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Phosphazene High Polymers with Bioactive Substituent Groups: Prospective Anesthetic Aminophosphazenes

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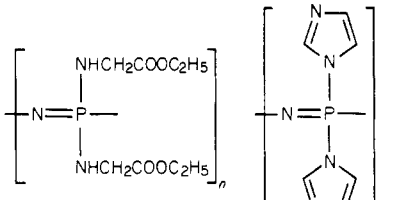
ABSTRACT: Anesthetic residues derived from procaine (4), benzocaine (5), chloroprocaine (6), butyl *p*-aminobenzoate (7), and 2-amino-4-picoline (8) have been linked to trimeric and high-polymeric phosphazene systems through the arylamino function by nucleophilic replacement of halogen in $(NPCl_2)_3$ or $(NPCl_2)_n$. Total halogen replacement occurred with the trimers and 99–100% replacement with the high polymers when forcing reaction conditions were employed. Mixed-substituent "copolymers" containing methylamino and procaino or 2-amino-4-picolino residues in a 50:50 ratio were also prepared in order to increase the solubility of the polymers in water. Comparisons are made between the small-molecule cyclotriphosphazene model systems and the high polymers.

Considerable interest exists in the synthesis of biologically active polymers.[1-4] One aspect of the field involves the attachment of biologically active small molecules to macromolecules in order to confer, for example, chemotherapeutic activity on the macromolecules themselves[5-7] or to generate a controlled-release system as the active small molecule is released from the polymer. Hydrolysis of the carrier polymer or the linkage between polymer and active agent is an attractive means for inducement of the release. The role of the macromolecule includes the immobilization of the active agent, a lowering of its diffusion or dialysis rate, and, in some cases, a control of the rate of release of the active small-molecule species.

Poly(organophosphazenes) are of particular interest as carrier macromolecules for biologically active agents. Amino acid ester (1) or imidazolyl (2) substituted poly-



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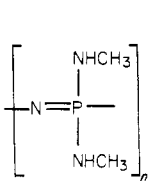

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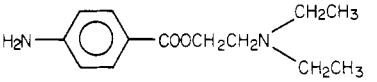
phosphazenes are hydrolytically sensitive, potentially biodegradable polymers,[8,9] and the water-soluble polymer 3 has been investigated as a polymeric coordination ligand for platinum antitumor complexes.[10] A similar polymer with pendent alkylimidazolyl cosubstituent units is an excellent water-soluble carrier molecule for metalloporphyrins.[11] Recently, we described the synthesis of steroid-linked polyphosphazenes.[12,13] Carrier molecules of these types have the advantages of apparent low toxicity, water or organic solubility, or biodegradability, depending on the specific side groups present.

In the present work, we have studied the attachment of the well-known local anesthetics procaine (4), benzocaine (5), chloroprocaine (6), butyl *p*-aminobenzoate (7), and 2-amino-4-picoline (8) to polyphosphazenes as a possible route to modification of their biological activity.



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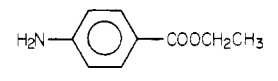

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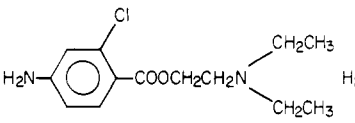

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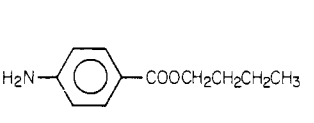

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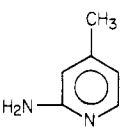

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Previous approaches for altering the activity of procaine-like compounds were based on changes in the molecular skeleton, such as increases in the size of the aminoalkyl group or the alkylene chain,[14-16] or the introduction of alkyl groups into the 4-amino unit.[17-19]

Here, the objective is to modify the duration of biological activity by linkage of the active molecule via the primary amino function to a polyphosphazene skeleton. Thus, compounds 4–8 were selected because they contain only

