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(33) High-resolution mass spectral data were obtained with the use of an AEI MS-902 mass spectrometer, linked to a PDP-8 computer.
(34) Elemental analysis data were obtained by Galbraith Laboratories.
(35) ^{31}P NMR data were recorded on a JEOL JNM-PS-100 spectrometer operating at 40 MHz in the Fourier transform mode. The samples were dissolved in THF (polymers) or $CHCl_3$ (cyclic model compounds). The data were processed on a Nicolet 1080 computer. Peak assignments were made on the basis of ^1H-decoupled and undecoupled spectra. Chemical shifts are based on the ppm scale; positive shifts are downfield from external H_3PO_4 used as a reference.
(36) ^1H NMR spectra were recorded on a JEOL JNM-PS-100 spectrometer operating at 100 MHz in the Fourier transform mode. The samples were dissolved in C_4D_8O (polymers) or $CDCl_3$ (cyclic species). The data were processed on a Nicolet 1080 computer. Peak assignments and coupling constants were determined on the basis of ^{31}P-decoupled and undecoupled spectra. Chemical shifts are on the δ scale and referenced to internal tetramethylsilane.
(37) The molecular weights were estimated by gel permeation chromatography, using polystyrene standards with 10^6, 10^5, 10^4, and 10^3 Styragel columns in series. The solvent was tetrahydrofuran.
(38) The glass transition temperatures (T_g) were measured with the use of a Chemical Instruments Corp. torsional braid analyzer, programmed to operate from −120 to +120 °C, with a temperature scan rate of 2.0 °C min^{-1}.

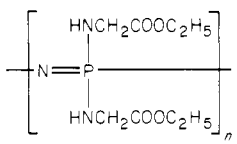
Phosphazene High Polymers with Steroidal Side Groups[1]

H. R. Allcock* and T. J. Fuller

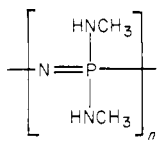
Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802. *Received June 5, 1980*

ABSTRACT: Steroidal residues derived from desoxoestrone (III), estrone (IV), 17β-estradiol (V), 17α-ethynylestradiol (VI), estradiol 3-methyl ether (VII), and 1,4-dihydroestradiol 3-methyl ether (VIII) have been linked to a polyphosphazene chain via the sodium salt of the steroidal hydroxy function. The degree of replacement of P–Cl bonds by P–OR units was in the range 0.5–40%, depending on the reaction conditions. The residual chlorine atoms were removed by reaction with methylamine, ethyl glycinate, or *n*-butylamine. Stable polymers of structure XIV were obtained when the steroidal units were linked to phosphorus through an aryloxy residue. However, linkage through an alkoxy residue led to instability and chain cleavage. The use of ethyl glycinato residues as cosubstituent groups yielded hydrolytically degradable polymers. Comparisons are made between these high-polymeric reactions and those of small-molecule cyclophosphazene models.

The use of macromolecules as carrier species for biologically active agents is a subject of growing interest.[2-4] Poly(organophosphazenes) are of particular interest in this respect. Amino acid ester substituted polyphosphazenes (I) are potential biodegradable polymers,[5] and the water-soluble polymer II has been investigated as a polymeric coordination ligand for platinum anticancer complexes.[6]



I

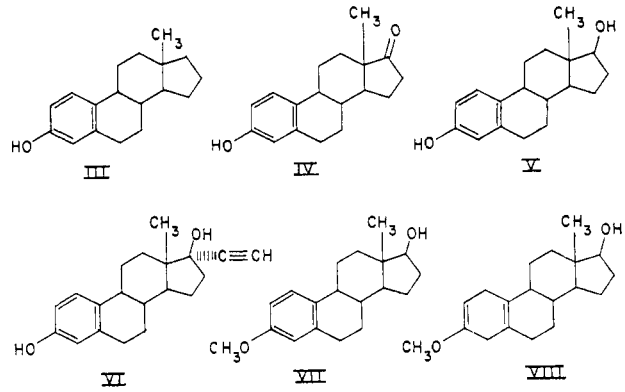


II

In this paper, we consider the prospect that poly(organophosphazenes) can be linked covalently to biologically active species, such as steroids. As a prelude to this study, we reported elsewhere the synthesis of several steroidal phosphazene model compounds based on the small-molecule cyclotriphosphazene framework XI.[7] In that work, we identified six steroid structures that were suitable for attachment to a phosphazene skeleton. These were desoxoestrone (III), estrone (IV), 17β-estradiol (V), 17α-ethynylestradiol (VI), estradiol 3-methyl ether (VII), and 1,4-dihydroestradiol 3-methyl ether (VIII). Here we extend those model reactions to the high polymers.

Steroids III, VII, and VIII were used because they contain only one active functional group and should not participate in cross-linking reactions. Steroid VIII was utilized because it can be converted, by treatment with acid, to 19-nortestosterone, a clinically important species.[8] Steroids IV–VI are also pharmacologically active. Although they are multifunctional, species IV–VI possess a 3-C-aromatic hydroxy function that should be more reactive than the hydroxy or keto groups at the 17-positions. Hence, cross-linking was expected to be minimal. The residues from III–VII were expected to confer a characterization advantage because their presence can be monitored by ultraviolet spectroscopy. Species IV–VI were expected to be biologically active, even in the polymer-bound form because the functionally active centers would remain exposed.

Chart I



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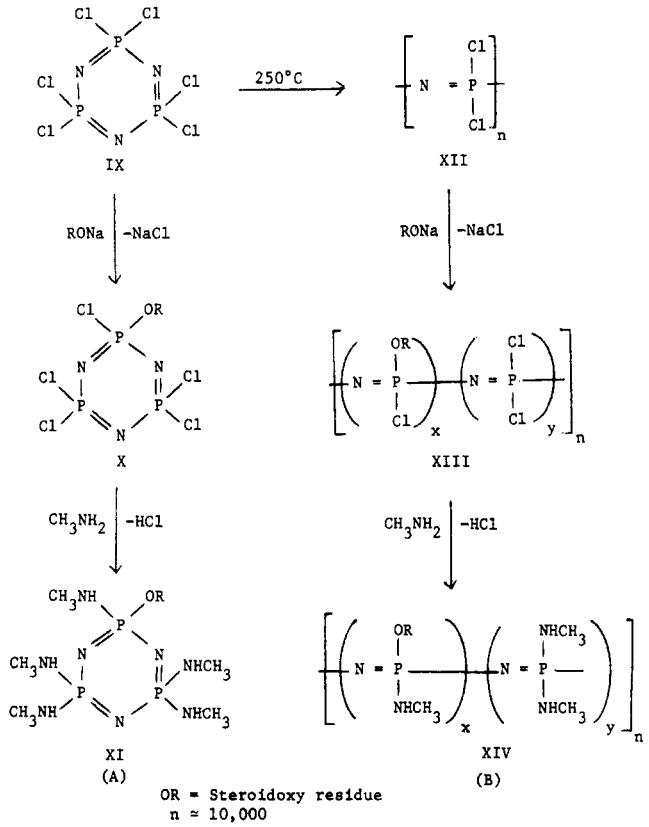
Scheme I



The overall synthetic strategy employed in the present study is outlined in pathway B of Scheme I. The model studies reported elsewhere[7] are summarized in pathway A of the same scheme. The synthesis involved a two-step substitution sequence. First, the sodium salt of the steroid was allowed to react with poly(dichlorophosphazene) (XII). Second, the remaining chlorine atoms in XIII were replaced by reaction with an amine in order to remove the hydrolytic lability associated with P–Cl bonds. In the model system studied previously,[7] it was found that the amino–steroidal cyclophosphazenes XI could be isolated and characterized much more readily than could compounds of structure X. Hence, it was anticipated that a similar advantage would be derived from the conversion of XIII to XIV. However, primary amines are known to react with the carbonyl group of estrone (IV).[7] Hence, in the present work, only the first step in the synthesis (the formation of XIII) was examined when this steroid was present.[9] Methylamine was chosen as a cosubstituent for three reasons. First, methylamine has a high reactivity toward P–Cl bonds,[10] and methylamino units can be attached to the phosphazene skeleton under relatively mild experimental conditions.[11] Second, because of its small steric size, methylamine is an excellent nucleophile for replacement of chlorine atoms that might be sterically shielded by bulky steroidal residues. Finally, the methylamino group is a water-solubilizing substituent. However, other cosubstituent groups, such as ethyl glycinato or *n*-butylamino, were also introduced in specific experiments. It should be noted that the cosubstituent group was attached to the phosphazene chain *after* the introduction of the steroidoxy unit in order to reduce the probability of homopolymer formation by the aminolysis reaction.

