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Synthesis of Sugar-Substituted Cyclic and Polymeric Phosphazenes and Their Oxidation, Reduction, and Acetylation Reactions

Harry R. Allcock* and Angelo G. Scopelianos

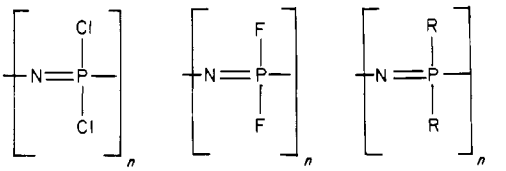
Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802. *Received June 29, 1982*

ABSTRACT: Sugar residues have been linked to cyclic and high-polymeric phosphazenes. Selective blocking of the 1,2- and 5,6-hydroxyl groups of α-D-glucose by acetone allowed linkage to the phosphazene via the remaining hydroxyl unit. Hydrolysis of the blocked, sugar-substituted phosphazenes brought about deprotection. The deprotected derivatives were then modified chemically by oxidation, reduction, and acetylation. The resultant high polymers are the first members of a new class of hydrophilic or water-soluble macromolecules. Their properties and structural characterization are discussed.

A need exists in several areas of science for new synthetic macromolecules that are hydrophilic, amphiphilic, or soluble in aqueous media. Polymers that contain sugar residues as side-group units are of special interest. Polymer-bound sugars are potential chiral templates for the asymmetric synthesis or optical resolution of organic molecules.[3-8] They are also of interest as intermediates in the synthesis of carbohydrates,[9-12] especially oligosaccharides,[13-16] as reverse osmosis membranes,[17] as selectively permeable membranes,[18] as tools for the examination of bioorganic mechanisms, and for pharmacological applications.[19] Such polymers may also be valuable as carrier ligands for transition metals or as binding sites for organic reagents.[20-24] Their potential role as affinity chromatography substrates or mordant films is also important.

The conventional approach to the synthesis of such macromolecules has been to use an organic polymer backbone such as those derived from polystyrene, poly(phenylene oxide), or polyacrylonitrile as a carrier for sugar-type side groups. The steps involved in such syntheses are often quite complex, and difficulties may be encountered with respect to skeletal degradation or incomplete linkage to the sugar.

We have developed a synthetic technique that allows a wide range of organic side groups to be linked to a stable, high-polymeric backbone.[25-34] The method makes use of nucleophilic substitution reactions carried out on the highly reactive macromolecular substrates poly(dichlorophosphazene) (**1**) or poly(difluorophosphazene) (**2**) to yield poly(organophosphazenes) (**3**). So far, a wide range of relatively simple side groups (R) has been incorporated into such polymers by the reactions of monofunctional nucleophiles with **1** or **2**. Here, we discuss an extension of this approach for the attachment of multifunctional sugar molecules to a phosphazene backbone.



1 **2** **3**, $n \simeq 15\,000$

Answers to the following questions were sought: (i) Will protected sugar molecules react efficiently with **1** to yield sugar-bound polyphosphazenes? (ii) Can subsequent chemistry such as hydrolysis of protecting groups or oxidation, reduction, or acetylation of the sugar units be carried out without destruction of the inorganic polymer skeleton? (iii) What are the unique properties of the derivative macromolecules and how do they differ from the properties of their small-molecule analogues.

As discussed in a recent review,[35] a prerequisite for the development of new reactions that involve **1** or **2** is an exploration of analogous reactions at the small-molecule, model compound level. This approach has been followed in the present work.

Results and Discussion

Model Reactions. The trial reaction strategy at the model compound level is outlined in Scheme I. α-D-Glucose was first protected by reaction with acetone to yield 1,2:5,6-di-*O*-isopropylidene-α-D-glucose. An excess of the sodium salt of this reagent was then allowed to react with hexachlorocyclotriphosphazene (**4**), with total replacement of the chlorine atoms by the protected sugar residues (**5**). The structure of **5** was confirmed by a combination of infrared, ^{31}P NMR, ^{13}C NMR, mass spectral, and microanalytical data. For example, the infrared

