Synthesis of Poly(alkylene phosphates) with Nitrogen-Containing Bases in the Side Chains. 1. N- and C-Substituted Imidazoles

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ABSTRACT: Poly(2,2-dihydro-2-oxo-1,3,2-dioxaphosphorinane) was quantitatively chlorinated; the resulting polymer was reacted with an excess of imidazole, giving the highly reactive poly(ester amide). This polymer was used to obtain polyphosphates containing N- or C-substituted imidazole in the side chains, by reacting the poly(ester amide) with N-(hydroxyethyl)imidazole or C-(hydroxyethyl)imidazole. The final polymers ($\bar{M}_n \geq 10^4$), stable in water solution, were characterized by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, indicating the structural uniformity of the prepared products.

Introduction

Successful preparation of models of biopolymers with polyphosphate main chains and bearing resemblance to nucleic acids (NA) and teichoic acids (TA) opened a possibility to the synthesis of polymers that may imitate some functions of biopolymers.

In these syntheses both polycondensation[1] and polymerization[2,3] methods were applied.

We have already reported on the synthesis of 2,2-dihydro-2-oxo-1,3,2-dioxaphosphorinane (1) and its polymerization to the high molecular weight polyphosphite (2) ($\bar{M}_n$ up to 10^5)[4]
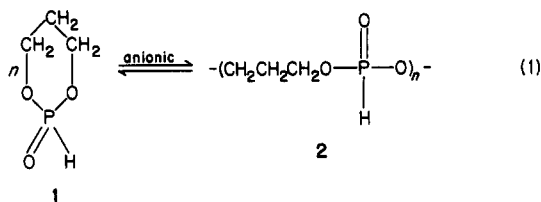

Several polyphosphites, similar to 2 but with much lower $\bar{M}_n$, were prepared by polycondensation by Petrov[5] and then by Vogt,[6] who has also established the chemical nature of the side reactions accompanying polycondensation and preventing the high polymer formation.

2 is a versatile starting material to prepare various polymeric derivatives. Its oxidation led to the first synthetic high molecular weight poly(alkylene phosphate)[7]

$$2 \xrightarrow{\text{oxdn}} -(\text{CH}_2\text{CH}_2\text{CH}_2\text{OP(O)(OH)O})_n- \quad (2)$$
3
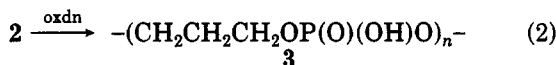
By the same methods, namely, the anionic polymerization of the corresponding cyclic phosphates, phosphites, and amides of the tricoordinate phosphorus followed by oxidation of the corresponding polymers, we recently prepared polyphosphates with backbones similar to 3 and containing elements of nucleic and teichoic acids, respectively[2,3]
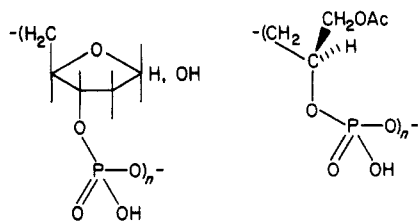
In this paper we use a similar approach to prepare poly(1,3-propylene phosphates) bearing imidazole units in the side chain and spaced similarly to the bases in the nucleic acids.

Experimental Section

2 was prepared by polymerization of 1 in CH_2Cl_2 solvent at 25 °C as described by us earlier.[4] $[1]_0 = 7.0$ mol/L and $[(i\text{-}C_4H_9)_3Al]_0 = 3 \times 10^{-2}$ mol/L were used. Polymerization came to equilibrium (according to ^{31}P NMR) after 24 h. 2 was isolated and freed from the monomer by precipitating from CH_2Cl_2 solvent into C_6H_6. All of the solvents used were thoroughly dried in order to prevent the polymer hydrolysis. Under the specified above conditions the yield of polymer, a white, powdery material, was about 50%.