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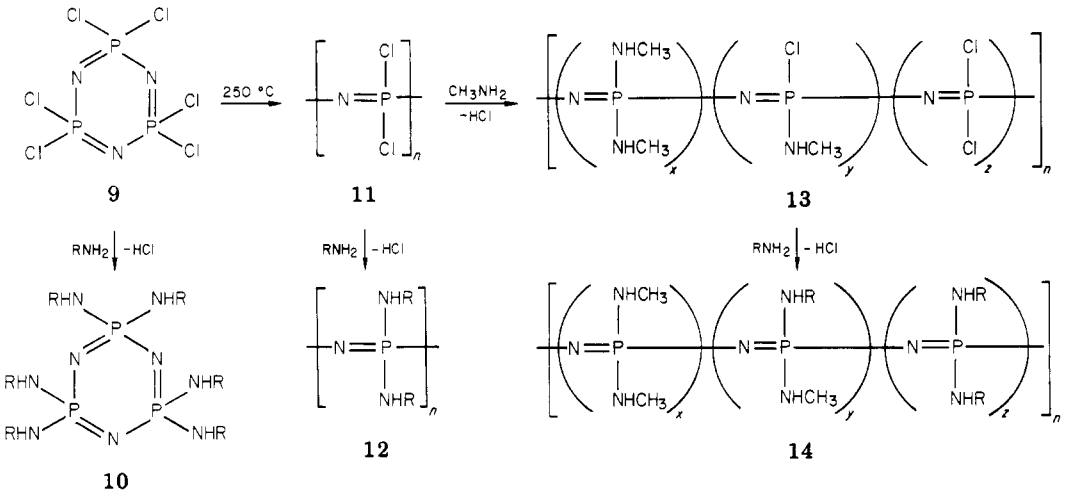
Scheme I[a]



[a] RNH_2 = 4–8.

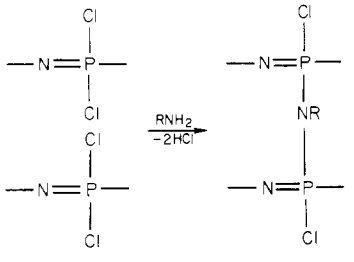
one linkage site. Cross-linking reactions would, therefore, be minimized. Residues 4–8 are detectable by ultraviolet spectroscopy. Moreover, polymer-bound derivatives of 4–8 linked to phosphorus through the primary amino units should retain their activity even in the polymer-bound form because the biologically active centers would remain exposed.[20]

Both cyclic trimeric and high-polymeric phosphazene skeletal systems were used. The cyclic trimeric derivatives served as small-molecule models for the preliminary examination of reaction conditions, monitoring of side reactions, and the development of analytical techniques. The overall synthetic strategy is outlined in Scheme I.

The objectives of this investigation were to answer the following questions: (1) Is the cyclic trimer (9) a valid model for predicting the reactivity of the high polymer (11), and do reactivity differences exist between 9 and 11 that might complicate the future use of 9 as a model system? (2) What effects do the various substituent groups derived from 4–8 exert on the physical properties of the polymer, and can solubilization in water be achieved with the use of methylamino cosubstituent groups? (3) How readily are the active side groups released from the trimeric or polymeric systems under hydrolytic conditions?

Results and Discussion

Reactions of $(NPCl_2)_3$ and $(NPCl_2)_n$ with Amines 4–8. Two problems were anticipated for the interaction of $(NPCl_2)_3$ or $(NPCl_2)_n$ with amines 4–8. First, the possibility exists that each primary amino unit could function as a cross-linking reactant, as shown in the conversion of 15 to 16. Such cross-linking reactions take place rapidly



15 16

when methylamine reacts with 11 under uncontrolled reaction conditions.[21] Cross-linking would prevent total halogen replacement. Second, it is known from earlier work that bulky secondary amines are unable to replace all the chlorine atoms in 11 because of steric hindrance effects[21] and the prospect existed that reactants 4 and 6 in particular might be affected by the same restrictions. However, in practice, these complications were not encountered, as will be illustrated in the following sections.

The syntheses of the cyclic trimeric derivatives 10 of amines 4–8 were accomplished in boiling toluene/tetrahydrofuran media with triethylamine as a hydrohalide acceptor. No cross-linked cyclomatrix species were detected. However, forcing reaction conditions were needed before complete replacement of the chlorine atoms could be accomplished. The products 10 were crystalline materials that were soluble in tetrahydrofuran, methylene chloride, or toluene but insoluble in water. No residual P–Cl bonds were detected by ^{31}P NMR analysis.

The high-polymeric analogues 12 were prepared in the same way, with forcing reaction conditions being needed for complete halogen replacement (see Experimental Section). No evidence was found for cross-linking during the high-polymer reactions, at least under the dilute reaction conditions employed. Thus, it seems clear that *aryl*amines of this type are not subject to the cross-linking side reactions that can occur with the lower primary alkylamines. Presumably this reflects a greater steric shielding by the aryl reagents. The high-polymeric species 12 were soluble in acetic acid or boiling dioxane but were only slightly soluble in water. They showed a higher solubility in aqueous acidic media.

