[C] = 4.0×10^{-3} mol/L, and t = 6 s, a value for k_p as high as 120 L/(mol s) at 0 °C. Considering the assumptions made, this value should be taken as a lower limit.

In conclusion, the anionic polymerization of ϵ-caprolactone in tetrahydrofuran represents a living ring–chain equilibrium system. The product distribution is essentially determined by the entropy term, the lower cyclics being favored over the linear polymers at higher dilution, as expected from the Jacobson–Stockmayer theory. The very fast equilibration, as shown in this paper, should be considered in studies concerned with either or both the thermodynamics of the ring-opening polymerization and the statistics of chain conformations of the species involved.

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Synthesis of Poly[(amino acid alkyl ester)phosphazenes][1-3]

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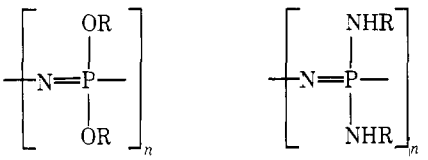
ABSTRACT: Phosphazene high polymers with glycino ethyl ester, leucino methyl ester, alanino methyl ester, and phenyl alanino methyl ester substituents have been synthesized by the interaction of poly(dichlorophosphazene) (IV) with amino acid esters. Total halogen replacement was achieved only with glycine ethyl ester, but replacement of the remaining chlorine could be effected by the subsequent introduction of methylamino groups as cosubstituents. In aqueous media the polymers were susceptible to a slow hydrolytic decomposition. In addition, a spontaneous chain cleavage process was detected that involved reactions of the substituent groups. All the polymers were basic and bound hydrogen chloride strongly. The physical properties and biomedical potentialities of the polymers are also discussed.

Although large numbers of synthetic high polymers are known, relatively few of these are suitable for use as biomedical implantation polymers or chemotherapeutic drug carrier molecules. Most synthetic organic polymers generate irritation responses which result in rejection of an implanted device or the clotting of blood. Moreover, few synthetic polymers can be absorbed by a living system as tissue regrowth occurs.

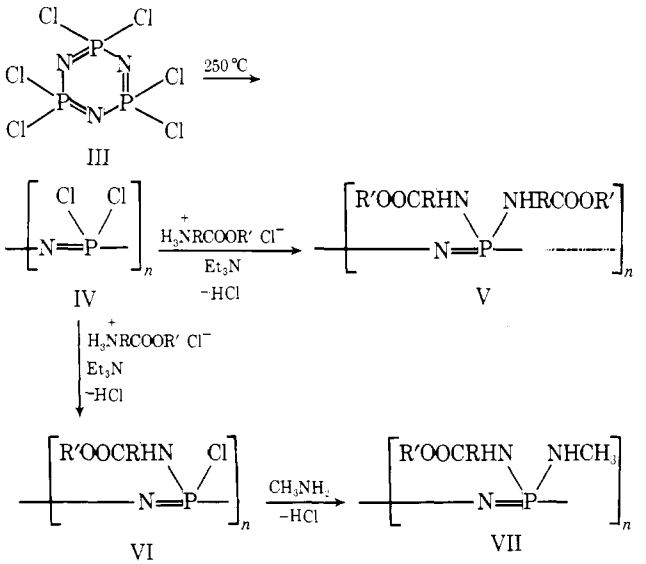
Stable phosphazene high polymers were first prepared by Allcock, Kugel, and Valan[4-6] and this work was extended by Allcock, Cook, and Mack.[7,8] Such polymers (I or II) are virtually unique with respect to the range of different properties that are accessible.[9] Specific phosphazene polymers with different substituent groups show a broad range of flexibilities, solubilities, and surface properties.[9-11] In many cases a judicious choice of the substituent groups can generate polymers with a precisely defined set of properties. For these reasons an attempt has been made to synthesize aminophosphazene polymers of structure II in which substituent groups are amino acid ester groupings alone or both amino acid ester and methylamino groups. It was anticipated that the polymers could be biocompatible as solids or biodegradable to the harmless hydrolysis products, amino acid, phosphoric acid, and ammonia. If the polymers proved to be soluble in aqueous media, they could possibly be used as plasma extenders or carrier molecules for chemotherapeutic drugs.



I II

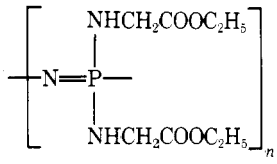
Results and Discussion

General Synthesis Route. The polymers were synthesized by the interaction of an amino acid ester with high molecular weight polydichlorophosphazene (IV) to yield V, or by a sequential introduction of amino acid ester groups (VI) and methylamino groups to yield VII. The polymers prepared are

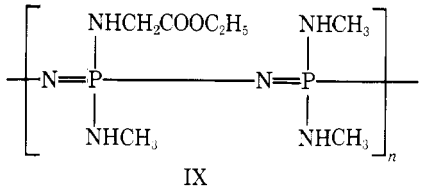


($n \approx 10\,000$)

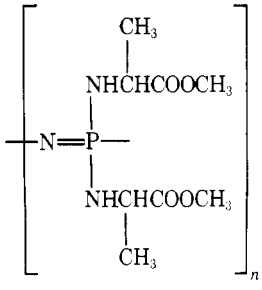
depicted as structures VIII–XV. Formulas VIII and IX represent actual structures, but X–XV are idealized representations since some of these polymers contained unreacted



VIII



IX



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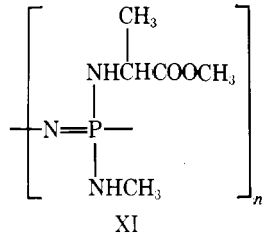
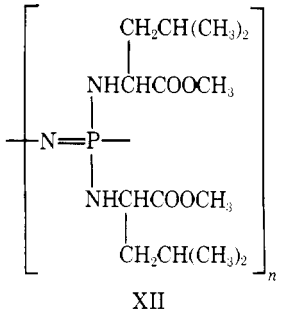
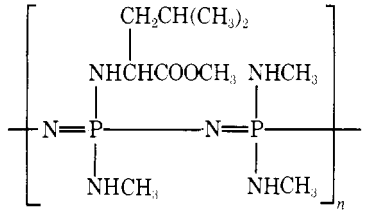