4 (poly(2-chloro-2,2-dihydro-2-oxo-1,3,2-dioxaphosphorinane)) was prepared by chlorination of 2 similarly to the known chlorination of the low molecular weight dialkyl phosphites.[8] 2 (15.2 g, 0.125 mol repeating units) and methylene chloride (400 g) were mixed at 25 °C under dry conditions until a clear solution was obtained. Then, dry Cl_2 was passed through the solution until a persistent yellow appeared. At this stage the original absorption in ^{31}P NMR at δ 8.8 (due to the $-\text{OP(O)(H)O}-$ unit) disappeared and instead a singlet at δ 3.54 appeared due to the formation of the ($-\text{OP(O)(Cl)O}-$ units). The excess of Cl_2 was then removed under vacuum until a colorless solution resulted. This solution of 4 was further used without polymer isolation.

5 was obtained according to the method reported previously:[9] ^{1}H NMR δ 8.1 (s, H_e), 7.5 and 7.6 (two lines, H_f or H_g), 5.3 (s, OH), 4.1–4.7 (m, H_c, H_d); the symbols are similar to these used in describing the NMR spectra of 8 (cf. Figure 1). ^{13}C NMR δ 136.7 (C_e), 126.5 and 119.0 (C_f, C_g), 59.6 (C_d), 47.8 (C_c). Before condensation (cf. eq 5) 5 was further purified by crystallization from THF and eventually heated at 100 °C for 8 h under vacuum.

6 was obtained according to ref 10: yield, 3%; ^{1}H NMR δ 7.6 (s, H_e), 6.8 (s, H_g), 6.6 (OH, NH), 3.8 (t, H_c), 2.8 (t, H_d); ^{13}C NMR δ 133.4 and 132.1 (C_e, C_f), 116.4 (C_g), 60.1 (C_c), 28.8 (C_d). Before condensation (cf. eq 6) 6 was heated at 100 °C for 8 h under vacuum.

7 (poly(2,2-dihydro-2-imidazolyl-2-oxo-1,3,2-dioxaphosphorinane)) was prepared by a direct reaction of 4 with an excess of imidazole. A solution of imidazole (14 g, 0.203 mol, 103 mol % excess over 4) in 150 g of CH_2Cl_2 was added dropwise at 25 °C to a 5% solution of 4 (15.6 g, 0.1 mol repeating units) over 1 h. The reaction mixture was kept for an additional hour at 0 °C to ensure the complete precipitation of imidazole hydrochloride (Im·HCl). Im·HCl was filtered off and the resulting solution of 7 was further used without polymer isolation. The degree of substitution was measured by ^{31}P NMR. Under the described above conditions only a new band at δ −5.88, due to the $-\text{OP(O)(Im)O}-$ unit, was observed.

8 (poly(2,2-dihydro-2-(2-N-imidazolylethoxy)-2-oxo-1,3,2-dioxaphosphorinane)) and 10 (poly(2,2-dihydro-2-(C^4-imidazolylethoxy)-2-oxo-1,3,2-dioxaphosphorinane)) were prepared by reacting 7 with N-(hydroxyethyl)imidazole (5) and C^4-(hydroxyethyl)imidazole (6), respectively.

Synthesis of 8. 5 (3.5 g, 0.03 mol) in 100 g of CH_2Cl_2 was added dropwise at 25 °C over 1 h to a solution of 7 (5.7 g, 0.03 mol repeating units) in 125 g of CH_2Cl_2. After 24 h the resulting solution of product was concentrated to 15–20% of its original volume and polymer precipitated to 100 g of acetone. After a few (3–5) cycles of dissolution in water and precipitation in acetonitrile 8 was dried under vacuum at 25 °C. The degree of substitution was measured by ^{31}P NMR. Only one singlet, δ −1.37, due to the repeating units of 8, was observed. When only partial substitution

was planned was the required amount of **5** used; then in ^{31}P NMR apart from a singlet at δ -1.37 a singlet at δ 0.42, due to the $-OP(O)(OH)O-$ unit, was observed in proportions close to the calculated ones on the basis of the starting [5]/[7] ratio.

Synthesis of 10. This was performed in a similar way to the synthesis of **8**, but **6** was used in a solution of DMF and **10** precipitated by itself from CH_2Cl_2 solution after 24 h of seasoning. Thus, after **10** was filtered off, it was further dissolved in water and precipitated in acetonitrile directly, omitting the stage of concentrating of the first solution.

