Equilibrium Cyclic Oligomer Formation in the Anionic Polymerization of ϵ-Caprolactone

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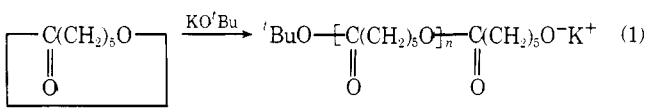
ABSTRACT: The anionic polymerization of ϵ-caprolactone in tetrahydrofuran with potassium *tert*-butoxide results in a living ring–chain equilibrium system. The product distribution is essentially determined by the entropy term, the lower cyclics being favored over the linear chains at higher dilution. Thus the equilibrium state is readily changed by dilution or concentration of the living system. The molar cyclization equilibrium constant decreased in proportion to the −2.5 power of the ring size, in accord with the Jacobson–Stockmayer theory, with the exception of the trimer which equilibrated at an appreciably lower concentration than expected. Terminating the reaction before establishment of the equilibrium provides direct evidence that the cyclic oligomers are produced by back-biting degradation from the initially formed linear polymers.

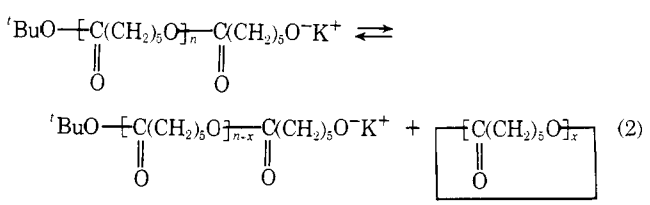
Recently formation of cyclic oligomers has been a matter of increasing concern particularly in the field of the cationic polymerization of heterocyclic monomers.[1] In contrast, little attention has been paid to anionic systems, except that some cyclic oligomers were found to occur as by-products in the anionic polymerization of ϵ-caprolactone.[2,3] In view of the very facile intra- and intermolecular transesterification reactions in this system,[3,4] it was thought interesting and important to study the product distribution with particular attention to the formation of cyclic oligomers. This paper shows that the anionic polymerization of ϵ-caprolactone can be described essentially as a thermodynamically controlled ring–chain equilibrium system. The lower cyclics are favored over the linear polymers with increasing dilution in accord with the Jacobson–Stockmayer theory.[5,6]

Experimental Section

All commercial reagents were purified by the usual procedures. Final purifications and reactions or polymerizations were performed in a high-vacuum system, pumped to 10^{-6} mm Hg, using a conventional breakable seal technique.[7] Tetrahydrofuran was distilled over lithium aluminum hydride and then from a blue colored solution containing sodium anthracene. ϵ-Caprolactone and *tert*-butyl alcohol were dried and distilled over calcium hydride. Potassium *tert*-butoxide was prepared by reaction of a potassium mirror and *tert*-butyl alcohol, with occasional degassing to remove the evolved hydrogen gas. The excess *tert*-butyl alcohol was evaporated by heating, and the resulting initiator, sublimed on the wall of the reaction flask, was dissolved in terahydrofuran. Its concentration was determined by titration of an aliquot with potassium hydrogen phthalate.