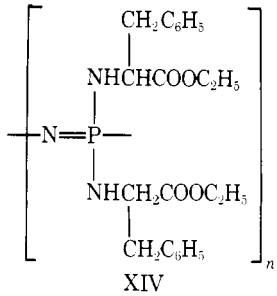
XI



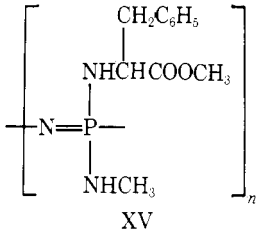
XII



XIII



XIV



XV

P–Cl bonds and others contained hydrogen chloride bound to the polymer as a hydrochloride salt.

The monomethylamino group was chosen as a cosubstituent because of its small dimensions and because it is a water-solubilizing substituent group for polyphosphazenes.[8] The choice of an amino acid *ester* as a substituent group, rather than an amino acid, was dictated by the expectation that free carboxylic acid groups would participate in chlorine substitution (to yield cross-links) and could also cause degradation of the polymer backbone.[12] A further restriction on the type of substituent group was provided by the fact that specific amino acid esters, such as esters of serine, threonine, cysteine, tyrosine, etc., contain two or more nucleophilic sites. Hence, the use of these reagents would be expected to lead to cross-linking. The choice of amino acid esters was further limited by the need to minimize steric hindrance effects which are known to lead to incomplete substitution[7,8] or to destabilization of phosphazene polymers.

The synthesis of mixed substituent polymers (IX, XI, XIII, and XV) was accomplished by introduction of the amino acid ester residue *first*, followed by treatment with methylamine, in an attempt to generate an approximately 1:1 molar ratio of the two groups. The alternative approach, which would involve a prior introduction of the methylamino residues, was unsuitable because of the high reactivity of methylamine[8] and the possibility that methylaminophosphazene homopolymer would be produced.

Table I
Intrinsic Viscosities, Molecular Weights, and Glass Transition Temperatures for Poly[(amino acid ester) phosphazenes]

Polymer	Intrinsic viscosity, dL/g	Estimated $\overline{M}_n \times 10^{6}$ [a,b]	Estimated T_g, °C[c]
VIII	2.0	2.0–5.0	−23
IX	1.4	6.0	40, 76
X	1.3	1.0–1.8	13–33
XI	1.0	1.0–10.0	95
XII	0.8	0.1–1.0	59, 110
XIII	0.8	1.0	87
XIII[d]			44
XIV	0.8	0.2–4.0	40, 65
XV	0.6	0.1–2.0	60
$[NP(NHCH_3)_2]_n$	>2.0	0.8–1.0	75

[a] The range of values shown represents the results from polymers prepared in different experiments. [b] Estimated from gel permeation chromatography curves. Since these values were based on polystyrene standards, the values are considered to be approximate. [c] By torsional braid analysis. [d] Polymer containing 25% methyl leucino and 75% methylamino residues.

Reactivity and Reaction Pattern. All four amino acid esters showed similar initial reactivities with $(NPCl_2)_n$ in benzene solution at 0 °C. In each case, the substitution reaction began almost immediately after mixing of the reagents and was complete within 16 h at 0 or 25 °C. However, steric hindrance effects involving the amino acid ester appeared to limit the degree of substitution. Ethyl glycinate yielded a homopolymer of structure VIII. Methyl alaninate replaced between 90 and 100% of the chlorine atoms in homopolymer formation, but excess methyl leucinate replaced only 50% of the available chlorine, and excess methyl phenylalaninate replaced only 75% of the chlorine atoms under the reaction conditions employed. The polymers that contained residual P–Cl bonds were surprisingly stable to hydrolysis, and the expected facile cross-linking behavior of such species was not observed.

In mixed substituent polymer formation, a 1:1 reactant ratio of amino acid ester to $(NPCl_2)_n$ did not result in replacement of one-half of the available chlorine. Instead, only ~25% chlorine replacement occurred with ethyl glycinate or methyl leucinate. A 3 or 4:1 excess of methyl alaninate or methyl phenyl alaninate to $(NPCl_2)_n$ was required before ~40–50% chlorine replacement could be effected (Tables II and III). These results strongly suggest that steric hindrance effects inhibit the replacement of more than one chlorine atom per phosphorus in $(NPCl_2)_n$, especially with branched amino acid esters. However, the presence of the bulky amino acid ester residues on the chain did not inhibit replacement of all or most of the remaining chlorine atoms by methylamino. Ethyl glycinate appears to have the highest over-all reactivity toward $(NPCl_2)_n$ of the four amino acid esters studied. It has been reported that the ethyl ester of glycine reacts with $(NPCl_2)_3$ (III) by a geminal mechanism,[13] but the results of this present

Table II
Synthesis Data for Poly(amino acid ester)phosphazenes[a]

Polymer	Method	Mol of amino acid ester·HCl	Mol of $N(C_2H_5)_3$	Mol of $(NPCl_2)_n$	Mol of CH_3NH_2	Polymer solubility[b]	Nonsolvents[b]	Yield, %
VIII	A	0.35	0.26	0.043		Benzene, acetone, THF	Hexane, water	57–64
IX	C	0.035	0.07	0.035	2.25	Ethanol, methanol, water	Benzene, heptane	71
IX	D	0.035	0.07	0.035	2.25	Ethanol, methanol, water	THF	70.4
X	A	0.18	0.135	0.023		Benzene	Heptane	
X	B	0.103	0.172	0.035		Benzene	Heptane	45.7
XI	C	0.18	0.135	0.045	0.90	Benzene, THF	Heptane	
XI	D	0.035	0.07	0.035	2.25	Benzene, THF	Heptane	18.2
XII	A	0.14	0.10	0.017		Benzene, THF	Heptane, water	
XII	B	0.10	0.17	0.035		Benzene, THF	Heptane, water	39.4
XIIIa	C	0.11	0.08	0.017	0.23	Ethanol, benzene	Acetone, heptane, water	
XIIIb	D	0.035	0.069	0.035	2.25	Ethanol, benzene	Acetone, heptane, water	42
XIIIb	D	0.035	0.035	0.035	2.25	Methanol	Heptane	38.4
XIV	A	0.09	0.07	0.012		Benzene, THF	Heptane, water	
XIV	B	0.103	0.172	0.035		Benzene, THF	Heptane, water	50
XV	C	0.86	0.07	0.022	0.22	Benzene, ethanol	Heptane, water	
XV	D	0.035	0.069	0.035	2.25	Benzene, ethanol	Heptane, water	67.6