High solubility in aqueous media was accomplished through the synthesis of mixed-substituent polymers containing methylamino groups as cosubstituents. Poly[bis(methylamino)phosphazene] homopolymer is soluble in water. Moreover, methylamine has a high reactivity toward P–Cl bonds and cosubstitutions can be carried out under mild reaction conditions. The small size of the methylamino group is an added advantage in cosubstitution reactions because steric hindrance effects are minimized.

The methylamino side groups were introduced into the mixed-substituent system first in order to avoid a possible reaction of the ester function of 4–7 with free methylamine. Mild reaction conditions (−50 to +25 °C in a THF/methylamine cosolvent system at 760 torr) allowed roughly 50% of the chlorine atoms in 11 to be replaced by methylamino groups to yield 13. Essentially all of the remaining chlorine atoms in 13 could then be replaced by treatment with procaine (4) or 2-amino-4-picoline under the more vigorous reaction conditions (40 °C) established earlier for the homopolymers. However, these conditions

Table I
Characterization Data for Cyclotriphosphazenes 10

RNH_2		microanalysis % C		% N	UV λ_{max}	IR ν(C=O), cm^{-1}	mp, °C	^{31}P NMR[a]	yield, %
4	calcd	60.58	5.37	15.59	294	1705	149-151	2.87	33
	found	60.78	5.70	15.70					
5	calcd	57.90	5.36	11.26	240	1675	198-200	2.94	35
	found	57.48	5.35	11.39					
6	calcd	53.42	6.16	11.98	310	1708	144-146	3.78	72
	found	53.39	6.33	10.37					
7	calcd	61.53	6.52	9.79	250	1705	204	3.12	68
	found	61.56	7.53	10.14					
8	calcd	55.59	5.40	27.02	255		138	3.45	42
	found	54.57	5.50	27.51					

[a] All samples were proton decoupled and were interpreted as A_3 spin systems. The solvent was dioxane. Chemical shift positions (in ppm) were relative to aqueous 85% H_3PO_4, where positive chemical shifts represent deshielding. A D_2O capillary lock was used.

Table II
Characterization Data for High Polymers 12 and 14

Compounds 12

RNH_2		microanalysis[a] % C	H %	% N	^{31}P NMR[b,c]	MW(GPC)[d]	T_g,[e] °C
4	calcd	60.58	5.37	15.59	2.5	$(4-5) \times 10^5$	50
	found	60.48	5.70	15.70			
5	calcd	57.90	5.36	11.26	6.8	$(4-5) \times 10^5$	47
	found	56.80	5.02	11.39			
6	calcd	53.42	6.16	11.98	4.7	$(4-5) \times 10^5$	55
	found	53.63	6.31	10.22			
7	calcd	61.53	6.52	9.79	2.7	$(4-5) \times 10^5$	48
	found	61.62	7.46	10.06			
8	calcd	55.59	5.40	27.02	0.7	$(4-5) \times 10^5$	27
	found	53.29	5.32	26.89			

Compounds 14

RNH_2		microanalysis % C	% H	^{31}P NMR[f]	MW(GPC)[d]	T_g,[e] °C	substituent ratio $x:y:z$[g,h]
4	calcd	55.19	7.62	8, 5, 2.5	5×10^5	58	1:1:1
	found	54.70	7.41				
8	calcd	44.20	7.20	8, 6, 0.7	5×10^5	44	1:1:1
	found	43.49	9.62				

[a] Analytical data were obtained by Galbraith Laboratories. [b] All samples were proton decoupled and were interpreted as A_n spin systems for the homopolymers. [c] Chemical shift positions (in ppm) were relative to aqueous 85% H_3PO_4. A D_2O capillary lock was used. [d] The range of values shown represents gel permeation chromatography results from different synthesis reactions. [e] By differential scanning calorimetry. [f] Three broad singlets were observed in the ^{31}P NMR due to the three different phosphorus environments corresponding to $NP(NHCH_3)_2$, $NP(NHCH_3)(NHR)$, and $NP(NHR)_2$. Each peak was well resolved. The peaks were of equal intensity and equal area integration. Thus, the cosubstituent ratio was assumed to be 1:1:1. [g] Substituent ratio and composition of the polymers were determined by graphical and computer-based fits to the analytical data. [h] Residual chlorine of <1% in all polymers was attributed to bound HCl, with the exception of the chloroprocaine derivatives. Evidence for this view was obtained from a correlation of the microanalysis, ^{31}P NMR data, and the decrease in the chlorine content following treatment with triethylamine.