Polymerizations or depolymerizations were usually carried out with samples of 0.2 to 2 g in 10 to 150 mL of tetrahydrofuran and 0.5 to 2 mol % initiator, corresponding to a total monomer concentration, $[M]_T$, of 0.07 to 0.5 M and an initiator concentration, $[I]_0$, of 0.7×10^{-3} to 8×10^{-3} M. The reaction was terminated by addition of excess 0.1 N hydrochloric acid in tetrahydrofuran, the solvent was evaporated under vacuum, and the product distribution was determined in chloroform by GPC with a Toyo Soda HLC 802 UR equipped with two columns, G2000 H8 (extrusion limit 2.5×10^2 Å). Flow rate was 1 mL/min. The peak position and intensity (area) were calibrated by using the monomer, the cyclic oligomers which had been isolated as described later, and a polymer with a number average molecular weight (measured by VPO) of 10 400 which had been reprecipitated from benzene into methanol. The peak area per unit weight, relative to that of the dimer, was as follows; $a_1/a_2 = 0.94$, $a_3/a_2 = 1.03$, $a_4/a_2 = a_5/a_2 = a_6/a_2 = 1.06$, and $a_p/a_2 = 1.11$, where a_i is the peak area per unit weight of the cyclic i mer, and a_p is the peak area of the polymer. Those of the tetramer, pentamer, and hexamer were assumed to be equal to each other, and those of the heptamer and the higher oligomers were assumed to be equal to the polymers. The relative errors involved in the determination of product distribution are believed to be within ±5% for the dimer, ±10% for the timer to hexamer, and ±30% for the higher cyclics and the polymers. Here the "polymers" in this report refer to those with molecular weights higher than about 2×10^3, based on the GPC calibration with standard polystyrene samples. They are reasonably assumed to be the linear polymers, since the weight fraction of cyclics in the equilibrated system should decrease according to −1.5 power of ring size[5,6] to be practically negligible at these molecular weight ranges.





A preparative experiment was carried out to isolate the cyclic oligomers by using 15 g of monomer (0.14 M) in 1.0 L of tetrahydrofuran with 0.86 mol % initiator. After equilibration for 2 h, the mixture was terminated and concentrated to about 80 mL by evaporating the solvent under reduced pressure until massive needle-like crystals precipitated out of the solution. They were filtered, washed with cold tetrahydrofuran, dried, and identified as the cyclic dimer: yield 8.7 g; mp (recrystallized from ethanol) 111.4–112.0 °C (lit.[8-10] 111–112 °C); NMR ($CDCl_3$) δ 2.36 (2 H, t, J = 6.0 Hz, α-CH_2), 1.78 (6 H, m, β,γ,δ-CH_2), δ 4.10 (2 H, t, J = 5.2 Hz, ϵ-CH_2); mass spectrum m/e 228. Anal. Calcd for $(C_6H_{10}O_2)_n$: C, 63.14; H, 8.83. Found: C, 63.42; H, 8.44. The filtrate was evacuated and subjected to distillation under high vacuum to give a fraction (1.6 g) boiled below 150 °C and that (1.9 g) boiled above 200 °C up to about 300 °C. The former liquid was identified essentially as the cyclic trimer (contaminated with 4 wt % dimer and 14 wt % tetramer based on GPC): bp[9] 190–205 °C (0.3 mm); NMR ($CDCl_3$) δ 2.28 (2 H, t, J = 6.0 Hz, α-CH_2), 1.48 (6 H, m, β,γ,δ-CH_2), 4.01 (2 H, t, J = 5.5 Hz, ϵ-CH_2); mass spectrum m/e 342 (trimer), 456 (tetramer). Anal. Found: C, 62.96; H, 8.58. The latter fraction (waxy solid) was a mixture of cyclic trimer (6 wt %), tetramer (50 wt %), pentamer (26 wt %), and hexamer (11 wt %) with small amounts of other higher members (7 wt %): NMR ($CDCl_3$) δ 2.28 (2 H, t, J = 6.0 Hz, α-CH_2), 1.50 (6 H, m, β,γ,δ-CH_2), 4.02 (2 H, t, J = 5.6 Hz, ϵ-CH_2); mass spectrum m/e 456 (tetramer), 570 (pentamer), 684 (hexamer). Anal. Found: C, 63.38; H, 8.62.

NMR and IR spectra of each fraction were fully consistent with the cyclic structure, without any indication of the end groups (CH_2OH, $OC(CH_3)_3$, double bonds) which would be possible in the linear chains. It is also to be noted that the yields of the isolated oligomers are almost consistent with the overall equilibrium distribution as will be described below.