[a] In each case the reaction solvent was benzene, the reaction temperatures varied from 0 to 25 °C, as described in the text, and the reaction times were in the range of 16–20 h. [b] For the purified, substituted polymers. With the exception of water, the solvents listed were used for reprecipitation purification.

Table III
Analytical Data[a]

Compd	C	H	N	P	Cl	A:B:C[b,c,g]	HCl[h,c,d]
VIII	38.64	6.41	16.48	12.30	0	100:0:0	0
IX	27.63	6.23	28.67	16.03	2.34	25:75:0[e]	11
X	37.02	6.33	15.42	12.33	3.83	90:0:10	10
XI	32.12	7.02	24.29	17.88	3.12	44:56:0[e]	16
XII	43.83	7.46	12.41	12.07	5.27	50:0:50	
XIIIa	38.00	7.55	20.62	17.29	2.64	32:68:0[e]	10
XIIIb	34.18	8.14	27.18	18.92	0.89	22:78:0[f]	4
XIV	57.03	5.69	10.68	9.49	2.08	75:0:25	
XV	46.46	6.36	16.12	14.66	4.35	41:59:0	28
						or 40:45:15	15

[a] Analytical data were obtained from Galbraith Laboratories and Chemalytics, Inc. [b] Substituent A = amino acid ester, B = methylamino, C = chlorine. [c] The actual composition of the polymers was deduced by graphical, trial and error, and computer-based best fits to the analytical data. [d] The chlorine content of polymers IX, XI, and XIII was attributed to salt-bound HCl rather than to residual P–Cl bonds on the basis of the combined analytical data and the fact that the chlorine content could be reduced by brief treatment of the polymers in organic media with anhydrous sodium carbonate or pyridine. [e] The reactant ratios had been arranged to generate a 50:50 substituent ratio. [f] The reactant ratios had been designed to yield a 25 75 substituent ratio. [g] Estimated proportion of substituents A:B:C. [h] Estimated number of molecules of HCl per 100 repeating units.

work imply that replacement of the first halogen atom at each phosphorus is a more facile step than replacement of the second.

Structure. The products were polymeric, as indicated by the molecular weight and intrinsic viscosity data (Table I). The cyclic trimer and tetramer, $(NPCl_2)_3$ and $(NPCl_2)_4$, react with ethyl glycinate by the expected route to yield species of structure $[NP(NHCH_2COOC_2H_5)_2]_{3\text{ or }4}$ (see Experimental Section). Hence, a similar basic repeating structure can be presumed for the polymeric analogues. Moreover, it was found that ethyl acetate does not react with $(NPCl_2)_n$ to yield acetyl chloride. Hence, a reaction of the ester component of the amino acid ester with P–Cl bonds appears to be unlikely.

Considerable difficulty was experienced in obtaining reproducible microanalysis data for these polymers.[14] All the polymers except VIII contained some chlorine. In specific cases (compounds X, XII, and XIV) this was attributed to incomplete chlorine replacement by the amino acid ester. In other cases, the chlorine analysis represented the presence of hydrogen chloride bound as a salt to the basic side group or (more likely) to the basic skeletal nitrogen atoms. Many oligomeric and polymeric aminophosphazenes are strong bases that release hydrogen chloride only with difficulty. The polymer compositions listed in Table III represent the best fit that could be obtained between the four variables (amino acid ester, methylamino, P–Cl, and HCl) and the analytical data.

Infrared spectra of the polymer showed a peak at 1200 cm^{-1} (from the phosphazene backbone). The remainder of each spectrum closely matched that of the appropriate amino acid ester and (with the ethyl glycinate derivatives) of the analogous cyclic trimer and tetramer. Thus, the integrity of the side group structures appeared to be retained in the polymers. The infrared spectra were not consistent with the structures in which the side group linkage was through the carboxylate group. Amino acid esters are susceptible to hydrolysis to the free acid. However, no spectral changes were evident after precipitation of the polymers into aqueous media, although low concentrations of free carboxylic acid residues could have remained undetected.

Physical Properties. Solution-cast films of the polymers were opaque and flexible. Those polymers that contained methylamino substituents were, in general, less flexible than the homopolymers. Polymers XII and XV did not swell significantly in water, although they became somewhat adhesive on exposure to atmospheric moisture. Polymer XI was swelled

by water and underwent partial dissolution. Polymer VIII was soluble in methanol, ethanol, acetone, and benzene but was insoluble in water. On the other hand, polymer IX was soluble in water, methanol, and ethanol but insoluble in acetone, chloroform, dioxane, tetrahydrofuran, and ether. Similar results were obtained from a 25% methylleucino–75% methylamino polymer. All the polymers were soluble in organic media (see Experimental Section).

Estimated molecular weights and glass transition temperatures are shown in Table I.

All the polymers were synthesized from virtually identical samples of poly(dichlorophospazene) (V) which had been prepared from one batch of $(NPCl_2)_3$ (III), with the polymerization tubes filled at the same time, evacuated and sealed together, and polymerized for the same time at the same temperature. Thus, at the start of each substitution reaction, all samples of $(NPCl_2)_n$ were assumed to have the same molecular weight and molecular weight distribution. Consequently, any differences in the intrinsic viscosities and $\overline{M}_n$ values must be attributed either to the different molecular masses of the substituent groups present or to molecular weight decreases incurred during substitution, purification, or storage.