The objectives of this investigation were to answer the following questions. (1) Do the model compound studies with compounds such as X or XI provide valid information that can be applied to the synthesis of the high polymers XIII and XIV; in particular, do significant reactivity differences exist between IX and XII that might complicate the future synthesis of a broad range of phosphazene polymer-bound drugs? (2) Does the attachment of the steroid residue to a high-polymeric phosphazene chain alter the stability or reactivity of the steroid function? (3) What effect does the cosubstituent group have on the physical and chemical properties of the polymer?

Results and Discussion

Linkage of the Steroid Residues to $(NPCl_2)_n$. The sodium salts of steroids III–VIII were prepared by a reaction with sodium hydride in tetrahydrofuran. The attachment of the steroidal residues to the polymer was limited both by the efficiency of preparation of the sodium salt from the free steroid and by the solubility of the steroidal salt in tetrahydrofuran.[7] The addition of dilute solutions of these steroid oxide salts to solutions of $(NPCl_2)_n$ yielded species of type XIII. As discussed in later sections, different degrees of chlorine replacement by steroidoxy units (over the range 0.5–40%) were obtained by changes in the reactant stoichiometry. Species XIII were not isolated or characterized fully because of their sensitivity to hydrolysis. Instead, with the exception of the estrone derivative,[9] they were converted immediately to XIV. Hence, the side-group ratios in species XIII were inferred indirectly from the structures of XIV.

It should be noted that aliphatic-type steroidal alcohols (V–VIII) or ketones (IV) are capable of side reactions with chlorophosphazenes. In particular, P–Cl bonds can induce the dehydration of V–VIII with the concurrent formation of hydroxyphosphazenes.[7,12] Species X or XIII are especially susceptible to this reaction, and this constitutes a second reason for the immediate direct aminolysis to XIV rather than an isolation of XIII.

Introduction of the Cosubstituent Group. It was anticipated that the steric bulk of the steroidal units might inhibit the replacement of nearby chlorine atoms by the cosubstituent nucleophile. For this reason, a series of control cosubstitutions were carried out with polymers of type XIII which contained OCH_2CF_3, OC_6H_5, or OC_6H_4Br-*p* substituents in place of the steroidoxy units. It was found that cosubstitution with methylamine was complete even when relatively mild reaction conditions were employed (−6 to +25 °C in a THF–methylamine cosolvent system at 760 torr). High-pressure autoclave reaction conditions were explored (see Experimental Section) but were not necessary for complete substitution.

With the steroidoxy units present, essentially all of the remaining chlorine atoms in XIII could be replaced by treatment with methylamine by using the mild reaction conditions established for the model polymers. The traces of residual chlorine (<1.5%) that were detected by elemental microanalysis were attributed to small amounts of hydrogen chloride bound as a salt to the skeletal or side-group nitrogen atoms. No residual P–Cl bonds could be detected by ^{31}P NMR analysis.[13]

Complete replacement of chlorine could also be obtained with the use of ethyl glycinato or *n*-butylamino cosubstituents in place of methylamino. The ethyl glycinato cosubstituent was expected to impart hydrolytic instability and biocompatibility to the polymer.[5] Higher temperatures (70 °C) were required for the cosubstitution reaction when butylamine was used.

No evidence was obtained that the cosubstitution reaction with methylamine, ethyl glycinate, or *n*-butylamine was accompanied by any displacement of the alkoxy or aryloxy groups already present. It has already been shown[5,10] that the reaction of $(NPCl_2)_n$ (XII) with these

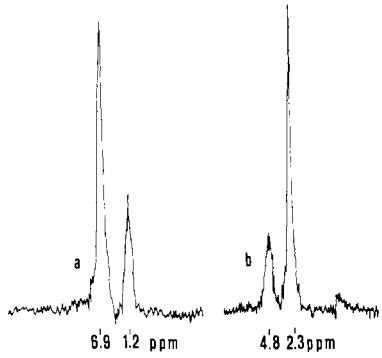


Figure 1. ^{31}P NMR spectra obtained for the compounds (a) $[NP(OR)_{0.2}(NHCH_3)_{1.8}]_n$, where ROH = ethynylestradiol (VI) (10–15%), and (b) $[NP(OR)_{0.7}(NHCH_3)_{1.3}]_n$, where ROH = estradiol (V) (35–40%).[15] Assignments for the chemical shifts are listed in Table II. The solvent was tetrahydrofuran.

amines does not lead to appreciable chain cleavage. Hence, any molecular weight decreases detected in the present work must be attributed to the presence of the steroidal units or to the side reactions that accompany the introduction of these units.

Structure of the Polymers. (1) Evidence for Steroid Attachment. Two analytical techniques—^{31}P NMR and ultraviolet spectroscopy—were used to confirm that the steroidoxy units were bound covalently to the phosphazene chain. The ^{31}P NMR approach will be described first.

The model homopolymers showed ^{31}P NMR peaks at the following chemical shift positions: −7.5 ppm, $[NP(OCH_2CF_3)_2]_n$; −19.7 ppm, $[NP(OC_6H_5)_2]_n$; −19.7 ppm, $[NP(OC_6H_4Br\text{-}p)_2]_n$; +7 to +8 ppm, $[NP(NHCH_3)_2]_n$; −0.8 ppm, $[NP(NHCH_2COOC_2H_5)_2]_n$; 4.4 ppm, $[NP(NHC_4H_9)_2]_n$. For model mixed-substituent polymers of type XIV, the following characteristic chemical shifts were identified: For $[NP(OCH_2CF_3)_x(NHCH_3)_y]_n$: 8.0 ppm, $P(NHCH_3)_2$; 3.0 ppm, $P(OCH_2CF_3)(NHCH_3)$; −6.7 ppm, $P(OCH_2CF_3)_2$. For $[NP(OC_6H_5)_x(NHCH_3)_y]_n$: 8.2 ppm, $P(NHCH_3)_2$; −0.9 ppm, $P(OC_6H_5)_2(NHCH_3)$. (See Table II for additional assignments.) These comparisons formed the basis of the proof for steroid attachment and, as described later, the evidence for the pattern of substitution.

Initially, it was shown that the polymer of type XIII, formed by the reaction of the sodium salt of estrone with $(NPCl_2)_n$, gave *two* closely spaced broad resonances in the region of −18 ppm [probably from PCl_2 and PCl(OR)]. However, it was clear that the similarity between the chemical shift positions of PCl_2 and PCl(OAryl) or P(OAryl)$_2$ precluded a definitive structural identification. Hence, the ^{31}P NMR spectra of species of type XIV were of greater value. The ^{31}P NMR spectra of species XIV were remarkably simple (Figure 1 and Table II). They showed two main peaks that were compatible with the presence of $P(NHCH_3)_2$ and $P(NHCH_3)(OAryl)$ units. Hence, the attachment of the steroidal component was confirmed.

