Conclusion

The hydrogenation of alternating butadiene–MMA copolymer gives a sequence-ordered copolymer which has repeating ethylene–ethylene–MMA sequences. It is a partially crystalline, soft, and tough material.

References and Notes

(1) Iwatsuki, S.; Yamashita, Y. *Prog. Polym. Sci.* **1971**, *2*, 1.
(2) Furukawa, J. In *Encycl. Polym. Sci. Technol.* **1971**, *15*, 137.
(3) Hirai, H. *J. Polym. Sci., Macromol. Rev.* **1976**, *11*, 47.
(4) Furukawa, J.; Iseda, Y.; Haga, K.; Kataoka, N.; Yoshimoto, T.; Imamura, T.; Shido, Y.; Miyagi, A.; Tanaka, K.; Sakamoto, K. *J. Polym. Sci., Part B* **1969**, *7*, 561.
(5) Irako, K.; Anzai, S.; Ohnishi, A.; Furukawa, J. *Nippon Kagaku Kaishi* **1976**, 670.
(6) Yokota, K.; Hirabayashi, T. *Polym. J.*, in press.
(7) Willstätter, R.; Waldschmidt-Leitz, E. *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 121.
(8) Furukawa, J.; Kobayashi, E.; Iseda, Y.; Arai, Y. *Polym. J.* **1970**, *1*, 442.
(9) Flory, P. J. *Trans. Faraday Soc.* **1965**, *51*, 848.
(10) Brandrup, J.; Immergut, E. H., Eds. "Polymer Handbook", 2nd ed.; Wiley: New York, 1975; Section III, p 61.
(11) Reference 10, Section V, p 16.
(12) Fox, T. G. *Bull. Am. Phys. Soc.* **1956**, *1*, 123.
(13) Reference 10, Section III, p 143.
(14) Reference 10, Section III, p 148.

Schiff Base Coupling of Cyclic and High-Polymeric Phosphazenes to Aldehydes and Amines: Chemotherapeutic Models

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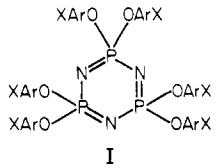
ABSTRACT: Prototype systems have been investigated for the synthesis of polymer-bound chemotherapeutic agents in which bioactive molecules are linked to poly(organophosphazenes) through Schiff base linkages. The sodium salts of the phenols 4-hydroxybenzaldehyde, 2-hydroxy-9-fluorenone, and 4-nitrophenol were allowed to react with hexachlorocyclotriphosphazene (III) to yield hydrolytically stable species of general formula $[NP(OArX)_2]_3$ (IV), where X = CHO, C=O, or NO_2. The 4-nitrophenolic group of IV was reduced to the corresponding 4-aminophenolic unit with PtO_2 and molecular hydrogen. Species IV formed Schiff base products with 2,4-dinitrophenylhydrazine, sulfadiazine, 3-hydroxytyramine, 2-amino-4-picoline, or citral. High-polymeric analogues of IV were synthesized with both phenoxy and OArX side groups (X = CHO, C=O, or NH_2) by techniques similar to those used for the cyclic trimers, and the macromolecules formed Schiff base species with 2,4-dinitrophenylhydrazine, sulfadiazine, phenylhydrazine, hydralazine, or citral. The physical and chemical properties of the Schiff base products are discussed.

Considerable interest exists in the use of synthetic macromolecules as carriers for the controlled release of chemotherapeutic agents.[1-3] Relatively few conventional polymers are suitable for this purpose because of the need for biocompatibility and facile side-group release mechanisms in aqueous media.

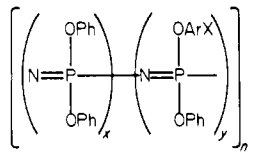
Poly(organophosphazenes) possess a number of advantages as potential carrier macromolecules. Synthetic routes are known for the introduction of a wide range of different substituent groups,[4-8] and the subtlety of structural variation is almost unique in macromolecular synthesis. Moreover, biodegradable polyphosphazenes have been prepared which can be designed to hydrolyze to innocuous small-molecule products.[9-11]

In this paper we explore the possibility that bioactive molecules might be attached to poly[(aryloxy)phosphazenes)] through a hydrolyzable Schiff base linkage. The reactions reported here are prototypes only since the use of aryloxy cosubstituent groups precludes the possibility of total biodegradation of these polymers. In later work we hope to extend these studies to systems that possess more biologically compatible spacer groups and cosubstituent units.

Inherent in our approach has been the need to perform exploratory reactions with small-molecule models, rather than with the high polymers themselves. Hence, cyclic trimeric phosphazenes such as I have been used as preliminary models for reactions with high polymers of type II. The group OArX represents a "spacer" aryloxy residues bearing a carbonyl or amino group X for reaction with amines or carbonyl compounds, respectively, to form Schiff bases. Because little was known about the reactivity or



I



II

stability of the carbonyl or amino units in molecules such as I or II, it was necessary to carry out preliminary reactions with nonchemotherapeutic analogues before extension of these coupling processes to more complex reactants.

Results and Discussion

Synthesis of Cyclic Trimeric Model Systems. The specific reaction sequences used for the phosphazene cyclic trimers are outlined in Scheme I.

