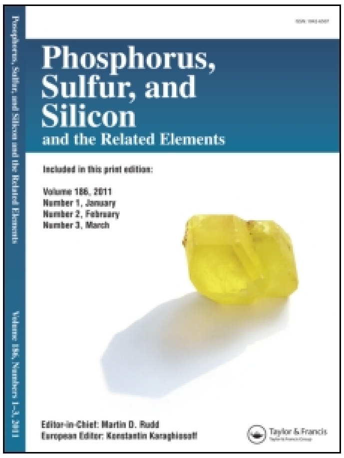

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ORGANOMETALLIC AND BIOACTIVE CYCLOPHOSPHAZENES, AND THE RELATIONSHIP TO INORGANIC MACROMOLECULES.

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Abstract Cyclophosphazenes have two relationships to linear high polymers: first, they may function as "monomers" for polymerization to high polymers; and second, they serve as small molecule reaction and structural models for the high polymers. These principles are illustrated by the behavior of cyclophosphazenes that bear organometallic side groups, and by species that have side units that are of biomedical interest. Some emerging applications of this chemistry are also mentioned.

INTRODUCTION

Inorganic ring systems have been studied in the past mainly from the viewpoints of their synthesis, structure, and reactivity. However, in recent years two additional purposes have appeared, and these now dominate research in specific fields such as cyclophosphazene, cyclosiloxane, cyclosilane, cyclosilazane, and borazine chemistry.

The first of these developments is based on the use of inorganic ring systems as starting points for the synthesis of inorganic high polymers. They are the "monomers" which undergo either ring-opening polymerization to macrocyclic or linear high polymers, or condensation to sheets or three-dimensional covalent solids en route to ceramics and other ultrastructure systems. The structure and reactivity of such small molecule inorganic rings are clearly inportant for understanding these transformations.

The second reason for the broadening interest in inorganic ring systems is that they serve as small-molecule structural and reaction models for the related macrocyclic or linear high polymers. Macromolecules are considerably more difficuly to characterize structurally than are small molecules. Distributions of different chain lengths are present rather than discrete, single molecular weight species. Bond angle, bond length, and conformational values for most high polymers must be derived from the limited data obtained from fiber X-ray diffraction, and this yields far less information than conventional single crystal X-ray studies. Hence, molecular structural information from small molecule X-ray studies often provides the only data available for estimating the structure of an inorganic macromolecule. NMR studies on small molecule model compounds often provide critical information for understanding the structures of the high polymers.

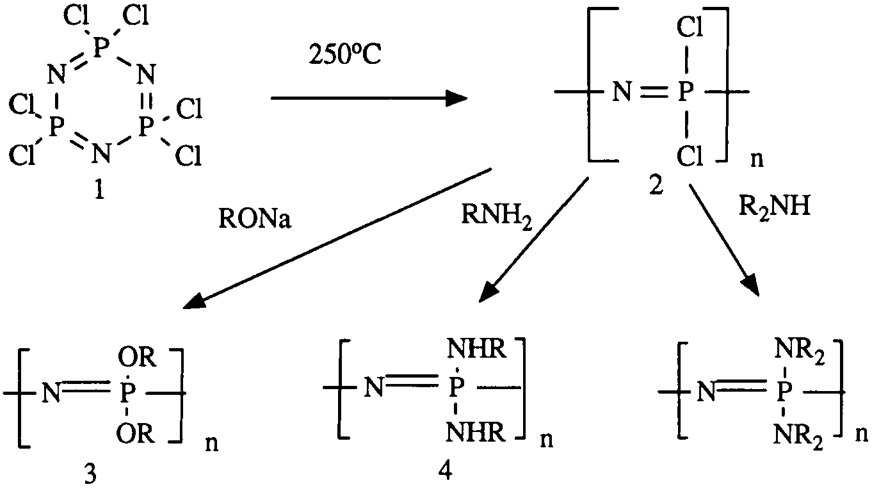
Finally, and perhaps most important of all, macromolecular structural diversity is increasingly being developed by chemical reactions carried out on preformed inorganic polymers. Such reactions can be exceedingly complex, and model reactions performed with small molecule counterparts may be an essential prerequisite as trial reactions or for understanding reaction mechanisms.

