Inorganic-Organic Polymers as a Route to Biodegradable Materials

Harry R. Allcock

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802, U.S.A

SUMMARY: The polyphosphazene platform allows the design and synthesis of a broad range of different polymers, some of which have special properties as biodegradable materials. Different polyphosphazenes are produced mainly by means of macromolecular substitution reactions carried out on a reactive polymeric intermediate, poly(dichlorophosphazene), $(NPCl_2)_n$. Organic side groups such as amino acid esters, glucosyl, glyceryl, glycolate, lactate, or imidazolyl sensitize the polymers to hydrolysis to benign materials such as phosphate, ammonia, and the free side unit. Other polymers are of interest as the basis for hydrogels and microencapsulation materials.

Introduction

Biodegradation, either in the environment or in implanted medical devices, can be designed into a polymeric material by the application of certain chemical principles. The main requirement is the ability of the polymer backbone to undergo hydrolytic or oxidative cleavage under enzymic or non-enzymic conditions. The side groups linked to the backbone may also play a part, but their role is often a secondary one via an influence on, for example, hydrophilicity or hydrophobicity or by providing sites for the initial reaction that precedes hydrolytic or oxidative attack on the backbone.

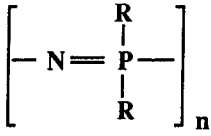
Examples of well-known backbones that readily undergo hydrolytic cleavage include classical organic polymer systems such as polyesters, polyamides, polyethers, or polyanhydrides, and a range of inorganic backbone macromolecules such as polysilicates, polyphosphates, and polyphosphazenes. The polyphosphazene platform provides many opportunities for the design and synthesis of biodegradable materials, and is readily tuned

 CCC 1022-1360/99/$ 17.50+.50/0

to control the conditions needed for hydrolytic chain cleavage and the rate at which degradation occurs. However, the phosphazene backbone is quite resistant to oxidative or photo-oxidative cleavage, as are most inorganic polymer systems.

General Features of the Polyphosphazene System

The polyphosphazenes consist of a series of several hundred different polymers with the molecular structure shown in **1**[1].



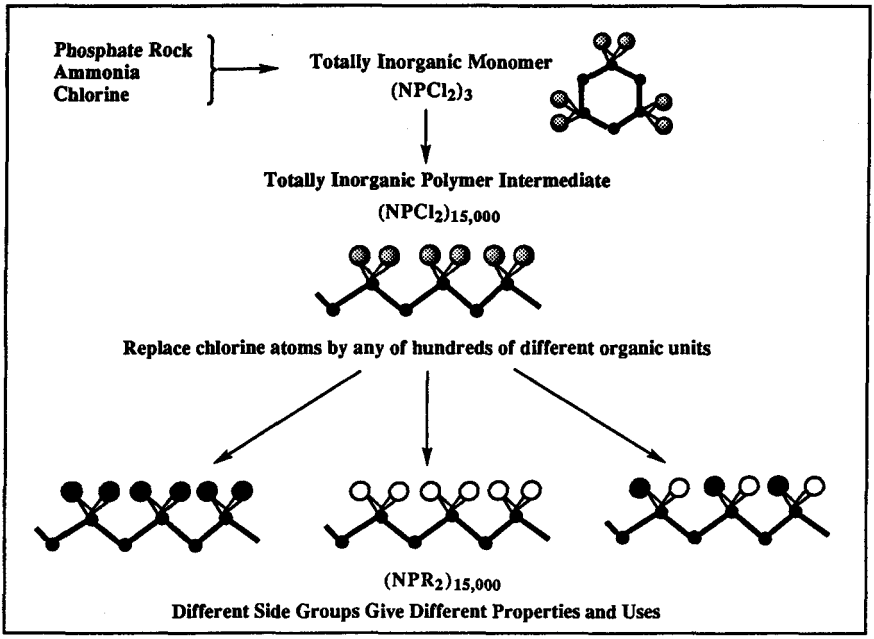
1

All these macromolecules have the same skeleton of alternating phosphorus and nitrogen atoms, but with different organic, organometallic, or inorganic side groups linked to the phosphorus atoms. The side groups strongly influence solubility, glass transition temperature, crystallinity, and many other properties including sensitivity to aqueous media. Most polyphosphazenes are biostable, but a number are sensitive to hydrolytic degradation under environmental or medical conditions[2-21]. Specific side groups, such as amino acid esters, glucosyl, glyceryl, glycolate, lactate, or imidazolyl units, sensitize the polymer to hydrolysis to benign materials such as the free side unit, phosphate and ammonia. The phosphate and ammonia constitute a buffered combination that is generally appropriate for both environmental and medical usage. On the other hand, hydrophobic side groups, such as aryloxy, fluoroalkoxy, alkyl ether, or C_4 and higher alkoxy units, protect the backbone against hydrolysis, or retard the hydrolysis rate when they are present as co-substituents along with hydrolysis-sensitizing units.