Additional confirmation was obtained by a combination of ultraviolet spectroscopy and gel permeation chromatography (GPC) separation. For example, a polymer of type XIV containing the steroidal residue derived from III was subjected to GPC fractionation. The high-polymeric fractions separated in this way (GPC molecular weight $\simeq 1 \times 10^6$) showed ultraviolet absorbance maxima at 278 and 272 nm (in ethanol). The steroid-free homopolymer $[NP(NHCH_3)_2]_n$ showed no detectable ultraviolet absorption in this wavelength region. Moreover, a *mixture* of III and $[NP(NHCH_3)_2]_n$ after GPC separation yielded a polymer that showed no ultraviolet absorbance. Hence, covalent linkage of the steroid had occurred in XIV. Moreover, the absorbance maxima of the bound steroid units differed slightly from those of the free steroid (III) (286.4 and 280 nm).

The ultraviolet and ^{31}P NMR spectra of species XIV, where OR is the residue from III, IV, V, or VI, were compatible with a linkage of the steroidal unit to phosphorus via an *aryloxy* residue. In each case a hypsochromic ultraviolet shift was detected when the polymeric species was compared with the free steroid. However, no hypsochromic shift occurred when steroid VII was linked (through position 17) to the polymer. The ^{31}P NMR spectra of the polymer-bound residues derived from VII and VIII were compatible with linkage through an *alkoxy*-type unit.

(2) Ratios of the Two Substituent Groups and Disposition of Steroidal Units. The substituent ratios were estimated by two methods—ultraviolet spectroscopy and ^{31}P NMR analysis. (The ^{13}C and ^1H NMR spectra of the polymers were too complex to permit an accurate assessment of the side-group ratios.) The ultraviolet analyses made use of controls for comparison with the absorbances measured for the polymers. As little as 0.5% substitution by steroidal units could be detected by this method. The ^{31}P NMR analyses involved comparisons of the peak areas derived from the $P(NHCl_3)_2$ and $P(NHCH_3)(OR)$ resonances. The NMR analysis method could be used only if 5% or more of the steroidal residues were present. These data are summarized in Table II and in the Experimental Section.

The ^{31}P NMR data showed clearly that the steroidal residues were arrayed *nongeminally* along the chains. This conclusion was based on the detection of resonances from $P(NHCH_3)_2$ and $P(NHCH_3)(OR)$ units and from the absence of detectable $P(OR)_2$ peaks. Of course, this characteristic pattern would not persist if the ratio of steroidal to amino side groups exceeded 1:1. The nongeminal replacement pattern in the conversion of XII to XIII can be explained in terms of steric hindrance effects.

Properties and Reactions of the Polymers. All the polymers were flexible or brittle film-forming materials. The solution properties depended on the ratio of the steroidal to amino side groups and on the nature of the amino residues. For species of formula XIV, the polymers were soluble in water or ethanol when less than 5% of the side groups were steroidal residues (for example, from III, VII, or VIII). These same products were insoluble in most organic media. Polymers with 5–20% of steroidal substituents (for example, from V or VI) were only slightly soluble in water and formed emulsions in aqueous media. However, they were soluble in tetrahydrofuran. Higher ratios of steroidoxy to methylamino units yielded materials that were soluble only in tetrahydrofuran.

The glass transition temperature (T_g) for $[NP(NHCH_3)_{1.3}(OR)_{0.7}]_n$ (where ROH = V) was 60 (DSC) or 68 °C (torsional pendulum). This is comparable to values for $[NP(NHCH_3)_2]_n$ of 58 (DSC) or ≃75 °C (torsional pendulum).

In general, polymers of type XIV were stable at room temperature in the atmosphere. However, the chain length varied (a) according to the type of steroid attached to the polymer and (b) with the ratio of steroidoxy to amino side groups. Steroidal substituents derived from III, IV, V, or VI yielded high molecular weight materials (GPC MW ≃ 10^6), even when 30–40% of the side groups were steroidal residues. However, the residues from steroids VII or VIII induced a marked decline in chain length, even when only one steroid unit was present per ten substituent units.

Higher ratios of steroid VII or VIII to amino residues were associated with progressively lower polymer molecular weights.

This phenomenon was attributed to the linkage of steroids VII or VIII to the phosphazene chain via the aliphatic sites of the steroids. In the earlier cyclophosphazene model compound studies, it was shown that aliphatic steroidal alcohols, such as V–VIII or cholesterol, are prone to undergo dehydration and chlorination reactions with IX, with the concurrent formation of hydroxyphosphazenes.[7] This reaction is facilitated by the presence of acid or by the effects of elevated temperatures. Strong evidence was obtained that VII or VIII underwent a similar reaction with XII at elevated temperatures.[14] The presence of hydroxyphosphazene residues along the polymer chain would almost certainly lead to chain cleavage, especially in the presence of moisture or at elevated temperatures.

Two other possibilities were considered for explaining the destabilizing influence of residues from VII or VIII. These were an O → N alkyl migration reaction similar to those reported for methoxy- or ethoxyphosphazenes[15–17] and hydrolysis of residual P–Cl bonds to P–OH units, followed by chain cleavage. No NMR evidence could be found to support the first possibility, and it seems unlikely that the residues from VII or VIII would inhibit the methylaminolysis of P–Cl bonds or facilitate their hydrolysis to a greater degree than is evident when residues from III–VI are present.

The conversion of XIV, in which OR was the residue from VIII, to its 19-nortestosterone analogue[8] by acidic hydrolysis accomplished the transformation of the steroidal residue but, at the same time, brought about a polymer molecular weight decrease from 1×10^6 to $\simeq 1 \times 10^4$.

The use of ethyl glycinato cosubstituent groups in place of methylamino yielded polymers that underwent chain cleavage in aqueous media. This is a charactristic of polyphosphazenes that contain amino acid ester substituents.[5] The effect was not observed when methylamino units were present as side groups.

Comparisons with Small-Molecule Models. The following similarities were found between the polymer of structure XIV and the cyclic model compounds XI. In both systems, steroids III–VI could be attached to the phosphazene skeleton via the aryloxy units to yield stable species. Steroid VII or VIII yielded stable derivatives of structure XI; however, they yielded derivatives of type XIV that were unstable because of side reactions that involved dehydration and chlorination of the aliphatic units. Both the cyclic and the polymeric systems permitted the attachment of multifunctional steroids such as IV, V, or VI without appreciable cross-linking. Moreover, the cosubstitution reactions with methylamine were not inhibited by the presence of the steroid residues in either the cyclic or the high-polymeric system.

On the other hand, the high-polymeric system is much more sensitive to chain-cleavage reactions. These would go unnoticed in the small-molecule cyclic species. This is particularly evident when opportunities exist for P–OH side group units to be formed by dehydration reactions with aliphatic steroidal hydroxy functions.