The absolute $\overline{M}_n$ values (determined by gel permeation chromatography) were considered to be less reliable than the intrinsic viscosity data. Nevertheless, most of the $\overline{M}_n$ values were in the range of 1×10^6 to 1.8×10^6, which corresponds roughly to about 5000–10000 repeating units per chain. Since the poly(dichlorophosphazene) used in such reactions generally yields alkoxyphosphazene polymers with about 10000–15000 repeating units per chain, it appears that substitution is accompanied by some decrease in chain length. The intrinsic viscosity values and molecular weights vary over an appreciable range (see Table I). The mixed substituent polymers containing methylamino units do not show molecular weights higher than those found for the bis(amino acid ester) derivatives. Hence, steric size alone cannot account for the molecular weight differences. As will be shown in the following section, the reactivity of the substituent groups to hydrolysis or rearrangement-depolymerization reactions probably has a greater influence on the molecular weight of each polymer.

Most of the polymers prepared in this work have glass transitions in the 25–100 °C temperature range. The principal exceptions are poly[bis(ethyl glycino)phosphazene] (VIII) (T_g −23 °C) and poly[bis(methyl alanino)phosphazene] (X) (T_g 13–33 °C). As might be expected, these two polymers are more flexible than the others. Methylamino residues probably raise the T_g values by intra- or intermolecular hydrogen bonding, an effect that has been observed for simple aminophosphazene homopolymers.[4,7,8] The presence of hydrogen chloride bound to the skeleton might also decrease the chain flexibility.

Stability and Mechanism of Molecular Weight Decline. All the amino acid ester containing polymers synthesized in this work underwent a slow decrease in molecular weight in solution and in the solid state at 25 °C. In this respect they differed from nearly all the organophosphazene polymers synthesized in earlier studies. For example, some samples of $[NP(NHCH_2COOC_2H_5)_2]_n$ (VIII) underwent a decrease in chain length from 8000 or 20000 repeating units to less than 1000 repeating units in 15 days in the solid state at 25 °C. The related mixed substituent polymer (IX) underwent a chain shortening from about 8000 to 1000 repeating units in 25–30 days. The other polymers behaved similarly. Cooling of the polymers to −32 °C considerably reduced the rate of decomposition.

All attempts to elucidate the degradation mechanism by identification of the reaction products were unsuccessful. Infrared spectra of the chain-shortened polymers were identical with those of the original materials. No changes in ^{31}P NMR spectra could be detected after degradation.[15] A molecular weight decline in chain length from 8000 repeating units to less than 1000 would have a marked effect on the polymer properties but would, nevertheless, generate a virtually undetectable concentration of end groups in the linear fragments. Gel permeation chromatography curves showed a broadening of the molecular weight distribution to encompass lower molecular weights as degradation occurred, but no cyclic trimers or tetramers were detected. Hence, a random chain cleavage process appeared to be operative, rather than an "unzipping" mechanism. Although such molecular weight declines at 25 °C would normally be considered disadvantageous for a synthetic polymer, they are a distinct advantage from the viewpoint of biomedical degradability. Hence, it was of interest to explore the mechanism of this process.

The following experimental observations provided clues to the degradation process:

(1) Solutions of the polymers in organic media showed a more rapid molecular weight decline than did the solid polymers, but the nature of the solvent appeared to have little effect. This suggests the involvement of an intramolecular degradation mechanism.

(2) Solid samples exposed to the air underwent a more rapid molecular weight decline than did those stored under vacuum. Thus, a reaction of the polymers with atmospheric moisture may initiate degradation.

(3) The partial replacement of amino acid ester residues by methylamino substituents resulted in only a marginal improvement in stability.

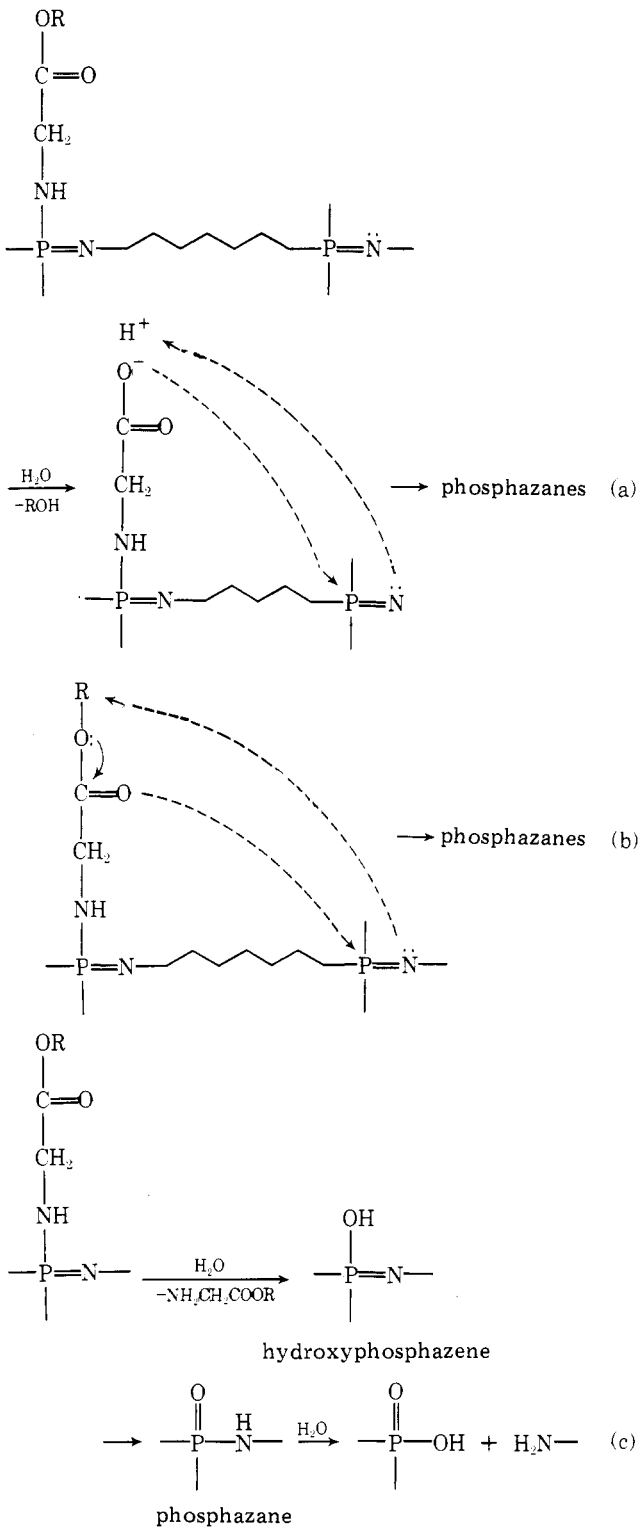
(4) The introduction of the bulkier substituent groups, e.g., phenyl alanino or methyl leucino, did not induce additional destabilization. Facts (3) and (4) suggest that the depolymerization is not simply a response to excessive steric hindrance in the polymer.