The cyclic model systems were synthesized by treatment of hexachlorocyclotriphosphazene (III) with the sodium salt of an aldehydic or ketonic phenol or of a nitrophenol. Specifically, one of three types of spacer units was introduced at this stage—those derived from the sodium salts of 4-hydroxybenzaldehyde, 2-hydroxy-9-fluorenone, or 4-nitrophenol. The 4-nitrophenoxy side groups were reduced with hydrogen over PtO_2 to the 4-aminophenoxy derivative. These derivatives are depicted in the general structures shown in IV, VI, and VII. The spacer units were chosen as the simplest aldehydic, planar ketonic, and amino derivatives that should form stable aryl Schiff bases. The 9-fluorenone unit had the added advantage that its reactions could be monitored readily by ultraviolet spectroscopy. The indirect formation of the 4-aminophenoxy

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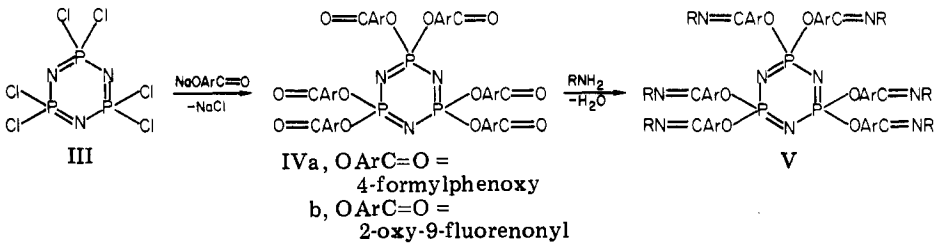
Scheme I



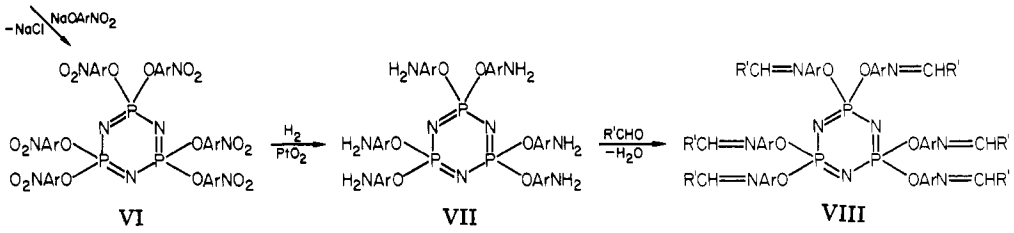
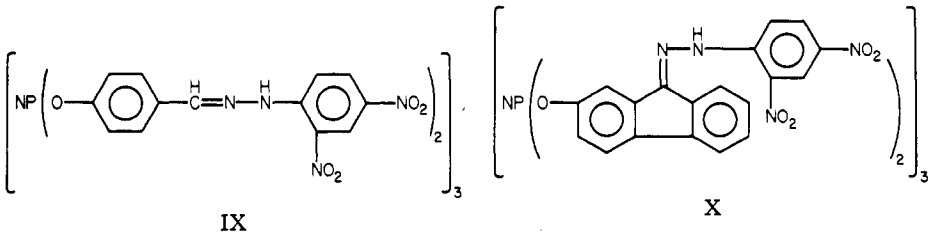
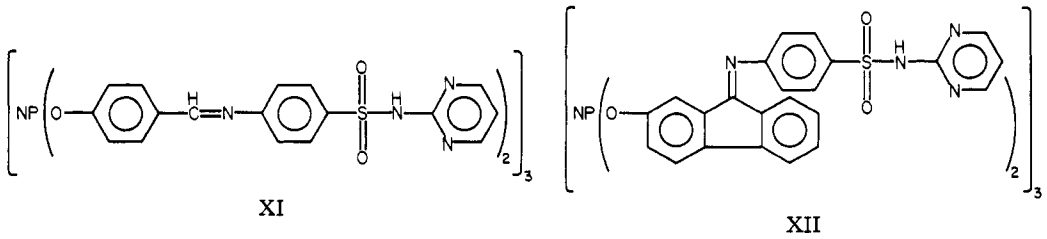
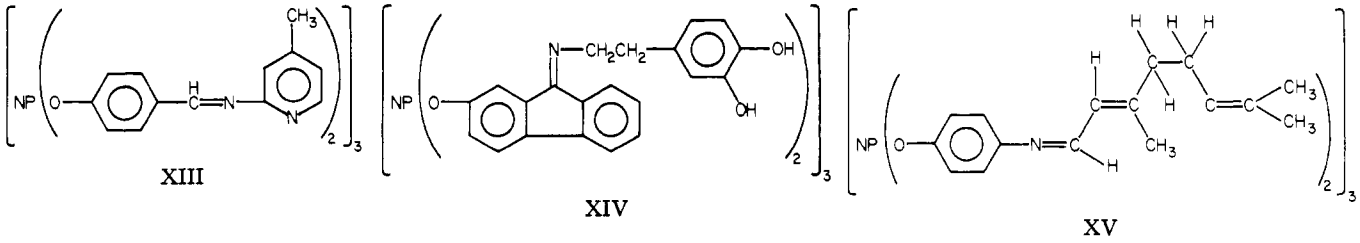


Chart I







unit was carried out to avoid possible intermolecular linkage reactions that would be expected if, for example, 4-aminophenol or its salts reacted with III. Similarly, the reaction conditions leading to the formation of IV were designed to avoid reaction of the second (nonhydroxy) functional group (see Experimental Section).

Subsequent coupling reactions were then induced between IV and 2,4-dinitrophenylhydrazine, sulfadiazine, 2-amino-4-picoline, or 3-hydroxytyramine to yield the Schiff bases of general structure V or between VII and citral to form a Schiff base of type VIII. The structures of the products are depicted in IX–XV (Chart I). 2,4-Dinitrophenylhydrazine was chosen as a coupling agent because of its known high reactivity in Schiff base formation and because of its use as a standard indicator for carbonyl units. Sulfadiazine provided an example of an antibiotic agent containing a primary *aryl*amino group. Similarly, hydroxytyramine (dopamine) is biologically active and possesses an *alkyl*amino coupling site. 2-Amino-4-picoline is an analgesic agent. Phenylhydrazine and hydralazine (an antihypertensive agent) provide examples of hydrazine-type coupling agents. Citral was used to monitor the ability of VII to yield Schiff base derivatives.

These results indicate that (1) aldehydic and ketone groups can survive the aryl oxide salt formation and linkage of the aryl oxide to the phosphazane (2) the phosphazene skeleton is unaffected by catalytic reduction of a nitro substituent to an amino group and (3) Schiff base compounds form readily with a variety of biologically active molecules.