Experimental Section

Reagents. Anhydrous methylamine (Linde or Matheson) was distilled directly from the cylinder and condensed over sodium. The formation of a blue color was considered to be evidence that the amine was dry. Triethylamine (Eastman) was distilled over barium oxide before use. Benzene and heptane (Fisher) were boiled at reflux over calcium hydride and distilled before use. Tetrahydrofuran (THF) (Fisher) was dried with lithium aluminum hydride or sodium/benzophenone. Sodium hydride, as a 50% dispersion in oil (Alfa), was washed with freshly distilled heptane before use. Estrone (Sigma or Aldrich), 17β-estradiol, 17α-ethynylestradiol, and estradiol 3-methyl ether (Sigma) were dried in vacuo for at least 8 h before use. Literature procedures were used to obtain desoxoestrone[7] and 1,4-dihydroestradiol 3-methyl ether.[8] Hexachlorocyclotriphosphazene (IX) (mp 110–112 °C) was obtained from a trimer–tetramer mixture (El Monte or Ethyl Corp.) after two vacuum sublimations at 60 °C (0.5 torr), two heptane recrystallizations, and two further vacuum sublimations. Poly(dichlorophosphazene) was prepared by the thermal polymerization of $(NPCl_2)_3$ at 250 °C for an 8–24-h period within a sealed Pyrex tube (20 cm × 2.5 cm). A less than 25% conversion of $(NPCl_2)_3$ to $(NPCl_2)_n$ was achieved to maximize the linearity of the polymer. The residual cyclic species were removed by sublimation at 60 °C (0.5 torr) over 12–24 h. The polymer was soluble in benzene or tetrahydrofuran.

Instrumentation. Proton-decoupled ^{31}P NMR spectra were obtained at 40.5 MHz with a JEOL PS100 FT spectrometer. The spectra were processed with a Nicolet 1080 data-processing system. Ultraviolet spectra were obtained with a Varian 634 or Cary 17 ultraviolet spectrometer. Infrared spectra were obtained with a Perkin-Elmer 267, 261, or 580 spectrophotometer. The wavelength maxima assignments were accurate to ± 5 cm^{-1}.

Elemental Analyses. Elemental analyses were performed by Galbraith Laboratories. Samples were dried for at least 8 h in vacuo at 40 °C before analysis. However, the microanalytical data were not as definitive as for the small-molecule model systems. This problem has been encountered with other *amino*phosphazene high polymers (especially with respect to nitrogen and phosphorus analyses) and has been attributed to the resistance of these species to total combustion or total digestion. The residual chlorine detected in XIV appeared to be present as coordinated hydrogen chloride rather than as P–Cl bonds. For these reasons, the NMR and ultraviolet data were considered to be more reliable indicators of composition and structure than the microanalytical results.

Gel Permeation Chromatography. Polymer separations and molecular weight approximations were carried out with a Waters Associates ALC/GPC 202 unit with columns consisting of 2-ft segments with 75A, 175A, 700A, and 2000A porous glass beads. Ethanol (95%) or methanol (75%) and water were used as the elution solvent. Fractions were analyzed by ultraviolet spectroscopy with ethanol or methanol as a reference. A mixture of estradiol 3-methyl ether (VII) and poly[bis(methylamino)phosphazene] was easily separated by this method.

Polymers that were soluble in THF were treated similarly with the exception that a Waters Associates ALC/GPC 501 gel permeation chromatography unit was used. This used a 4-ft, 10^5- or 10^6-Styragel column, with THF as the solvent. Comparisons were made with the elution times for polystyrene standards.

Reactions between the Sodium Salt of Estrone (IV) and $(NPCl_2)_n$ (XII). Under nitrogen, estrone (1 g, 3.7 mmol) was dissolved in THF (250 mL), and excess sodium hydride was added. After 4 h, the suspension was filtered, and the filtrate was added dropwise to a solution of $(NPCl_2)_n$ [0.107 (0.93), 0.215 (1.85), 0.286 (2.47), 0.430 (3.7), 0.859 (7.41), or 2.15 g (18.5 mmol)] dissolved in THF (150 mL). The reaction mixtures were stirred for 8 h, concentrated, and analyzed by ^{31}P NMR techniques.

Preparation of $[NP(NHCH_3)_2]_n$ as a Control. A solution of poly(dichlorophosphazene) (2 g, 0.0172 mol) in THF (250 mL) was cooled to 0 °C. Methylamine (300 mL) was condensed into the reaction vessel by means of a dry ice/acetone condenser and was maintained there for 4 h. The reaction mixture was stirred for 24 h under nitrogen while unreacted methylamine was permitted to escape through a silicone oil bubbler. The solvent was then removed with a rotary evaporator, and the residue was dissolved in ethanol (200 mL). The solution was filtered, and the filtrate was purified by dialysis against ethanol, water, and finally ethanol. The polymeric solution was filtered and concentrated. Evaporation of the solvent left a white film of $[NP(NHCH_3)_2]_n$ (1.0 g). The ^{31}P NMR spectrum of this product was a singlet (Table II). The glass transition temperature of this polymer was 58 °C (DSC). Anal. Calcd: Cl, 0.0. Found: Cl, 0.15.

Preparation of $[NP(OC_6H_4Br\text{-}p)_{0.7}(NHCH_3)_{1.3}]_n$ as a Control. A solution of *p*-bromophenol (1.49 g, 8.62 mmol) in THF (150 mL) was added dropwise under nitrogen to a stirred suspension of excess sodium hydride (5 g, 0.208 mol) in THF (100

Table I
Polymer Solubilities, Molecular Weights, and Spectroscopic Data

polymer product	OR steroid unit derived from	% of side groups as steroidoxy[a-c]	UV absorbance max,[d] nm	IR $\nu_{P=N}$,[e] cm^{-1}	GPC MW[f]	suitable solvents
$[NP(NHCH_3)_2]_n$				1180-1250	1×10^6	ethanol, H_2O
$[NP(OCH_2CF_3)_2]_n$				1270-1280	1×10^6	THF
$[NP(OC_6H_4Br\text{-}p)_2]_n$				1240	1×10^6	THF
$[NP(OC_6H_5)_{0.19}(NHCH_3)_{1.81}]_n$		9.5[b]	265, 260, 255[g]	1200-1260	1×10^6	ethanol, H_2O
$[NP(OC_6H_4Br\text{-}p)_{0.7}(NHCH_3)_{1.3}]_n$		32-37,[b] 34[c]		1200-1260	1×10^6	THF
$[NP(OCH_2CF_3)_{0.084}(NHCH_3)_{1.916}]_n$		4.2[b]		1180-1250	1×10^6	ethanol, H_2O
$[NP(OCH_2CF_3)_{0.374}(NHCH_3)_{1.626}]_n$		19[b]		1180-1280	1×10^6	THF
$[NP(OR)_{0.1}(NHCH_3)_{1.9}]_n$	III	2,[a] 4.7,[b] 5[c]	278, 273, 270[g]	1180-1250	1×10^6	ethanol, H_2O
$[NP(OR)_{0.26}(NHCH_3)_{1.74}]_n$	V	11-14,[b] 13[c]	278, 273, 270	1180-1250	1×10^6	ethanol, H_2O
$[NP(OR)_{0.7}(NHCH_3)_{1.3}]_n$	V	40,[b] 35[c]		1200-1260	1×10^6	THF
$[NP(OR)_{0.2}(NHCH_3)_{1.8}]_n$	VI	12-15,[b] 10[c]		1180-1250	1×10^6	THF, ethanol
$[NP(OR)_{0.024}(NHCH_3)_{1.976}]_n$	VII	1.2[c]	290-283		1×10^4	ethanol, H_2O
$[NP(OR)_{0.1}(NHCH_3)_{1.9}]_n$	VII	4,[a] 5[c]	290, 283	1250	1×10^6	ethanol, H_2O
$[NP(OR)_{0.25}(NHCH_3)_{1.75}]_n$	VII	10.8-14.2[b]		1260	1×10^5	THF
$[NP(OR)_{0.01}(NHCH_2COOCH_2CH_3)_{1.99}]_n$	VII	≤ 0.5[a]	290, 283	1200	1×10^6[i]	THF, ethanol, H_2O
$[NP(OR)_{0.01}(NHCH_2CH_2CH_2CH_3)_{1.99}]_n$	VII	≤ 0.5[a]	290-283	1260	1×10^4	THF
$[NP(OR)_{0.036}(NHCH_3)_{1.964}]_n$	VIII	1.8[c]		1220-1250	1×10^6	ethanol, H_2O
			243[g,h]		1×10^4-1×10^5	ethanol, H_2O