must not be so forcing that the methylamino side groups already present can generate cross-links by reaction with P–Cl groups still present. After completion of the reactions, no residual P–Cl bonds were detected by ^{31}P NMR analysis. The trace amounts of residual chlorine (<1%) 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 evidence was found that the cosubstitution reaction was accompanied by displacement of methylamino groups already present.

Structural Characterization of the Cyclotriphosphazenes. Species **10** were characterized by a combination of ^{31}P NMR, ^1H NMR, infrared, and ultraviolet spectroscopy and elemental analysis (see Table I and Experimental Section). The ^{31}P NMR spectra were singlets, indicative of hexasubstitution. The ^{31}P chemical shifts were similar when the side-group residues were derived from **4–8**, presumably because of the separation between the variable units and the skeletal phosphorus atoms. However, these ^{31}P chemical shifts (2.9–3.8 ppm) were quite different from those for $(NPCl_2)_3$ (+19 ppm). The ^1H NMR spectra were complicated, but the integrated ratios of aliphatic to aromatic protons were consistent with residues derived from **4–8**.

Infrared spectra showed evidence for the survival of the phosphazene ring in **10**, with characteristic maxima in the 1150–1200-cm^{-1} region. Aromatic C–H bonds were detected from peaks in the 3000–3100-cm^{-1} region, the amino N–H groups were evident from peaks at 3500–3200 cm^{-1}, and P–N or C–N stretching modes were detected in the 925–960-cm^{-1} region.

Characterization of the High Polymers. All the polymers were soluble in organic solvents. Only the mixed-substituent polymers **14** were appreciably soluble in neutral aqueous media. Evidence for polyelectrolyte behavior was found when the polymers were dissolved in aqueous acid. As shown in Table II, the elemental mi-

croanalyses corresponded to structures 12–14. (The ratios of the different substituent groups in 14, deduced by microanalysis, are shown in Table II.)

^{31}P NMR spectra of the homopolymers 12 showed a sharp singlet only, with chemical shifts at 2.5 (procaino derivative), 6.8 (benzocaine derivative), 0.7 (picolino derivative), 2.7 (butyl *p*-aminobenzoate derivative), and 2.5 ppm (chloroprocaino derivative). The spectra of the mixed-substituent polymers 14 were remarkably simple. They showed three equivalent ^{31}P NMR peaks that were compatible with the presence of equal concentrations of $P(NHCH_3)_2$, $P(NHCH_3)(NHR)$, and $P(NHR)_2$ units.

The infrared spectra for all the polymers showed characteristic –P=N– "stretching" absorptions between 1320 and 1100 cm^{-1} plus carbonyl bands in the 1675–1708-cm^{-1} region.

The GPC-average molecular weights were in the range 4×10^5 to 5×10^5, values that are somewhat lower than those normally found for poly[(arylamino)phosphazenes].[22,23] This may reflect a tendency for depolymerization as a consequence of the forcing reaction conditions needed for complete halogen replacement.

Glass transition temperatures are listed in Table II. They are in the range 27–58 °C and can be compared to the value of 91 °C for $[NP(NHC_6H_5)_2]_n$. Hydrogen bonding undoubtedly plays a part in reducing the torsional mobility of polyphosphazenes of this type, compared to, say, $[NP(OC_6H_5)_2]_n$ (T_g = –8 °C).

Additional Conclusions. The utility of the model compound approach to polyphosphazene synthesis is well illustrated by these results. The resemblance between the reactions of the cyclic trimeric ring system and the linear high-polymeric analogue is striking. The hydrolysis behavior and bioactivity of the cyclic and polymeric derivatives have not yet been examined in detail. However, preliminary experiments indicate that the procaino-substituted high polymers undergo a slow hydrolysis in buffered aqueous media at pH 7.