Structural Characterization of the Cyclic Phosphazenes. Species IV, VI, VII, and IX–XV were characterized by a combination of ^{31}P NMR, ^{1}H NMR, and infrared spectroscopy, mass spectrometry, and elemental microanalysis (see Table I and II and the Experimental Section). For example, the ^{31}P NMR spectra were singlets for species IV–VIII, with the chemical shift position varying with the nature of the para-substituent groups. The chemical shift for $[NP(OC_6H_4CHO\text{-}p)_2]_3$ appeared at 7.19 ppm and changed to between 9 and 10.2 ppm when the Schiff base derivatives IX–XIV were formed (Table I).

Table I
Characterization Data for Cyclic Trimers

compound		microanalysis % C	% H	% N	% P	IR, cm^{-1}	mp, °C	MW, mass spec *m/e*	^{31}P NMR,[c,d] ppm	% yield
IVa	calcd	58.50	3.48	4.78	10.80			861		
	found	58.41	3.73	4.36	10.60	1705[a]	154-156	861	7.19	90
IVb	calcd	71.01	3.67	3.12	7.12			1306		
	found	70.06	4.59	3.12	7.03	1715[a]	231-234	1306	8.19	55
VI	calcd	44.85	2.49	13.08	9.65			963		
	found	44.96	2.57	12.93	9.80		263-265	963	6.99	90
VII	calcd	55.10	4.59	16.09	11.87			783		
	found	54.97	4.58	15.88	12.06		189-190	783	11.22	70
IX	calcd	48.22	2.78	19.47	4.79					
	found	48.16	2.81	19.43	4.82	1618[b]	325[d]		7.63	78
X	calcd	57.35	2.76	15.85	3.89					
	found	56.98	3.11	15.61	3.80	1615[b]	240[d]	*m/e* above MS limit	7.78	70
XI	calcd	59.04	4.34	18.23	4.48					
	found	59.16	4.20	17.95		1615[b]	235[d]		10.20	93
XII	calcd	60.40	3.33	14.10	3.70					
	found	59.09	3.73	14.62		1650[b]	220[d]		7.90	59
XIII	calcd	66.80	4.71	14.98	6.63			1401		
	found	66.70	4.43	15.12		1670[b]	88-89	1401	8.80	70
XIV	calcd	71.48	4.53	5.95	4.39					
	found	69.52	4.50	5.17		1685[b]	205[d]		7.11	68
XV	calcd	72.58	7.56	7.93	5.86					
	found	72.64	7.32	9.24	5.70	1650[b]	270[d]		11.07	88

[a] C=O. [b] C=N. [c] All samples were proton decoupled and were interpreted as A_3 spin systems. [d] Each sample was dissolved in THF. Chemical shift positions were relative to aqueous 85% H_3PO_4. A D_2O capillary lock was used.

Table II
Characterization Data for High Polymers

compound		microanalysis[a] % C	% H	% N	% P	substituent ratio A:B:C[b-e]	GPC[f] MW × 10^{-5}	T_g,[g] °C	^{31}P NMR, ppm (cosubstituent ratio)
XVIIa	calcd	61.15	4.06	5.68	12.58	73:0:27			
	found	61.12	4.08	5.62	12.60		5.0-7.1	-15	-16, -21 (1:2.7)
XVIIb	calcd	65.59	3.98	5.09	11.23	78:0:22			
	found	65.58	3.94	5.05	11.10		6.0-7.0	35	-19 to -20[h]
XIX	calcd	56.40	3.70	8.44	12.14	73:0:27			
	found	56.41	3.68	8.40	11.90		4.8-5.0	-14	-17, -21 (1:2.7)
XX	calcd	60.22	4.41	9.10	12.97	73:0:27			
	found	60.01	4.01	9.01	12.82		4.8-5.0	46	-8, -21 (1:2.7)
XXII	calcd	55.10	3.54	12.98	9.02	73:27:0			
	found	55.15	3.54	12.88	9.08		5.0-7.1	-18	-18, -21 (1:2.7)
XXIII	calcd	59.80	3.55	10.90	8.73	78:22:0			
	found	59.88	3.55	10.82	8.50		5.6-6.0	56	-19 to -20[h]
XXIV	calcd	59.40	3.94	9.09	10.27	73:15:12			
	found	59.36	3.60	10.08	10.22		5.0-5.3	0	-16, -21 (broad)
XXV	calcd	62.62	3.83	8.68	9.07	78:14:8			
	found	61.04	3.60	8.72	9.11		5.6-6.0	28	-19 to -20[h]
XXVI	calcd	63.95	4.45	9.48	10.80	73:24:3			
	found	63.90	4.40	9.45	10.70		5.0-6.0	-12	-17, -21 (1:2.7)
XXVII	calcd	66.34	4.27	8.21	9.88	78:21:1			
	found	66.02	4.26	8.19	9.68		5.6-6.0	38	-19 to -20[h]
XXVIII	calcd	62.44	4.09	12.52	10.04	73:22:5			
	found	62.40	4.08	12.49	10.02		4.8-6.0	-12	-16 (broad), -21 (1:2.7)
XXIX	calcd	66.64	5.73	7.64	10.12	73:25:2			
	found	66.21	5.43	7.00	9.96		4.8-5.0	25	-10, -21 (1:3)

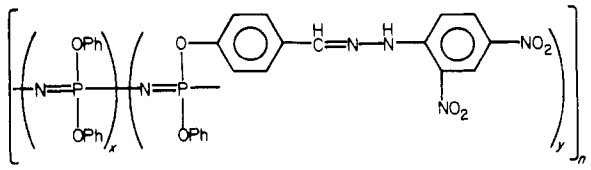
[a] Analytical data were obtained by Galbraith Laboratories. [b] Substituent: A = phenoxy, B = Schiff base, C = unreacted aldehydic-, ketonic-, or amino-type side group. [c] The composition of the polymers was determined by graphical, trial and error, and computer-based best fits to the analytical data. [d] Residual chlorine in these polymers was attributed to HCl bound as a salt rather than to unreacted PCl groups. Evidence for this view was obtained from a correlation of the microanalyses, ^{31}P NMR data, and the reduction of the chlorine content following treatment with tertiary amines. [e] The reactant ratios had been designed to yield a 75:25 substituent ratio. [f] The range of values shown represents gel permeation chromatography results from different syntheses. The values shown were obtained by comparison with polystyrene standards. [g] From torsional pendulum analysis. [h] Schiff base formation brought about no further shift in the peak positions although some peak broadening was observed.

