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Poly(dialkyl phosphates) Based on Deoxyribose[1]

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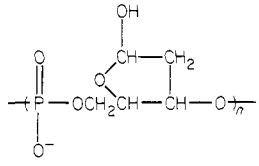
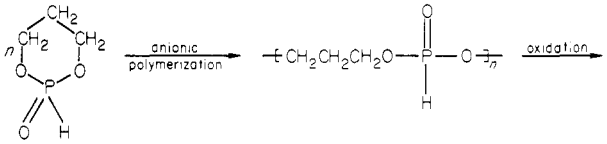
ABSTRACT: Anionic polymerization of α(and β)-methyl-2-deoxy-D-ribofuranoside cyclic diethylphosphoramidite initiated by *t*-BuOK gives polymers with molecular weights up to 9×10^3 ($n = 46$). The subsequent rearrangement of the resulting polyamide leads to the poly(dialkylphosphoric acid) containing α(and β)-methyl-2-deoxy-D-ribofuranoside (I) in the main chain. The structure of the resulting polyacid and of the intermediate products was established on the basis of the analysis of their ^1H, ^{31}P, and ^{13}C NMR spectra. Thus the obtained polymer has a structure similar to deoxyribonucleic acid devoid of base.

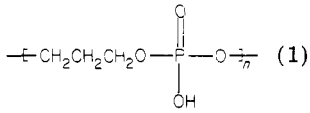


I

Introduction

Previously, we described the polymerization of five- and six-membered cyclic phosphorus-containing monomers, leading to the high molecular weight polyphosphates or polyphosphites.[2-5] Further reactions of these polymers allowed the preparation of macromolecules with backbones similar to those of nucleic acids and with molecular weights exceeding 10^5; e.g.[3]

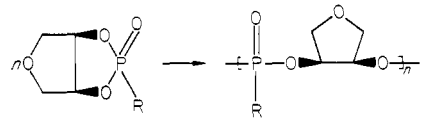




(1)

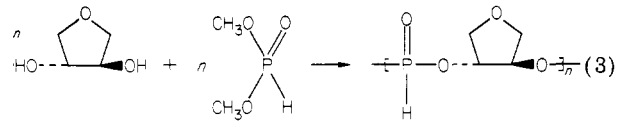
In order to come closer to the structures of natural polymers, we prepared polymers containing tetrahydrofuran rings (analogues of furanoside rings) in the backbone. These polymers were obtained by anionic polymerization of bicyclic phosphorus compounds (eq 2) and/or by polycondensation of the corresponding diol with dialkyl phosphite, as shown in eq 3.[6]

Following this approach, we have undertaken an attempt to polymerize bicyclic monomers bearing deoxyribose units in order to prepare the corresponding model of the nucleic acid, namely, the deoxyribonucleic acid devoid of base:



(2)

R = H, OCH_3



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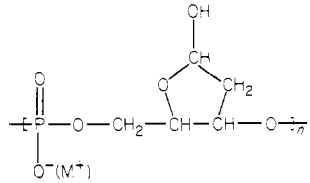

The present paper describes the synthesis of this polymer.

Results and Discussion

Synthesis of Monomer 3. Condensation of α(and β)-methyl-2-deoxy-D-ribofuranose (1) and phosphorous hexaethyltriamide (2) leads to a mixture containing among other products described below *trans*-3-(diethylamino)-8-methoxy-2,4,7-trioxa-3-phosphabicyclo[4.3.0]nonane (α-(and β)-methyl-2-deoxy-D-ribofuranoside cyclic diethyl-

