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# Small-Molecule Phosphazene Rings as Models for High Polymeric Chains

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A growing belief exists that the special chemical and physical properties of synthetic macromolecules may provide a vehicle for important advances in catalysis, in chemotherapy, and in the understanding of chemical and biological reaction mechanisms. These properties are also of interest for future developments in biomedical artificial organ research and in high-temperature and electronic technology. Although most of the known polymers are synthesized by the polymerization of organic monomers, future advances may require a greater emphasis on the use of preformed macromolecules that can be modified extensively by chemical reactions.

Macromolecules are inherently more difficult to synthesize, characterize, or modify chemically than are most small-molecule compounds. These difficulties stem from the long molecular chain lengths, the coiling of these chains, the resultant molecular shielding, and the multitudinous opportunities that exist for inter- and intramolecular interactions along the length of each chain. In practice, these factors become manifest in serious complications when attempts are made to use macromolecules as reaction substrates or when the polymers must be purified and characterized.

Specifically, three problems are associated with the use of macromolecules as starting materials for synthesis. First, the coiling of the polymer chains in solution affects the reactivity of the side groups, often in unexpected ways. Second, macromolecules are infinitely more sensitive to coupling side reactions than are small molecule systems. Assume that in a certain substitution process a side reaction causes the loss of 1% of the product by the coupling of two molecules. In a small-molecule system, the 1% side product can be discarded and the yield of the main product is 99%. The same side reaction occurring in a macromolecular system, where each molecule may contain 10 000 or 15 000 repeating units, would generate 100 or 150 *cross-links* per chain. This would give rise to an insoluble matrix, and the yield of the linear polymer would be 0%. Hence, reactions that employ macromolecules as substrates must be much "cleaner" than those that are adequate for small-molecule reactions. Third, macromolecules are extremely sensitive to chain cleavage reactions. The advantageous properties of polymers depend directly on the long chain length. Thus, any side reaction that induces even a low percentage of chain cleavage will have a catastrophic effect on the physical properties of the polymer. Ten chain cleavage reactions per 10 000 repeating units may yield a product that has no worthwhile macromolecular properties at all.

In conventional macromolecular synthesis these problems are usually minimized by avoiding the need to perform reactions on high polymers themselves. The synthesis of a new organic polymer is often restricted to a search for new monomers and investigations into ways in which those monomers may be polymerized. However, this approach is not possible for some of the newer inorganic-based polymer systems now being explored. Hence, the question of polymer reactivity and sensitivity to side reactions constitutes a serious problem.

One solution to this problem is the use of small-molecule "model" systems as synthetic, mechanistic, or structural substitutes for high polymers. The objective is to use the easily purified and readily characterized small molecules for the rapid exploration of new reactions, reactivities, and structural phenomena that could be accomplished only slowly and with considerable difficulty with the analogous high polymers. The information derived from the most successful model-compound experiments can then be applied to the more challenging large-molecule systems. This idea has considerable appeal both for studies relating to known polymers and for those that have not yet been synthesized. This Account explores the validity of this approach for a new and intriguing macromolecular system—the polyphosphazenes. However, the experience gained with this one system is expected to be of general value for the planning of a synthetic attack on other still unexplored macromolecular systems.

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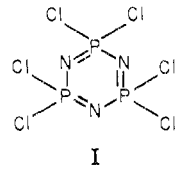
## Phosphazene High Polymers

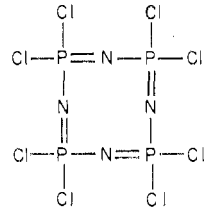
The long search for new high polymers that possess inorganic elements as skeletal atoms has been under way for at least 40 years. The motivation for this search has been the recognition that inorganic-backbone polymers should possess unusual chemical and physical properties that would be of fundamental scientific and technological interest.

Up to the present time only two classes of polymers—the poly(organosiloxanes) and the poly(organophosphazenes)—have fulfilled the promise of the inorganic polymer approach. Poly(organophosphazene) research and technology are still in their infancy, but even now it is clear that these macromolecules rival conventional organic polymer systems in their synthetic scope, structural diversity, theoretical challenge, and, in some cases, practical utility. The first syntheses of these polymers by my co-workers and me was a direct result of the use of the model compound concept.

Phosphazenes are cyclic or linear molecules that contain a framework of alternating phosphorus and nitrogen atoms, with two substituent groups attached to each phosphorus. The earliest known compounds of this type were the cyclic chlorophosphazenes, I and II, which can be converted by heating to the insoluble, rubbery poly(dichlorophosphazene) (III). In the 1930s



I



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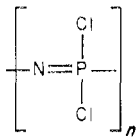


III

a few individuals examined the properties of this polymer but were discouraged by its insolubility and hydrolytic instability. Thus, for the next 30 years it remained simply a laboratory curiosity.