[a] The approximate steroid substitution in XIII was determined by ultraviolet spectroscopy. [b] The steroid percentage was estimated by ^{31}P NMR spectroscopy. [c] The steroid percentage was estimated by elemental microanalysis. [d] Cyclic and polymeric phosphazenes generally have no appreciable absorbance in the ultraviolet region above 220 nm. [e] In general, the "P=N" infrared stretching frequencies for XIV resembled those of the homopolymers with the cosubstituent that was present in the greater concentration. For $[NP(NHCH_3)_2]_n$, $\nu_{P=N} = 1250\ cm^{-1}$ and for $[NP(OCH_2CF_3)_2]_n$, $\nu_{P=N} = 1270$-$1280\ cm^{-1}$. [f] Molecular weights were determined by gel permeation chromatography. [g] The following ultraviolet absorbance maxima (nm) were observed: phenol, 275, 270, and 215 (ethanol); steroid III, 286.5 and 280 (ethanol) or 291 and 282 (THF); steroid VII, 290 and 283 (ethanol and THF); testosterone, 241 (ethanol). [h] The sample was prepared by the hydrolysis of XIV, where HOR is the residue from VIII, in 3 N hydrochloric acid (15 min at 50 °C). The ultraviolet absorbance was compatible with the presence of testosterone (see *g*). [i] The molecular weight decreased after 2 weeks in aqueous ethanol to 5×10^4 (THF).

mL). After 4 h at 25 °C the mixture was filtered, and the filtrate was added dropwise to a stirred solution of poly(dichlorophosphazene) (1 g, 8.62 mmol) in THF (150 mL). The mixture was stirred for 4 h and then cooled with an ice bath. Methylamine (200 mL) was condensed into the reaction vessel. After 4 h the reaction mixture was allowed to return to 25 °C under nitrogen, while unreacted methylamine gas was permitted to escape through a silicone oil bubbler. Stirring was maintained for 72 h. The solvent was removed with a rotary evaporator, and liquid methylamine (200 mL) was added to the residue. Triethylamine (200 mL) was then added as a hydrochloride acceptor and the methylamine was removed with a rotary evaporator. The polymeric residue was collected and was dissolved in THF. After filtration and reprecipitation from THF into ethanol and then into pentane, a white polymeric product was obtained (0.6 g). The molecular weight and spectroscopic data for the polymer are listed in Table I. A ^{31}P NMR spectrum of the product was consistent with the structure XIV, where OR = $OC_6H_4Br\text{-}p$ (35 ± 3%). More than 30% of the substituent groups were arrayed along the polymer chain in a nongeminal fashion (see Table II). However, some geminal $NP(OC_6H_4Br\text{-}p)_2$ residues (<3%) were also detected. The microanalytical data for C, H, and Cl were compatible with a substituent ratio of 34.1:65.9 *p*-bromophenoxy groups to methylamino residues. Anal. Calcd for $[NP(OC_6H_4Br\text{-}p)_{0.682}(NHCH_3)_{1.318}]_n$: C, 32.17; H, 3.47; N, 16.10; P, 15.37; Cl, 0.0; Br, 26.99. Found: C, 32.12; H, 3.76; N, 14.60; P, 15.04; Cl, 0.12; Br, 21.92.

Preparation of $[NP(OCH_2CF_3)_{0.084}(NHCH_3)_{1.916}]_n$ (XIV, Where OR = OCH_2CF_3, 4.2%) and $[NP(OCH_2CF_3)_{0.374}(NHCH_3)_{1.626}]_n$ (XIV, Where OR = OCH_2CF_3, 18.7%) as Controls. Excess sodium (1.15 g, 0.050 mol) was added to a solution of 2,2,2-trifluoroethanol (0.65 g, 6.5 mmol) dissolved in THF (50 mL). The mixture was filtered under nitrogen, and the filtrate was added to a solution of poly(dichlorophosphazene) (1.5 g, 0.0129 mol) in THF (100 mL). Constant stirring was maintained for the duration of the reaction. After 2 h, the reaction mixture was cooled with an ice bath, and methylamine (100 mL) was condensed into the reaction vessel and maintained there for 4 h by means of a dry ice condenser. When methylamine (liquid) was present in sufficient quantity (50 mL), the entire mixture became clear and colorless. The reaction mixture was allowed to warm to 25 °C under nitrogen, and unreacted methylamine vapor was permitted to escape through a silicone oil bubbler over a period of 48 h. Two fractions were isolated. A THF-soluble portion was separated from an insoluble residue by filtration. This latter product was partially soluble in ethanol and was analyzed by ^{31}P NMR methods (see Table II). The integrated ^{31}P NMR spectrum was consistent with the presence of 4.2% trifluoroethoxy residues and with the formula $[NP(OCH_2CF_3)_{0.084}(NHCH_3)_{1.916}]_n$. The THF-soluble fraction (after filtration) was reprecipitated twice from THF into heptane to yield a pale yellow elastomer (0.16 g). The ^{31}P NMR spectrum of this material (see Table II) was compatible with the formula $[NP(OCH_2CF_3)_{0.374}(NHCH_3)_{1.626}]_n$ (with the presence of 18.7% trifluoroethoxy groups). The molecular weights (as determined by gel permeation chromatography) for both fractions are listed in Table I.

Preparation of $[NP(OC_6H_5)_{0.19}(NHCH_3)_{1.81}]_n$ as a Control. Phenol (0.809 g, 8.61 mmol) was dissolved in THF (30 mL), and excess sodium hydride was added. After 6 h at 25 °C, the suspension was filtered under nitrogen, and the filtrate was added to poly(dichlorophosphazene) (5 g, 0.0431 mol) dissolved in THF (200 mL). Constant stirring was maintained for the duration of the reaction. After 8 h, the reaction mixture was cooled with an ice bath. Methylamine gas (300 mL) was condensed into the reaction vessel and maintained there for 2 h with a dry ice condenser. Unreacted and undissolved methylamine gas was then allowed to escape over a 2-h period. The reaction mixture was transferred to a Magnedrive autoclave,[19] and an atmosphere of methylamine and nitrogen was introduced. (The resultant pressure was 250 psi.) After 2.5 h at 30 °C, the autoclave was

Table II
^{31}P NMR Chemical Shifts[a]