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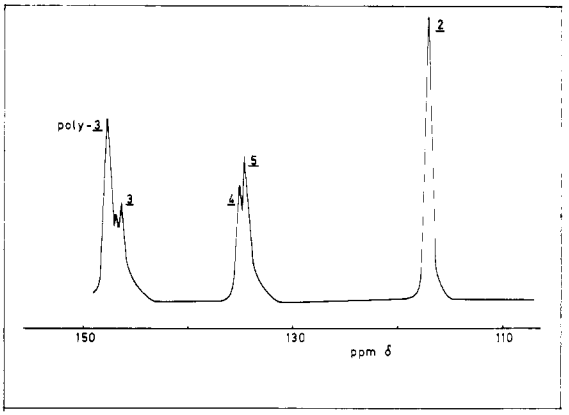
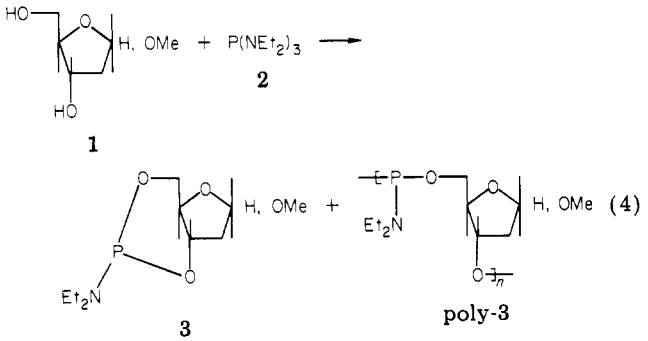
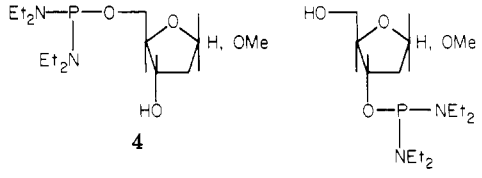


Figure 1. $^{31}P\{^1H\}$ NMR spectrum of the reaction mixture (eq 4) in dioxane.

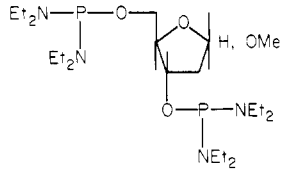
phosphoramidite) (**3**) and its polymer, poly-**3**. The conditions of reaction 4 are given in the Experimental Part.



In the $^{31}P\{^1H\}$ NMR spectrum of the reaction mixture at the early stage of the condensation (eq 4), three signals were observed: at 117.4 ppm for **2** and at 134.2 and 135.1 ppm for monosubstituted amides **4** and **5**. It is difficult



to assign specifically the 134.2- and 135.1-ppm signals to the monosubstituted compounds **4** or **5**. Moreover, compound **6** should have the same chemical shifts as both **4**



6

and **5**. A typical $^{31}P\{^1H\}$ NMR spectrum of the reaction mixture at the early stage of reaction is shown in Figure 1. During further heating at ~100 °C of this mixture, signals belonging to **2**, **4**, and **5** slowly disappeared, with the simultaneous appearance of those from **3** and poly-**3**. Both **3** and poly-**3** are very sensitive to moisture (hydrolysis) and oxygen and even a very short contact with air causes oxidation to the appropriate phosphoramidates ($\delta_{^{31}P}$ = 22.1). **3** was isolated from the reaction mixture by distillation [120 °C (10^{-2} mm)].

3, which has not previously been known, gives two pairs of signals in the $^{31}P\{^1H\}$ NMR spectrum (Figure 2a), namely, at 146.6 and 146.1 ppm and at 137.8 and 137.3

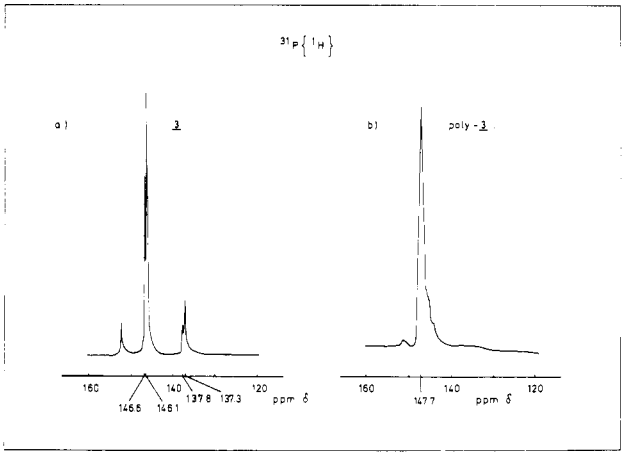
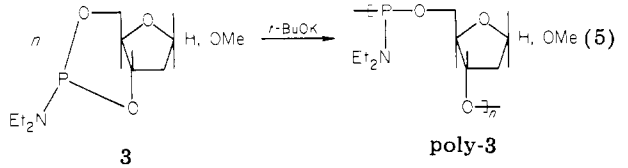