Several mechanistic possibilities exist. These are: (a) a mechanism involving prior hydrolysis of ester linkages to yield carboxylic acid groups; (b) an attack on the skeleton by the carbonyl groups of the substituent units; (c) a hydrolytic cleavage of the bond connecting the side group to phosphorus; or (d) mechanisms involving either the salt-bound hydrogen chloride or the residual P–Cl bonds.

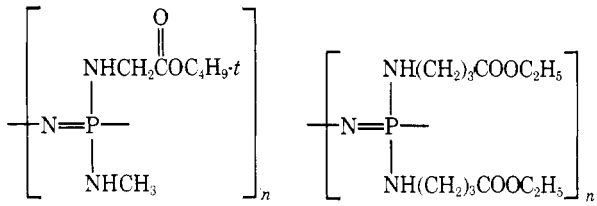
First, it must be emphasized that polymer VIII contained no P–Cl residues and no bound hydrogen chloride, and yet it underwent a molecular weight decline faster than any of the other polymers. Hence, option (d) does not explain the behavior of this polymer. Because of the absence of P–Cl bonds and bound HCl in VIII, the behavior of this particular polymer is considered in greatest detail in the following sections. Those polymers that contain residual P–Cl bonds can almost certainly degrade by hydrolysis of P–Cl to P–OH bonds, followed by proton migration to skeletal nitrogen to yield hydrolytically unstable phospha*zane* linkages (–$P(R_2)$(O)–NH–). Thus, conventional hydrolytic chain cleavage mechanisms can be presumed for polymers XII, XIV, and perhaps XV. The remaining likely degradation pathways are illustrated in Scheme I.

Reaction (a) is plausible for all the amino acid ester polymers synthesized in this work. It is well known that amino acid esters are susceptible to hydrolysis to the free amino acid. Moreover, commercial amino acid ester hydrochlorides may contain traces of the free amino acid which could be carried through the synthetic sequences. Poly[bis(ethyl glycinato)phosphazene] prepared from rigorously purified ethyl glycinate and protected from atmospheric moisture declined less in molecular weight[16] than did polymer prepared with the use of less stringent techniques. Hence, the possibility exists that the final number of polymer fragments depends on the number of carboxylic *acid* residues in the polymer. Added

Scheme I



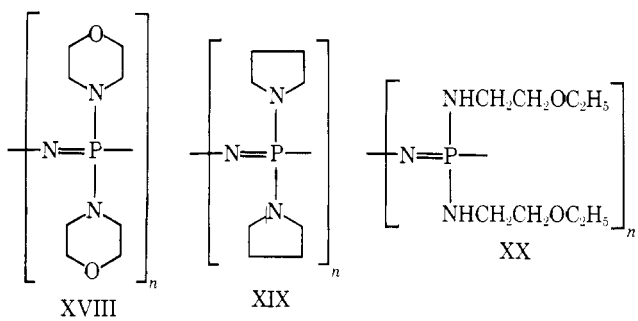
benzoic acid or benzoyl peroxide markedly enhanced the rate of chain cleavage. Moreover, these reagents induced molecular weight decreases in conventional (normally stable) organophosphazenes, such as $[NP(OCH_2CF_3)_2]_n$ or $[NP(NC_5H_{10})_2]_n$ (XXI). The microanalytical discrepancies for some batches of the amino acid ester substituted polymers could be explained in terms of the presence of small amounts of free COOH groups in the polymers. Moreover, the polymers which appeared to be the most resistant to chain cleavage were those which contained phenylalanine ester, and these might be expected to be more hydrophobic than, for example, polymers that contained ethyl glycinate residues. However, protection



of the ester grouping against hydrolytic attack by the synthesis of a *tert*-butyl glycino-substituted polymer (XVI) had no perceptible influence on the rate of molecular weight decline. Although side group ester hydrolysis provides a plausible mechanism for the initiation of chain cleavage, the experimental results indicate that other mechanisms are probably involved as well.

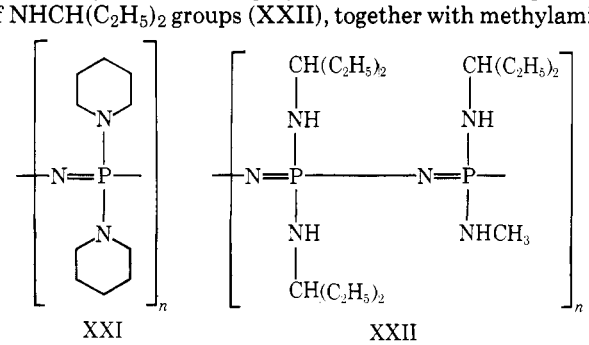
Attack by a side group carbonyl unit (mechanism b) is compatible with the experimental data. Butyramide causes extensive decomposition and chain cleavage during reactions with $(NPCl_2)_n$. Separation of the ester function from the amino function (as in XVII) did not prevent a spontaneous molecular weight decline.