Synthesis of Polyphosphazenes, and Molecular Tailoring

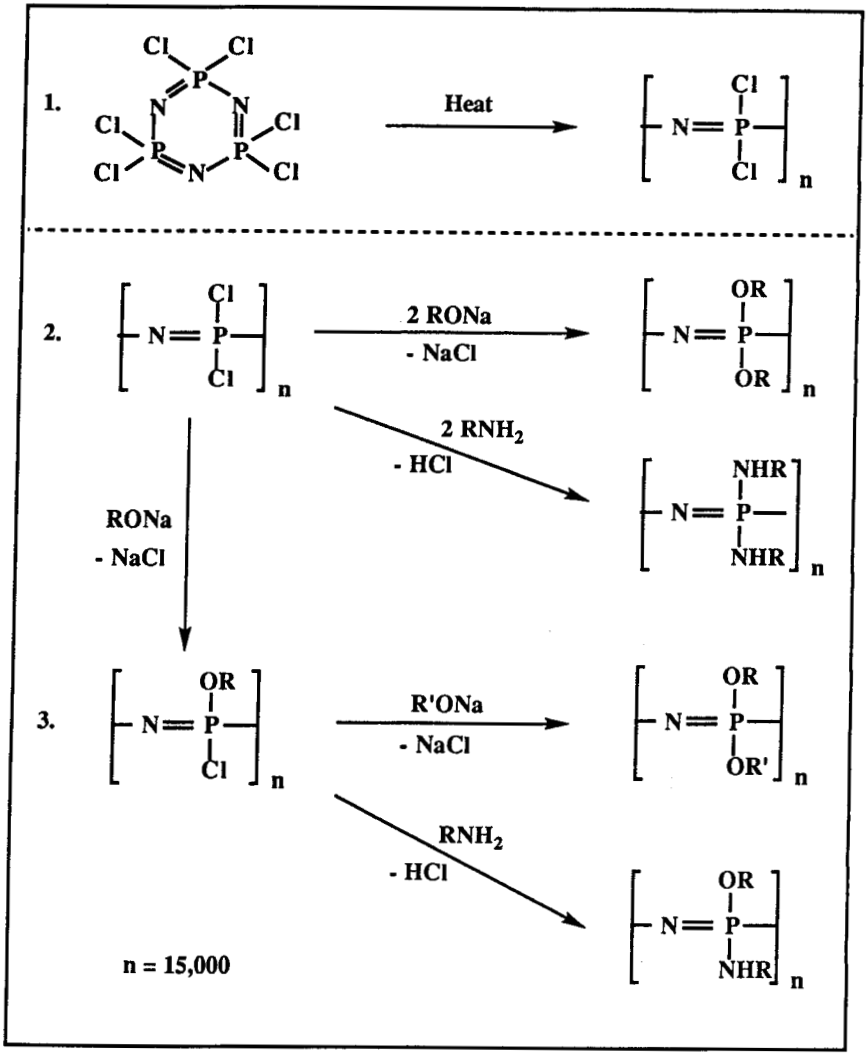
The wide range of different polymers accessible in the polyphosphazene series is mainly a result of a synthetic method developed in our program[22-24]. This is based on the macromolecular substitution protocols shown in Schemes 1-3.