Trimer $[NP(OC_6H_4NO_2\text{-}p)_2]_3$ showed a chemical shift of 6.99 ppm, which changed to 11.2 ppm for $[NP(OC_6H_4NH_2)_2]_3$ and 11.07 ppm for species XV.

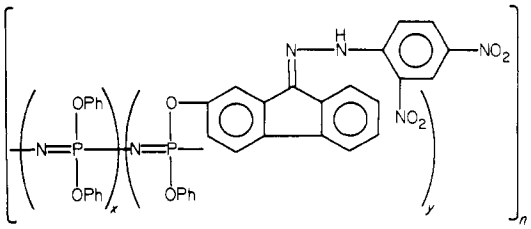
The ^1H NMR spectra were complicated, but the integrated ratios of aliphatic to aromatic protons were consistent with structures $[NP(OC_6H_4CHO\text{-}p)_2]_3$, $[NP(OC_6H_4NH_2)_2]_3$, IX, X, XIII, or XIV. For species XV, disappearance of the amino proton signal followed Schiff base formation.

Infrared spectra showed evidence for retention of the cyclotriphosphazene ring in all cases, with maxima in the 1150–1200-cm^{-1} range. Aromatic C–H bonds were detected

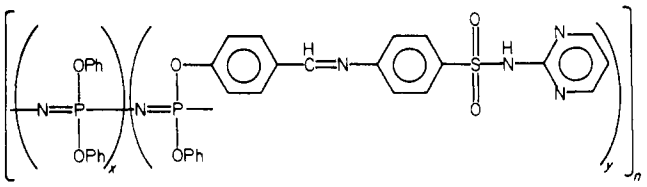
Chart II



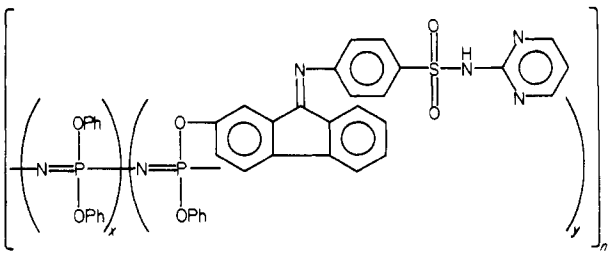
XXII



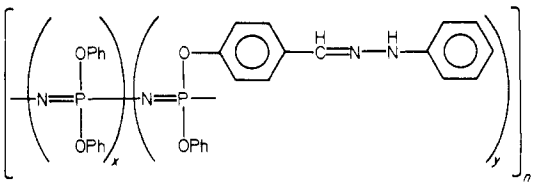
XXIII



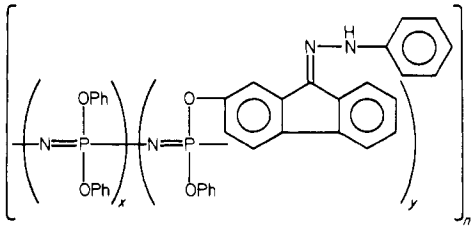
XXIV



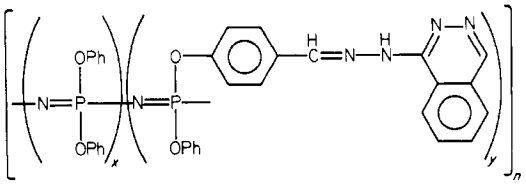
XXV



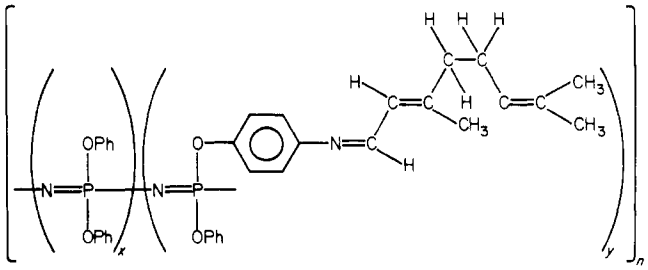
XXVI



XXVII



XXVIII



XXIX

from peaks in the 3000–3100-cm^{-1} region, and the carbonyl groups in IV were detected at 1705 (C_6H_4CHO) and 1715 (fluorenone) cm^{-1}. These carbonyl peaks disappeared following Schiff base formation, accompanied by the appearance of C=N stretching frequencies in the 1615–1690-cm^{-1} region.

The mass spectra of compounds IV, VI, and VII showed parent ions that corresponded to the expected molecular weights, but the Schiff base derivatives had molecular weights too high to be measured in this way. Schiff base formation was accompanied by a color change to yellow or bright orange, as would be expected from the formation of a conjugated C=N bond.

Synthesis of the High-Polymeric Derivatives. High-polymeric analogues of types XVIII and XXI were prepared by the reaction sequences shown in Scheme II. As in the cyclic trimeric model compounds, the "spacer" linkages comprised the 4-oxybenzaldehyde, 2-oxy-9-fluorenone, and 4-aminophenoxy units. Schiff base formation was then attempted with 2,4-dinitrophenylhydrazine, sulfadiazine, phenylhydrazine, hydralazine, or citral. The macromolecules formed are shown in XXII–XXIX (Chart II).