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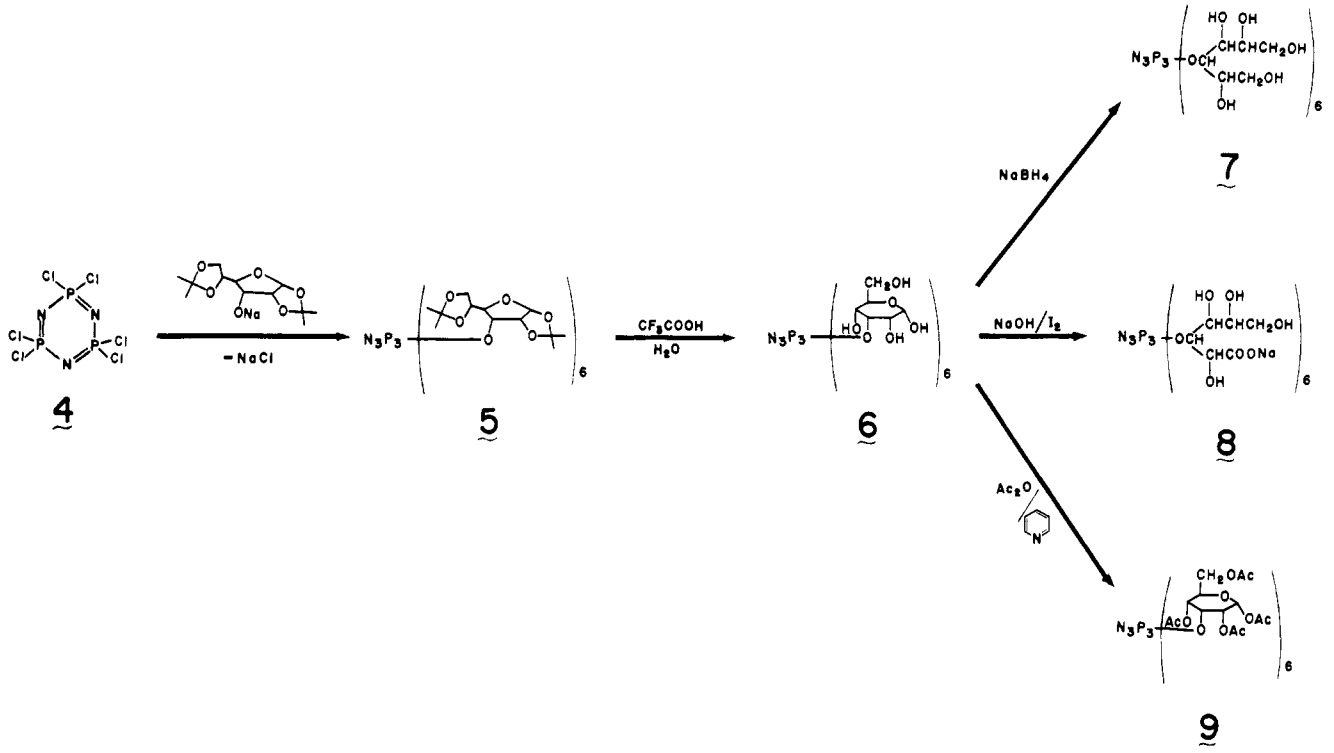
Scheme I



spectrum contained peaks at 3000–2900 (s) (C–H) (KBr disk), 1375 (s) (*gem*-dimethyl), 1250 (br) (P=N), and 1050 (br) (C–O) cm^{-1}. The ^{31}P NMR spectrum consisted of a single peak centered at 15.7 ppm. Other characterization data are summarized in the Experimental Section.

Acetal units are among the most useful protecting groups in sugar and nucleoside chemistry. Their rapid removal from **5** was accomplished by the use of 90% trifluoroacetic acid in water at 25 °C to yield analytically pure **6**. The structure of **6** was confirmed by infrared, ^{31}P NMR, mass spectral, and microanalytical techniques. The infrared spectrum showed peaks at 3300 cm (s) (OH) (in KBr disks), 2900 (w) (C–H), 1250 (br) (P=N), and 1050 (br) (C–O) cm^{-1}. The ^{31}P NMR spectrum consisted of a single peak centered at 16.5 ppm.