Scheme 1. Principle of Polyphosphazene Macromolecular Substitution

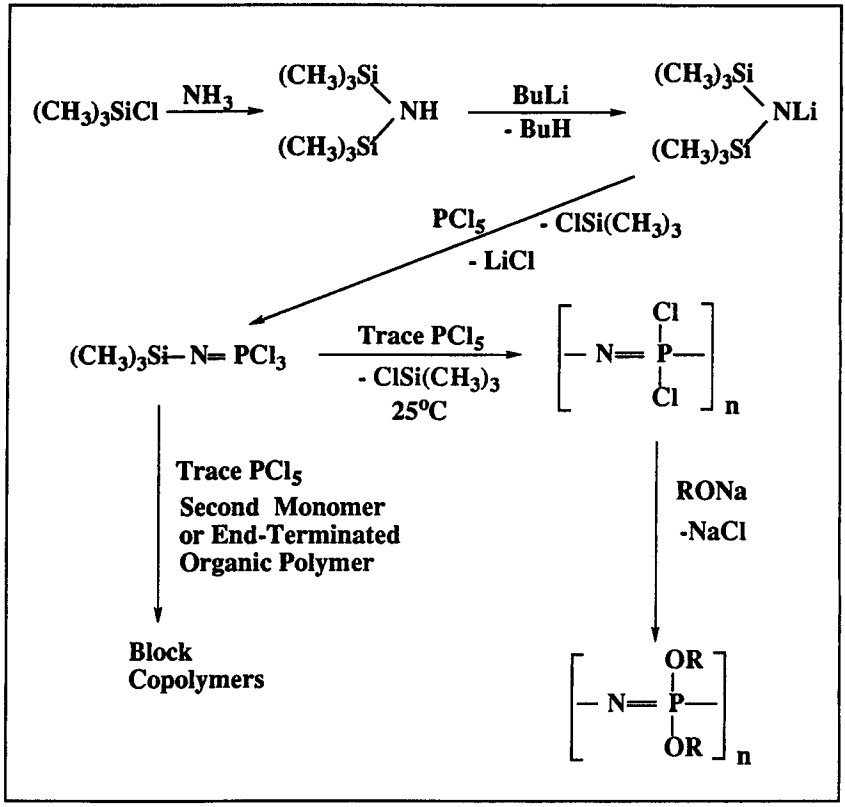


This approach is based on the high reactivity of the key macromolecular intermediate, poly(dichlorophosphazene), which can be produced by two alternative routes. The traditional route to poly(dichlorophosphazene) is by the ring-opening polymerization of the cyclic trimer, hexachlorocyclotriphosphazene at 250°C in the molten phase (Scheme 2)[22-24] This method gives polymer with weight average molecular weights in the range of 1 to 3 x 10^6, but with a broad molecular weight distribution and little control over the chain length. The second method, discovered only recently [25-29], is a "living" cationic condensation process that takes place in solution at 25°C and yields narrow molecular weight distribution polymers, with excellent control of the molecular weight and access to block copolymers (Scheme 3).

Scheme 2. Three-Step Synthesis of Poly(organophosphazenes)



Scheme 3. New Method for the Preparation of Phosphazene Polymers



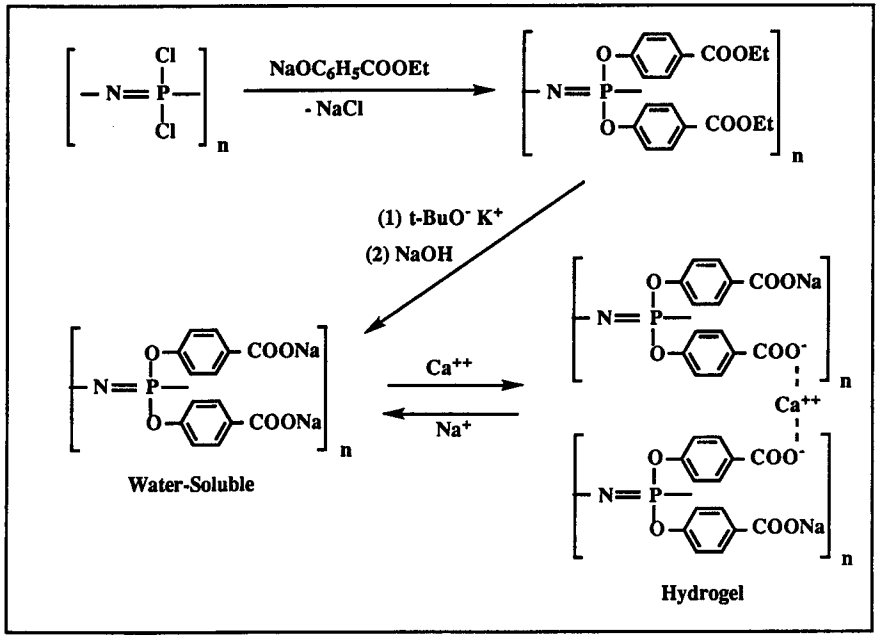
All the chlorine atoms in poly(dichlorophosphazene) can be replaced by reaction of the polymer with nucleophiles such as primary or secondary amines or the sodium salts of alcohols or phenols. Because the highest molecular weight $(NPCl_2)_n$ polymers contain 15,000 or more repeating units, this means that 30,000 or more chlorine replacement reactions take place on each macromolecule. The large number of different reagents that will participate in this reaction underlies the broad range of different polymers that are accessible. Different side groups give rise to different physical and chemical properties, and the range of properties is illustrated by Chart 1.