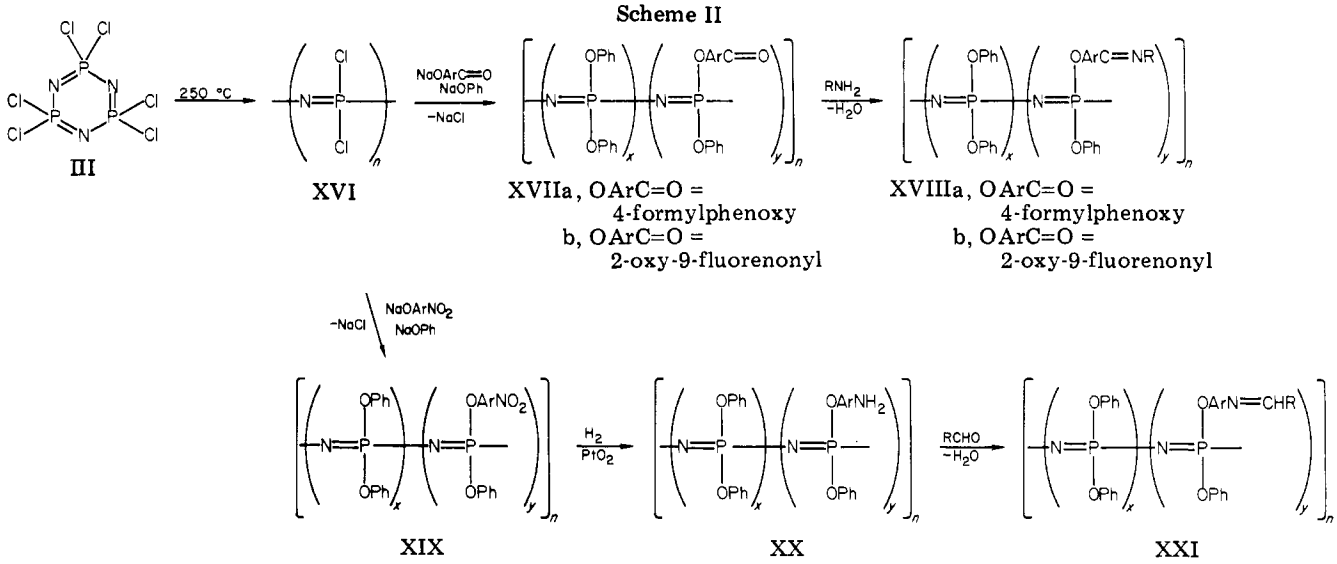
These polymers are mixed-substituent derivatives in which approximately 75% of the side groups were phenoxy residues and only 25% of the side groups bore the Schiff base linkages. It was anticipated that attempts to prepare high polymers in which every aryloxy side group bore a pendent Schiff base unit might lead to difficulties because of the excessive steric hindrance effects that would be generated.[12]

Characterization of the High Polymers. All the polymers were soluble in organic media and were, therefore, un-cross-linked. As shown in Table II, the microanalyses corresponded to structures XXII–XXIX. (The actual ratios of the different substituent groups deduced by microanalysis are listed in Table II.) Less than 1% residual chlorine was detected in the polymers, an indication of the high efficiency of substitution in the conversion of XVI to XVII or XIX.

The ^{31}P NMR spectra of the polymers provided confirmatory evidence for the substituent ratios.

The ^{31}P NMR spectra for the polymers were less definitive than those obtained for the cyclic trimer, due mainly to peak broadening and the existence of different phosphorus environments. However, polymer XIX showed two peaks, one at −21 ppm from $P(OPh)_2$ residues and the other centered at −17 ppm from $P(OPh)(OC_6H_5NO_2\text{-}p)$ units. The two peaks were in a ratio of 3:1. Following reduction of the NO_2 group to NH_2, the peak at −17 ppm

Scheme II



moved to −8 ppm. The integrated peak ratios remained at 3:1. Schiff base formation to yield XXIX brought about no further shift in the peak positions. Species XVII and XVIII showed only one broad peak centered at −20 ppm. Thus, although a nongeminal substitution pattern seemed evident for XIX–XXI, no evidence about the disposition of substituents could be obtained for XVII or XVIII.

Infrared spectra of the polymers were consistent with the expected structures. All the polymers showed a characteristic P=N "stretching" absorption between 1320 and 1100 cm^{-1}. The characteristic disappearance of the carbonyl (C=O) and the appearance of C=N in the region of 1600 and 1700 cm^{-1} were indicative of Schiff base formation. So, too, was the color change from colorless to yellow or orange.

The GPC average molecular weights were in the range 4.5×10^5 to 7.1×10^5, values that are lower than those normally found for poly[(aryloxy)phosphazenes] such as $[NP(OPh)_2]_n$. (Aryloxy)phosphazene high polymers are known to be sensitive to cyclization–depolymerization reactions at elevated temperatures,[13] and it is speculated that the attachment of the bulky amines via Schiff base formation further favors depolymerization.[14]

Glass transition temperatures are listed in Table II. Poly(diphenoxyphosphazene), $[NP(OPh)_2]_n$, has a T_g value of −8 °C.[5] The polymers synthesized here showed glass transitions in the range −24 to +56 °C, an indication that the torsional mobility of the backbone bonds is affected markedly by the introduction of the bulky Schiff base substituent groups.

Hydrolysis of the Schiff Base Linkages. Most compounds containing carbon–nitrogen double bonds can be hydrolyzed to the corresponding aldehydes or ketones. For imines the hydrolysis is easy and can be carried out with water, although hydrolysis of Schiff bases containing an aryl group bound directly to the C=N grouping is more difficult and requires acidic or basic catalysis. For example, the polymer XXVII, containing the fluorenone-phenylhydrazine imine linkage, hydrolyzed in the presence of dilute aqueous base to yield the free ketone and phenylhydrazine. Thorough extraction (Soxhlet) of the polymer removed all traces of phenylhydrazine from the polymer matrix and afforded species XVIIIb. Infrared spectra of the resulting polymer showed the appearance of a prominent peak at 1715 cm^{-1} due to the regenerated ketone and a peak at 1200 cm^{-1} from the phosphazene backbone. Gel permeation chromatography revealed no evidence of backbone chain shortening during the hydrolysis reaction. This hydrolysis appears to be typical of the behavior of all the Schiff base compounds prepared in this work.