compound	OR steroid unit derived from	$P(NHCH_3)_2$ (integration)	$P(OR)(NHCH_3)$ (integration)	$P(OR)_2$ (integration)	% OR
		Control Compounds			
$[NP(NHCH_3)_2]_n$[b]		8.0			0
$[NP(NHCH_2COOCH_2CH_3)_2]_n$[c]		−0.80			0
$[NP(NHCH_2CH_2CH_2CH_3)_2]_n$[b]		4.5			0
$[NP(OC_6H_4Br\text{-}p)_2]_n$ or $[NP(OC_6H_5)_2]_n$[c]				−19.7	100
$[NP(OC_6H_5)_{0.19}(NHCH_3)_{1.81}]_n$[b]		8.2 (0.8)	−0.9 (0.19)		9.5
$[NP(OC_6H_4Br\text{-}p)_{0.7}(NHCH_3)_{1.3}]_n$[c]		4.6 (0.325)	−2.4 (0.60)	−17.5 (0.071)	35 ± 3
$[NP(OCH_2CF_3)_2]_n$[c]				−7.5	100
$[NP(OCH_2CF_3)_{0.084}(NHCH_3)_{1.916}]_n$[b]		8.0 (0.94)	3.0 (0.027)	−6.7 (0.029)	4.2
$[NP(OCH_2CF_3)_{0.374}(NHCH_3)_{1.626}]_n$[c]		7.9 (0.74)	3.0 (0.13)	−6.7 (0.12)	18.7
		$[NP(OR)_x(NHCH_3)_y]_n$			
$[NP(OR)_{0.1}(NHCH_3)_{1.9}]_n$[b]	III	7.4 (0.91)	0.14 (0.093)		4.7[d]
$[NP(OR)_{0.26}(NHCH_3)_{1.74}]_n$[b]	V	7.2 (0.78)	−0.71 (0.22)		11-14
$[NP(OR)_{0.7}(NHCH_3)_{1.3}]_n$[c]	V	4.76 (0.175)	−2.3 (0.70)		40
$[NP(OR)_{0.20}(NHCH_3)_{1.8}]_n$[c]	VI	6.87 (0.709)	−1.2 (0.29)		12-15
$[NP(OR)_{0.024}(NHCH_3)_{1.976}]_n$[b]	VII	7.9			0[e]
$[NP(OR)_{0.1}(NHCH_3)_{1.9}]_n$[b]	VII	7.9			0[f]
$[NP(OR)_{0.25}(NHCH_3)_{1.75}]_n$[c]	VII	7.4 (0.73)	3.0 (0.2)		12 ± 3
$[NP(OR)_{0.01}(NHCH_2COOCH_2CH_3)_{1.99}]_n$	VII	−0.80			0[e]
$[NP(OR)_{0.01}(C_4H_9)_{1.99}]_n$	VII	4.5			0[e]
$[NP(OR)_{0.036}(NHCH_{1.964}]_n$	VIII	8.0			0[e]
$[NP(OH)_{0.2}(NHCH_3)_{1.8}]_n$	VIII	8.65	3.5		ca. 10

[a] The reference was external 85% H_3PO_4 with a D_2O capillary for lock. Values are in ppm. [b] In ethanol. [c] In tetrahydrofuran. [d] Ultraviolet spectroscopy was used to estimate the OR side group concentration as 2% of the total.[31] [e] Below the detectable limits by ^{31}P NMR methods. [f] Ultraviolet spectroscopy was used to estimate the OR side group concentration as 4% of the total side groups present.[21]

Table III
Reaction Conditions for the Synthesis of Poly(organophosphazenes) with Steroidoxy Side Groups

product	steroid: OR residue derived from	steroid	$(NPCl_2)_n$	exposure time to excess methylamine,[a] h	yield of polymer, g
$[NP(OR)_{0.26}(NHCH_3)_{1.74}]_n$ (13%)	V	1 g (0.00368 mol)[b] in THF (250 mL)	0.853 g (0.00735 mol) in THF (150 mL)	72	0.3
$[NP(OR)_{0.7}(NHCH_3)_{1.3}]_n$ (35%)	V	1 g (0.00368 mol)[b] in THF (300 mL)	0.427 g (0.00368 mol) in THF (150 mL)	336	0.5
$[NP(OR)_{0.2}(NHCH_3)_{1.8}]_n$ (10%)	VI	1 g (0.00338 mol)[b] in THF (250 mL)	0.784 g (0.00676 mol) in THF (150 mL)	336	0.2
$[NP(OR)_{0.024}(NHCH_3)_{1.976}]_n$ (1.2%)	VII	0.5 g (0.00175 mol)[c] in THF (100 mL)	2.00 g (0.0172 mol) in THF (150 mL)	60	0.5
$[NP(OR)_{0.25}(NHCH_3)_{1.75}]_n$ (12.5 ± 3%)	VII	3.7 g (0.013 mol)[c] in THF (250 mL)	1.50 g (0.0129 mol) in THF (150 mL)	60	3.2
$[NP(OR)_{0.036}(NHCH_3)_{1.964}]_n$ (≤1.8%)	VIII	0.74 g (0.0026 mol)[c] in THF (100 mL)	1.50 g (0.0129 mol) in THF (150 mL)	60	0.61

[a] Methylamine (200 mL) was added by means of a dry ice condenser. [b] The sodium salts of steroids V and VI were formed in a suspension with excess sodium hydride in tetrahydrofuran (THF) at 25 °C for 4 h (by the same procedure used to prepare $[NP(OC_6H_4Br\text{-}p)_{0.682}(NHCH_3)_{1.318}]_n$). [c] The sodium salts of these steroids were prepared in a suspension of excess of sodium hydride with tetrahydrofuran (THF) that was refluxed for at least 5 h. (The same procedure was used to prepare $[NP(OR)_{0.1}(NHCH_3)_{1.9}]_n$, where OR is the steroid residue derived from VII.)

allowed to vent for 1 h. Tetrahydrofuran and methylamine were removed by means of a rotary evaporator to leave an ethanol-soluble residue. After dialysis against ethanol, water, and ethanol, the polymeric solution was filtered. The solvent was evaporated, and a clear, pliable film-forming polymer (1 g) remained. The molecular weight data (GPC in ethanol), ultraviolet spectrum (in ethanol), and infrared spectrum (film on KBr) are summarized in Table I. A ^{31}P NMR spectrum of the product was compatible with the structure $[NP(OC_6H_5)_{0.19}(NHCH_3)_{1.81}]_n$ (see Table II).

Preparation of $[NP(OR)_{0.1}(NHCH_3)_{1.9}]_n$ (XIV), Where OR Is the Steroid Unit Derived from III (5%). Desoxoestrone (III) (1 g, 3.9 mmol) was dissolved in THF (250 mL), and excess sodium hydride was added. The suspension was boiled at reflux for 3 h, and the mixture was filtered under nitrogen. The filtrate was added dropwise to a solution of poly(dichlorophosphazene) (2.26 g, 19.5 mmol) dissolved in THF (300 mL). The stirred reaction mixture was then refluxed for 10 h. It was then cooled with an ice bath, and methylamine gas (200 mL) was condensed into the reaction vessel by means of a dry ice condenser. After 4 h, the reaction mixture was permitted to warm to 25 °C. It was then stirred for 48 h. The solvent was removed with a rotary evaporator, and the residue was dissolved in ethanol. After filtration, the solution was dialyzed against water and then against ethanol.[20] The solvent evaporated from the viscous solution to yield a light yellow polymeric film (0.3 g). The molecular weight and spectroscopic properties of the product are listed in Table I. A Beer–Lambert plot (based on the ultraviolet absorbance of III) was used to determine the degree of steroid attachment to polymer XIV. The steroidal residues constituted 2% of the total side groups present. A ^{31}P NMR spectrum (see Table II) and the elemental analysis were consistent with the presence of 5% of the side groups as steroid units derived from III. Anal. Calcd for $[NP(OR)_{0.1}(NHCH_3)_{1.9}]$, where OR is the steroid unit derived from III: C, 34.82; H, 7.76; Cl, 0.0. Found: C, 34.84; H, 8.28; Cl, 0.82.

Preparation of $[NP(OR)_{0.26}(NHCH_3)_{1.74}]_n$ Where OR Is the Steroid Unit Derived from V (13%). The synthetic procedures used for the synthesis of this compound were similar to those used to prepare $[NP(OC_6H_4Br\text{-}p)_{0.7}(NHCH_3)_{1.3}]_n$. The experimental details are summarized in Table III. The solvent

was removed from the reaction mixture with a rotary evaporator. Liquid methylamine (200 mL) was added to redissolve the polymeric residue, and triethylamine (200 mL) was then added. The methylamine was removed with a rotary evaporator. The portion of the residue that was insoluble in the triethylamine was collected, and the procedure was repeated. The residue was dissolved in ethanol and precipitated into water. It was then dried in vacuo. The molecular weight and spectroscopic properties are listed in Table I. A ^{31}P NMR spectrum of the material (see Table II) was consistent with the replacement of 11–14% of the chlorine atoms of XII by the steroidal unit from V. The elemental analysis was compatible with the presence of 13% of the steroid units from V. Anal. Calcd for $[NP(OR)_{0.26}(NHCH_3)_{1.74}]_n$, where OR is the steroid unit derived from V: C, 45.95; H, 7.72; Cl, 0.0. Found: C, 46.03; H, 8.37; Cl, 3.34.