These principles are illustrated most clearly in phosphazene chemistry, and the examples given below provide a case study of what may be expected in the future for other inorganic ring systems and their polymers

BACKGROUND

The early history of cyclophosphazene chemistry revolves around the synthesis of cyclic halogenophosphazenes, such as $(NPCl_2)_3$ or $(NPCl_2)_4$, and the reactions of these species with alkoxides, aryloxides, and primary or secondary amines, Much effort has been devoted to the elucidation of the reaction mechanisms of these substitutions and to the identification of gem-, non-gem-, cis-, or trans- halogen replacement patterns.[1-3] Earlier[4-6]we discovered a method by which hexachlorocyclotriphosphazene (**1**) can be polymerized to a macrocyclic or open chain high polymer, simply by heating the molten trimer under controlled conditions at 250°C. The resultant high polymer (**2**) was free from crosslinks and was therefore soluble in several organic solvents. In solution it functions as a reactive macromolecular intermediate and undergoes halogen replacement reactions when treated with a wide variety of organic nucleophiles. These reactions are illustrated in Scheme I.

Scheme I



In recent years this approach has been extended to the polymerization of cyclic phosphazenes that bear both halogen and alkyl, aryl, or organometallic units linked as side groups to the phosphorus atoms of the ring. Subsequent replacement of the halogen atoms in the high polymer by organic nucleophiles is then carried out as illustated in Scheme I. In addition, a direct synthesis route to alkyl- and aryl-phosphazene polymers has been developed.[7] The progression of these developments has been described elsewhere.[8]

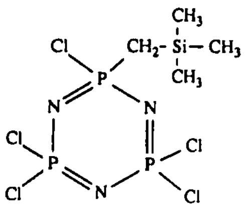
These reaction sequences have been developed to the point where at least 300 different types of stable, high molecular weight polyphosphazene systems are now known, each with different side groups or combinations of different groups. The macromolecular properties change with each modification of the side groups, and the range of properties now accessible rivals and sometimes surpasses that found in classical organic polymer systems. For these reasons, several poly(organophosphazenes) are now produced on a manufacturing scale[9] for use in advanced engineering applications, and this aspect of the field continues to grow. By the middle of 1988, well over 1000 publications dealing with the synthesis and uses of polyphosphazenes had appeared.

In the following sections a few selected developments from our laboratory will be discussed. The theme of the comments will involve two questions. First, what molecular structural features in a cyclic phosphazene favor polymerization or prevent it? Second, to what degree can secondary reactions be carried out on the cyclic trimers or high polymers to modify side groups already present? For a more general overview the reader is referred to several recent surveys.[7-11]

POLYMERIZABILITY

Although halogenocyclophosphazenes, such as $(NPCl_2)_3$, $(NPCl_2)_4$, $(NPF_2)_3$, and $(NPBr_2)_3$ polymerize when heated, their counterparts in which all the halogen atoms have been replaced by organic groups do not polymerize. They may undergo ring-ring equilibration to yield higher cyclic oligomers, but no genuine high polymers are obtained.

It follows, then, that considerable interest revolves around the behavior of cyclic trimers that contain both halogen and organic side units. The structures shown in **5-13** illustrate the types of compounds within this class that do polymerize when heated.



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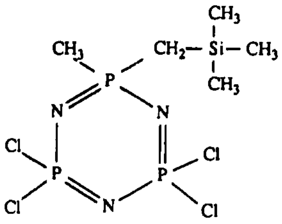

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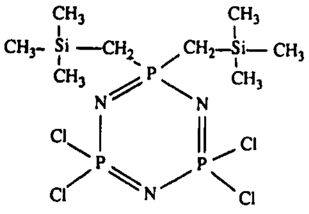

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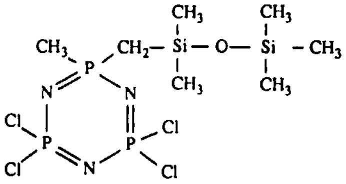

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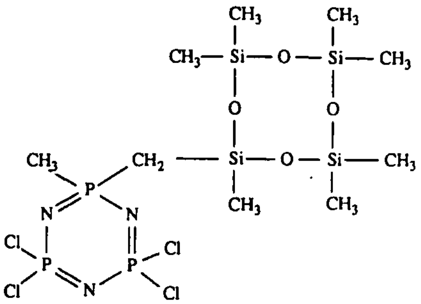