Results and Discussion

The anionic polymerization of ϵ-caprolactone in tetrahydrofuran with potassium *tert*-butoxide was conducted at a variety of conditions, and the product distribution was analyzed by GPC. Figure 1 shows typical GPC chromatograms, and the results are summarized in Table I. The cyclic dimer, trimer, and a mixture of tetramer to hexamer, isolated by a

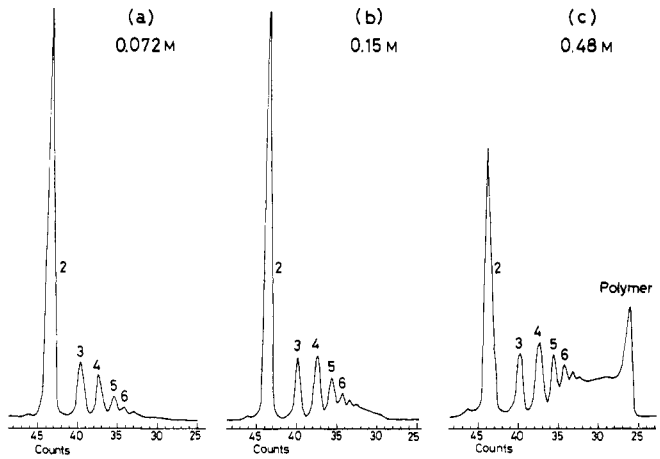


Figure 1. Typical GPC chromatograms of the products equilibrated at a total monomer unit concentration: (a) 0.072 M (run 1); (b) 0.15 M (run 12-1); (c) 0.48 M (run 11-1). The number on each peak indicates the degree of polymerization of the corresponding cyclic oligomer.

preparative experiment, were identified by elemental analyses, NMR, IR, and mass spectra. The monomer peak at 48 counts in GPC could not be detected in all runs listed in Table I, indicating its final distribution should be less than 1 wt % at most.

Attempts to follow the reaction with time (runs 2, 3, and 4) revealed surprisingly that the monomer consumption was completed in a few minutes, thereafter the product distribution changed very little with standing times as long as several days. The reaction mixture remained nevertheless an active living system, because additional monomer was also completely converted to give a different product distribution (run 10-2). In fact, the product distribution could be readily changed simply by dilution (run 11-2) or by concentration of the living system (run 12-2). The lower cyclics were more favored over the polymers with increasing dulution. The lower cyclics were more favored over the polymers with increasing dilution. Therefore, the present system, very soon after the introduction of the initiator solution, can be essentially represented by the living ring–chain equilibrium given in eq. 2.

As expected from the equilibrium equation and also from the Jacobson–Stockmayer theory,[5,6] the concentration of each product at equilibrium was influenced exclusively by the concentration of the total monomer units present. Figure 2 clearly proves this situation, because the plots are independent of the history of the experiments including not only the conventional polymerization of monomer (runs 1–6), but also depolymerization of a polymer (run 7), polymerization of dimer (runs 8, 9), polymerization of additional monomer (run 10), dilution with additional solvent (run 11), and concentration by solvent evaporation (run 12). In this figure, a critical monomer unit concentration is apparent at about 0.25 unit mol/L, below which the polymers are effectively absent, and above which the polymers appear in proportion to the concentration whereas the concentrations of the cyclic oligomers are levelled off.

The molar cyclization equilibrium constant[6,11] is defined by

$$-M_n- \rightleftarrows -M_{n-x}- + c\text{-}M_x \tag{3}$$

and

$$K_x = \frac{[-M_{n-x}-][c\text{-}M_x]}{[-M_n-]} = \frac{[c\text{-}M_x]}{p^x} \tag{4}$$

where $-M_n-$ and $-M_{n-x}-$ are the linear n and $n-x$ mer, and $c\text{-}M_x$ the cyclic x mer, and p is the ratio of the concentration