Preparation of $[NP(OR)_{0.7}(NHCH_3)_{1.3}]_n$, Where OR Is the Steroid Unit Derived from V (35%). The synthetic procedure used to prepare this polymer was similar to the one used to synthesize $[NP(OC_6H_4Br\text{-}p)_{0.7}(NHCH_3)_{1.3}]_n$. The specific reaction conditions used and the yield are listed in Table III. The solvent was removed from the reaction mixture with a rotary evaporator. The residue was dissolved in THF and the solution was filtered. The polymer was reprecipitated twice from THF into water, followed by a reprecipitation from THF into pentane. The spectral properties and molecular weight are listed in Table I. A ^{31}P NMR spectrum of the material was compatible with the presence of steroid units derived from V as 40% of the total number of side groups (see Table II). An elemental analysis suggested that the number of steroidal groups in XIV was 35% of the total substituent groups. Anal. Calcd for $[NP(OR)_{0.7}(NHCH_3)_{1.3}]_n$, where OR is the steroid unit derived from V: C, 60.94; H, 7.78; N, 11.76; P, 11.33; Cl, 0.0. Found: C, 59.61; H, 7.35; N, 9.90; P, 10.61; Cl, 0.15. The replacement of chlorine by methylamine groups was apparently unaffected by the presence of the bulky steroid groups. The glass transition temperature for this polymer was 60 °C (as determined by differential scanning calorimetry).

Preparation of $[NP(OR)_{0.2}(NHCH_3)_{1.8}]_n$, Where OR Is the Steroid Unit Derived from VI. The synthetic method used to prepare this compound was similar to the one used to prepare $[NP(OC_6H_4Br\text{-}p)_{0.7}(NHCH_3)_{1.3}]_n$. The experimental details are listed in Table III. After removal of the solvent from the reaction mixture with a rotary evaporator, the polymeric residue was purified by reprecipitation twice from ethanol into water. The water-insoluble material was collected and was redissolved in THF. After filtration, the solution was reprecipitated into pentane. The ^{31}P NMR spectrum was compatible with a composition in which 12–15% of the side groups were the steroidal units (Table II). An elemental microanalysis was used to estimate that 10% of the side groups were steroidal groups. Anal. Calcd for $[NP(OR)_{0.2}(NHCH_3)_{1.8}]_n$, where OR is the steroid unit derived from VI: C, 44.05; H, 7.47; Cl, 0.0. Found: C, 42.40; H, 5.11; Cl, 2.28.

Preparation of $[NP(OR)_{0.024}(NHCH_3)_{1.976}]_n$ (XIV), Where OR Is the Steroid Unit Derived from VII (1.2%). The synthetic method used to prepare this polymer was similar to the one employed to prepare $[NP(OR)_{0.1}(NHCH_3)_{1.9}]_n$, where OR is the steroid unit derived from VII (see below). The experimental details are summarized in Table III. The polymer was purified by dialysis as described previously. The ^{31}P NMR spectrum consisted of a singlet at 8 ppm (see Table II). The degree of steroid attachment was less than the limits detectable by ^{31}P NMR methods. Hence, elemental analysis was used to determine the ratio of steroidal to methylamino units. The data were compatible with a structure in which 1.2% of the side groups were derived from VII. Anal. Calcd for $[NP(OR)_{0.024}(NHCH_3)_{1.976}]_n$, where OR is the steroid unit derived from VII: C, 26.26; H, 7.66; Cl, 0.0. Found: C, 26.02; H, 7.29; Cl, 0.20.

Preparation of $[NP(OR)_{0.1}(NHCH_3)_{1.9}]_n$ (XIV), Where OR Is the Steroid Residue Derived from VII. A solution of estradiol 3-methyl ether (2.0 g, 6.98 mmol) in THF (100 mL) was boiled at reflux for 5 h with sodium hydride (10 g, 0.21 mol) (added as a 50% dispersion in oil). The suspension was filtered under nitrogen, and the filtrate was added to a vigorously stirred solution of poly(dichlorophosphazene) (4.1 g, 35.3 mmol) in THF (150 mL). After 12 h at 25 °C the mixture was cooled with an ice bath, and methylamine (200 mL) was condensed in the reaction vessel by means of a dry ice condenser. After 4 h, the mixture was allowed to warm to 25 °C. It was then stirred for 60 h. Unreacted methylamine gas was allowed to escape through a silicone oil bubbler. The solvent was then removed with a rotary evaporator. Ethanol was added to dissolve the residue, and the resultant polymeric solution was dialyzed first in ethanol, then in water (1 wk), and then in an ethanol–2-propanol mixture.[20] The solvent was evaporated from the viscous solution to yield a white, polymeric film (1.9 g). The polymer was moderately soluble in water and very soluble in ethanol. The molecular weight and spectroscopic properties of the polymer are listed in Table I. A Beer–Lambert plot based on the ultraviolet absorbance of the steroid VII and elemental analysis data were used to estimate that approximately 5% of the side groups in XIV were steroidal units. Anal. Calcd for $[NP(OR)_{0.1}(NHCH_3)_{1.9}]_n$, where OR is the residue derived from VII: C, 34.93; H, 7.74; Cl, 0.0. Found: C, 34.89; H, 7.49; Cl, 4.36. (The presence of chlorine was attributed to salt formation with HCl.) A ^{31}P NMR spectrum consisted of a singlet at 8.0 ppm. This indicated that the number of steroidal residues attached to XIV was below the 5% limit of detection for the ^{31}P NMR method.

Preparation of $[NP(OR)_{0.25}(NHCH_3)_{1.75}]_n$, Where OR Is the Steroid Unit Derived from VII. The procedure used for the synthesis of this polymer was similar to the one used to prepare the polymer $[NP(OR)_{0.1}(NHCH_3)_{1.9}]_n$, where OR is the steroid unit derived from VII (5%). The experimental details are listed in Table III. The solvent was removed from the reaction mixture, and the residue was dissolved in THF. The solution was filtered, and the polymer was reprecipitated twice from THF into heptane. The molecular weight and spectral properties of the material are listed in Table I. A ^{31}P NMR spectrum of the product was compatible with the structure $[NP(OR)_{0.25}(NHCH_3)_{1.75}]_n$, i.e., a polymer that had 12.5 ± 5% of the side groups as steroidal residues. The ^{31}P NMR chemical shifts for the repeating units, $NP(OR)(NHCH_3)$, were similar when OR was OCH_2CF_3, the residue derived from VII, or OH (see Table II). Thus, the detection of P–OH groups would be masked by other peaks in the ^{31}P NMR spectra. The elemental analysis was in reasonable agreement with the ^{31}P NMR data. Anal. Calcd for $[NP(OR)_{0.25}(NHCH_3)_{1.75}]_n$, where OR is the residue derived from VII (12.5%): C, 46.22; H, 7.85. Found: C, 47.09; H, 6.39.