Our interest in this topic was stimulated by the recognition of two facts. First, it appeared that the hydrolytic instability of III was a consequence of the presence of P–Cl bonds rather than an intrinsic feature of the skeleton. If analogous high polymers could be synthesized that possessed nonhydrolyzable organic side groups in the place of chlorine, an unusual new class of macromolecules would be accessible. The prospect that this could be accomplished by the polymerization of organic-substituted trimers and tetramers was found to be experimentally unfeasible. An alternative approach to achieve the same end was by a direct replacement of the chlorine atoms in III by organic nucleophiles. Second, it was recognized that this could not be accomplished with the insoluble form of III, because substitution reactions cannot be carried out to completion with an insoluble reactant. However, nearly all linear, covalent polymers are soluble, and the fact that the known forms of III imbibed solvents such as benzene suggested that the polymer possessed a cross-linked structure. Thus, it appeared possible that the cross-linked form might have been derived from a soluble, un-cross-linked species that would be a more suitable substrate for substitution reactions.

Two serious problems remained. It was not known initially if halogen replacement reactions with chlorophosphazenes were feasible without cleavage of the inorganic skeleton, and it was not clear how an un-cross-linked form of III might be prepared. Model compound studies yielded the vital data needed to solve the first problem; a chance observation provided the answer to the second.

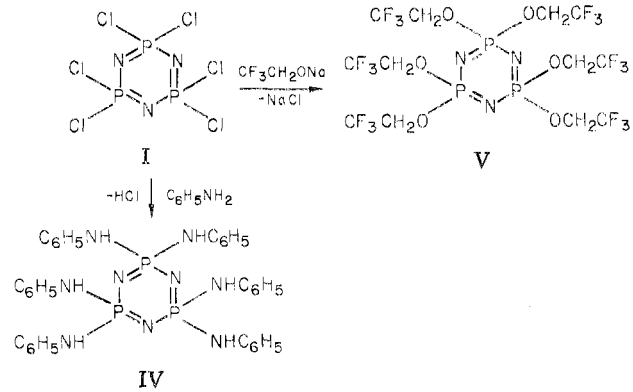
## Models for Poly(dichlorophosphazene)

Earlier X-ray structural work on the cross-linked form of III[1] had suggested that the basic structural unit is a linear repetitive arrangement of $NPCl_2$ residues, as shown in III. The analogous cyclic trimer (I) and tetramer (II) appeared to be plausible models for the high polymer. These cyclic species are readily prepared (from phosphorus pentachloride and ammonium chloride), are easily purified by recrystallization or sublimation, and might be expected to react in a similar manner to the high polymers.

However, the geometry of a small ring is different from that of a short segment of a high polymer. Ideally, better reaction models would be provided by higher cyclic species, such as $(NPCl_2)_{5-10}$, but such compounds are difficult to isolate. Short-chain models of structure $Cl_4PN{=}P(Cl_2)N{=}PCl_3$ or $Cl_4P(N{=}PCl_2)_2N{=}PCl_3$ would mimic the linear geometry of a high polymer, but the ratio of end units to middle units would be unsatisfactory. Moreover, such compounds are difficult to isolate and purify. Hence, the cyclic trimer and tetramer (I and II) provide a compromise between an ideal model and the experimental constraints.

## Early Model Reactions and Polymer Substitution

The first organic substitution reactions were described by Hofman, Couldridge, and Bode.[2] They involved the interaction of I with aniline to yield IV.



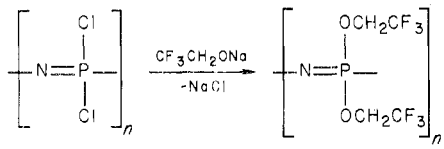
IV

This reaction provided the first evidence that the skeleton could survive nucleophilic replacement of the halogen atoms. The second (and critical) set of small-molecule reactions was not carried out until 1956.[3]

(1) Meyer, K. H.; Lotmar, W.; Pankow, G. W. *Helv. Chim. Acta* **1936**, *19*, 930.
(2) Bode, H.; Butow, K.; Lienau, G. *Chem. Ber.* **1948**, *81*, 547.
(3) McBee, E. T.; Allcock, H. R.; Caputo, R.; Kalmus, A.; Roberts, C. W. U.S. Govt. Astia Rep. AD 209,669 (1956–1959).

They involved the interactions of the sodium salts of fluoro alcohols with I or II to yield compounds such as V. The products were hydrolytically stable. Especially important was the discovery that these substitution reactions are surprisingly "clean", with very high yields being accomplished, no evidence of ring cleavage, and no tendency for rearrangement or decomposition of the products being found at temperatures as high as 250 °C.