Chart 1. Range of Properties that can be Generated in Polyphosphazenes by Side Group Changes

A. *Materials Properties*	
Physical State	**Viscous liquids, elastomers, glasses, ceramics**
Glass transition temperature	**From -100°C to +180°C**
Crystallinity	**From 100% amorphous to 80% crystalline**
Melting temperature	**From -30°C to +250°C**
Surface character	**From hydrophilic (c.a. 35°) to highly hydrophobic (120°)**
Fire resistance	**From marginally flammable to powerful flame retardants**
Thermal stability	**From 150°C to >300°C**
Solubility	**From water-soluble to hydrocarbon-soluble**
Radiation stability	**From crosslinkable to radiation resistant (>2 Mrad)**
Coordination power for metal ions	**From non-coordinative to binding strongly to metals**
B. Biomedical and Environmental Properties	
Bioerosion	**From infinitely stable to controlled bioerosion**
Biological activity	**From "bioinert" to biologically active**
Surfaces	**From highly hydrophobic to hydrogel**
Gels	**From hydrogels to organogels**
Hydrogel LCST	**From 30°C to 65°C**
Bio-immobilization potential	**From surface immobilization to hydrogel entrappment and microencapsulation**

Several of the side groups that are of interest for biodegradable properties bear functional groups such as OH, NH_2, or COOH at their terminus, and the application of the above synthesis could lead to crosslinking when a reagent molecule reacts with two separate polymer chains. Thus, a number of the difunctional reagents employed in the macromolecular synthesis must have one of the functional groups protected before linkage of the other to the polymer. The final derivatized macromolecule is then generated by deprotection of the pendent functional units. An example is shown in Scheme 4. Thus, the use of the *esters* of p-hydroxybenzoic acid, amino acids, glycolic and lactic acids, rather than the free carboxylic acids is an essential requirement to prevent crosslinking during the synthesis [30]. Hydroxyl groups must be protected by tetrahydropyranyl or isopropylidene groups, and amino units by "BOC" groups.

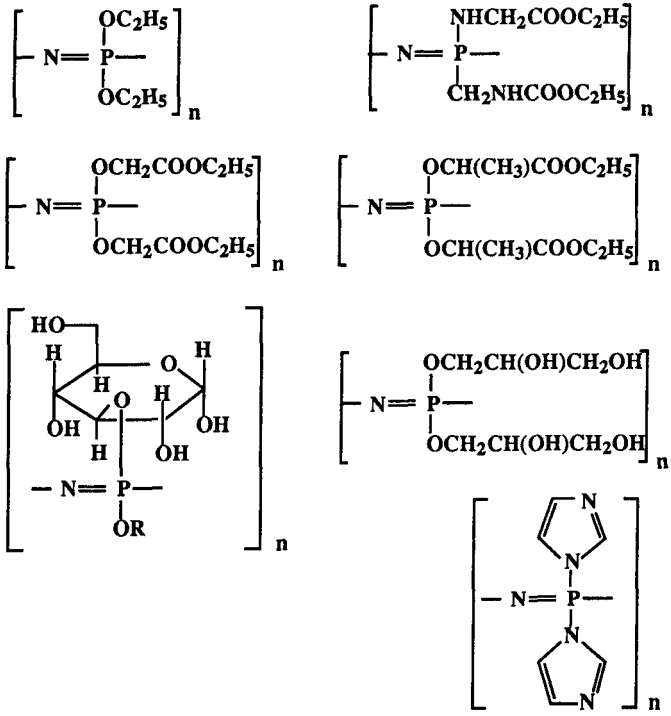
Scheme 4. Protection and Deprotection of a Functional Side Group