Figure 2. $^{31}P\{^1H\}$ NMR spectra of **3** (a) and poly-**3** (b), ~50%, in C_6H_6; 25 °C.

ppm, with the ratio of intensities (4.4–6.6):1 and with equal intensities of signals within the pairs. It is known that the dialkylamino group in the dioxaphosphorinane ring can be placed in the axial or equatorial position.[7,8] ^{31}P NMR chemical shifts for isomers with the NMe_2 group in the equatorial and axial position are in 2-(dimethylamino)-5-*tert*-butyl-1,3,2-dioxaphosphorinane: 142.4 and 135.4 ppm, respectively,[7] with the ratio of intensities of signals 4.88:1. In 2-(dimethylamino)-4-methyl-1,3,2-dioxaphosphorinane the same absorptions are at 142.6 and 138.2 ppm, with the intensity ratio 5.66:1 at the conditions of the thermodynamic equilibrium.[8] Similar values of 144.9 and 139.6 ppm were reported by Bajwa and Bentrude[9] for 3′,5′-thymidine cyclic phosphodimethylamidite.

In all the works mentioned above, the configuration at the carbon atoms of the dioxaphosphorinane ring was identical for both isomers and the only difference was in the configuration at the phosphorus atom. However, since **1** exists in α and β anomeric forms with different positions of the methoxy group at C-1, the monomer molecule **3** can exist in four diastereoisomeric forms (taking into account the relative positions of the methoxy and diethylamino groups). Thus we suppose that the signals at 146.6 and 146.1 ppm belong to the more stable isomers with the NEt_2 groups in the equatorial positions (known to be more stable thermodynamically[8]) and the signals at 137.8 and 137.3 ppm to the less stable monomer isomers with the NEt_2 groups in the axial positions. The observed pairs of signals are due to the presence of α and β anomers within the above-described isomers. The chemical shifts of the C-3 and C-5 atoms in the $^{13}C\{^1H\}$ NMR spectrum of **3** depend also on the equatorial or axial position of the NEt_2 group (Figure 3). In Table I, ^1H and ^{13}C chemical shifts and ^1H–^1H, ^1H–^{31}P, and ^{13}C–^{31}P coupling constants of **1**, **2**, and **3** are given with the tentative assignment of the signals to isomers with the equatorial and axial diethylamino group.

Polymerization of 3. Polymerization of **3** was carried out at room temperature in bulk in NMR tubes.



The conversion of monomer was monitored by ^{31}P NMR. The corresponding absorptions can be used to determine the proportions of both **3** and poly-**3** in the mixture.

On the basis of the observed changes of the relative absorptions, we roughly estimated the rate coefficients of

Table I
^1H and ^{13}C NMR Data of 1, 2, and 3[a]

group[b]	1 ($CDCl_3$) ^1H[c,d]	1 ($CDCl_3$) ^{13}C[c,d]	2 (neat) ^1H[c]	3 (C_6D_6) ^1H[c]	3 (C_6D_6) ^{13}C[c,d]
CH(1)	5.04-5.15	103.6		4.59-4.89	104.1 104.4
CH_2(2)	1.95-2.25	39.4 40.0		1.76-2.36	~38[e]
CH(3)	4.31-4.57	69.9 70.3		3.93-4.42	72.6 (11.7)
CH(4)	3.90-4.20	84.7 85.2		3.93-4.42	75.3 (9.8) (eq) 76.5 (9.8) (ax)
CH_2(5)	3.64 (d, 4.0)	60.8 61.7		3.51-3.90	67.6 (6.0) (ax) 68.6 (7.8) (eq)
OCH_3	3.52 3.35	53.0 53.4		3.16 3.21	54.7 55.4
NCH_2			4.15 (8.0)	2.99 (~7.0)	38.8 (21.5)
NCH_2CH_3			1.25 (6.8)	0.99 (7.1)	15.3 (3.9)