Nearly 10 years elapsed before model reactions of this type could be transposed to the macromolecular system. A method for the isolation of soluble poly(dichlorophosphazene) was developed during a kinetic and mechanistic study of the polymerization of I to III.[4,5] The observation was made that the cross-link density of the polymer increased with polymerization time. By inference, if the polymerization could be terminated at an early enough stage, no cross-links at all should be present. This interpretation was found to be correct. The polymer obtained up to the point at which 70–75% of the trimer had reacted was soluble in benzene, tetrahydrofuran, and a number of other solvents. Treatment of this polymer with sodium trifluoroethoxide yielded the fully substituted macromolecule VI.[5,6]




III VI

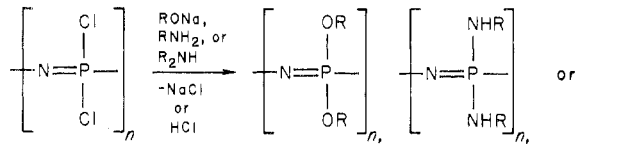
This organophosphazene polymer was stable to air, moisture, aqueous acid, and base. It did not burn. It could be fabricated into films and flexible fibers. The molecular weight values indicated that the average chain length exceeded 15 000 repeating units. It was clear to us that we had discovered a synthetic route that could lead to the preparation of an almost unprecedented range of new polymers, each with different substituent groups (as homopolymers or mixed substituent species) and different physical and chemical properties.

The unique feature of this synthesis route is the use of a highly reactive, *unstable, polymeric intermediate* (III) as a substrate for the introduction of different substituent groups. The phosphazene backbone functions as a stable "framework" to which the substituent groups are selectively attached. Hence, different polymer structures can be "tailor-made" for specific laboratory or technological purposes.

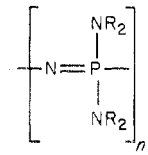
Following this initial discovery, high polymers of formula $[NP(OCH_3)_2]_n$, $[NP(OC_2H_5)_2]_n$, $[NP(OC_6H_5)_2]_n$, $[NP(NHC_6H_5)_2]_n$, $[NP(NHC_2H_5)_2]_n$, $[NP(N(CH_3)_2)_2]_n$, and $[NP(NC_5H_{10})_2]_n$ were synthesized with the use of similar techniques,[5-7] and in recent years work in our laboratory and elsewhere has increased this number to more than 80 different examples.[8-11] Meanwhile, the chemistry of small-molecule cyclic phosphazenes has expanded to a remarkable degree, with detailed mechanistic and structural interpretations emerging from a number of research groups as well as from our own. Hence, phosphazene chemistry is now in the position that information is available about the polymers as well as the models. In the remainder of this Account, it is my intention to use the knowledge now available to answer the question: "How valid is the model compound approach, and how much can really be predicted from the reactions and structures of small-molecule cyclic compounds that can then be applied to the behavior of macromolecules?"

## Comparison of Reactivity Patterns

One of the characteristic features of small-molecule cyclophosphazene chemistry is the ease with which chlorine atoms in I or II can be replaced by a wide variety of alkoxy, aryloxy, or amino residues to yield species such as $[NP(OR)_2]_{3 \text{ or } 4}$, $[NP(NHR)_2]_{3 \text{ or } 4}$, or $[NP(NR_2)_2]_{3 \text{ or } 4}$. In all these reactions, partly organo-substituted derivatives, as well as fully substituted species, can usually be isolated. Moreover, two or more different organic substituents can be attached to the same ring. Comprehensive reviews on these reactions are in the literature.[12-16] These reactions can be viewed as models for the analogous interactions between poly(dichlorophosphazene) and nucleophiles, with the same prospects for partial or full substitution by one or more organic reactants. Enough information is now available to permit close comparisons to be made between the polymers and the analogous cyclic species.




III VII VIII



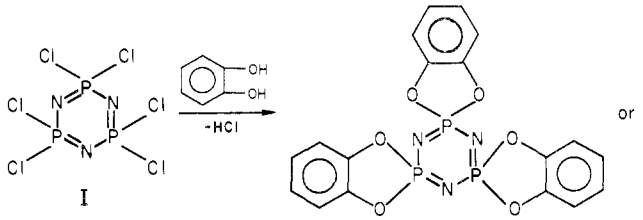

IX

First, a wide variety of alkoxy, aryloxy, and amino groups can be linked to both the cyclic and polymeric phosphazene skeletons (VII–IX). These groups include $OCH_3$, $OC_2H_5$, $OCH_2CF_3$, $OCH_2CF_2CF_3$, $OC_6H_5$, $OC_6H_4X$, $NHCH_3$, $NHC_2H_5$, $NHC_3H_7$, etc., $NHC_6H_5$, $NHC_6H_4X$, $N(CH_3)_2$, $NC_5H_{10}$, $NHCH_2COOR$, etc. For substituents of these types, close similarities seem to exist between the ease of halogen replacement in both the cyclic oligomeric and the high polymeric systems. Even unexpected peculiarities derived from electronic effects appear to be transposed from the cyclic systems to the high polymer. For example, the ability of amines to replace only one fluorine per phosphorus in