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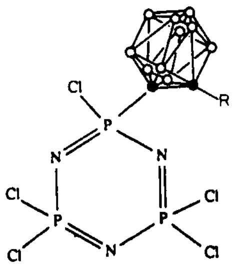

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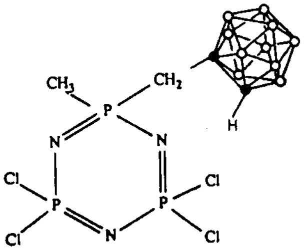
R = Me or Ph



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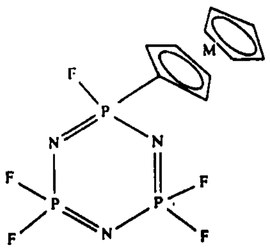

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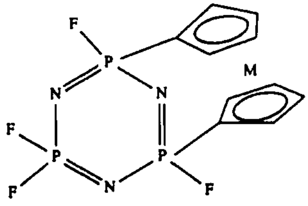


M = Fe or Ru

13

Most of these compounds were prepared by organometallic chemistry. For example, species **5-8** were synthesized by the reactions of organosilyl or organosiloxyl Grignard reagents with $(NPCl_2)_3$.[12] The geminal methyl groups in **6**, **8**, and **9** were introduced by subsequent treatment with methylmagnesium chloride. The carboranyl derivatives **10** were prepared by the interaction of $(NPCl_2)_3$ with the appropriate lithiocarborane.[13] Species **11** was accessible via the reaction of $(NPCl_2)_3$ with an organocopper reagent derived from methylmagnesium chloride, followed by treatment with propargyl bromide.[14] Reaction of the resultant gem-methyl-propynylphosphazene with $B_{10}H_{12}(CH_3CN)_2$ yielded **11**. Compound **11** undergoes Hawthorne-type chemisty to form nidocarboranyl anions and tungsten or molybdenum carbonyl adducts. The metallocenylphosphazenes, **12**, were isolated from the reaction of $(NPF_2)_3$ with lithioferrocene or lithioruthenocene, while species **13** were prepared by the interaction of $(NPF_2)_3$ with dilithioferrocene or dilithioruthenocene.[15]

Although the organosilicon derivatives **5-9** undergo phosphazene ring-opening polymerization to high polymers with pendent organosilicon side groups, other related derivatives do not.[16] For example, the analogues of **8** and **9**, with a chlorine atom in place of the geminal methyl group, undergo silicon-oxygen bond cleavage reactions rather than polymerization. The presence of two linear siloxane units geminal to each other, or two geminal cyclotetrasiloxane groups, inhibits polymerization, probably for reasons connected with steric hindrance during the polymerization steps.

Species **10** and **11** undergo polymerization to polyphosphazenes, although the steric bulk of the carborane units appears to favor a shift in the ring-polymer equilibria to favor medium molecular weight (1×10^5) rather than high molecular weight (1×10^6) macromolecules.

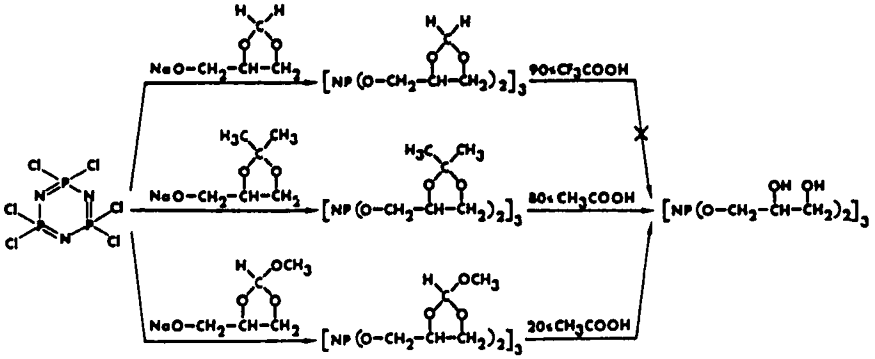
The metallocenyl derivatives **12** and **13** illustrate the role played by a strained transannular ring. Both compounds polymerize by opening of the phosphazene ring at 250°C. However, species **13** polymerizes faster. Opening of the phosphazene ring in **13** allows a release of the ring strain, and this favors linear or macrocyclic polymer formation over recyclization to small rings.