Compound **6** could be reduced to **7** in high yield by treatment with aqueous sodium borohydride solution. The infrared spectrum of **7** was similar to that of **6** but with a stronger OH band at 3300 cm^{-1} and a sharper P=N stretch at 1250 cm^{-1}. However, the ^{31}P NMR spectrum consisted of a singlet shifted to −1.2 ppm.

Oxidation of **6** was accomplished by treatment with aqueous hypoiodite solution. The infrared spectrum of the product (**8**) showed evidence for a carboxylate group at 1750 cm^{-1} and a retention of the OH and P=N peaks at 3300 and 1250 cm^{-1}, respectively. A slight shift in the position of the ^{31}P NMR singlet had occurred, to −0.2 ppm.

Acetylation of **6** was accomplished with pyridine and acetic anhydride to yield **9**. The presence of the acetyl groups was confirmed by the strong infrared absorbance at 1720 cm^{-1}. The ^{31}P NMR spectrum of **9** consisted of a single peak at 14.2 ppm. Mass spectral, ^{13}C NMR, and microanalytical characterization data for compounds **6–9** are summarized in the Experimental Section.

In none of these reactions was evidence obtained that the formation of **5–9** was accompanied by skeletal cleavage reactions or (in the formation of **6–9**) by P–O bond cleavage. Thus the prospect for an extension of these procedures to the analogous high polymers appeared promising.

Table I
Molecular Weight and Glass Transition Data

polymer	mol wt[a]	T_g,[c] °C
10	8×10^5	87
11	7×10^5	92
12	6.8×10^5	79
13	*b*	72
14	6.8×10^5	47

[a] By gel permeation chromatography with the use of tetrahydrofuran solvent. [b] This polymer was insoluble in tetrahydrofuran. [c] By differential scanning calorimetry.

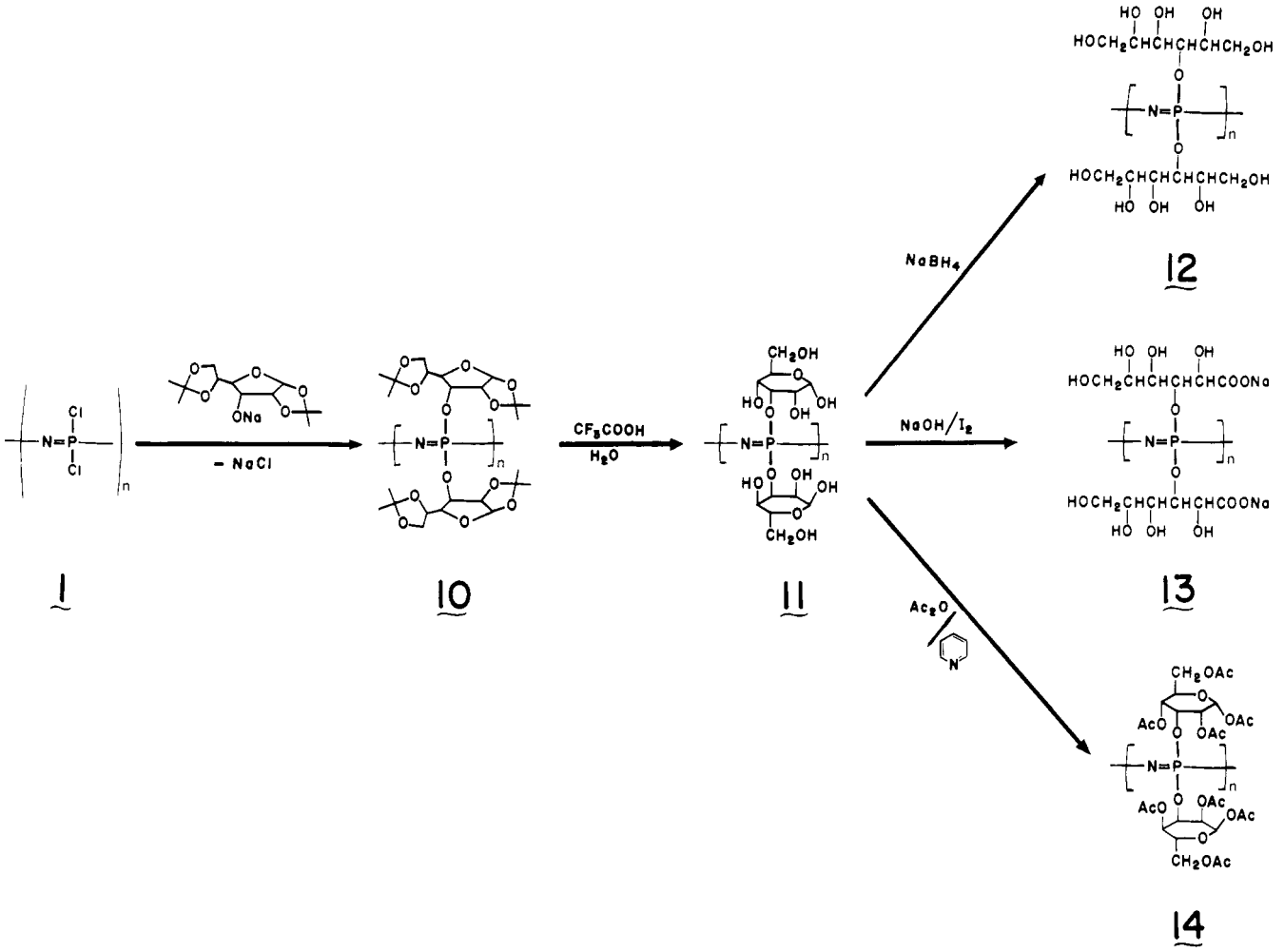
High-Polymeric Reactions. The sodium salt of 1,2:5,6-di-*O*-isopropylidene-α-D-glucose reacted with poly(dichlorophosphazene) (**1**) to yield the hydrolytically stable high polymer **10** (Scheme II). Structural characterization of **10** was accomplished by a combination of infrared, ^{31}P NMR, ^{13}C NMR, and microanalytical data (see Experimental Section). In fact, the infrared and ^{31}C NMR spectra of **10** were almost identical with those of **5**, except for the broader peaks in **10**. The ^{31}P NMR spectrum of this polymer consisted of a broad, single peak centered at −11 ppm. GPC molecular weight and glass transition data are given in Table I.