Results and Discussion

Polymers prepared throughout this work were mostly characterized by ^{1}H, ^{13}C, and ^{31}P NMR. The chemical shifts of a given group usually depend slightly on the polymer concentration in solution. Thus, the chemical shifts are mostly given for 15 wt % solutions.

Poly(2,2-dihydro-2-oxo-1,3,2-dioxaphosphorinane) (**2**) was prepared by polymerization of its monomer (**1**), as described earlier.[4] Polymers with $\bar{M}_n$ ranging from 2×10^4 to 4×10^4 (measured by membrane osmometry) were used throughout this work. Since **2** is hydrolytically unstable, it is essential to handle this polymer with the exclusion of water and in the highly purified solvents. **2** is soluble in CH_2Cl_2 and $CHCl_3$ and can be freed from its monomer by precipitation from CH_2Cl_2 solution into C_6H_6. Monomer **1** is soluble in the resulting mixture.

^{1}H, ^{31}P, and ^{13}C NMR spectra clearly indicate the structural uniformity of **2** used in further synthesis. In ^{31}P NMR there are two quintets, reduced to one sharp signal in the ^{31}P{^{1}H} NMR spectrum at δ 8.8 (in CH_2Cl_2 solvent). In ^{13}C NMR two groups of signals appear, a doublet at δ 59.6 (POCH$_2$, $^2J_{PC}$ = 5.5 Hz) and a triplet at δ 29.3 (POCH$_2$CH$_2$CH$_2$OP, $^3J_{PC}$ = 6.7 Hz).

2 was reacted with Cl_2 in CH_2Cl_2 solution, giving the corresponding poly(2-chloro-2,2-dihydro-2-oxo-1,3,2-dioxaphosphorinane) (**4**)

$$-(CH_2CH_2CH_2OP(H)(O)O)_n- \xrightarrow[CH_2Cl_2]{Cl_2}$$
$$-(CH_2CH_2CH_2OP(Cl)(O)O)_n- \quad (3)$$
$$\textbf{4}$$
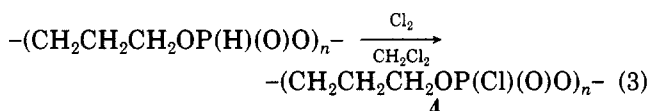
In the ^{31}P{^{1}H} NMR spectrum a gradual disappearance of a signal at δ 8.8 (OP(O)(H)O unit) is followed by the appearance of a new signal at δ 3.54 (OP(O)(Cl)O unit). Eventually, this signal became the only one in the product, indicating complete transformation of **2** into **4**.

Vogt[6] attempted to prepare poly(2-chloro-2,2-dihydro-2-oxo-1,3,2-dioxaphospholane) but obtained, according to his analysis, exclusively its isomeric polyphosphate: poly(2-chloroethyl phosphate), due to the fast internal chain transfer. A polymer similar to **2** (from hexamethylenediol) was obtained earlier by Petrov[4] by polycondensation with dialkyl phosphites.

4 was further used for the preparation of various derivatives, taking advantage of its high reactivity. In this paper synthesis of polymers bearing imidazole (Im) in the side groups is described, namely the N- and C-substituted imidazoles. Since the P–N bond resulting from a direct coupling of imidazole to phosphorus is not stable enough for further applications of the poly(ester amide) in the water solutions, we linked imidazole to **4** by using the hydroxyethyl spacer. Thus, the starting compounds were N-(hydroxyethyl)imidazole (**5**) and C^4-(hydroxyethyl)-imidazole (**6**).