Experimental Section

Reagents. Hexachlorocyclotriphosphazene (9) (mp 110–112 °C) was obtained from a trimer–tetramer mixture (Ethyl Corp.) after two vacuum sublimations at 60 °C (0.5 torr), two recrystallizations from heptane, and two additional vacuum sublimations. Poly(dichlorophosphazene) (11) was prepared by the thermal polymerization of $(NPCl_2)_3$ at 250 °C for an 8–24-h period in a sealed Pyrex tube (20 × 2.5 cm). Typically, less than 25% conversion to the high polymer was attempted, and the unreacted trimer was then recovered by sublimation at 60 °C (0.5 torr) during 12–24 h. The polymer was soluble in organic media such as toluene or tetrahydrofuran.

Toluene was refluxed over and distilled from CaH_2 before use. Triethylamine was refluxed over and distilled from BaO before use. Tetrahydrofuran (THF) (Fisher) was dried and distilled from sodium/benzophenone. Procaine, benzocaine, and butyl *p*-aminobenzoate were obtained as the free bases from Sigma Chemical Co. 4-Amino-2-picoline was obtained from Aldrich. 2-Chloroprocaine hydrochloride was kindly provided by Pennwalt Corp.

Instrumentation. Proton-decoupled ^{31}P NMR spectra were obtained at 40 MHz with a JEOL PS100FT spectrometer equipped with a Nicolet 1080 data processing system. Ultraviolet spectra were obtained with a Hewlett-Packard 8450A spectrometer. Infrared spectra of samples as KBr disks or thin films on NaCl plates were obtained with a Perkin-Elmer 580 spectrometer. Approximate polymer molecular weights were estimated by using a Waters Associates ALC-201 gel permeation chromatography instrument fitted with a 122 cm × 1 cm 10^5-Å Styragel column for use with THF solvent at a flow rate of 2.4 mL/min. Approximate calibration of the columns was accomplished by means of narrow molecular weight distribution polystyrene standards obtained from Waters Associates. Glass transition temperatures were measured with a Perkin-Elmer DSC20 instrument.

Reactions of $(NPCl_2)_3$ with Procaine (4), Benzocaine (5), Chloroprocaine (6), Butyl *p*-Aminobenzoate (7), and 2-Amino-4-picoline (8). The following general procedures were used. Hexachlorocyclotriphosphazene (9) (2 g, 5.83×10^{-3} mol) was dissolved in dry toluene (100 mL). To this were added dropwise a solution of the free amine (4 equiv for each chlorine atom) in dry THF (100 mL) and excess freshly distilled triethylamine. The solution was heated slowly to reflux, and heating was continued for 96 h. A white precipitate of triethylamine hydrochloride formed slowly. The progress of each reaction was monitored by ^{31}P NMR spectroscopy, with completion of the substitution being indicated by the appearance of a singlet in the 0–4-ppm region. The reaction mixture was then cooled and filtered, and solvent was removed from the filtrate at reduced pressure to leave a yellow oil. Methylene chloride was added and the solution was extracted twice with water and dried with anhydrous magnesium sulfate. The organic layer was then added slowly to hexane to bring about precipitation of an adhesive yellow solid. Trituration with hot hexane (to remove residual free base) followed by column chromatography of the residue through silica gel (or neutral alumina) (CH_2Cl_2/ethyl acetate eluent) yielded the hexaaminocyclotriphosphazenes as off-white needles (30–70% yields).

The synthesis of the chloroprocaine derivative differed from the procedure described above because the amine was received as its hydrochloride salt. This was treated first with an excess of triethylamine in boiling THF, and the solution was then filtered through a glass coarse fritted funnel into the solution of the cyclotriphosphazene. The reaction of 2-amino-4-picoline (8) with $(NPCl_2)_3$ required only 48 h at the solvent reflux temperature. In all of these reactions, the cosolvent ratios were not critical, but a 1:1 ratio of toluene to THF gave the best results. Melting points and other characterization data are listed in Table I.