Experimental Section

Reagents and Solvents. Hexachlorocyclotriphosphazene (mp 110–112 °C) was obtained from a trimer–tetramer mixture (Ethyl Corp.) after two fractional vacuum sublimations at 60 °C (0.5 torr), two recrystallizations from heptane, and two further vacuum sublimations. 2-Hydroxy-9-fluorenone, 4-hydroxybenzaldehyde, 4-nitrophenol, and phenol (Aldrich) were sublimed and stored in vacuo. 2,4-Dinitrophenylhydrazine, 3-hydroxytyramine, 2-amino-4-picoline, phenylhydrazine, hydralazine, and citral (Aldrich) were used as received. Sulfadiazine was obtained from Sigma Chemical Co. Xylene or heptane (Fisher) were boiled at reflux and distilled from CaH_2 before use. Tetrahydrofuran and dioxane (Fisher) were distilled from sodium–benzophenone. Sodium hydride, as a 50% dispersion in oil (Alfa), was washed with dry heptane before use.

Analytical Techniques. Proton-decoupled ^{31}P NMR spectra were obtained in the FT mode at 40.5 MHz with a JEOL JNM-PS-100 spectrometer equipped with a Nicolet 1080 data processing system. Infrared spectra were obtained with a Perkin-Elmer 580 spectrometer. Polymer separations and molecular weight approximations were by gel permeation chromatography with the use of a Waters Associates ALC-201 instrument. A 4 ft × $^3/_8$ in. 10^5 Styragel column was used with a tetrahydrofuran solvent flow rate of 2.4 mL/min. Approximate calibration of the columns was accomplished by means of narrow molecular weight polystyrene standards obtained from Waters Associates. The physical properties of the polymers were monitored by torsional braid analysis with the use of a modified Chemical Instruments Corp. unit. Mass spectra were obtained with an AEI MS 902 mass spectrometer operated at an ionization potential of 20 eV. Elemental analyses were obtained by Galbraith Laboratories on samples that were dried for at least 8 h in vacuo at 40–80 °C.

General Synthetic Route to IV or VI. All cyclic trimeric compounds of structure IV or VI were prepared in the same manner. The following procedure is typical. A mixture of sodium hydride (0.91 g, 0.037 mol), 4-hydroxybenzaldehyde (5.27 g, 0.038 mol), and hexachlorocyclotriphosphazene (2 g, 0.0057 mol) in tetrahydrofuran (200 mL) was stirred at reflux for 48 h. The mixture was then cooled and filtered via Schlenk techniques, and the filtrate was concentrated to a volume of 40 mL and added slowly to hexane (300 mL) to yield a precipitate of IVa (4.5 g, 90%). The white solid was recrystallized twice from ethyl acetate. The melting points and characterization data for this and related compounds are listed in Table I.

General Synthetic Route to Schiff Bases V. The following procedure is typical. The cyclic trimer IVa (0.75 g, 0.0008 mol) was dissolved in tetrahydrofuran (35 mL). 2,4-Dinitrophenylhydrazine (0.2 g, 0.001 mol) was added, and the mixture was stirred

at 25 °C for 2 h. After addition of approximately 1.5 mL of concentrated hydrochloric acid, the solution changed to an orange color and a red-orange precipitate formed. This was collected by suction filtration, washed with ethanol (30 mL), and dried in vacuo. The yield was 1.2 g (78%). The characterization data are listed in Tables I and II. This compound underwent a vigorous decomposition when heated to 325 °C in a melting point capillary. *In view of this observation, care should be taken to avoid the possibility of heating preparative quantities of this compound to temperatures above 250 °C.*

Hexakis(4-aminophenoxy)cyclotriphosphazene (VII). A 1000-mL autoclave was charged with hexakis(*p*-nitrophenoxy)-cyclotriphosphazene (VI) (16 g, 0.016 mol), aniline as a solvent (100 mL), and PtO_2 (0.01 g). The autoclave was charged with hydrogen (50 psi), agitated, and heated to 50 °C for 24 h. No drop in pressure took place after this time. The solution was concentrated to 50 mL under reduced pressure and then added slowly to benzene (400 mL). The white precipitate was recrystallized from *o*-dichlorobenzene to yield VII (9.1 g, 70%); mp 189 °C (lit.[15] mp 189–190 °C).

Reactions of VII with Citral. Hexakis(4-aminophenoxy)-cyclotriphosphazene (VII) (1.0 g, 0.0012 mol) was dissolved in diethylene glycol (35 mL) and the solution was treated with 3,7-dimethyl-2,6-octadienal (citral) (2,3 g, 0.015 mol). The mixture was stirred for 2 h at 25 °C. Concentrated hydrochloric acid (0.018 mol) was then added and the reaction mixture was warmed. A deep red color formed. Additional citral (2.3 g, 0.015 mol) was added slowly to compensate for any loss due to cyclization of the aldehyde. The mixture was allowed to react at 25 °C for 15 min before addition of water (10 mL). The red precipitate was removed by filtration, washed with ethanol (30 mL), and recrystallized from acetone; yield 1.7 g (88%). The characterization data are listed in Table I.

Poly(dichlorophosphazene) (XVI). The cyclic trimer $(NPCl_2)_3$ (200 g) was polymerized in evacuated, sealed glass tubes at 250 °C for 8 h. The tube was rocked continuously during polymerization to ensure agitation of the contents. The tube was then cooled and residual cyclic oligomers were removed by sublimation at 55 °C (0.7 torr). All the poly(dichlorophosphazene) used in this work was prepared from one batch of purified cyclic trimer, with a number of trimer polymerization tubes being filled and evacuated and trimer polymerized in an identical manner.

Poly[(4-formylphenoxy)phenoxyphosphazene] (XVIIa). Poly(dichlorophosphazene) (13.5 g, 0.116 mol) dissolved in dioxane (1000 mL) was added slowly to a stirred solution of sodium phenoxide prepared from phenol (16.4 g, 0.174 mol) and sodium hydride (8.379 g, 0.174 mol) in dioxane (150 mL). The ratio of reactants was designed to bring about replacement of only 75% of the chlorine atoms by phenoxy groups. The mixture was stirred at reflux for 48 h, cooled to 25 °C, and treated dropwise with a solution of sodium 4-formylphenoxide prepared from 4-hydroxybenzaldehyde (35.5 g, 0.29 mol) and sodium hydride (13.92 g, 0.29 mol) in dioxane (150 mL). This was a 300% excess of the aryl oxide over that required to remove the remaining chlorine atoms. The reaction mixture was then stirred at reflux for an additional 48 h, cooled to 25 °C, and filtered to remove sodium chloride. The filtrate was then treated with an additional 0.1 mol of sodium phenoxide at 100 °C for 24 h to ensure maximum removal of chlorine atoms from the polymer. The polymer was purifed by dropwise addition of the reaction mixture (at 25 °C) into water and subsequent reprecipitation of the solid product three times from tetrahydrofuran into water. Drying in vacuo yielded 22.1 g (81%) of the polymer. Characterization data are listed in Table II.