Table I
Equilibrium Product Distribution

Run	$[M]_T$,[h] unit M	$[I]_0$, 10^3M	Temp, °C	Time	Product distribution, wt %[i] $x = 2$	$x = 3$	$x = 4$	$x = 5$	$x = 6$	$x \geq 7$	Polymers
1[a]	0.072	0.67	0	7 h	73	10	8	5	2	2	0
2-1[a]	0.13	1.5	0	0.5 h	57	11	11	8	5	8	0
2-2[a]	0.13	1.5	0	50 h	60	11	11	7	4	7	0
2-3[a]	0.13	1.5	0	406 h	60	11	10	7	4	8	0
3-1[a]	0.21	4.0	0	26 s	45	10	11	9	6	19	0
3-2[a]	0.21	4.0	0	2 h	45	10	11	8	6	20	0
4-1[a]	0.32	3.5	0	95 s	39	9	11	8	5	14	14
4-2[a]	0.34	3.5	0	5 h	40	8	10	8	5	13	16
5[a]	0.42	7.1	0	2 h	31	6	8	6	4	11	34
6-1[a]	0.26	5.2	−78	7.5 h	36	8	11	8	7	17	13
6-2[a]	0.27	5.0	0	7 h	41	9	11	8	6	16	9
6-3[a]	0.26	4.4	50	6.5 h	41	12	10	8	5	14	10
7-1[b]	0.11	0.92	−78	20 h	67	10	10	6	4	3	0
7-2[b]	0.10	0.85	0	20 h	67	11	9	6	2	5	0
7-3[b]	0.10	0.81	50	20 h	65	12	8	5	3	7	0
8[c]	0.12	2.6	0	7 h	62	11	10	6	3	8	0
9[c]	0.46	7.9	0	7 h	28	7	8	5	3	9	40
10-1[a]	0.16	5.9	0	1 h	53	11	11	8	5	12	0
10-2[d]	0.50	5.7	0	2 h	26	6	8	5	3	7	45
11-1[a]	0.48	8.8	0	1 h	29	7	9	6	4	10	35
11-2[e]	0.12	2.2	0	2 h	63	11	10	7	4	5	0
12-1[a]	0.15	2.5	0	1 h	57	11	11	8	4	9	0
12-2[f]	0.48	7.3	0	2 h	26	7	9	6	4	10	38
12-3[g]	0.28	2.2	0	20 h	42	9	10	8	5	14	12

[a] Polymerization of ϵ-caprolactone monomer. [b] Depolymerization of a polymer with $\bar{M}_n$ = 10 400. [c] Polymerization of cyclic dimer. [d] Addition of monomer to the run 10-1. [e] Dilution with solvent added to the run 11-1. [f] Concentration of the run 12-1 by evaporation of solvent. [g] Simultaneous additions of monomer and solvent to the run 12-2. [h] The concentration of the total monomer units in the equilibrated mixture. [i] The monomer could not be detected in GPC in all runs so that its equilibrium distribution should be less than 1 wt %.

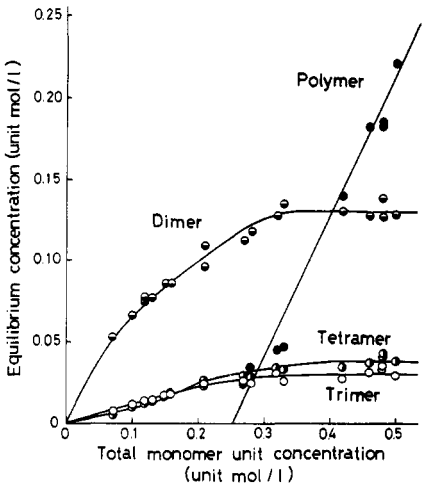


Figure 2. Equilibrium concentrations of cyclic dimer (⊖), trimer (○), tetramer (◑), and linear polymers (●) as a function of total monomer unit concentration at 0 °C.