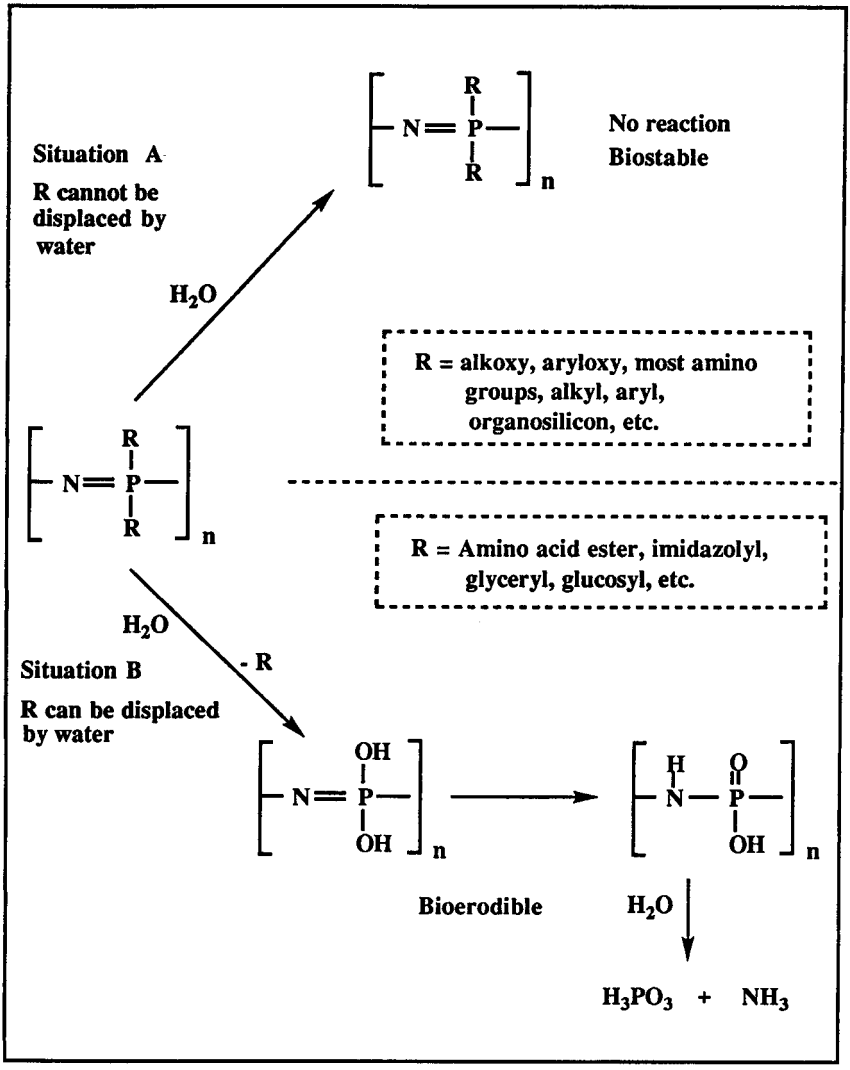
Mechanism of Hydrolysis

In polyphosphosphazenes hydrolytic breakdown of the skeleton requires the presence of a hydroxyl side group linked directly to phosphorus. Such a structure is highly sensitive to two sequential reactions - rearrangement of the proton from oxygen to skeletal nitrogen, followed by attack on the (now saturated) skeleton by water. Thus, hydrolytic breakdown requires the presence of side groups that can be displaced from phosphorus by water, leaving hydroxyl groups in their place (Scheme 5). On the other hand, if the side group cannot be displaced from phosphorus, either because it is a poor leaving group or because water cannot penetrate to the skeleton because of side group steric bulk or hydrophobicity, then the polymer will be hydrolytically stable.