[a] Different chemical shifts observed for the same carbons can be ascribed to α- and β-anomeric forms and two isomers of 3 with the NEt_2 group in the axial (ax) or equatorial (eq) position. [b] The number related to the carbon atom in the ring is given in parentheses. [c] Chemical shifts in ppm; coupling constants in hertz (in parentheses). [d] Analysis was made by comparing the data published for 1 (^1H NMR[10,11] and ^{13}C NMR[12]) and for the similar cyclic phosphoramidites.[9,13] [e] Partly covered by NCH_2 signals.

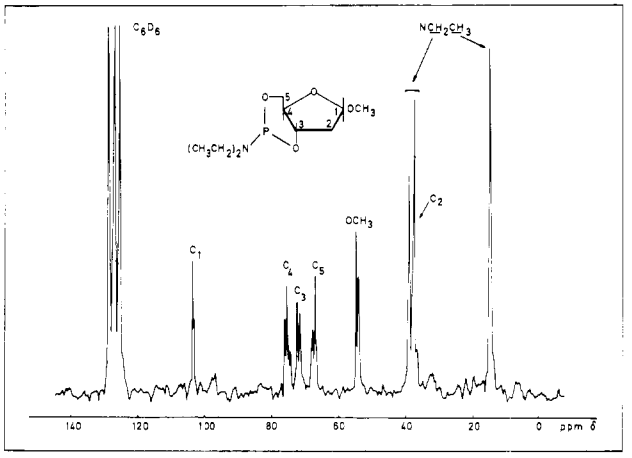


Figure 3. $^{13}C\{^1H\}$ NMR spectrum of 3, 50%, in C_6D_6; 25 °C.

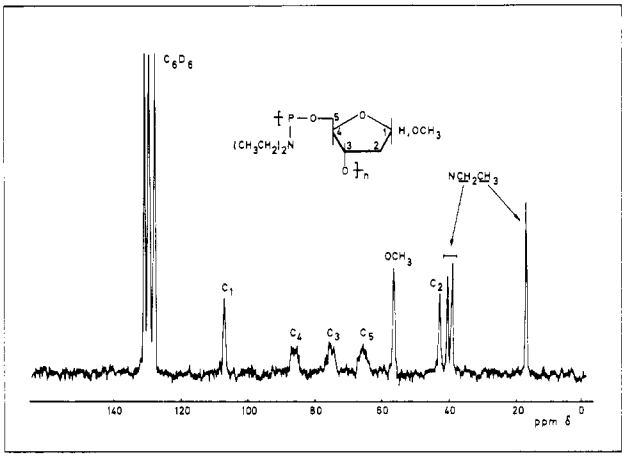
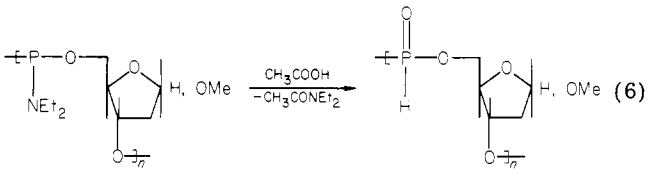


Figure 4. $^{13}C\{^1H\}$ NMR spectrum of poly-3, 50%, in C_6D_6; 25 °C.

propagation and termination, assuming that polymerization consists of fast initiation, propagation, and irreversible unimolecular termination. This scheme fits best the kinetic data. Other schemes, including various bimolecular terminations, gave larger deviations.