Preparation of $[NP(OR)_{0.01}(NHCH_2COOC_2H_5)_{1.99}]_n$, Where OR Is the Steroid Unit Derived from VII (<0.5%). Estradiol 3-methyl ether (1 g, 3.5 mmol) was dissolved in THF (25 mL), and excess sodium hydride (10 g, 0.208 mol) was added. The suspension was boiled at reflux for 0.5 h, and more THF (75 mL) was added. The reaction mixture was filtered under nitrogen, and the filtrate was added to a stirred solution of poly(dichlorophosphazene) (2 g, 0.017 mol) in THF (50 mL). After 4 h, the mixture was cooled with an ice bath. A filtered solution of ethyl glycinate was added [prepared by the boiling of a suspension of glycine ethyl ester hydrochloride (10 g, 0.072 mol) and triethylamine (14.6 g, 21 mL, 0.145 mol) in THF (200 mL) for 0.5 h]. The polymer solution was allowed to cool to 25 °C. It was then stirred for 72 h. After filtration, the solvent was removed with a rotary evaporator until approximately 25 mL remained. After two reprecipitations from THF into heptane and from benzene into heptane, a white polymer was obtained (1.0 g). The spectroscopic properties and the molecular weight of the polymer are listed in Table I. The ultraviolet spectrum was consistent with the presence of VII as ≤0.5% of the total side groups present. The steroidal units could not be detected by ^{31}P NMR methods. This polymer underwent a molecular weight decrease in aqueous media in a manner reminiscent of $[NP(NHCH_2COOC_2H_5)_2]_n$.[5]

Preparation of $[NP(OR)_{0.01}(NHC_4H_9)_{1.99}]_n$, Where OR Is the Steroid Unit Derived from VII (<0.5%). Estradiol 3-methyl ether (1.0 g, 3.51 mmol) in THF (100 mL) was stirred for 8 h with excess sodium hydride. After 8 h at reflux, the suspension was filtered under nitrogen. The filtrate was added to poly(dichlorophosphazene) (2.00 g, 17.2 mmol) in THF (50 mL). After 16 h, the reaction mixture was cooled by means of an ice bath, and *n*-butylamine (33 g, 0.452 mol) was added. The reaction mixture was allowed to warm to 25 °C and stirred for 8 h. It was then refluxed for 12 h. The mixture was filtered, concentrated, and reprecipitated three times from THF into heptane. The residue was precipitated from THF into water to give yellow

product (0.34 g). The molecular weight and spectroscopic properties of the polymer are listed in Table I. Ultraviolet spectroscopy was used to show that approximately 0.5% of the side groups were steroidoxy. The number of steroid units attached to XIV was less than the detectable limits of ^{31}P NMR methods.

Preparation of $[NP(OR)_{0.036}(NHCH_3)_{1.964}]_n$, Where OR Is the Steroid Unit Derived from VIII. This polymer was prepared by a procedure similar to the one used for $[NP(OR)_{0.1}(NHCH_3)_{1.9}]_n$, where OR is the steroid unit derived from VII (1.8%). The reaction conditions used for the synthesis are listed in Table III. The polymer was purified by dialysis as described previously. The molecular weight and spectroscopic properties of this polymer are listed in Table I. The number of steroid units attached to XIV was below the detectable limits of ^{31}P NMR methods. Thus, an elemental analysis was used to estimate the number of steroid units attached to XIV. Anal. Calcd for $[NP(OR)_{0.036}(NHCH_3)_{1.964}]_n$, where OR is the steroid unit derived from VIII (1.8%): C, 27.82; H, 7.70; Cl, 0.0. Found: C, 27.82; H, 7.12; Cl, 4.60. (The presence of chlorine was attributed to salt formation with HCl).

Acidic Hydrolysis of $[NP(OR)_{0.036}(NHCH_3)_{1.964}]_n$ (XIV), Where OR Is the Steroid Unit Derived from VIII. Several high molecular weight fractions of this polymer in ethanol were collected by gel permeation chromatography and combined. A concentrate of this solution was heated (<50 °C) in 3 N hydrochloric acid for 15 min. The solution was then neutralized with sodium hydroxide and reseparated by gel permeation chromatography. An absorbance in the ultraviolet spectrum of the acid-treated high molecular weight fraction appeared at 243 nm (vs. 241 nm for testosterone; see Table I). The 1,4-dihydro ring of the steroid unit VIII had hydrolyzed to an α,β-unsaturated ketone.[8] However, the molecular weight of the polymer had decreased from 10^6 to 10^4–10^5. This molecular weight decrease may have resulted from a thermal elimination of the steroidal units from XIV in acid or to a hydrolytic chain-cleavage process.

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(11) In fact, the homopolymer $[NP(NHCH_3)_2]_n$ can be prepared by the interaction of XII with methylamine at −6 to 25 °C.[10]
(12) These reactions involve dehydration reactions of the steroid,[7] a process that is accelerated by heat or the presence of hydrochloric acid.
(13) A conservative estimate of the limit of detection of P–Cl bonds was less than 5% (or 5 P–Cl residues for every 100 substituent groups or 50 P=N repeat units).
(14) Cholesterol and mestranol (the 3-methyl ether of VI) underwent dehydration reactions with XII or IX[7] at elevated temperatures to form hydroxyphosphazenes. The reaction occurred even when sodium hydride was present. Cholesteryl chloride was one of the products formed by the reaction between cholesterol and XII.
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(19) The Magnedrive autoclave was manufactured by Autoclave Engineers, Inc. The autoclave unit (1-L capacity) and stirrer assembly were made of Hastalloy B. The unit was externally cooled (−50 °C), and methylamine (Linde) was condensed into the vessel through stainless steel tubing.
(20) A final separation of cyclic, trimeric, and tetrameric species not removed by dialysis was effected by a reprecipitation from ethanol (or an ethanol–water mixture) into an organic solvent such as benzene, tetrahydrofuran, or heptane.
(21) The percent of a substituent group is for the formula $[NP(OR)_x(NHR)_{2-x}]_n$.

Thermal Rearrangement of $[NP(OCH_3)_2]_3$ and $[NP(OCH_3)_2]_4$[1]

W. T. Ferrar, F. V. DiStefano, and H. R. Allcock*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802. *Received April 3, 1980*

ABSTRACT: The thermal rearrangements of $[NP(OCH_3)_2]_3$, $[NP(OCD_3)_2]_3$, and $[NP(OCH_3)_2]_4$ in the molten state or in *o*-dichlorobenzene to yield $[RNP(O)OR]_{3\text{ or }4}$ have been studied. The rearrangement reaction is accelerated by the formation of the products. Moreover, evidence was obtained that the rearrangement is *inter*molecular since the reaction rates are concentration dependent and "cross alkylation" products were detected from the interaction of $[NP(OCH_3)_2]_3$ with $[NP(OCD_3)_2]_3$. The rearrangement of the tetramer, $[NP(OCH_3)_2]_4$, yields first a kinetically preferred geometric isomer of $[CH_3NP(O)OCH_3]_4$ (VII) which is subsequently converted to the thermodynamically preferred isomer (VIII). The ^1H, ^{31}P, and ^{13}C NMR spectra of the starting materials and products are discussed.

Cyclic and high polymeric phosphazenes that contain alkoxy groups attached to phosphorus (I) have been known for many years.[2–6] It has also been recognized since the early 1960s[7–9] that alkoxyphosphazene cyclic trimers and tetramers which contain methoxy, ethoxy, propoxy, or benzyloxy side groups attached to phosphorus can undergo a thermal-rearrangement reaction in which alkyl groups migrate from oxygen to skeletal nitrogen to yield cyclophosphazanes (II). The sensitivity of the high polymers of formula $[NP(OCH_3)_2]_n$ or $[NP(OC_2H_5)_2]_n$ to high-temperature or high-energy decomposition processes[6,10] has been ascribed to such a rearrangement reaction. The value

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