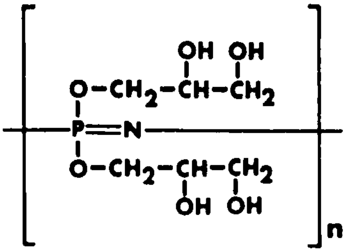
REACTIONS OF SIDE GROUPS

Organic side groups linked to a polyphosphazene by means of the chemistry shown in Scheme I can function as sites for further chemical reactions. A critical requirement for this type of structural diversification is that the reagents used for side group modification should not bring about cleavage of the phosphorus-nitrogen skeletal bonds. Thus, such reactions are usually explored first with cyclic trimeric or tetrameric model compounds as a prelude to experiments with the high polymers. Two examples will be given, both related to the syntheses of high polymeric phosphazenes that are of interest in biomedical research.

The first example involves the deprotection of glyceryl units attached to a phosphazene skeleton.[17] Glycerol was first protected by reactions with formaldehyde, acetone, or trimethylorthoformate to yield reagents that were converted to the sodium salts shown in Scheme II. The sodium salts were then allowed to react with $(NPCl_2)_3$ to form the hexaglyceryl cyclotriphosphazenes shown. Attempts to deprotect these side groups with a variety of reagents showed

Scheme II





$$\left[-P(O\text{-}CH_2\text{-}CH(OH)\text{-}CH_2OH)_2{=}N- \right]_n$$

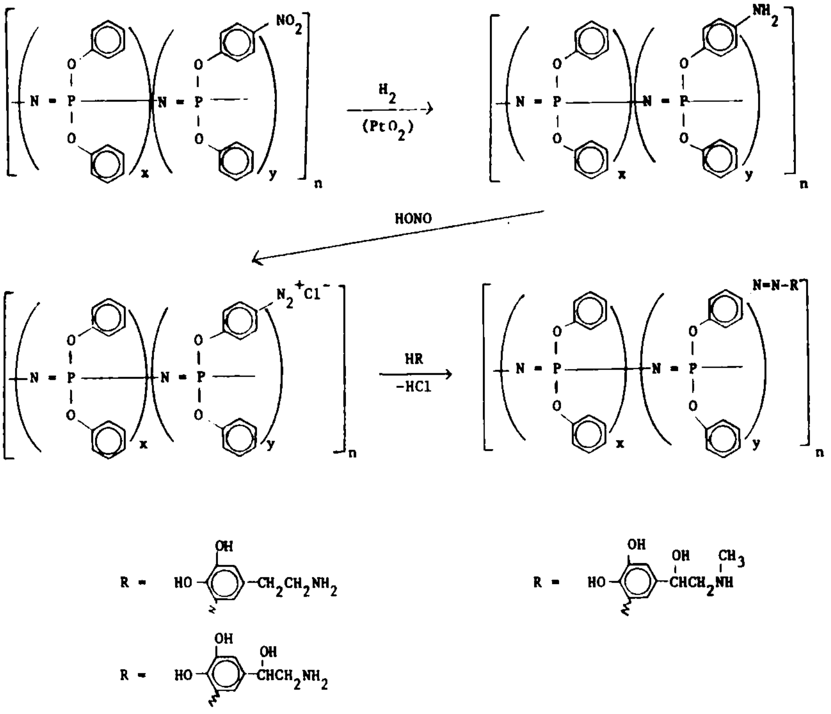
14

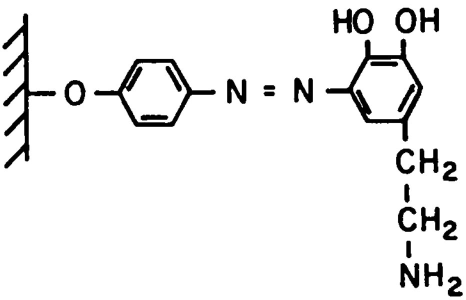
that the reaction conditions were quite critical if phosphorus-nitrogen bond cleavage was to be avoided. After many trial experiments it was found that the isopropylidene protecting group could be removed cleanly by treatment with 80% acetic acid, without skeletal decomposition. The same conditions were then used for deprotection of the analogous high polymer to yield the poly(glycerylphosphazene) shown as **14**. Polymer **14** is a water-soluble, biodegradable macromolecule that hydrolyzes slowly to phosphate, ammonia, and glycerol, and is a candidate as a substrate for controlled drug release applications.