Thus the rate coefficient for propagation is in the range 10^{-3}–10^{-4} L·mol^{-1}·s^{-1} and that of termination close to 10^{-5} s^{-1} (both at 25 °C).

Synthesis of Poly(phosphite diester) Poly-7. The polyamide poly-3 was converted into poly(phosphite diester) with dry acetic acid (eq 6). The progress of ace-



poly-3 poly-7

tolysis was recorded by ^{31}P NMR. $^{13}C\{^1H\}$ NMR spectra of poly-3 and poly-7 are given in Figures 4 and 5. The ^{31}P NMR spectrum of pure poly-7 shows one broad signal at 6.75 ppm split with $^1J_{PH}$ = 717.8 Hz (in the ^1H NMR spectrum, $^1J_{PH}$ = 718.8 Hz; cf. Table II).

As we have shown previously, high molecular weight poly(trimethylene phosphite) gives also in the $^{31}P\{^1H\}$ NMR spectrum only one singlet at 5.3 ppm split into a

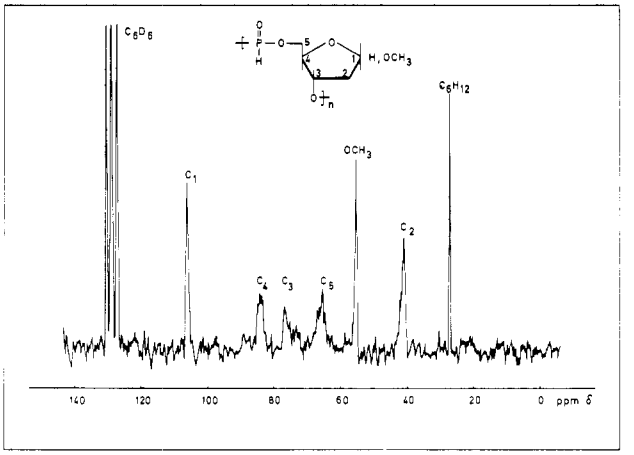


Figure 5. $^{13}C\{^1H\}$ NMR spectrum of poly-7, ~50%, in $CDCl_3$; 25 °C.

doublet with $^1J_{PH}$ = 675.8 Hz.[3]

Molecular weight of the resulting polymers was measured only for poly-7 because poly-3, as we have mentioned already, was too sensitive to water and oxygen to be measured at the available conditions by vapor pressure osmometry.

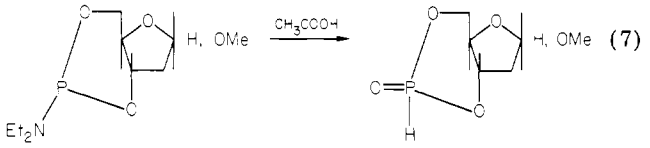
After acetolysis of poly-3, apart from signals of poly-7, two peaks were observed, representing approximately 25%

Table II
^1H and ^{13}C NMR Data for Polymers Bearing Deoxyribose Units[a]

	poly-3 (C_6D_6)		poly-7 ($CDCl_3$)		poly-8		poly-9	
group	^1H	^{13}C	^1H[c]	^{13}C	^1H (Me_2SO-d_6)	^{13}C (CD_3OD)	^1H (Me_2SO-d_6)	^{13}C (D_2O)
CH(1)	4.77-5.09	106.0 106.2	4.75-5.45	105.0 105.3	5.16-5.60	106.7	4.70-5.19	97.7
CH_2(2)	1.93-2.40	41.8	2.09-2.60	40.2	1.52 (t, 6.6)	41.2	1.36 (t, 6.6)	39.4
CH(3)	4.09-4.70	73.4[b] 74.7	4.75-5.45	75.4 76.1	4.09-4.79	78.1 79.5	4.35-4.70	75.5
CH(4)		84.4[b] 86.0	3.74-4.75	82.2 82.8		83.9	4.00-4.35	82.4
CH_2(5)	3.55-4.09	63.7 64.5		64.0 64.7	3.45-4.00	68.4	3.58-4.00	65.6
OCH_3	3.15	55.4	3.30	55.1	3.60	55.6		
NCH_2	2.65-3.20	38.7 (19.5)						
NCH_2CH_3	0.9 (7.0)	15.9						
PH			6.96 (718.8)					