Reactions of High-Polymeric $(NPCl_2)_n$ with Procaine (4), Benzocaine (5), Chloroprocaine (6), Butyl *p*-Aminobenzoate (7), and 2-Amino-4-picoline (8). Poly(dichlorophosphazene) (11) (15 g, 0.13 mol) was dissolved in toluene (900 mL) to yield a clear, viscous solution. Excess triethylamine was distilled directly into this reaction mixture. A solution of the free base amine (3 equiv per chlorine atom) in dry THF (400 mL) was added dropwise to the cooled polymer solution. The solution was then heated slowly to reflux, and heating was continued for 168 h, with moisture being rigorously excluded throughout this period. Evidence that the reaction was complete was obtained from the appearance of a singlet at 0–7 ppm in the ^{31}P NMR spectrum. The reaction mixture was then cooled to 25 °C and filtered to remove hydrochloride salts and, on some occasions, the polymer. The clear, yellow filtrate was concentrated in a rotary evaporator. The polymer was isolated by precipitation of the concentrate into hexane or by washing the filter cake with water. Two reprecipitations from dioxane into pentane, followed by thorough Soxhlet extraction with pentane, yielded the polymers as pale yellow, film-forming materials. For elemental analysis, the polymer was reprecipitated one more time from dioxane into pentane.

Again, the procedures used for the reaction with chloroprocaine were slightly different. The hydrochloride salt of chloroprocaine was first treated with triethylamine in boiling THF. The mixture was then filtered through a coarse fritted funnel, under strictly anhydrous conditions, into the solution of poly(dichlorophosphazene). The characterization data are listed in Table II.

Synthesis of Mixed-Substituent Methylamino/Procaino and Methylamino/2-Amino-4-picolino Polymers. Poly(dichlorophosphazene) (29 g, 0.25 mol) was dissolved in dry toluene (1500 mL), under strictly anhydrous conditions, in a 3-L, three-necked flask equipped with an overhead stirrer, dry ice condenser, and nitrogen inlet. Triethylamine (70 mL) was distilled directly into this solution, followed by methylamine (16.6 mL, 0.375 mol), previously condensed at –78 °C over sodium spheres. During these additions the temperature of the reaction mixture was maintained at 0 °C. The mixture was stirred for 2 h, during which time a copious precipitate of triethylamine hydrochloride was formed.

The solution was then divided equally into two three-necked, 3-L flasks, each equipped with a condenser, a nitrogen inlet, and a mechanical stirrer. To one flask was added procaine (free base) (82.3 g, 0.35 mol) in THF (500 mL). The temperature of the

reaction mixture was maintained at 2 °C or lower during the addition. The mixture was then stirred at 0 °C for 24 h, allowed to warm to 25 °C, and stirred at this temperature for 180 h. ^{31}P NMR spectroscopy at this point showed three distinct sets of resonances, none of which could be ascribed to P–Cl units. The reaction mixture was filtered and the filtrate concentrated under reduced pressure to a volume of 300 mL. The concentrate was added to hexane to precipitate the polymer as an off-white powder. This was Soxhlet extracted with hexane and precipitated twice from THF or dioxane into pentane.

The second half of the initial reaction mixture was treated with 2-amino-4-picoline (35 g, 0.324 mol) in dry THF (500 mL). The subsequent steps were similar to those described above. The product was a white powder.

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References and Notes

(1) Hall, C. E.; Hall, O *Experienta* **1961**, *17*, 544; **1962**, *18*, 38.
(2) Cornell, R. J.; Donaruma, L. G. *J. Polym. Sci., Part A* **1965**, *3*, 827.
(3) Donaruma, L. G.; Razzano, J. *J. Med. Chem.* **1966**, *9*, 258.
(4) Donaruma, L. G.; Vogl, O., Eds. "Polymeric Drugs"; Academic Press: New York, 1978.
(5) Merigan, T. C.; Finkelstein, M. S. *Virology* **1968**, *35*, 363.
(6) Minor, W.; Alfrey, T.; Koehler, J.; Zimmerman, R. *Bacteriol. Proc.* **1971**, *225*.
(7) Lampson, G. P.; Field, A. K.; Tytell, A. A.; Nemes, M. M.; Hilleman, H. R. *Proc. Soc. Exp. Biol. Med.* **1970**, *135*, 911.
(8) Allcock, H. R.; Fuller, T. J.; Mack, D. P.; Matsumara, K.; Smeltz, K. M. *Macromolecules* **1977**, *10*, 824.
(9) Allcock, H. R.; Fuller, T. J. *J. Am. Chem. Soc.* **1981**, *103*, 2250.
(10) Allcock, H. R.; Allen, R. W.; O'Brien, J. P. *J. Am. Chem. Soc.* **1977**, *99*, 3984, 3987.
(11) Allcock, H. R.; Greigger, P. P.; Gardner, J. E.; Schmutz, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 606.
(12) Allcock, H. R.; Fuller, T. J. *Macromolecules* **1980**, *13*, 1338.
(13) Allcock, H. R.; Fuller, T. J.; Matsumura, K. *J. Org. Chem.* **1981**, *46*, 13.
(14) Einhorn, A.; Fiedler, K.; Ladisch, C.; Uhlfelder, E. *Justus Liebigs Ann. Chem.* **1909**, *371*, 142.
(15) Smitz, H. L.; Loevenhart, A. S. *J. Pharmacol. Exp. Ther.* **1924**, *24*, 159, 167.
(16) Schulemann, W. *Klin. Wochenschr.* **1924**, *3*, 676.
(17) I. G. Farbenindustrie, A. G. German Patent 582715, 1933.
(18) Fussganger, R.; Schumann, O. *Arch. Exp. Pathol. Pharmakol.* **1931**, *160*, 53.
(19) Bonica, J. J. *Curr. Res. Anesth. Analg.* **1951**, *30*, 1, 76.
(20) Weiner, B. Z.; Zilka, A. *J. Med. Chem.* **1973**, *16*, 573.
(21) Allcock, H. R.; Cook, W. J.; Mack, D. P. *Inorg. Chem.* **1972**, *11*, 2584.
(22) Allcock, H. R.; Kugel, R. L. *Inorg. Chem.* **1966**, *5*, 1320.
(23) White, J. E.; Singler, R. E.; Leone, S. A. *J. Polym. Sci., Polym. Chem. Ed.* **1975**, *13*, 2531.