Evidence was also found to support mechanism c. The hydrolytic cleavage of a P–N side group bond would be facilitated by a high leaving group ability of the side group. Thus, ethyl glycinate[17,18] has a pK_a at 25 °C of 7.75, whereas butylamine has a pK_a value of 10.78. Poly[bis(butylamino)phosphazene is an especially stable polymer.[8] Similarly, poly[bis(morpholino)phosphazene] (XVIII) underwent a skeletal cleavage reaction in the atmosphere, but poly[bis(pyrrolidino)phosphazene] (XIX) and poly[bis(piperidino)phosphazene] (XXI)[6] did not. The pK_a value for morpholine at 25 °C is 8.33, whereas the values for pyrrolidine and piperidine are 11.27 and 11.12, respectively. Polymer XX underwent



chain cleavage, a result that can be related to a pK_a value of 9–10 for $H_2NCH_2CH_2OC_2H_5$.[17] This rough correlation of polymer instability with leaving group ability provides a valuable guidance for the tailored synthesis of hydrolytically degradable polymers.

Earlier work has stressed the role played by steric hindrance in the destabilization of poly(organophosphazenes) at elevated temperatures.[19,20] Steric crowding does not explain the breakdown of the polymers discussed here in the 25–50 °C temperature range. Polymer XXI[6] appears to be stable almost indefinitely at 25 °C, and polymers that contained up to 78% of $NHCH(C_2H_5)_2$ groups (XXII), together with methylamino



or chloro cosubstituent groups, were found to be stable for long periods of time, even in contact with atmospheric moisture.

The proposed degradation mechanisms a, b, and c lead to the formation of phosphaz*anes*. The resultant phosphazane linkages would in all three cases constitute sites for rapid hydrolytic chain cleavage. Thus, in view of the mechanistic likelihood of reactions a, b, and c, it is perhaps surprising that the experimental results for the degradation process can be explained by an average of only 5 to 10 reactions per chain during a 15–30 day period.

Hydrolytic Breakdown and Biomedical Potential. A goal of this work was the synthesis of polymers that would degrade in the body to harmless or even metabolizable products. The spontaneous molecular weight decline has already been described. This leads to a very slow change in physical properties rather than to dissolution of the polymers. Prolonged exposure of polymer VIII to the atmosphere did not generate free glycine. Although this polymer is insoluble in neutral aqueous media and in aqueous phosphate buffer (pH 7.5) at 25 °C, a very slow liberation of glycine occurred in these media, accompanied by slow dissolution of the polymer over a period of several weeks. The free glycine was detected by the ninhydrin test. Hydrolysis and dissolution were more rapid in strong aqueous acid or base. A similar pattern of hydrolysis and glycine liberation was observed with the cyclic tetramer, $[NP(NHCH_2COOC_2H_5)_2]_4$. Polymer IX, which is soluble in neutral aqueous media, underwent rapid chain cleavage and glycine liberation in a pH 7.4 buffer at 60–70 °C.

It seems clear from these preliminary hydrolysis tests that the polymers offer the prospect for biological degradation to amino acid, phosphate, and ammonia. In vivo animal implantation tests are now in progress.

Experimental Section

Materials. Benzene (Fisher) was dried by boiling at reflux over calcium hydride, followed by distillation over molecular sieves. Tetrahydrofuran (Baker) was distilled from lithium aluminum hydride. Acetone (Baker) was used as received. Hexane (Baker) was distilled from calcium sulfate and stored over molecular seives. Glycine ethyl ester hydrochloride, alanine methyl ester hydrochloride, leucine methyl ester hydrochloride, and phenyl alanine methyl ester hydrochloride (Sigma) were dried in a vacuum cabinet at 25 °C for 24 h before use. Methylamine gas (Matheson) was condensed over sodium spheres into a graduated flask and then allowed to recondense into the reaction mixture. Triethylamine (Eastman) was dried by boiling at reflux over barium oxide and was then distilled just before use. Hexachlorocyclotriphosphazene (III) (El Monte Chemical Co.) was sublimed from the crude trimer–tetramer mixture at 50 °C (0.7 Torr). The product was recrystallized from dry hexane, dried in vacuo, and resublimed at 50 °C (0.7 Torr). The melting point of the purified trimer was 111–112.5 °C.

Equipment. Solution viscosity measurements were made with a Cannon Ubbelohde 75-E-157 viscometer in a constant temperature bath at 30 °C. Benzene or tetrahydrofuran was used as the solvent.

Gel permeation chromatograms were obtained with the use of a Waters Associates ALC201 instrument fitted with a refractive index detector. Tetrahydrofuran containing 0.25 g/L tetrabutylammonium bromide was used as the solvent. Sample concentrations were 0.16–0.25%. Separation was carried out on 120 cm × 0.8 cm 10^6 Styragel columns, calibrated with narrow molecular weight polystyrene standards. Thus, the $\overline{M}_n$ values are considered to be approximate. Typical analyses were conducted with 4× attenuation, positive polarity, 600–700 psi pressure, and a flow rate of 1.8 mL/min.

Infrared spectra were measured with a Perkin-Elmer 621 instrument. Spectra of polymer samples were taken as films cast on silver chloride or sodium chloride plates. Spectra of the amino acid ester hydrochloride salts were taken as a Nujol mull between salt plates.

The glass transition temperatures (T_g) were measured with the use of a Chemical Instruments Corp. torsional braid analyzer programmed to operate from −190 to +190 °C with a temperature variation rate of 1.5–2.0 °C min^{-1}. The samples were maintained in a dry nitrogen atmosphere during each experiment. Successive cycles up to +190 °C showed an increase in T_g values for polymer XIV and this effect was attributed to thermal decomposition. Glass transition temperatures measured over a 1-week period showed no variations that could be ascribed to changes in chain length.