[a] Chemical shifts in ppm; coupling constants in hertz (in parentheses). [b] Positions of C-3 and C-4 were assigned on the basis of the analysis of the ^{13}C NMR spectrum of the ribitol teichoic acid[16] and salmon sperm DNA.[17] [c] Chemical shifts of protons at C-3 and C-4 are uncertain.

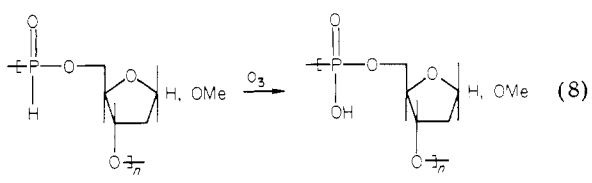
of the total, at $\delta_{^{31}P}$ = 1.61 and 0.40, with $^1J_{PH}$ = 620.1 and 620.2 Hz, respectively. These signals belong to two isomers of the cyclic product **7**, with the phosphoryl oxygen atom placed in the equatorial and axial positions. This was confirmed by the acetolysis of **3** alone in a separate experiment.



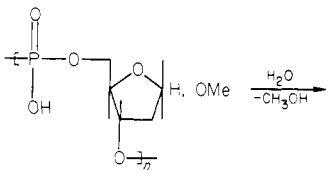
In the ^{31}P NMR spectrum of λ^5-2-oxo-4,6-dimethyl-1,3,2-dioxaphosphorinane, signals were observed at +3.1 ppm, with $^1J_{PH}$ = 664 Hz for the isomer with the equatorial phosphoryl group, and at 1.2 ppm, with $^1J_{PH}$ = 719 Hz for the isomer with the axial phosphoryl group.[14]

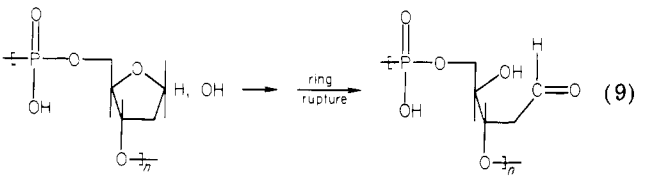
Apparently, during reaction 6 depolymerization of poly-**3** occurred followed by acetolysis of **3** into **7**. **7** may also arise by depropagation of the already formed poly-**7**. This alternative has not yet been resolved. A similar behavior (appearance of monomeric phosphite in the mixture during the acetolysis of polyamide freed from its monomer) was also observed in our laboratory in the acetolysis of poly(trimethylene diethylphosphoramidite).[15] It is possible, in principle, to obtain **7** by direct condensation of **1** with dimethyl phosphite, but we failed in a few attempts because such condensation was always accompanied by decomposition of **1**.

Synthesis of Poly(dialkyl phosphate) Bearing Deoxyribose Units. Oxidation of poly-**7** was carried out with different oxidizing agents, namely, peracetic acid, nitrogen tetraoxide, or ozone in CH_2Cl_2 solution. The best results were obtained with ozone:



Poly-**8** is a white powder stable at room temperature in dry methanolic solution ($\delta_{^{31}P}$ = 2.9). Dry poly-**8** was stable in the refrigerator but darkened after a few days when it was kept at room temperature. This change of color may be due to losing the blocking methoxy group in aqueous solutions (the presence of methanol was detected in the reaction mixture by GLC) and further opening of the deoxyribose ring, eventually followed by formation of the carbonyl group (the presence of a C=O band at 1700 cm^{-1} in the IR spectrum was detected):