Chart 2. Bioerodible Polyphosphazenes

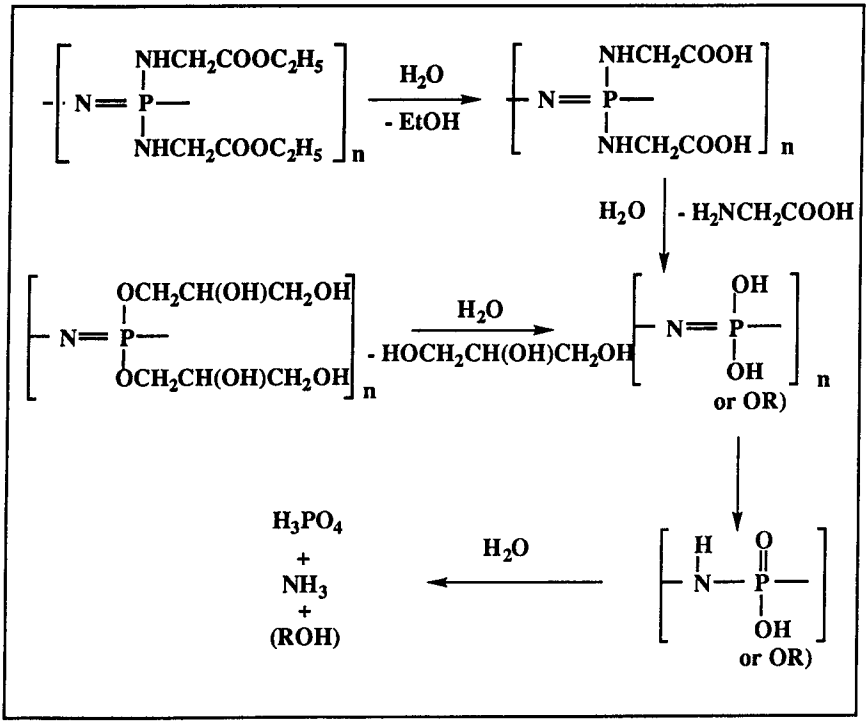


Scheme 5. Influence of Side Groups on Bioerodibility



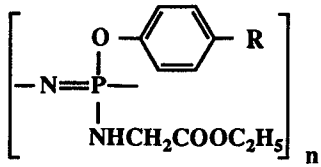
Examples of organic side groups that can be displaced under hydrolytic conditions are shown in Chart 2. It is no coincidence that all of these are hydrophilic units or species that can themselves be hydrolyzed to hydrophilic moieties. Thus, Scheme 6 illustrates two cases that, by a sequence of reactions, lead to the introduction of a hydroxyl group on phosphorus and subsequent skeletal breakdown. Once a P-OH unit has been introduced, skeletal cleavage takes place via the rearrangement to a phosphaz*a*ne, followed rapidly by hydrolytic cleavage of the backbone.

Scheme 6. Hydrolysis Pathway



By contrast, if the side groups are highly hydrophobic, and especially if they are bulky, they protect the P-side group bond against the initial attack, and the polymer is infinitely stable in an aqueous environment. The presence of hydrolyzable *and* poorly-hydrolyzable groups linked to the same chain as, for example, in species **2**, allows

considerable freedom for controlling the rate of hydrolysis through changes in the ratio of the two side groups.



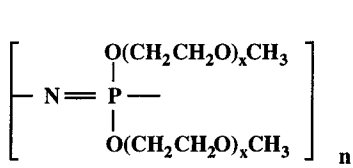
2

So too does the presence of a hydrophobic ester group (phenyl instead of ethyl in structure **2**), or the use of phenylalanine instead of glycine, etc. Moreover, the different types of dispaceable side groups shown in Chart 3 add another level of control, since each has a different sensitivity to hydrolytic displacement from phosphorus.

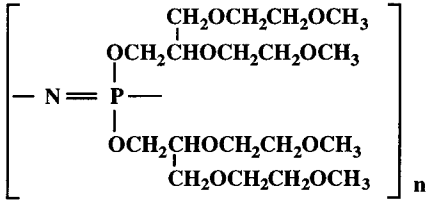
The organic side group that is displaced most rapidly from a phosphazene chain is the imidazolyl unit. The polymer that has all-imidazolyl side groups is so sensitive to atmospheric moisture that it cannot be handled in the air for more than a few minutes before degradation begins. However, in tandem with aryloxy co-substituent groups, it forms a series of polymers that are stable in the atmosphere but slowly bioerode in a biological environment [6].

The Special Case of Hydrogels and Microspheres

Hydrogels can be produced by crosslinking a water-soluble polymer and allowing it to absorb water. Such materials can be used for the immobilization of enzymes, for the controlled release of bioactive agents, or for the capture of metal cations. The group of polyphosphazenes that have the greatest utility as hydrogels are species with either linear or branched oligo-ethyleneoxy side chains [31-36]. Two examples are shown as **3** and **4**.