Poly[(2-oxy-9-fluorenonyl)phenoxyphosphazene] (XVIIb). Poly(dichlorophosphazene) (13.5 g, 0.116 mol) was dissolved in dioxane (100 mL), and to this solution was added slowly a solution of sodium phenoxide prepared from phenol (16.4 g, 0.174 mol) and sodium hydride (8.379 g, 0.174 mol) in dioxane (150 mL). This ratio of reactants was designed to replace 75% of the available chlorine atoms in $(NPCl_2)_n$. This reaction mixture was stirred at reflux for 48 h, cooled to 25 °C, and treated with a solution of sodium 9-fluorenone 2-oxide prepared from 2-hydroxy-9-fluorenone (56.8 g, 0.29 mol) and sodium hydride (13.92 g, 0.29 mol) in dioxane (200 mL). This was a 300% excess over that needed to replace the remaining chlorine atoms in the polymer. The reaction mixture was then stirred at reflux for 56 h, cooled to 25 °C, filtered to remove sodium chloride, and treated with a further 0.1 mol of sodium phenoxide at 100 °C for 24 h to ensure total chlorine replacement. The mixture was cooled to 25 °C, and the polymer was precipitated by dropwise addition into water. Subsequent reprecipitation was carried out three times from THF into water and twice from THF into acetone before drying in vacuo; yield 17.2 g (55%).

Poly[(4-nitrophenoxy)phenoxyphosphazene] (XIX). Poly(dichlorophosphazene) (13.5 g, 0.116 mol) was dissolved in dioxane (1000 mL) and this was treated dropwise with a solution of sodium phenoxide prepared from phenol (16.4 g, 0.174 mol) and sodium hydride (8.379 g, 0.174 mol) in dioxane (150 mL). Again, this represented an attempt to replace 75% of the chlorine atoms in XVI. After 48 h of boiling at reflux, the mixture was added slowly to a solution of sodium 4-nitrophenoxide prepared from 4-nitrophenol (40.31 g, 0.29 mol) and sodium hydride dispersion in oil (13.92 g, 0.29 mol) in dioxane (400 mL). This mixture was stirred at 65 °C for 96 h (the relatively low temperature was used to minimize the possibility of cross-linking). After filtration to remove sodium chloride, the polymer was isolated by slow addition of the solution to water, followed by precipitation from THF into water a total of six times and precipitation twice from THF into acetone. Residual solvent was removed in vacuo; yield 18.7 g (61.9%).

Poly[(4-aminophenoxy)phenoxyphosphazene] (XX). A 1000-mL autoclave was charged with XIX (15 g), aniline (300 mL), and PtO_2 (0.1 g). The autoclave was pressurized with hydrogen to 50 psi and agitated at 50 °C for 96 h. The resultant reaction mixture was filtered to remove the catalyst, and the filtrate was added dropwise to ethanol (1500 mL). The solid precipitate was then reprecepitated four times from THF into ethanol and twice from THF into benzene. The yield of vacuum-dried polymer was 10 g (72%).

Synthesis of Polymeric Schiff Bases XVIII. The following procedure is typical. Poly[phenoxy(4-formylphenoxy)phosphazene] (XVIIa) (0.5 g, 0.001 mol) in THF (50 mL) was treated with 2,4-dinitrophenylhydrazine (0.812 g, 0.004 mol). The reaction mixture was first stirred at reflux for 30 min, then cooled to 25 °C, and treated slowly with concentrated hydrochloric acid (0.015 mol). An immediate color change to orange occurred. After an additional 2 h of reaction at 25 °C, the mixture was filtered and the polymer was isolated by dropwise addition of the filtrate into aqueous ethanol. Purification was effected by three precipitations from THF into absolute ethanol; yield of XXII, 0.518 g (75%).

The Schiff bases from the fluorenone-substituted polymer were prepared in a similar way. For example, polymer XVIIb (0.5 g) was treated in a similar manner with phenylhydrazine (0.8 mL, 0.008 mol) to yield XXVII. Final purification by five precipitations from THF into absolute ethanol yielded 0.49 g (84%) of the yellow polymer.

Synthesis of Polymeric Schiff Base XXIX. Poly[(4-aminophenoxy)phenoxyphosphazene] (VII) 0.5 g, 0.001 mol) in a 1:1 mixture of dioxane and xylene (50 mL) was treated with 3,7-dimethyl-2,6-octadienal (citral) (1 g, 0.006 mol). The mixture was stired at reflux for 30 min, cooled to 25 °C, and treated dropwise with concentrated hydrochloric acid (0.015 mol.). A color change to orange occurred immediately. Additional citral (3 g, 0.018 mol) was added slowly to compensate for a possible loss of this reactant through cyclization. After being stirred for 2 h at 25 °C, the mixture was filtered and the polymer precipitated by dropwise addition of the filtrate into aqueous ethanol. Three subsequent precipitations from dioxane into absolute ethanol followed by drying in vacuo at 50 °C (1 torr) for 8 h yielded XXIX; yield 0.32 g (62%).

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References and Notes

(1) Donaruma, L. G. *Prog. Polym. Sci.* **1975**, *4*, Chapter 1.
(2) Batz, H. G. *Adv. Polym. Sci.* **1975**, *23*, 25.
(3) Schuerch, C. *Adv. Polym. Sci.* **1972**, *10*, 173–94.
(4) Allcock, H. R.; Kugel, R. L. *J. Am. Chem. Soc.* **1965**, *87*, 4216.
(5) Allcock, H. R.; Kugel, R. L.; Valan, K. J. *Inorg. Chem.* **1966**, *5*, 1709.