Deprotection of **10** to yield **11** was accomplished by the use of 90% trifluoroacetic acid in water. Longer reaction times were needed than with the cyclic analogue. Polymer **11** was soluble in water, tetrahydrofuran, ethanol, and pyridine. It showed no evidence of cross-linking. The ^{31}P NMR spectrum consisted of a single, broad peak centered at −7 ppm. Other spectroscopic data were consistent with species **11** (see Experimental Section). The infrared spectrum was similar to that of the cyclic analogue, **6**.

Reduction of **11** by aqueous sodium borohydride yielded the water-soluble polymer **12**, which could be purified by dialysis. Again, the ^{31}P NMR spectrum consisted of a broad singlet, located this time at −2.8 ppm. As before, the infrared spectrum of **12** resembled that of **7**, except for an increase in peak width.

Oxidation of **11** by means of sodium hypoiodite yielded

Scheme II



13, a water-soluble polymer that could also be purified by dialysis. However, the saltlike nature of this product reduced its solubility in common organic media. The infrared spectrum of **13** was similar to that of the cyclic analogue, **8**. The ^{31}P NMR peak was shifted to −1.0 ppm.

Acetylation of **11** to give **14** also proceeded in a similar manner to that found for the small-molecule system. The ^{31}P NMR spectrum of **14** showed a single peak at −6.0 ppm. ^{13}C NMR and microanalytical characterization data are summarized in the Experimental Section.

Unique Features of the High Polymers. As shown in Table I, the sequence of organic transformations that starts with **10** does not result in appreciable skeletal cleavage. The conversion of **1** to **10**–**14** results in a dramatic rise in the glass transition temperature from −66 °C (for **1**) to the 50–90 °C region. This is consistent with a reduction in backbone torsional freedom that would be expected from the presence of bulky organic substitutent groups, especially these that are capable of hydrogen bonding.