Polymerization Technique. Polymerization of $(NPCl_2)_3$ (III) was carried out in degassed, sealed glass tubes, each containing about 200 g of purified III. The sealed tubes were heated in a Freas Model 104 thermoregulated oven at 250 °C for 120 h. Agitation of the tubes during polymerization was accomplished by means of a wire which extended from a geared-down electric motor and arm assembly into the oven and was attached to one end of a wire basket containing the tubes. A rocking motion of the tubes was completed about once each minute.

After completion of the polymerization, residual cyclic oligomers were removed by vacuum sublimation at 55 °C/0.7 Torr. To reduce differences in the poly(dichlorophosphazene) samples used in the different substitutions, a number of polymerization tubes were filled, evacuated, and sealed at the same time with the use of trimer from one uniform batch. These tubes were stored in the dark and were polymerized as needed at the same time and temperature.

Substitution Reactions. General. Four variations on the substitution technique were employed. Methods A and B applied to the preparation of the homopolymers. In method A, sufficient triethylamine was present to liberate the amino acid ester from its salt, and the excess amino acid ester then functioned as the hydrohalide acceptor during reaction of this reagent with $(NPCl_2)_n$. In method B, additional triethylamine was present both to release the amino acid ester from its salt and to function as a hydrohalide acceptor during the substitution step. Methods C and D applied to the synthesis of the mixed substituent polymers. In method C, the $(NPCl_2)_n$ solution was added to the amino acid ester solution, whereas in method D the amino acid ester solution was added to the $(NPCl_2)_n$ solution. Method D would, therefore, be expected to yield a polymer with a more even distribution of amino acid ester groups along the chain. (The T_g values listed in Table I were for mixed substituent polymers made by method D.) Two problems were encountered during the purification stages. First, it was considered advisable, when possible, to avoid the use of water as a precipitation medium. Second, because of this restriction, difficulty was sometimes experienced in the removal of hydrogen chloride bound to the polymer. However, some hydrogen chloride could be removed by treatment of solutions of the polymers in anhydrous organic media with solid alkali metal carbonate, pyridine, or triethylamine.

The synthesis procedures were very similar for the use of different amino acid esters. Typical preparative procedures are described in the following sections, and the details for other syntheses are summarized in Table II.

Poly[bis(ethylglycino)phosphazene (VIII) (Method A). Glycine ethyl ester hydrochloride (48.4 g, 0.35 mol) was dried in a vacuum oven at 25 °C and then transferred to a 1000-mL flask containing dry benzene (450 mL) and triethylamine (36.4 mL, 0.26 mol). The mixture was stirred at reflux for 3.5 h, and a small amount of benzene was distilled off to remove traces of water azeotropically. The mixture was cooled and was filtered in a dry nitrogen atmosphere into a 3000-mL flask. The filtrate was then cooled at 0 °C and was stirred as a solution of poly(dichlorophosphazene) (5.0 g, 0.043 mol) in benzene (500 mL) was added dropwise. Stirring was continued first at 0 °C for 6 h then at 25 °C for 10 h. After removal of the insoluble hydrochloride salts by filtration, a viscous polymer solution was isolated by vacuum evaporation of solvent at 25 °C on a rotary evaporator. Precipitation of this viscous solution into *n*-heptane yielded a solid polymer. This was then reprecipitated from benzene into *n*-heptane. Reprecipitation techniques were occasionally sufficient to remove the last traces of hydrochloride salts. If not, treatment of a benzene solution of the polymer with potassium carbonate yielded polymer that gave a negative Beilstein test for chlorine. The yields of polymer varied from 57 to 64% based on $(NPCl_2)_n$. The polymer was soluble in benzene, tetrahydrofuran, and acetone. It was insoluble in water, although it did swell and absorb water when immersed in aqueous media for several hours.

Poly[(ethyl glycino)(methylamino)phosphazene] (IX) (Method C). A suspension of glycine ethyl ester hydrochloride (5.82 g, 0.035 mol) and triethylamine (10.3 mL, 0.074 mol) was stirred in boiling benzene (500 mL) for 3.5 h. The mixture was cooled to 0 °C and filtered within an atmosphere of dry nitrogen to remove triethylamine hydrochloride. The filtrate was transferred to a 2000-mL three-necked flask cooled to 0 °C. *To* this was added dropwise with stirring a solution of poly(dichlorophosphazene) (4.0 g, 0.035 mol) in benzene (500 mL) under an atmosphere of dry nitrogen. The mixture was stirred at 0 °C for 6 h and then allowed to warm slowly to 25 °C as stirring continued for an additional 10 h. The mixture was cooled again to 0 °C, and methylamine (100 mL, 2.25 mol) was added by

means of a dry ice condenser. The suspension was stirred at 0 °C for 10 h and then filtered. Evaporation of solvent from the filtrate yielded an adhesive solid. This was purified by precipitation twice from ethanol or methanol into benzene (yield 71%). The white polymer was only slightly soluble in benzene or tetrahydrofuran, but a final purification was effected by precipitation from benzene into hexane.

Poly[(ethyl glycino)(methylamino)phosphazene] (IX) (Method D). This procedure differed from the preceding one by addition of the free amino acid ester *to* the poly(dichlorophosphazene) to ensure an even distribution of these substituents along each chain. Dry glycine ethyl ester hydrochloride (4.8 g, 0.035 mol) was suspended in dry benzene (450 mL) and treated with triethylamine (6.96 g, 0.069 mol). The mixture was stirred at reflux for 3.5 h, cooled to 0 °C, filtered in a dry nitrogen atmosphere, and then added dropwise to a stirred solution of poly(dichlorophosphazene) (4.0 g, 0.035 mol) in benzene (500 mL) at 0 °C. After 6 h reaction at 0 °C and 10 h at 25 °C, the mixture was recooled to 0 °C and treated rapidly with a large excess of liquid methylamine (100 mL, 2.25 mol). The methylamine addition was carried out quickly in order to reduce the possibility of cross-linking by this reagent. After 10 h additional reaction, the mixture was filtered to remove the solid polymer and hydrochloride salts. These latter were removed by a series of reprecipitations from methanol into tetrahydrofuran. The yield was 70.4%.