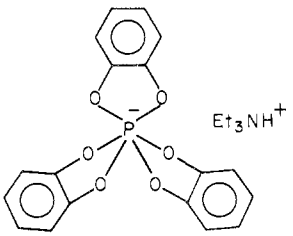
(4) Allcock, H. R.; Best, R. J. *Can. J. Chem.* **1964**, *42*, 447.
(5) Allcock, H. R.; Kugel, R. L. *J. Am. Chem. Soc.* **1965**, *87*, 4216.
(6) Allcock, H. R.; Kugel, R. L.; Valan, K. J. *Inorg. Chem.* **1966**, *5*, 1709.
(7) Allcock, H. R.; Kugel, R. L. *Inorg. Chem.* **1966**, *5*, 1716.
(8) Allcock, H. R. *Science* **1976**, *193*, 1214.
(9) Allcock, H. R. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 147.
(10) Tate, D. P. *J. Polym. Sci., Polym. Symp.* **1974**, *48*, 33.
(11) Singler, R. E.; Schneider, N. S.; Hagnauer, G. *Polym. Eng. Sci.* **1975**, *15*, 321.
(12) Allcock, H. R. "Phosphorus-Nitrogen Compounds", Academic Press: New York, 1972.
(13) Allcock, H. R. *Chem. Rev.* **1972**, *72*, 315.
(14) Pantel, S.; Becke-Goehring, M. "Six and Eight-Membered Ring Systems in Phosphorus-Nitrogen Chemistry"; Springer: Berlin, 1969.
(15) Shaw, R. A.; Keat, R.; Hewlett, C. In "Preparative Inorganic Reactions"; Jolly, W. L., Ed.; Interscience: New York, 1965; Vol. 2, pp 1–191.
(16) Krishnamurthy, S. S.; Sau, A. C. *Adv. Inorg. Chem. Radiochem.* **1978**, *21*.

$(NPF_2)_{3 \text{ or } 4}$ is matched almost exactly in the reactions of $(NPF_2)_n$.[17] Although much is known about the reaction pathways followed in the cyclic systems ($S_N2$, $S_N1$, gem, non-gem, cis, or trans),[12,13] virtually nothing is known about the mechanistic details of the polymeric reactions. In the absence of firm data, the assumption is often made that the mechanisms are similar.

However, striking differences are evident when the reactions of cyclic or polymeric chlorophosphazenes with dinucleophiles are compared. For example, catechol reacts with I to yield either X or XI, depending on the reaction conditions.[18]



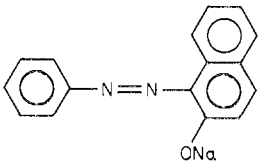

I X



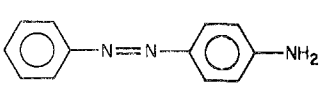

XI

The high polymer III interacts with catechol and triethylamine to yield a cross-linked matrix, together with XI. The cyclic tetramer II has so far failed to yield a spirocyclic phosphazene analogous to X and, in this respect, the tetramer constitutes a better model for the polymer than does the cyclic trimer. Cross-linking reactions also take place when III reacts with ammonia, even though the cyclic trimer and tetramer (I and II) give the normal products of formula $[NP(NH_2)_2]_{3 \text{ or } 4}$. This interchain linkage is inhibited by steric effects. Methylamine yields a cross-linked polymer at 25 °C, but gives the open-chain species, $[NP(NHCH_3)_2]_n$, at 0 °C or below. Longer chain primary amines show no tendency to participate in cross-linking, and the polymer substitution reactions are similar to those of the small cyclic species.[19]

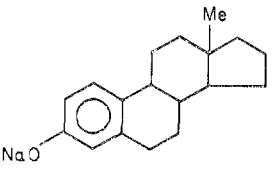
High polymeric poly(dichlorophosphazene) appears to be much more sensitive to side-group steric effects than is the cyclic trimer or tetramer. This is especially obvious when the nucleophile is a secondary amine, such as diethylamine, *N*-methylamine, or diphenylamine. Diethylamine replaces only one chlorine per phosphorus in III, even under forcing experimental conditions, whereas total replacement can be effected with the cyclic trimer I. The steric effect of the nucleophile is also obvious when azo dyes, such as XII or XIII or the steroid-type molecule shown in XIV, react with chlorophosphazenes. No more than two halogen atoms are replaced with the trimer,[20,21] and it is generally difficult to replace more than one halogen atom per nine or ten repeating units in the polymer.




XII




XIII




XIV

One reason for these reactivity differences between the cyclic oligomers and the linear high polymers appears to be connected with the molecular geometries. In the cyclic trimer, the side groups on different phosphorus atoms point away from each other; hence, steric effects are minimized. By contrast, irrespective of the precise extended conformation adopted, the side groups in the high polymer are closer to each other or are oriented toward the nearby skeletal atoms. Thus, in the polymer a bulky substituent group already present will exert a powerful shielding effect on the nearby P–Cl bonds.

The replacement of *halogen* substituents by organic nucleophiles has been discussed. However, organic substituents already present can also be replaced by other organic units in metathetical side-group exchange processes. These reactions have been examined in some detail for cyclic trimers and tetramers,[22] but the analogous reactions with the high polymers have been explored only for fluoroalkoxy group exchangers.[23] An extension of such exchange processes to the high polymeric systems would have a significant synthetic value.