Perhaps the most interesting feature of macromolecules **11**–**13** is their solubility in water and their apparent stability in this medium. This raises the prospect that such polymers may be appropriate as biomedical molecules, and this possibility is being investigated.

Experimental Section

Equipment. Infrared spectra were recorded by means of a Perkin-Elmer 580 spectrometer. ^{31}P NMR spectra were obtained in the FT mode with a JEOL PS-100 spectrometer. ^{13}C NMR spectra (FT) were obtained with a Bruker WP-200 FT NMR spectrometer operated at 52 MHz. Approximate polymer molecular weights were determined with a Waters Associates ALC/GPC 201 instrument fitted with a 120 cm × 1 cm, 10^6-Å Styragel column with calibration with polystyrene standards. Microanalyses were obtained by Galbraith Laboratories.

Materials. Most experimental manipulations were performed under an atmosphere of dry nitrogen (Matheson). Tetrahydrofuran (THF) (Fisher) was freshly distilled under nitrogen from sodium–benzophenone ketyl. α-D-Glucose was obtained from Sigma and was used as received. Trifluoroacetic acid, sodium borohydride, and sodium hydride (50% dispersion in mineral oil) were obtained from Aldrich and were used as received. Iodine (Eastman), sodium hydroxide pellets, pyridine (Fisher), and acetic anhydride (Baker) were used as received. Hexachlorocyclotriphosphazene (Ethyl Corp.) was sublimed and recrystallized from hexane.

Poly(dichlorophosphazene) (**1**) was prepared by the polymerization of $(NPCl_2)_3$ (**4**) at 250 °C. An average of 30–40% conversion to the linear polymer was obtained.

Synthesis of 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose. This reagent (diacetone glucose) was prepared by methods described by other workers.[36]

Reaction of the Sodium Salt of Diacetone Glucose with $(NPCl_2)_3$. Hexachlorocyclotriphosphazene (**4**) (2.5 g, 7.20×10^{-3} mol) and diacetone glucose (15.0 g, 5.76×10^{-2} mol) were dissolved in dry tetrahydrofuran (200 mL). To this solution was added 3.5 g of sodium hydride (50% oil dispersion, 7.30×10^{-2} mol) over a period of 15 min. The mixture was stirred at room temperature for 0.5 h and was then refluxed for 48 h. The reaction mixture was cooled and filtered. The filtrate was concentrated in a rotary evaporator and was washed with 500 mL of water to remove unreacted diacetone glucose. The crude product was recrystallized from hexane to yield a white crystalline compound (**5**), mp 198–200 °C. The mass spectrum of this compound consisted of a parent

peak at m/e 1689 (mol wt for **5** = 1689), with peaks corresponding to the successive loss of six diacetone glucose groups. ^{13}C NMR ($CDCl_3$) 112.34, 109.07 (>C(O)(O)), 104.96 (α-furanose C-1), 83.12, 81.08, 80.50, 72.48 (C-2 to 5), C- 66.85 (C-6), 26.72, 26.21, 25.60 (CH_3). Anal. Calcd. for $C_{72}H_{114}O_{16}N_3P_3$: C, 51.15; H, 6.75; O, 34.10; N, 2.48; P, 5.51. Found: C, 51.02; H, 6.74; O, 34.14; N, 2.43; P, 5.67.

Reaction of 5 with CF_3COOH.[37] Compound **5** (1.00 g, 5.92×10^{-4} mol) was dissolved in 10 mL of a 9:1 (v/v) trifluoroacetic acid–water mixture. The mixture was maintained at room temperature for 10 min, and the solvent was then removed by evaporation in vacuo. The residue was washed with diethyl ether to yield a white crystalline compound (**6**), mp 99 °C. The mass spectrum of this compound showed a parent peak at m/e 1209 (mol wt **6** = 1209), with peaks corresponding to the successive loss of six glucose groups. ^{13}C NMR (Me_2SO-d_6) 97.08 (α-pyranose C-1), 92.50 (β-pyranose C-1), 76.89 (α-pyranose C-3), 75.14 (β-pyranose C-3), 73.39, 72.18, 70.60 (C-2, C-4, C-5), 61.52 (C-6). Anal. Calcd. for $C_{36}H_{66}O_{36}N_3P_3$: C, 35.73; H, 5.46; O, 47.64; N, 3.47; P, 7.69. Found: C, 35.97; H, 5.22; O, 47.79; N, 3.43; P, 7.59.