3



4

Many of these species show lower critical solution temperature behavior both in aqueous solution and as hydrogels. Thus, the hydrogels contract and expel water when heated above the LCST, which can be within the range of 30°C to 65°C depending on the structure of the side groups. This provides a mechanism for the expulsion of small-molecule biologically active agents at a certain temperature, or for the activation or deactivation of enzymes trapped in the hydrogel [34]. These materials are not hydrolytically degradable in neutral aqueous media, but the introduction of hydrolysis-sensitizing co-substituent groups provides a mechanism for polymer breakdown at a controlled rate. Moreover, the presence of $-OC_6H_4COOH$ co-substituents allows the swelling or contractile behavior of the hydrogel to be controlled by changes in pH [36].

The polyphosphazene in which all the side groups are $-OC_6H_4COOH$ units is soluble in water as its sodium or potassium salt, but becomes insoluble in aqueous media in the presence of calcium ion or other multivalent cations [30]. The insolubility is a consequence of ionic crosslinking by the calcium ions (Scheme 4). This phenomenon is being developed as a method for the microencapsulation of sensitive biologically active agents such as mammalian cells, proteins, or vaccines for use in biomedicine, biotechnology, and agriculture [37-42].

Final Comments

What does this chemistry mean for future developments in environmental science, agriculture, or medicine? First, it must be emphasized that polyphosphazenes will probable never be as inexpensive as the common commodity organic polymers. Thus, it is unlikely that they will replace the classical organic polymers that are of environmental concern. On the other hand, they have powerful advantages over other polymer systems when precisely tuned properties are needed, especially for degradation to harmless products in the environment or in medicine. Thus, the most promising near-term prospects lie in the

controlled release of pharmaceuticals, insecticides, and herbicides or as components in composites with less expensive polymers. Polyphosphazenes of the types shown in **3** and **4** are being developed as solid polymer electrolytes in batteries, and these may help to replace liquid electrolytes, especially acids, in a variety of energy storage devices. In medicine, possible uses for bioerodible polyphosphazenes are foreseen as structural materials such as sutures, staples, and other devices, and especially in tissue engineering as substrates for the growth of mammalian cells.

The polyphosphazenes are the first inorganic-organic polymers to be developed through the macromolecular substitution route, but they provide many lessons on how the same principles may be applied in the future to other macromolecules that contain inorganic elements in the backbone structure

References

1) J. E. Mark, H. R. Allcock, R. West, *"Inorganic Polymers"*, Prentice Hall, Englewood Cliffs, New Jersey, 1992, Ch. 3
2) H. R. Allcock, T. J. Fuller, D. P. Mack, K. Matsumura, K. M. Smeltz, *Macromolecules* **10**, 824 (1977)
3) H. R. Allcock, T. J. Fuller, *J. Chem. Soc.* **103**, 2250 (1981)
4) H. R. Allcock, T. J. Fuller, K. Matsumura, *Inorg. Chem.* **21**, 515 (1982)
5) H. R. Allcock, A. G. Scopelianos, *Macromolecules* **16**, 715 (1983)
6) C. Laurencin, H. J. Koh, T. X. Neenan, H. R. Allcock, R. S. Langer, *J. Biomed. Mater Res.* **21**, 1231 (1987)
7) H. R. Allcock, S. Kwon, *Macromolecules* **21**, 1980 (1988)
8) H. R. Allcock, S. R. Pucher, *Macromolecules* **24**, 23 (1991)
9) H. R. Allcock, S. R. Pucher, R. J. Fitzpatrick, *Biomaterials* **13**, 857 (1992)
10) S. R. Pucher, H. R. Allcock, *Polym. Prepr.* **33**, 108 (1992)
11) C. T. Laurencin, M. E. Norman, H. M. Elgendy, S. F. El-Amin, H. R. Allcock, S. R. Pucher, A. M. A. Ambrosio, *J. Biomed. Mater. Res.* **27**, 963 (1993)
12) H. R. Allcock, S. R. Pucher, A. G. Scopelianos, *Biomaterials* **15**, 563 (1994)
13) H. R. Allcock, S. R. Pucher, A. G. Scopelianos, *Macromolecules* **1**, 1 (1994)
14) H. R. Allcock, S. R. Pucher, A. G. Scopelianos, *Macromolecules* **27**, 1071 (1994)
15) S. E. M. Ibim, S. F. El-Amin, A. M. A. Ambrosio, H. R. Allcock, C. T .Laurencin, *Proc. Intern. Symp. Control. Rel. Bioact. Mater.* **21**, 266 (1994)
16) C. S. Reed, K. S. TenHuisen, P. W. Brown, H. R. Allcock, *Chem. Mater.* **8**, 440 (1996)
17) S. M. Ibim, A. M. A. Ambrosio, D. Larrier, H. R. Allcock, C. T. Laurencin, *J. Control. Rel.* **40**, 31 (1996)
18) C. T. Laurencin, S. F. El-Amin, S. E. Ibim, D. Willoughby, D. A. Attawia, A. M. A. Ambrosio, H. R. Allcock, *J. Biomed. Mater. Res.* **30**, 133 (1996)
19) H. R. Allcock , *Annals of the New York Academy of Sciences* **831**, 13 (1997)