## Hydrolysis and the Biomedical Problem

One of the most challenging chemical problems for the future is the synthesis of macromolecules that have biomedical compatibility—either total inertness in contact with tissues or blood, or biological degradability to nontoxic small-molecule products. Poly(organophosphazenes) have a number of attractive features for such biomedical uses, not the least of which is the broad synthetic versatility and the wide range of chemical and physical properties that can be built into specific macromolecules. However, any advances in this area must be preceded by a knowledge of the hydrolysis behavior of the different classes of phosphazene high polymers, with an emphasis on the nature of the intermediate and final hydrolysis products. As mentioned earlier, detailed reaction mechanism studies are exceedingly difficult to carry out with macromolecules. Hence, the first line of attack must involve studies with small-molecule model systems. It should be kept in mind that the small-molecule reactions can be followed readily for *solutions* of the phosphazenes whereas, in many cases, the analogous polymers will be totally

(17) Allcock, H. R.; Patterson, D. B.; Evans, T. L. *Macromolecules* **1979**, *12*, 172. *Inorg. Chem.*, in press.
(18) Allcock, H. R. *J. Am. Chem. Soc.* **1964**, *86*, 2591.
(19) Allcock, H. R.; Mack, D. P.; Cook, W. J. *Inorg. Chem.* **1972**, *11*, 2584.
(20) Allcock, H. R.; Wright, S. D.; Kosydar, K. M. *Macromolecules* **1978**, *11*, 357.
(21) Allcock, H. R.; Fuller, T. J.; Matsumura, K. Unpublished results.
(22) Allcock, H. R.; Smeltz, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 4143.
(23) Allcock, H. R.; Moore, G. Y. *Macromolecules* **1975**, *8*, 377.

insoluble in solvent systems that contain even small amounts of water. Hence, discrepancies between the reaction rates (though perhaps not the products) of the models and the polymers must be expected.

No reaction conditions (except the use of concentrated sulfuric acid) have yet been found for the hydrolytic decomposition of polyphosphazenes that contain fluoroalkoxy or phenoxy side groups. These polymers show the greatest promise as inert biomedical materials. This stability may be mainly a consequence of the insolubility of the polymers, because the cyclic model compounds, $[NP(OCH_2CF_3)_2]_{3 \text{ and } 4}$, $[NP(OCH_2C_2F_5)_2]_3$, and $[NP(OCH_2C_3F_7)_2]_{3 \text{ and } 4}$, are hydrolyzed rapidly in basic aqueous-organic media.[24] The hydrolysis of $[NP(OC_6H_4R)_2]_{3 \text{ or } 4}$ is accelerated by electron-withdrawing groups (R) attached to the phenyl ring.[25] Spiroaryloxy derivatives, such as X, are especially sensitive to hydrolysis.[25] Although the results of these model reactions cannot be applied directly to the polymeric systems, they do indicate that specific substituent groups (such as nitroaryloxy or spiroarylenedioxy) should be avoided if hydrolytic stability is the principal objective.

Ethyl glycinate and the esters of leucine, alanine, or phenylalanine react with poly(dichlorophosphazene) to yield polymers with amino acid ester side groups.[26] These polymers are hydrolytically unstable and are promising candidates for biological degradative uses. The hydrolysis behavior of such polymers is still under investigation, but the use of model compounds such as $[NP(NHCH_2COOC_2H_5)_2]_3$ has shown[27] that the hydrolysis is rapid and leads to the formation of ethanol, phosphate, amino acid, and ammonia. If the same mechanistic pathway is followed during the hydrolysis of the macromolecules, these polymers may function as carriers for the controlled release of chemotherapeutic agents.

## The Organometallic Problem

It will be clear that a broad range of different polymers can be prepared by the interactions of $(NPCl_2)_n$ with alkoxides, aryloxides, or amines. Yet one important class of high molecular weight polyphosphazenes has so far proved difficult to synthesize—those polymers that possess alkyl or aryl groups bonded directly to the skeleton through P–C bonds. Polymers of this structure should be much more stable at high temperature than those that contain oxygen or nitrogen as linkage atoms in the side group structure.

In principle, the synthesis of such polymers should be straightforward. Nucleophilic reactions between organometallic reagents, such a Grignard or organolithium species, and $(NPCl_2)_n$ would be expected to yield the appropriate poly(organophosphazenes). In practice, serious complications exist, *even with model compound reactions*. Chlorophosphazenes contain two types of potential nucleophilic cleavage sites—the P–Cl and P–N bonds. Grignard and organolithium reagents can cleave both. For poly(dichlorophosphazene) the seriousness of the chain cleavage process is illustrated