Reduction of 6. Compound **6** (0.50 g, 4.13×10^{-4} mol) was dissolved in water (100 mL). To this solution was added 2.0 g of sodium borohydride, and the mixture was stirred at room temperature for 60 h. The insoluble residue was filtered off, the filtrate was concentrated, and the residue was suspended in pyridine and filtered. The filtrate was concentrated to yield the semicrystalline product, **7**. The mass spectrum of this compound showed a parent peak at m/e 1221 (mol wt for **7** = 1221). ^{13}C NMR (Me_2SO-d_6) 79.92 (C-3), 73.12, 70.67 (C-2, C-4, C-5), 64.02 (C-1), 62.09 (C-6). Anal. Calcd. for $C_{36}H_{73}O_{36}N_3P_3$: C, 35.38; H, 6.39; O, 47.17; N, 3.44; P, 7.62. Found: C, 35.46; H, 6.46; O, 47.55; N, 3.21; P, 7.32.

Oxidation of 6.[38] Compound **6** (0.50 g, 4.13×10^{-4} mol) was dissolved in water (100 mL). This solution was treated alternately and dropwise with aqueous 0.1 N iodine solution and 0.1 N sodium hydroxide solution. A total of 40 mL of the iodine and 60 mL of the sodium hydroxide solution was added during 1.5 h. The solution was concentrated and the residue was suspended in pyridine and filtered. The filtrate was concentrated to yield compound **8**, mp >350 °C. ^{13}C NMR (Me_2SO-d_6) 176.46 (C-1), 73.01 (C-3), 72.04 (C-2), 71.36 (C-4), 70.37 (C-5), 62.94 (C-6). Anal. Calcd. for $C_{36}H_{60}O_{42}N_3P_3Na_6$: C, 30.06; H, 4.18; O, 46.76; N, 2.92; P, 6.47; Na, 9.60. Found: C, 31.12; H, 4.47; O, 48.34; N, 2.62; P, 6.11; Na, 7.34.

Acetylation of 6.[39] Compound **6** (0.50 g, 4.13×10^{-4} mol) was dissolved in pyridine (80 mL) and was treated with 80 mL of acetic anhydride at 70 °C for 48 h. The insoluble residue was removed by filtration and the filtrate was concentrated to yield the crude compound **9**. Recrystallization from a methylene chloride–hexane mixture yielded the semicrystalline product, **9**. ^{13}C NMR ($CDCl_3$) 169.21, 168.10 (C=O), 90.93 (β-anomer C-1), 88.34 (α-anomer C-1), only discernible peaks besides $CDCl_3$. Anal. Calcd. for $C_{84}H_{114}O_{60}N_3P_3$: C, 45.47; H, 5.14; O, 43.30; N, 1.89; P, 4.19. Found: C, 45.63; H, 5.47; O, 42.96; N, 1.82; P, 4.12.

Reaction of the Sodium Salt of Diacetone Glucose with High-Polymeric $(NPCl_2)_n$. Diacetone glucose (9.0 g, 3.46×10^{-2} mol) was dissolved in 100 mL of dry tetrahydrofuran and was treated with sodium hydride (1.0 g, 4.1×10^{-2} mol, 50% dispersion in mineral oil), and the mixture was stirred at room temperature for 12 h. Stirring was then stopped and the excess sodium hydride was allowed to settle. The clear supernatant solution was removed by syringe and was added dropwise to a solution of poly(dichlorophosphazene) (**1**) (1.5 g, 1.30×10^{-2} mol) in 100 mL of tetrahydrofuran. The reaction mixture was refluxed for 72 h. The mixture was cooled and concentrated, and the product (**10**) was isolated by reprecipitation into water. Further purification was carried out by precipitation from THF into water (twice) and from THF into hexane (twice). ^{13}C NMR ($CDCl_3$) 112.00, 108.82 (>C(O)(O)), 104.52 (α-furanose C-1), 82.92, 80.82, 80.41, 72.02 (C-2 to C-5), 66.59 (C-6), 26.70, 25.20 (CH_3). Anal. Calcd. for $C_{24}H_{38}O_{12}NP$: C, 51.15; H, 6.75; O, 34.10; N, 2.48; P, 5.51. Found: C, 51.28; H, 6.87; O, 34.05; N, 2.32; P, 5.48.