20) S. M. Ibim, S. F. El-Amin, M. E. P. Goad, A. M. A. Ambrosio, H. R. Allcock, C. T. Laurencin, *Pharm. Develop. & Technol.* **3(1)**, 55 (1998)
21) C. T. Laurencin, S. E. M. Ibim, H. R. Allcock, A. M. A. Ambrosio, S. El-Amin, M. S. Kwon, *Bioact. Mater.* **24**, 971 (1997)
22) H. R. Allcock, R. L. Kugel, *J. Am. Chem. Soc.* **87**, 4216 (1965)
23) H. R. Allcock, R. L. Kugel, K. J. Valan, *Inorg. Chem.* **5**, 1709 (1966)
24) H. R. Allcock, R. L. Kugel, *Inorg. Chem.* **5**, 1716 (1966)
25) C. H. Honeyman, I. Manners, C. T. Morrissey, H. R. Allcock, *J. Am. Chem. Soc.* **117**, 7035 (1995)
26) H. R. Allcock, C. A. Crane, C. T. Morrissey, J. M. Nelson, S. D. Reeves, C. H. Honeyman, I. Manners, *Macromolecules* **29**, 7740 (1966)
27) H. R. Allcock, J. M. Nelson, S. D. Reeves, *Macromolecules* **29**, 7740 (1997)
28) J. M. Nelson, H. R. Allcock, *Macromolecules* **30**, 1854 (1997)
29) H. R. Allcock, S. D. Reeves, J. M. Nelson, C. A. Crane, *Macromolecules*,**30**, 2213 (1997)
30) H. R. Allcock, S. Kwon, *Macromolecules* **22**, 75 (1989)
31) H. R. Allcock, S. Kwon, G. H. Riding, R. J. Fitzpatrick, J. L. Bennett, *Biomaterials* **19**, 509 (1988)
32) J. L. Bennett, A. A. Dembek, H. R. Allcock, B. J. Heyen, D. F. Shriver, *Chem. Mater.* **1**, 14 (1989)
33) H. R. Allcock, S. R. Pucher, M. L. Turner, R. J. Fitzpatrick, *Macromolecules* **25**, 5573 (1992)
34) H. R. Allcock, S. R. Pucher, K. B. Visscher, *Biomaterials* **15**, 502 (1994)
35) H. R. Allcock, G. K. Dudley, *Macromolecules* **29**, 1313 (1996)
36) H. R. Allcock, A. M. A. Ambrosio, *Biomaterials* **17**, 2295 (1996)
37) S. Cohen, M. C. Bano, K. B. Visscher, M. Chow, H. R. Allcock, R. Langer, *J. Am. Chem. Soc.* **112**, 7832 (1990)
38) M. C. Bano, S. Cohen, K. B. Visscher, H. R. Allcock, R. Langer, *Biotechnology* **9**, 468 (1991)
39) S. Cohen, M. C. Bano, L. G. Cima, H. R. Allcock, J. P. Vacanti, C. A. Vacanti, R. Langer, *Clinical Materials* **13**, 3 (1993)
40) A. Andrianov, S. Cohen, R. Langer, K. B. Visscher, H. R. Allcock, *J. Control. Rel.* **27**, 69 (1993)
41) S. Cohen, H. R. Allcock, R. Langer, *Minutes (Editions de Sante, France)* 36 (1993)
42) A. K. Andrianov, L. G. Payne, K. B. Vissscher, H. R. Allcock, R. Langer, *J. Appl. Polym. Sci.* **53**, 1573 (1994)