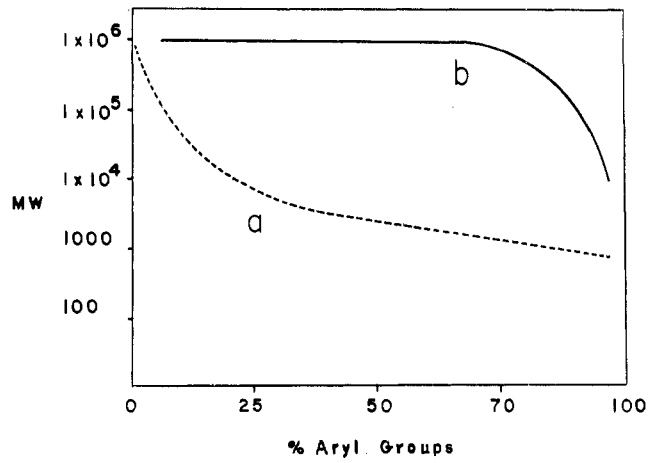
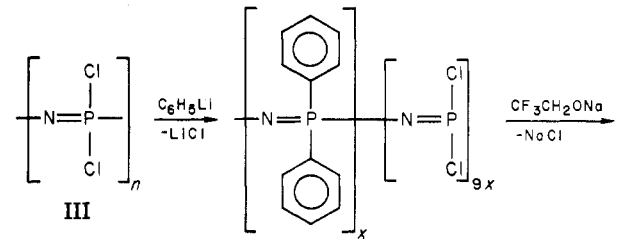
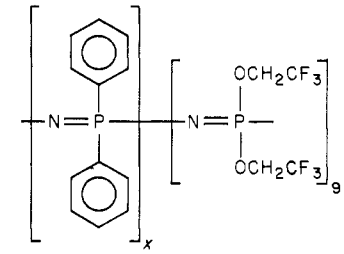



**Figure 1.** Halogen substitution *and* chain cleavage occur when high polymeric $(NPCl_2)_n$ reacts with phenyllithium (curve a), but halogen replacement predominates with $(NPF_2)_n$ until roughly 75% of the fluorine atoms have been replaced by phenyl groups (curve b).

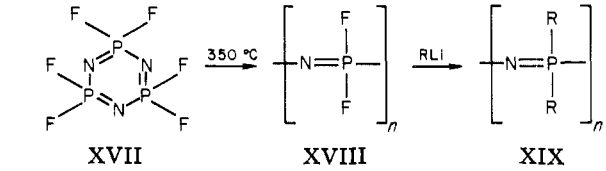
by curve a in Figure 1. With phenyllithium used as a reagent, only about 10% of the chlorine atoms in $(NPCl_2)_n$ can be replaced by phenyl groups (XV) before




the average chain length falls to an unacceptably low value. However, if the reaction is terminated at this stage, the remaining chlorine atoms can be replaced by other side groups, such as trifluoroethoxy (XVI), to stabilize the polymer against hydrolysis.

Moeller,[28] Allen,[29] and Paddock[30] have shown that small-molecule *fluoro*cyclophosphazenes are less susceptible to chain cleavage by organometallic reagents than are the analogous chlorocyclophosphazenes. Thus, it appeared possible that high polymeric fluorophosphazenes might behave similarly (XIX). The




(24) Allcock, H. R.; Walsh, E. J. *J. Am. Chem. Soc.* **1972**, *94*, 119.
(25) Allcock, H. R.; Walsh, E. J. *J. Am. Chem. Soc.* **1972**, *94*, 4538.
(26) Allcock, H. R.; Fuller, T. J.; Mack, D. P.; Matsumura, K.; Smeltz, K. M. *Macromolecules* **1977**, *10*, 824.
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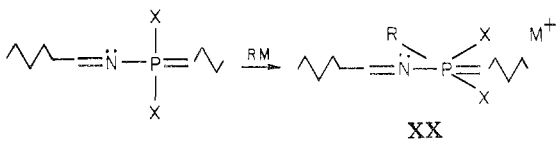
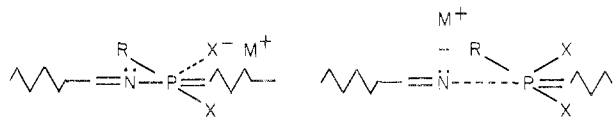
synthesis of an un-cross-linked poly(difluorophosphazene) (XVIII) was accomplished by the high-temperature, high-pressure polymerization of hexafluorocyclotriphosphazene (XVI).[31] Polymer XVIII is soluble only in fluorinated media such as perfluorobutyltetrahydrofuran or perfluorodecalin, solvents in which most organometallic reagents are insoluble. Hence, heterophase substitution techniques are needed. The differences between the behavior of $(NPF_2)_n$ and $(NPCl_2)_n$ under organometallic substitution conditions are illustrated in Figure 1. Chain cleavage does not become serious with $(NPF_2)_n$ until more than 75% of the fluorine atoms have been replaced by the organic unit. An explanation for these differences is as follows.

The reaction of a halophosphazene with an organometallic reagent probably involves the formation of a pentacoordinate intermediate, as shown in XX.



