of this reaction, the amino acid would be released and a hydrolytically-sensitive phosphazane formed. In a third mechanism, water would displace the amino acid esters from the phosphorus atoms to form a hydroxyphosphazene. This species could rearrange in the presence of water to a phosphazane. The phosphazane would then react with water to yield phosphates and ammonia.

Conclusions

Several prospective biomedical uses exist for these polymers. The most obvious is in the field of erodible bioreinforcing or biostructural materials. Several of the polymers (5, 6, 8, 9, and 15) are microcrystalline and others (10, 12, 13, 14, and 15) possess relatively high glass transition temperatures. Both of these properties are

appropriate for the preparation of sutures and perhaps bone regeneration substrates, since they would permit facile processing and provide dimensional stability at body temperature. Another possible application would be in erodible wound coverings. Finally, the use of these polymers as drug delivery platforms is of some interest. Poly[bis(ethyl glycinat-*N*-yl)phosphazene] (**3**) has already been investigated for this purpose.[4] The use of different amino acid esters might allow a fine-tuning of the rate of drug delivery in a monolithic system.

Experimental Section

Reagents and Equipment. All reactions were carried out under a dry nitrogen atmosphere (Matheson) using standard Schlenk line techniques. Tetrahydrofuran (Omnisolv) was distilled from sodium benzophenone ketyl under an atmosphere of dry nitrogen. Hexane, toluene, and triethylamine (Aldrich) were distilled from CaH_2 under nitrogen. The amino acid ester hydrogen chloride salts (Sigma) were used as received. Hexachlorocyclotriphosphazene (Ethyl Corp.) was purified by two sublimations of a trimer–tetramer mixture (30 °C/0.1 mm Hg). Poly(dichlorophosphazene) was prepared by the thermal ring-opening polymerization of the cyclic trimer in an evacuated Pyrex tube at 250 °C.[13] All ^{31}P NMR spectra were obtained with a JEOL FX-90Q (36.23 MHz) or a Bruker 360 WM (145 MHz). ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker 360 WM operated at 360 and 99 MHz, respectively. Glass transition temperatures were determined with a Perkin-Elmer DSC-7 apparatus with TAS-7 software. Molecular weights were estimated by gel permeation chromatography using a Hewlett-Packard LC 1090 unit and a polystyrene stationary phase. Polystyrene standards were used to calibrate the columns. Sample concentrations were ca. 1.5% (w/v) in THF. Elemental analyses were obtained by Galbraith Laboratories (Knoxville, TN).

Synthesis of Polymers 2–16. The syntheses of these polymers were carried out in a similar manner. The procedure for polymer **5** is given as a typical example. Poly(dichlorophosphazene) (**1**) (2.0 g, 0.017 mol) was dissolved in dry THF (250 mL). Benzyl glycinate hydrogen chloride salt (17.4 g, 0.087 mol) was suspended in toluene (250 mL) with triethylamine (13 mL, 0.087 mol). This suspension was boiled at reflux for 6 h. It was then cooled, filtered, and added to the stirred polymer solution. The reaction mixture was then warmed at 35 °C for 36 h. The solution was then cooled to room temperature. The reaction mixture was filtered to remove the salts formed during the reaction and was concentrated under vacuum. Polymer **5** was isolated and purified by successive precipitations into hexane (3×) and pentane (2×). The product was an off-white tough material.

Crystallinity Studies for Polymers 2–16. Each polymer (0.2 g) was dissolved in THF (5 mL). A film was then cast on a glass slide and was placed in a drybox under a nitrogen flow to allow the solvent to evaporate. The films were examined by means of a polarizing microscope (Unitron MPS) with a temperature control stage. Each polymer, if crystalline, was heated to 20 °C above its melting transition as determined previously by DSC analysis. Solid polymer samples on glass slides in a Fisher-Johns melting point apparatus were also monitored as the temperature was raised. The temperature was increased at a rate of 10 °C/min.

Hydrolysis Studies. (I) Solution State. An initial gel permeation chromatogram of each polymer in THF was obtained. Deionized water (0.2 mL) was then added to each sample (polymer concentration 1.5% w/v in THF). The chromatogram of each polymer was then monitored after 1 week and then biweekly over a 5-week period to follow the molecular weight change.

Hydrolysis Studies. (II) Solid State. Samples of each polymer (0.5–0.75 g) were immersed in deionized water (30 mL). After 3 weeks and then after every 2-week period, solid polymer samples (20–50 mg) were dissolved in THF. GPC chromatograms were then obtained for each of these THF solutions. In addition, inspections were made of the physical appearance of each polymer. All the experiments continued for 7 weeks.

Detection of Hydrolysis Products. Phosphates were detected by the addition of zirconyl chloride or silver nitrate to the hydrolysis media and the precipitation of white zirconyl phosphate or yellow silver phosphate, respectively. The ninhydrin test was used to detect amino acids and ammonia. The alcohols were detected by ^{1}H NMR spectroscopy.

Acknowledgment. The authors thank Ethicon, Inc. (a Johnson and Johnson Company), for generous financial support of this project.

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