Coupling of Cyclic and High-Polymeric [(Aminoaryl)oxy]phosphazenes to Carboxylic Acids: Prototypes for Bioactive Polymers

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ABSTRACT: Prototypical polymer-bound chemotherapeutic or herbicidal systems have been synthesized in which bioactive molecules are linked to poly(organophosphazenes) by peptide-coupling techniques. The synthetic procedures were developed first through the use of cyclotriphosphazene small-molecule model systems and with the initial use of simple nonbioactive carboxylic acids. These reactions were then utilized for the synthesis of high-polymeric analogues containing bioactive side groups. The sodium salts of 4-cyanophenol and phenol were allowed to react with $(NPCl_2)_3$ or $(NPCl_2)_n$ to yield derivatives of type $[NP(OPh)_x(OC_6H_4CN)_y]_{3 \text{ or } n}$. The 4-cyano groups were then reduced to 4-(aminomethyl)phenoxy units with the use of BH_3·THF. Condensation of the pendent amino groups with acetic, propionic, benzoic, acrylic, and nicotinic acids, *N*-acetylglycine, *N*-acetyl-DL-penicillamine, *p*-(dipropylsulfamoyl)benzoic acid, and 2,4-dichlorophenoxyacetic acid was accomplished with the use of dicyclohexylcarbodiimide. The physical and chemical properties of the products are discussed.

Many advantages can be foreseen for the use of synthetic macromolecules as carriers and controlled-release substrates for bioactive agents.[1] However, relatively few conventional polymers are appropriate for this purpose, primarily because of their bioincompatibility or resistance to hydrolytic breakdown. As discussed by us in other papers,[2-8] poly(organophosphazenes) possess a number of almost unique characteristics that may favor their use as carrier species. These features include the ease with which bioactive agents can be linked covalently or coordinatively to the macromolecular system and the wide choice of side-group structures that can impart water solubility, hydrophilic or hydrophobic insolubility, or, in special cases, biodegradability to nontoxic molecules.

In the present paper we describe a new option for the attachment and hydrolytic release of bioactive side groups. It makes use of an amide linkage between an aryloxy spacer group attached to the phosphazene chain and a carboxylic acid. The polymers described here are prototypes in the sense that they illustrate the range of structures that can be synthesized. However, they are water-insoluble systems that are not designed as facile biodegradable species. Biodegradability requires the use of cosubstituent groups, such as amino acid ester or imidazolyl units.[9] Water solubility requires the presence of methylamino or related cosubstituent groups.[2,10]

As discussed earlier,[11] our preferred route to the synthesis of new phosphazene high polymers involves a prior exploration of new reactions using small-molecule cyclic trimeric phosphazene models. This is the route followed in this work also. The carboxylic acids chosen for these coupling studies include a number of simple molecules such as acetic, propionic, and benzoic acids that were employed as preliminary models for reactions with more complex species. The coupling studies were then extended to reactions of the phosphazenes with acrylic and nicotinic

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