Poly[bis(ethyl 4-aminobutyro)phosphazene], $[NP(NHCH_2CH_2CH_2COOEt)_2]_n$. Ethyl 4-aminobutyrate hydrochloride (10 g, 0.06 mol) was stirred with dry triethylamine (4.2 mL, 0.03 mol) in dry benzene (300 mL). To this was added dropwise, with constant stirring, a solution of poly(dichlorophosphazene) (2.3 g, 0.02 mol as $NPCl_2$) in dry benzene (500 mL). The mixture was stirred at 25 °C for 24 h and was then filtered to remove triethylamine hydrochloride. Evaporation of the solvent yielded a polymer film. Precipitation from tetrahydrofuran into water yielded a polymer that contained no residual chlorine (Beilstein test).

Reactions of Ethyl Glycinate with $(NPCl_2)_3$ and $(NPCl_2)_4$. Dry ethyl glycinate hydrochloride (24.6 g, 0.176 mol) was stirred for 3.5 h in dry boiling benzene (300 ml) with dry triethylamine (18.5 mL, 0.13 mol), before cooling to 0 °C and filtration to remove hydrochloride salts. The filtrate was then treated with hexachlorocyclotriphosphazene (2.5 g, 0.0 2 mol as $NPCl_2$) in dry benzene (200 mL). After the mixture had been stirred at 0 °C for 6 h and at 25 °C for 10 h, the white solid was filtered off and dried (mp 145–146 °C). Evaporation of the filtrate at reduced pressure yielded a yellow oil. Mass spectral analysis of the oil showed the presence of $(NPCl_2)_3$, $[NP(NHCH_2COOC_2H_5)_2]_3$, and all the possible mixed substituent trimers.

A similar reaction was performed with the use of ethyl glycinate hydrochloride (24.6 g, 0.176 mol), triethylamine (18.5 mL, 0.135 mol), and $(NPCl_2)_4$ (2.5 g, 0.022 mol as $NPCl_2$). The filtrate from the reaction mixture was evaporated to leave a pale yellow solid which, when recrystallized from benzene, gave crystals, mp 106–107 °C. The material contained no chlorine (Beilstein test). Its mass spectrum showed a parent peak at 997 amu (the mol wt of $[NP(NHCH_2COOC_2H_5)_2]_4$ is 996). The infrared spectrum was consistent with the same compound.

Poly[(*tert*-butyl glycino)(methylamino)phosphazene]. Glycine *tert*-butyl ester hydrochloride (5.0 g, 0.03 mol) was stirred in dry benzene (300 ml) with dry triethylamine (4.2 mL, 0.03 mol). The mixture was stirred at reflux for 3.5 h and then cooled to 0 °C. To this was added dropwise, with constant stirring, a solution of poly(dichlorophosphazene) (1.43 g, 0.012 mol) in dry benzene (150 mL). The mixture was stirred at 0 °C for 6 h and then allowed to warm slowly to 25 °C for an additional 10 h. A sample of polymer isolated from this reaction mixture and purified still contained unreacted chlorine (Beilstein test). The main reaction mixture was then cooled to 0 °C and methylamine (5 mL, 0.123 mol) was added. The reaction mixture was stirred at 0 °C for 10 h and at 25 °C for 6 h. The polymer was then isolated by filtration and removal of solvent from the filtrate. Final purification was effected by reprecipitation from THF into water.

Poly[bis(1-ethoxyethyl-2-amino)phosphazene] (XX). The reaction was carried out in a similar manner to those described above between aminodiethyl ether (15 g, 0.17 mol), poly(dichlorophosphazene) (3.95 g, 0.034 mol), and triethylamine (20 mL, 0.134 mol) in dry benzene (800 mL).

Poly[bis(3-aminopentyl)phosphazene] and Poly[(3-aminopentyl)(methylamino)phosphazene] (XXII). A solution of dry 3-amino pentane (25 g, 0.288 mol) and dry THF (300 mL) was stirred with triethylamine (82.5 mL, 0.6 mol). To this was added dropwise with stirring a solution of poly(dichlorophosphazene) (13.4 g, 0.115 mol) in THF (700 mL). The mixture was stirred at 45 °C for 16 h and then at 65 °C for 75 h. One-half of this reaction mixture was filtered, and the filtrate was concentrated at reduced pressure. Purification was effected by precipitation from THF into water. Residual halogen was detected by a Beilstein test. The intrinsic viscosity was 0.48 dL/g and the approximate $\overline{M}_n$ value was 400 000. A sample isolated after the 16-h step at 45 °C had an intrinsic viscosity of 1.52 dL/g and an $\overline{M}_n$ value of 1 250 000. Hence, the "forcing" conditions caused some depolymerization.

The second half of the reaction mixture was treated at 0 °C with methylamine (50 mL, 1.15 mol) in THF (500 mL). The mixture was stirred at 0 °C for 6 h and 25 °C for 10 h. Filtration, followed by repeated reprecipitation of the filtrate from THF into water, yielded a white brittle polymer. Traces of chlorine could still be detected by a Beilstein test. The intrinsic viscosity in THF was 0.56 dL/g. The microanalysis corresponded closest to a polymer that contained 52% $NHCH(C_2H_5)_2$, 44% $NHCH_3$, and 4% Cl groups, although similar reactions yielded polymers that contained up to 78% of the substituent groups as $NHCH(C_2H_5)_2$ units. It should be noted that the detection of chlorine does not necessarily indicate incomplete substitution. These polymers are strong bases, and hydrogen chloride is strongly bound, especially to the skeletal nitrogen atoms.

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References and Notes

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