Table II
Molar Cyclization Equilibrium Constant at 0 °C

x	$K_x \times 10^2$, M	ΔG, kcal/mol	ΔS, cal/(mol deg)
2	6.50	1.48	−5.4
3	1.07	2.46	−9.0
4	0.98	2.51	−9.2
5	0.60	2.78	−10.2
6	0.34	3.09	−11.3

of the living linear chains of $n+1$ mer to that of n mer. Since p should approach unity at the condition $n \gg 1$, K_x should be given directly by the limiting equilibrium concentration of the corresponding cyclic x mer which formed at a monomer concentration appreciably higher than the critical 0.25 unit mol/L. The result is given in Table II, together with the corresponding change in free energy and entropy, calculated by

$$-RT \ln K_x = \Delta G = -T\Delta S \quad (5)$$

The enthalpy term ΔH was neglected because the product distribution changed very little by equilibration at −78, 0, and 50 °C (Table I, runs 6 and 7). In fact, ΔH was estimated to be less than ±0.6 kcal/mol at most, which corresponds to an observed maximum difference of 20% in the product distributions at 0 and 50 °C. Thus it may be concluded that the cyclic oligomers of $x \geq 2$ and the linear polymers differ little in their enthalpy contents.

Since eq 2 or 3 also stands for the equilibrium, from right to left hand side, for the polymerization of the respective cyclic x mer, it is to be noted that the reciprocal K_x is identified as the equilibrium constant for polymerization, $-\Delta G$ and $-\Delta S$ being the free energy and entropy changes for polymerization. It is therefore concluded that the polymerization–depolymerization equilibrium involved is essentially determined by the entropy difference among the cyclic oligomers of $x \geq 2$ and the linear polymers. Log–log plots in Figure 3 show that K_x decreases in proportion to −2.5 power of x, in accord with the Jacobson–Stockmayer theory[5,6] which assumes Gaussian chain statistics. This relation does not hold for the trimer which equilibrates at a considerably lower concentration than expected, suggesting some unfavored ring conformation. However, its fraction, as compared to those of higher oligomers, was found to increase, even though very slightly, with increasing dilution (runs 1-5) and increasing equilibration temperatures (runs 6 and 7) to approach a concentration expected by the theory.

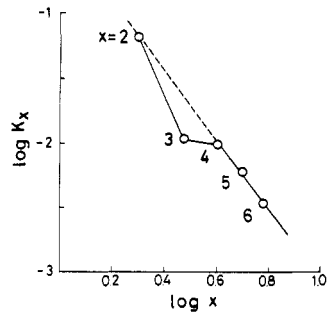


Figure 3. Log–log plot of molar cyclization equilibrium constant (K_x) against ring size (x). The slope of the linear broken line is −2.5.

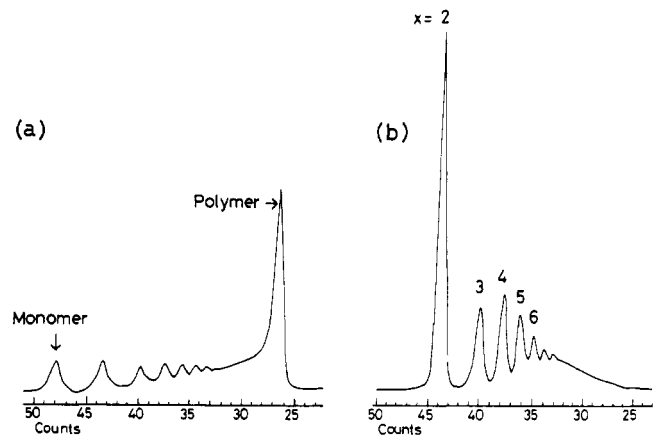


Figure 4. GPC chromatograms of the products obtained before and after establishment of equilibrium: polymerization time (a) 6 s (run 3); (b) 26 s (run 3-1). $[M]_0 = 0.21$ M, $[I]_0 = 4.0 \times 10^{-3}$ M.