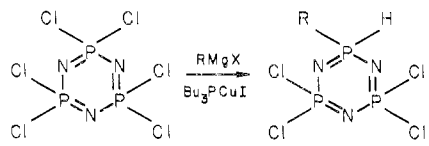
XX



XXI XXII

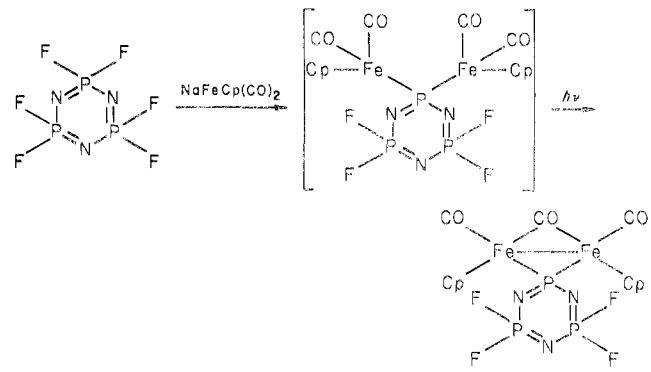
Separation of the halide ion, $X^-$ (as shown in XXI), would be favored by a high electronegativity in X (hence, fluorine is more effective than chlorine). Moreover, a highly electronegative substituent would withdraw electron density from the lone-pair orbital at nitrogen and discriminate against chain cleavage (XXII). Presumably, these effects are responsible for the behavior shown in curve b of Figure 1. Chain cleavage becomes serious with $(NPF_2)_n$ only when a substantial number of strongly electron-withdrawing ligands (F) have been replaced by weaker electron-withdrawing or even electron-supplying groups (R). One further factor complicates the reactions of poly(dihalophosphazenes) with organometallic reagents. Alkyl groups attached to the polyphosphazene chain are susceptible to metallation by the organometallic reagent, and this can lead to the formation of cross-links.

A number of unusual organometallic reactions have recently been discovered for cyclophosphazene model systems. Hexachlorocyclotriphosphazene (I) reacts with alkylcopper reagents to yield *hydrido*phosphazenes (XXIII) via a complex mechanism.[32] The hydrogen



I XXIII

atom is introduced by hydrolytic cleavage of an N–Cu bond. Hexafluorocyclotriphosphazene interacts with sodium cyclopentadienyldicarbonylferrate to form a remarkable derivative (XXIV).[33] This is the first



XXIV

phosphazene reported that possesses a P–metal side group bond and a three-membered ring at skeletal phosphorus.

These model reactions are currently being extended in our laboratory to the analogous high polymeric systems, with the prospect that the polymers may show unique electrical or catalytic properties.

## Coordination Chemistry

Phosphazenes possess skeletal nitrogen atoms that are potential donor ligand sites for transition metals. Moreover, side groups that possess donor sites can be attached to the backbone. It has been known for a number of years that cyclophosphazenes can undergo protonation at the skeletal nitrogen atoms,[12,34,35] but the study of cyclo- and polyphosphazenes as ligands for transition metals is still in its infancy. A few systems are known in which *cyclic* phosphazenes are coordinated via the skeletal nitrogen atoms to transition metals,[36,37] but in this Account the discussion will be confined to three recent developments from our laboratory that are particularly related to the high polymers. The first of these illustrates the use of the skeletal nitrogen atoms as donor sites, and the second and third examples illustrate how specific side-group structures can be utilized for transition-metal binding.

Macromolecular ligands that are soluble in water have potential uses in biomedicine. It is well-known that a number of small-molecule square-planar platinum complexes, such as $PtCl_2(NH_3)_2$, are anticancer agents,[38] but that the clinical effectiveness of these compounds is offset by their capacity to be excreted rapidly through the renal system, with concurrent kidney damage. Macromolecules cannot normally penetrate semipermeable membranes. Hence, the prospect exists that the side effects might be reduced if the platinum unit can be coordinated to a water-soluble polymer. The possibility also exists that the polymer itself might provide a mechanism for directing the complex to the sites where the maximum chemotherapeutic effect could be achieved, for example, by concentration at

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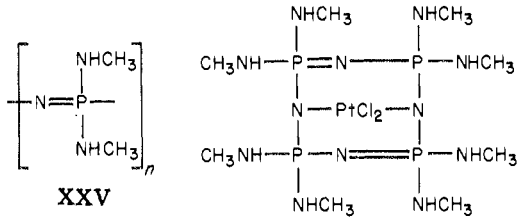
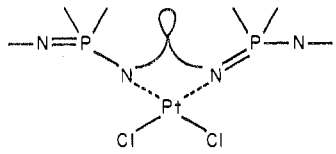
acidic sites in the body. The polymer chosen as an initial trial carrier ligand is shown in XXV. The re-



XXV



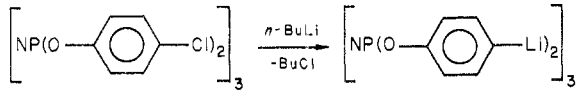
XXVI



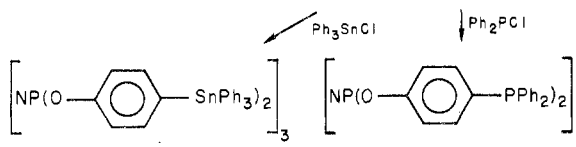
XXVII

action of XXV with $K_2PtCl_4$ and 18-crown-6 ether in chloroform yields a polymeric complex of formula $[NP(NHCH_3)_2]_n(PtCl_2)_x$ (where the ratio of $n$ to $x$ is roughly 17:1).[39] This species is nondialyzable in in vitro tests and shows a similar antitumor activity to the small-molecule analogue. The structure of the polymeric complex was deduced by the synthesis of a model system based on the analogous cyclic tetramer. A single-crystal X-ray analysis revealed that the platinum is bound in a transannular fashion to two *skeletal* nitrogen atoms (XXVI).[40] The spectroscopic similarities between the polymeric complex and the model suggest that the macromolecular system has a similar mode of binding (XXVII).