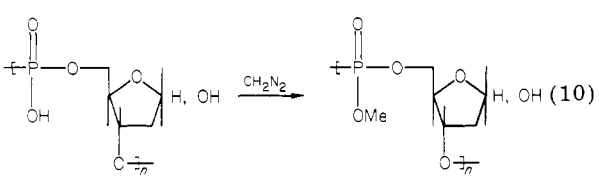




The structure of poly-**8** and poly-**9** ($\delta_{^{31}P}$ = −1.2 in H_2O) was confirmed by the analysis of ^1H and ^{13}C NMR spectra (shown in Figures 6 and 7). The ^1H and ^{13}C NMR data of poly-**9** together with those for poly-**3**, poly-**7**, and poly-**8** are collected in Table II.

Poly-**9** is an oily or semisolid substance. Vapor pressure osmometry could not be used to measure $\bar{M}_n$ of either poly-**8** or poly-**9** because these polymers are only soluble in ionizing solvents. The light scattering method was useless because the $\bar{M}_n$ of these polyacids was too low.

Thus we converted the final polyacid into a polyester and measured its molecular weight. Poly-**9** ($\bar{M}_n$ = 6100, n = 31.5 measured for poly-**7**) was converted into its methyl polyester (poly-**11**) by diazomethane and the final molecular weight was found to be $\bar{M}_n$ = 4300 (n = 19). In



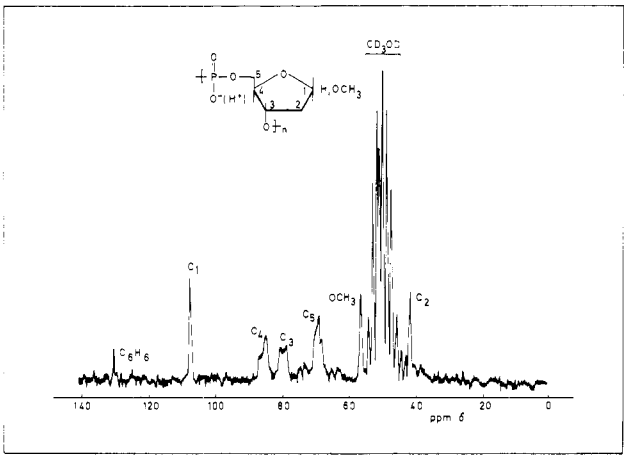


Figure 6. $^{13}C\{^1H\}$ NMR spectrum of poly-**8**, ~30%, in CD_3OD; 25 °C.

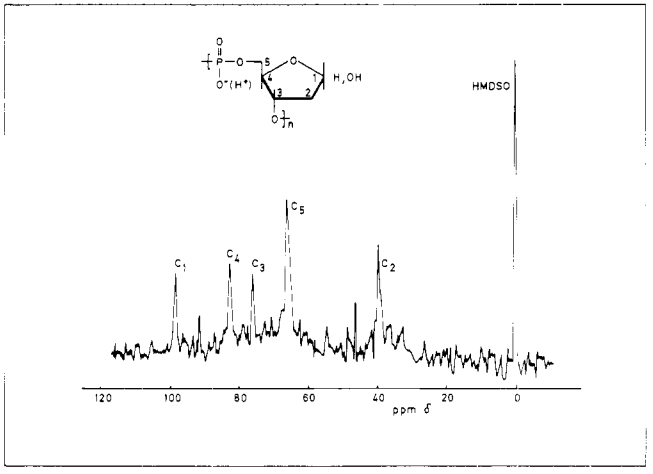


Figure 7. $^{13}C\{^1H\}$ NMR spectrum of poly-**9**, ~30%, in D_2O; 25 °C.