Finally, kinetic aspects of the present system should be mentioned in connection with the very high rate of monomer conversion. Monomer could not be detected to any appreciable amount in the equilibrated mixture. Upon terminating the reaction as soon as possible (6 s after the introduction of the initiator solution), a nonequilibrium product distribution could be observed such as shown in Figure 4a. A peak at 26 counts due to the polymers is most prominent (68%) in comparison to those due to unreacted monomer (6%) and other oligomers (26% in total). After reaction for 26 s the equilibrium was already reached, as shown in Figure 4b (run 3-1). Exactly the same distribution resulted after reaction for 2 h (Table I, run 3-2). Since the condition was such that the high polymers could never occur at equilibrium, as is obvious from Figure 4b, this result provides direct evidence that the cyclic oligomers are produced by degradation from the initially formed linear polymers. Therefore it is reasonable to suppose that the highly reactive monomer is first very rapidly polymerized to give essentially the living linear chains which, having almost lost their ability to propagate further, are left either to degrade through back-biting reactions to give the cyclic oligomers, or to undergo intermolecular interchange reactions. Thus, it is to be noted that all of the reactions are either intra- or intermolecular transesterifications involving alkoxide anions and reach equilibrium in less than 1 min.

It may be now appropriate to estimate the propagation rate constant, k_p, for the ε-caprolactone polymerization by applying the result in Figure 4a to eq 6

$$\ln [M]_0/[M] = k_p[C]t \quad (6)$$

where $[M]_0$ is the initial monomer concentration and [M] that at time t, and [C] is the concentration of living ends. Assuming a living system with an instantaneous and quantitative initiation coupled with no termination gives, with $[M]/[M]_0 = 0.06$,

[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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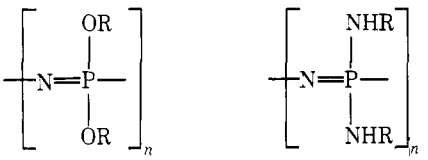
ABSTRACT: Phosphazene high polymers with glycino ethyl ester, leucino methyl ester, alanino methyl ester, and phenyl alanino methyl ester substituents have been synthesized by the interaction of poly(dichlorophosphazene) (IV) with amino acid esters. Total halogen replacement was achieved only with glycine 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.

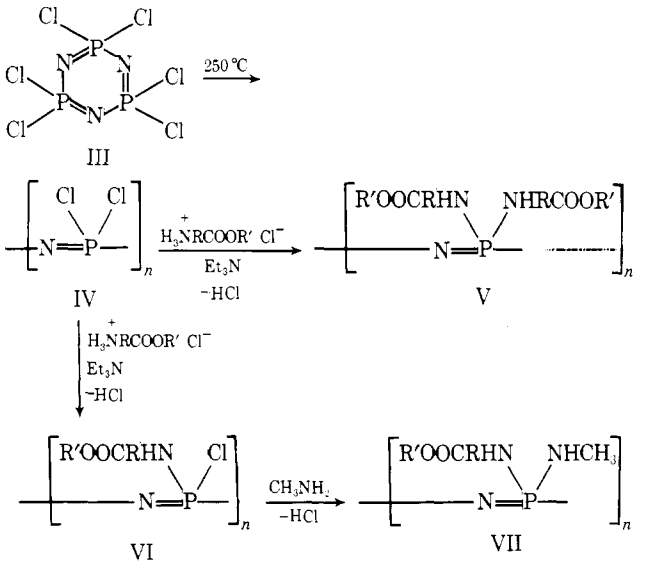
Stable phosphazene high polymers were first prepared by Allcock, Kugel, and Valan[4-6] and this work was extended by Allcock, Cook, and Mack.[7,8] Such polymers (I or II) are virtually unique with respect to the range of different properties that are accessible.[9] Specific phosphazene polymers with 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