(6) Allcock, H. R.; Kugel, R. L. *Inorg. Chem.* **1966**, *5*, 1716.
(7) Allcock, H. R. "Phosphorus-Nitrogen Compounds"; Academic Press: New York, 1972.
(8) Allcock, H. R. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 147.
(9) Allcock, H. R.; Fuller, T. J.; Mack, D. P.; Matsumura, K.; Smeltz, K. M. *Macromolecules* **1977**, *10*, 824.
(10) Allcock, H. R.; Fuller, T. J. *Macromolecules* **1980**, *13*, 1338.
(11) Allcock, H. R.; Fuller, T. J. *J. Org. Chem.*, in press.
(12) Allcock, H. R.; Cook, W. J.; Mack, D. P. *Inorg. Chem.* **1972**, *11*, 2584.
(13) Allcock, H. R.; Moore, G. Y.; Cook, W. J. *Macromolecules* **1974**, *7*, 571.
(14) Allcock, H. R. *J. Macromol. Sci., Rev. Macromol. Chem.* **1970**, *C4*, 149.
(15) Kober, E.; Lederle, H. J.; Ottmann, G. *Inorg. Chem.* **1966**, *5*, 2239.

Diazo Coupling Reactions with Poly(organophosphazenes)

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ABSTRACT: Polymer-bound dyes have been prepared by the diazotization of high-polymeric $[NP(OC_6H_5)_x(OC_6H_4NH_2\text{-}p)_y]_n$, followed by coupling to phenol, β-naphthol, 6′-NaO_3S-β-naphthol, and (*p*-aminophenyl)naphthalene. These reactions were preceded by model compound studies with the cyclic trimer $[NP(OC_6H_4NH_2\text{-}p)_2]_3$. In both cases, the aminophenoxy units were generated by reduction of 4-nitrophenoxy groups with PtO_2 and hydrogen. The phosphazene skeleton was unaffected by the reduction, diazotization, and diazo coupling processes. The physical characteristics of the trimers and high polymers are described.

Polymer-bound dye systems are of interest in photochemical research, in photographic processes, and in a number of biologically related applications.[1-3] As part of our general interest in the reactions of cyclic and high-polymeric phosphazenes,[4-6] we have examined the possibility that diazo-linked polyphosphazenes can be prepared by side-group construction reactions carried out on a preformed poly(organophosphazene).

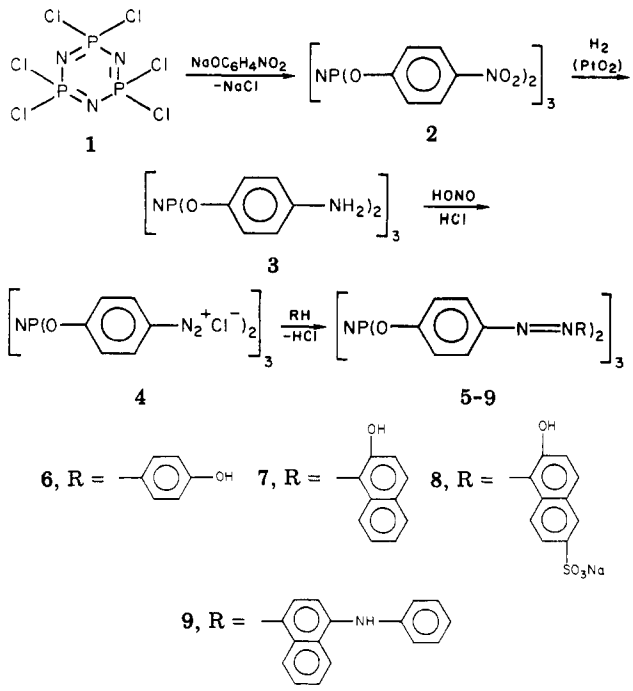
Polyphosphazenes are appealing carrier molecules for chromophores because of their general transparency, the photochemical stability of the backbone,[7] the possibility of electronic interactions between the backbone and the chromophore, and the ease with which different side groups can be incorporated into the macromolecule by substitutive techniques.[4-6,8-10] Previous attempts to link preformed chromophores to a phosphazene chain[11] suffered from steric hindrance and ligand displacement problems which, together, allowed the introduction of relatively few chromophoric units per chain.

In the present approach, we have used polyphosphazenes that contain both phenoxy and 4-nitrophenoxy side groups, with the latter being used as sites for chromophore construction. Because of the usual problems involved in the molecular characterization of new high polymers, the high-polymeric reactions were preceded by a series of model compound studies with small-molecule cyclotriphosphazenes in order first to optimize the synthetic and characterization procedures.[6]

Results and Discussion

Model Compound Studies. The overall reaction sequence for the model compound studies is outlined in Scheme I. Thus, hexachlorocyclotriphosphazene (**1**) reacted with sodium 4-nitrophenoxide to yield hexakis(4-nitrophenoxy)cyclotriphosphazene (**2**), which could be reduced catalytically to hexakis(4-aminophenoxy)cyclotriphosphazene (**3**). No evidence of catalyst poisoning by the phosphazene was found, and this was important for the later polymer synthesis. Compound **3** was converted to the diazonium salt **4** under standard reaction conditions

Scheme I



and without any evidence of phosphazene skeletal cleavage. Subsequent coupling of the diazonium salt to four representative aromatic units yielded **5–9**.

These model compounds were characterized by a variety of techniques. First, the strong characteristic colors of **5–9** were indicative of azo compound formation. Ultraviolet–visible absorptions were detected at the following wavelengths: **6**, 348 nm; **7**, 330 and 370 nm; and **8**, 325 and 342 nm. Species **9** can exist in either a protonated (cyanine type) or unprotonated form which yields either a purple color (λ_{max} 574 nm) in acidic solution or an orange color (λ_{max} 347 nm) in basic media. Elemental analysis, ^{31}P NMR, ^{1}H NMR, melting point, and mass spectrometric

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