The second example involves two related reactions of aryloxy side groups attached to a phosphazene skeleton and the transposition of these reactions to the surface chemistry of polyphosphazene solids.

Nitro-aryloxyphosphazenes can be prepared by two different routes: by the reaction of a sodium nitroaryloxide with, for example, $(NPCl_2)_3$ or $(NPCl_2)_4$; or by the nitration of aryloxyphosphazenes such as $[NP(OC_6H_5)_2]_3$ or $[NP(OC_6H_5)_2]_n$. The nitro groups then serve as reactive sites for the attachment of biologically active agents. One such reaction pathway is shown in Scheme III, in which the nitro groups are introduced via a nitroaryloxide at the initial macromolecular substitution step, and are converted in solution first to amino- and then to diazonium halide units. These couple with catecholamines such as dopamine to yield a polymer which, in the solid state (**15**), shows a surface bioogical activity toward rat pituitary cells in culture similar to that found for free dopamine in solution.[18] This, then, is a prototype for devices in which biological responses are obtained without release of the small molecule bioagent into the living organism. Needless to say, the reaction pathways used for the synthesis of the polymer were

Scheme III





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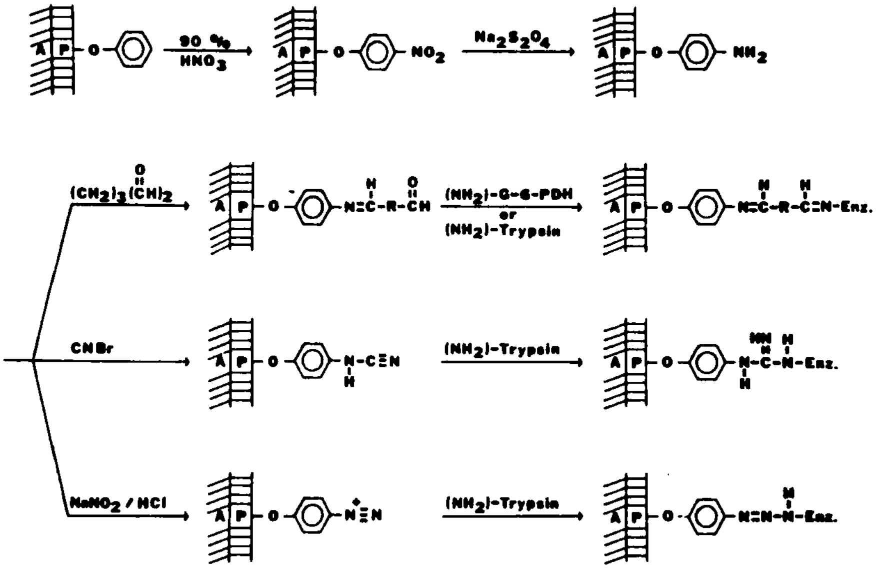
Scheme IV



A = Alumina, P = Polyphosphazene, R = $(CH_2)_3$

developed initially at the small molecule cyclic phosphazene level.

A related development involves reactions carried out totally at the surface of a solid poly(aryloxyphosphazene), reactions that have no counterpart at the small molecule level. Thin surface coatings of $[NP(OC_6H_5)_2]_n$ were deposited on particles of porous alumina powder. The polymer surface was then nitrated in a heterophase reaction, and the nitro groups then reduced to amino units with dithionite. Treatment of the surface with glutaric dialdehyde, followed by glucose 6-phosphate dehydrogenase or trypsin, resulted in covalent linkage of the enzymes to the surface.[19] Enzymic activity was retained (and indeed the enzyme longevity was enhanced) to the point that the enzyme-solid conjugates could be used for biochemical transformations in a continuous flow reactor. The advantage of the phosphazene as an immobilization substrate is that the surface character of the polymer can be changed readily by means of the chemistry shown in Scheme I.

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