4 was either used as such or first converted into the corresponding poly(ester amide) (**7**) in reaction with an excess of imidazole, and only the resulting **7** was reacted with the (hydroxyethyl)imidazoles. This latter path is preferred, because the imidazole hydrochloride could easily

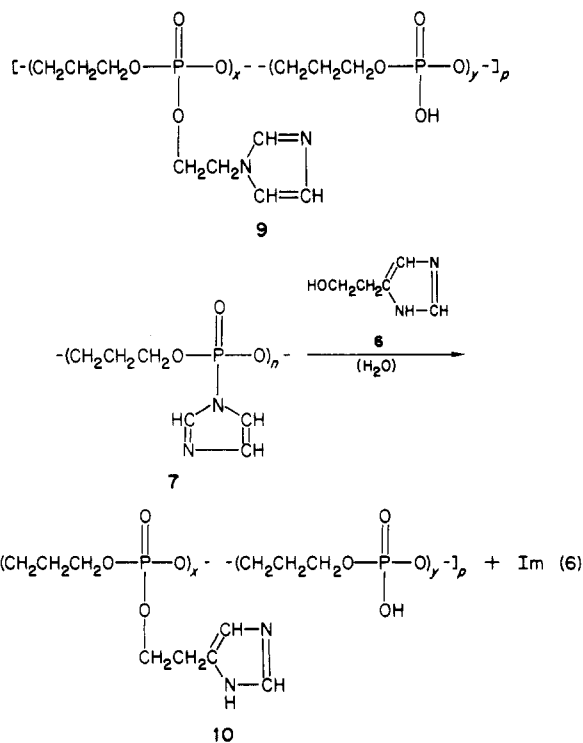be removed and in the second step product of higher purity was obtained.

First Step
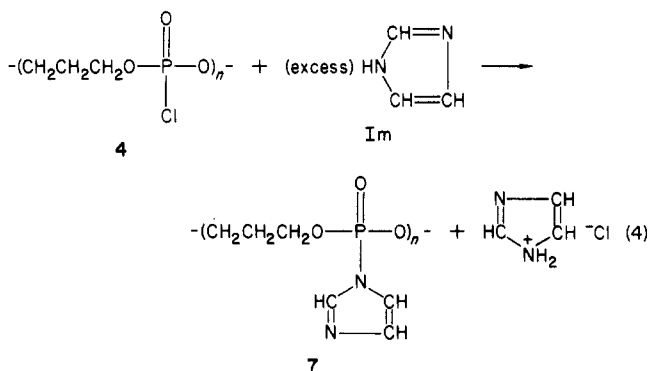
Second Step
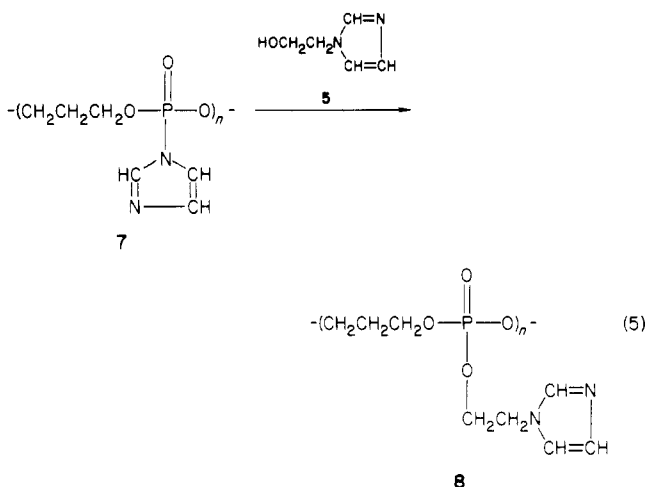
8 with various degrees of substitution was obtained; the unsubstituted units were converted, after the polymer workup, into the acidic units