Hydrolysis of Polymer 10.[37] Polymer **10** (0.50 g) was dissolved in 10 mL of a 9:1 (v/v) trifluoroacetic acid–water mixture. The solution was held at room temperature for 8 h, diluted with 125 mL of water, and dialyzed in a cellulose tube for 48 h. After concentration of the solution, the polymeric product (**11**) was isolated as a white brittle material. ^{13}C NMR (Me_2SO-d_6) 96.78 (β-pyranose C-1), 92.93 (α-pyranose C-1), 76.12 (β-pyranose C-3), 75.37 (α-pyranose C-3), 73.42, 72.10, 70.82 (C-2, C-4, C-5), 61.34 (C-6). Anal. Calcd. $C_{12}H_{22}O_{12}NP$: C, 35.73; H, 5.46; O, 47.64; N, 3.47; P, 7.69. Found: C, 36.27; H, 5.37; O, 47.93; N, 3.22; P, 7.21.

Reduction of Polymer 11. Compound **11** (0.50 g) was dissolved in water (100 mL). To this solution was added 2.5 g of sodium borohydride, and the mixture was stirred at room temperature for 60 h and then dialyzed in a cellulose tube for 120 h. The insoluble residue was filtered off, and the filtrate was concentrated to yield the white polymeric material, **12**. ^{13}C NMR (Me_2SO-d_6) 77.81 (C-3), 74.63, 69.91 (C-2, C-4, C-5), 62.29 (C-1), 59.88 (C-6). Anal. Calcd. for $C_{12}H_{28}O_{12}NP$: C, 35.38; H, 6.39; O, 47.17; N, 3.44; P, 7.62. Found: C, 36.47; H, 6.42; O, 46.76; N, 3.21; P, 7.14.

Oxidation of Polymer 11. Compound **11** (0.50 g) was dissolved in water (150 mL). This solution was treated alternately and dropwise with aqueous 0.1 N iodine solution and 0.1 N sodium hydroxide solution during 1.5 h. The solution was dialyzed for 96 h in a cellulose tube and was then concentrated to yield the white polymer **13**. ^{13}C NMR (Me_2SO-d_6) 176.12 (C-1), 73.12 (C-3), 72.14 (C-2), 71.32 (C-4), 70.39 (C-5), 63.01 (C-6). Anal. Calcd. for $C_{12}H_{20}O_{14}NPNa_2$: C, 30.06; H, 4.18; O, 46.76; N, 2.92; P, 5.77; Na, 9.60. Found: C, 31.48; H, 4.39; O, 48.52; N, 2.57; P, 5.93; Na, 7.11.

Acetylation of Polymer 11. Compound **11** (0.50 g) was dissolved in pyridine (80 mL) and was treated with 80 mL of acetic anhydride at room temperature. The solution was then heated at 70 °C for 24 h. The insoluble residue was removed by filtration, and the filtrate was concentrated, dissolved in methylene chloride, and precipitated into methanol (twice) to yield polymer **14**. ^{13}C NMR ($CDCl_3$) 168.92 (C=O), the only peak that was clearly seen except $CDCl_3$. Anal. Calcd. for $C_{28}H_{38}O_{20}NP$: C, 45.47; H, 5.14; O, 43.30; N, 1.89; P, 4.19. Found: C, 45.12; H, 5.28; O, 43.72; N, 1.56; P, 4.32.

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Registry No. **1**, 26085-02-9; **4**, 940-71-6; **5**, 85066-73-5; **α-6**, 85048-96-0; **β-6**, 85048-97-1; **7**, 85048-98-2; **8**, 85048-99-3; **α-9**, 85049-00-9; **β-9**, 85066-74-6; **10**, 85048-90-4; **α-11**, 85066-72-4; **β-11**, 85048-91-5; **12**, 85048-92-6; **13**, 85048-93-7; **α-14**, 85048-94-8; **β-14**, 85048-95-9; 1,2:5,6-diacetone glucose, 582-52-5.