A second example of metal binding by phosphazenes makes use of a side-group coordination site. Significant chemical advantages can be foreseen for homogeneous catalysts that are bound to a macromolecule. The polymeric ligand could function as a "dog leash" to prevent the loss of the catalyst in solution, and perhaps to modify its activity. Polyphosphazenes offer a number of potential advantages as polymeric ligands, but probably *not* by utilization of the skeletal nitrogen atoms. Instead, phosphine residues have been attached to phosphazenes at the model system level via the hexa(lithiophenoxy)cyclotriphosphazene shown in XXVIII.[41] Compound XXIX has been used as a co-



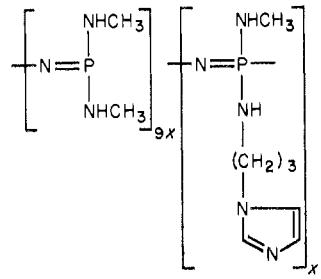
XXVIII



XXX XXIX

ordination ligand for osmium cluster compounds.[42] Work on the polymeric analogue of XXXIX is in progress. Moreover, other organometallic species can be synthesized readily from XXVIII, as illustrated by the formation of the stannane derivative, XXX.

Finally, the prospect exists that water-soluble polyphosphazenes may be employed as models for biological macromolecules, with the use of pendent coordination sites for the binding of, for example, metalloporphyrins. Synthetic, water-soluble polymers that are suitable for such model studies are quite rare. Polymers XXV and XXXI have been examined as



XXXI

possible water-soluble carrier ligands for hemin (iron(III) protoporphyrin IX) and heme (iron(II) protoporphyrin IX).[42] These investigations were preceded by trial studies with cyclophosphazene models.

Polymer XXV does not coordinate to the Fe(III) or Fe(II) atoms of hemin or heme in aqueous media. It merely anchors these metalloporphyrins by acid–base interactions through the carboxylic acid residues. On the other hand, polymer XXXI coordinates strongly to the iron of hemin or heme to yield 6-coordinate complexes. Although the complex with heme does not bind dioxygen reversibly in aqueous solution or in solid films, the Fe(III) species formed from it in the presence of oxygen is reduced back at the Fe(II) species *by the polymer*. Thus, the polymer functions as a reducing agent to give the *appearance* of reversible oxygen uptake. It is our intention to modify these polymer structures to a more subtle degree in an attempt to favor oxygenation–deoxygenation behavior.

## Validity and Weakness of the Model Compound Concept

It will be obvious from this Account that small-molecule cyclic phosphazenes have played a vital role in the design and synthesis of high polymeric phosphazenes. Although not discussed here, the small-molecule rings have also served as essential *structural* models for the molecular structure determination of polyphosphazenes—a subject that is just starting to gather momentum.

However, certain items of data derived from small-molecule studies have proved, in retrospect, to be actually misleading when applied to the polymers. For example, thermal stability studies carried out with the cyclic trimer, $[NP(OC_6H_5)_2]_3$, showed that this compound has a remarkably high stability at temperatures of 400 °C or above. Yet the analogous high polymer, $[NP(OC_6H_5)_2]_n$, *depolymerizes* to its cyclic oligomers, $[NP(OC_6H_5)_2]_{3,4,5...etc.}$, when heated at 200 °C and, in so doing, loses its valuable high polymeric properties.[43] Similarly, ultraviolet irradiation studies of cyclic phosphazenes, such as $[NP(OCH_2CF_3)_2]_4$, $[NP(OCH_2CH_3)_2]_4$, or $[NP(OC_6H_5)_2]_4$, overestimate the stability

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of the high polymers.[44] On the other hand, the hydrolytic stability of many poly(organophosphazenes) in the solid state is much greater than is implied by the hydrolytic behavior of the cyclic models. The early structural studies with cyclic trimers and tetramers provided no hint of the unusual torsional flexibility of the skeletal bonds in the polymer—a feature that is responsible for most of the current technological interest in these materials. In general, the cyclic compounds are unsatisfactory as models when they fail to reveal the seriousness of minor side reactions that could lead to chain scission or cross-linking in the high polymers.

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Provided these limitations are recognized, the small-molecule, model-compound approach to polymer synthesis has considerable merit. It seems likely that the polyphosphazene system is simply one of the first of many new macromolecular series that will be based on the inorganic elements. The periodic table is replete with examples of elements and element pairs that show a strong tendency to form small-molecule rings, and the study of these ring systems will probably provide the clues needed for the design and synthesis of the corresponding high polymers.

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