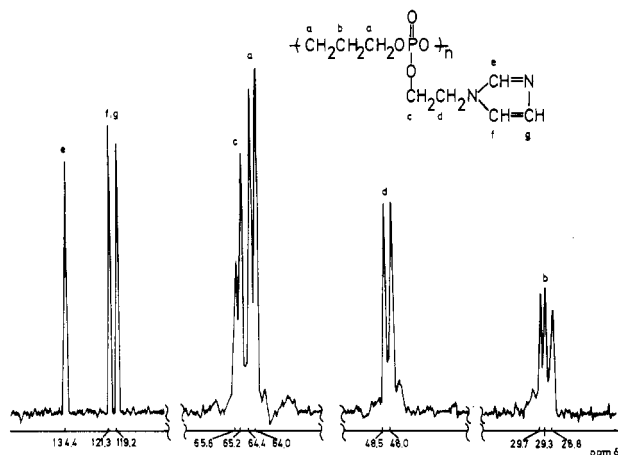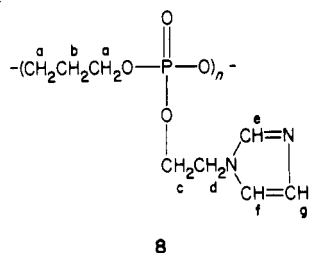Polymer **10** with 85% substitution by C^4-(hydroxyethyl)-imidazole was obtained with 5–50% excess of **6**. In the

Figure 1. $^{13}C\{^1H\}$ NMR spectrum of **8** in D_2O solution.

NMR spectra of **8** ($\bar{M}_n = 12\,400$) the following signals were observed (chemical shifts, multiplicity and assignments given in this order):
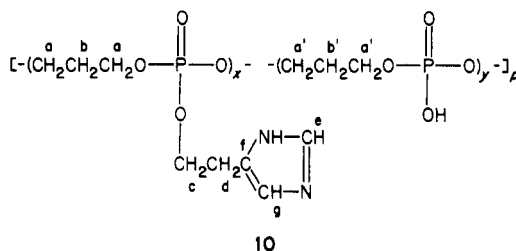

8

^1H NMR δ 9.45 (s, H_e), 8.15 (two superimposed signals H_f, H_g), 5.3–4.9 (m, H_c, H_d), 4.9–4.4 (m, H_a), 2.8–2.2 (m, H_b).

$^{13}C\{^1H\}$ NMR spectrum is shown in Figure 1, where the assignments are given directly.

$^{31}P\{^1H\}$ NMR gives one sharp line at δ –1.37 (s).

The NMR spectra of **10** ($M_n = 9500$, 85% substitution) were recorded in D_2O solution.

10

The following chemical shifts and multiplicities were observed: ^1H NMR δ 9.1 (s, H_e), 7.8 (s, H_g), 4.6 (m, H_a, $H_{a'}$, H_c), δ 3.6 (m, H_d), δ 2.37 (m, H_b, $H_{b'}$); $^{31}P\{^1H\}$ NMR δ 0.42 (s, OP(O)(OH)O), –1.21 (s, OP(O)(OCH$_2$CH$_2$Im)O), $^{13}C\{^1H\}$ NMR 132.4 (s, C_e), 128.8 (s, C_f), 115.9 (s, C_g), 65.4 (d, J_{PC} = 5.8 Hz, C_c), 64.5 (d, J_{PC} = 5.9 Hz, C_a), 29.6 (t, J_{PC} = 6.8 Hz, C_b), 24.3 (d, J_{PC} = 7.8 Hz, C_d). Signals due to $C_{a'}$ and $C_{b'}$ have also been observed.

The composition of the mixed products like **9** was judged on the basis of proportion of the acidic (–OP(O)(OH)O–) units (δ 0.42 in ^{31}P NMR) and the substituted units, measured in ^{31}P NMR. Products with 50% and 75% of the substituted units were prepared. Their ^1H and ^{13}C NMR spectra were mostly the superposition of the spectra of the corresponding homopolymers; no other P atoms were observed than these at δ 0.42 and –1.37 Apparently, the distance of eight bonds is too large for our instrument to distinguish between the hetero- and homodiads.

The elaborated method opened a way of preparing a new family of hydrophilic polymers with bases in the side chains, spaced similarly to their natural counterparts, and complement in this way synthetic polymers containing nucleic and related bases[11] and used also to mimic the functions of enzymes.

Solutions of **8** and **10** in water (1% solution) showed a relative viscosity within a range from 1.1 to 1.2. Viscosities of these solutions did not change for several months at room temperature. The ^{31}P NMR spectra did not reveal either any hydrolysis in solutions of **8** in water (15%) for at least 30 days.

References and Notes

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