References and Notes

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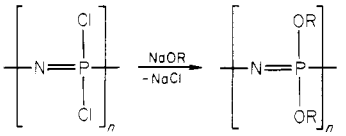
Improved Method for the Synthesis of Poly(organophosphazenes) and Hindered Cyclophosphazenes

Paul E. Austin, Geoffrey H. Riding, and Harry R. Allcock*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802. *Received September 8, 1982*

ABSTRACT: The use of tetra-*n*-butylammonium chloride or bromide as a solid/liquid phase-transfer agent and ion-pair separation catalyst has a dramatic accelerating effect on the reactions of poly(dichlorophosphazene) with sodium alkoxides or aryl oxides. This allows the synthesis of hitherto inaccessible high molecular weight polyphosphazenes or the preparation of known polymers under unusually mild experimental conditions. The same principles apply to the preparation of small-molecule cyclophosphazenes.

A large number of poly(alkoxyphosphazenes) and poly[(aryloxy)phosphazenes] (**2**) have been synthesized by the interaction of alkali metal alkoxides or aryl oxides with poly(dichlorophosphazene) (**1**) in organic media.[1-11]



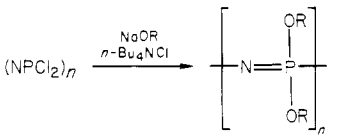
1 **2**

However, this method works well only when both the nucleophile and poly(dichlorophosphazene) are soluble in the same organic medium. If this requirement is not met, incomplete replacement of the halogen atoms may occur.

Many alkali metal alkoxides and aryl oxides are essentially insoluble in nonpolar organic media, and this restricts the number of different poly(organophosphazenes) that can be prepared. In addition, the attachment of bulky organic side groups such as aryloxy units to a phosphazene ring or chain requires the use of forcing reaction conditions that may cause partial depolymerization of the high polymer to cyclic oligomeric analogues.

We have now developed a modification to the conventional substitution process which overcomes both of the problems mentioned above. The method makes use of tetra-*n*-butylammonium chloride or bromide as a catalyst for use with sodium alkoxides or aryl oxides.[12] The tetraalkylammonium counterion serves to increase the lipophilicity and nucleophilicity of the oxyanions. Moreover, the interaction of a poorly soluble sodium alkoxide or aryl oxide with the tetraalkylammonium halide solubilizes the alkoxide as its alkylammonium salt. The result is a catalysis of the nucleophilic substitution process.

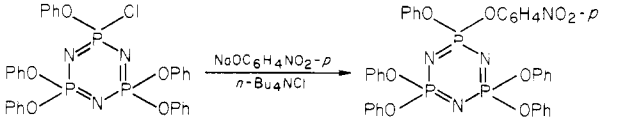
Scheme I



5, OR = OC_6H_5
6, OR = $OC_6H_4NO_2$-*p*
7, OR = OC_6H_4CHO-*p*
8, OR = $OC_6H_4COCH_3$-*p*
9, OR = OCH_2CF_3 and $OCH_2(CF_2)_5CF_2H$

Results

Model Reaction. The role of *n*-Bu_4NCl was monitored first for the model cyclic trimeric compound **3**. In the



3 **4**

absence of the alkylammonium halide, the interaction of **3** with sodium *p*-nitrophenoxide in dioxane resulted in no detectable formation of **4** after 1 week at 100 °C. The addition of *n*-Bu_4NCl to the reaction mixture was followed by a quantitative conversion of **3** to **4** within 30 min at the same temperature. The nonreactivity of **3** in the presence of sodium *p*-nitrophenoxide in dioxane is ascribed to both the insolubility of the nucleophile and its low nucleophilic character. Addition of the alkylammonium halide serves both to assist solubilization and to enhance its nucleophilicity through ion-pair separation.

High-Polymeric Reactions. Similarly, the presence of *n*-Bu_4NCl or *n*-Bu_4NBr has a powerful effect on the

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