thus-obtained poly-**11** we observed in the ^1H NMR spectrum a doublet at 3.93 ppm and $^3J_{PH}$ = 11.2 Hz arising from the $POCH_3$ group. This is in good agreement with the chemical shift of $POCH_3$ in poly(λ^5-2-methoxy-2-oxo-1,3,2-dioxaphosphorinane) (3.8 ppm and $^3J_{PH}$ = 11.0 Hz) we described previously.[18] Comparison of the integration of $POCH_3$ and CH_2 (2) groups in the ^1H NMR spectrum of poly-**11** indicates that the methylation has been virtually quantitative. Comparison of the polymerization degrees of poly-**7** and poly-**11**, $n \approx 30$ and ~20, respectively, indicates that there is some, but not very extensive, chain scission. It is not clear, however, whether it takes place at the stage of oxidation or during further reactions.

Experimental Part

Solvents. All solvents were purified by common methods.[19] THF and benzene were purified as described[19] and finally stored on a high-vacuum line over Na–K alloy.

Reagents. $\alpha(\beta)$-Methyl-2-deoxy-D-ribofuranoside (**1**) was obtained in the reaction of 2-deoxy-D-ribose with CH_3OH containing 0.1% hydrogen chloride as described:[20] yield 87%; bp 80 °C (6 × 10^{-2} mm) (lit.[20] yield 63%; bp 115–125 °C (bath temperature) (4.5 × 10^{-1} mm)); $[\alpha]^{25}_D$ +62.83° in CH_2Cl_2. Anal. Calcd: C, 48.65; H, 8.11. Found: C, 48.56; H, 8.11.

Phosphorous hexaethyltriamide (**2**) was prepared as described for phosphorous hexamethyltriamide[21] (bp 57 °C (9 × 10^{-2} mm); lit.[21] bp 120–122 °C (10 mm)); ^1H NMR 4.15 (J = 8.0 Hz, CH_2), 1.25 (J = 6.8 Hz, CH_3) ppm; ^{31}P NMR 117 (lit.[22] 117.5 ppm).

Peracetic acid solution in acetic acid (about 1 M solution) was prepared as described[23] and used without further purification. N_2O_4 was used in CH_2Cl_2 solution. CH_3COOH after preliminary purification was distilled off from phosphorus pentoxide before use. t-BuOK was prepared as described previously.[24] CH_2N_2 was used in Et_2O solution.

Condensation of 1 with 2. Equimolar amounts of **1** and **2** (e.g., 1.74 and 2.90 g, i.e., about 10^{-2} mol) were mixed with 80 mL of dioxane under an Ar atmosphere. Then the mixture was stirred and refluxed at about 600 mm of pressure, with simultaneous cooling of the receiver flask in a CO_2/acetone mixture. The bath temperature was kept sufficiently high to maintain reflux but below 120 °C to avoid distillation of dioxane. After 5 h the pressure was lowered and dioxane was distilled off at a bath temperature of about 80 °C. Then the mixture was placed in an NMR tube and further heated to ≤102 °C. During heating, the ^{31}P NMR spectra of the reaction mixture were measured. After several hours the reaction was completed (according to the ^{31}P NMR spectra) and the resulting monomer **3** (colorless oil, yield ≤20%) was distilled from the mixture (bath temperature 120 °C (10^{-2} mm)). The remaining polyamide poly-**3** was a slightly yellow semisolid product. In the $^{31}P\{^1H\}$ NMR spectrum of the resulting **3** there were observed besides the major peaks at 146.6, 146.1, 137.8, and 137.3 ppm two other peaks at 154.3 and 152.3 ppm; the peak area of these impurities was 8% of the major peaks of **3**.

Polymerization of 3. Polymerization of **3** was carried out at room temperature in C_6D_6 solution in tubes closed with a Teflon stopcock; t-BuOK was used as initiator (≤8 mol %). Usually after several days polymerization was complete (100% conversion, followed by ^{31}P NMR method) (cf. Figure 2b).

Acetolysis. To poly-**3**, obtained by polycondensation or polymerization methods in benzene or THF solution, was added dry acetic acid (equimolar amount or 10% excess) at room temperature and the mixture was left for 24 h. Then all volatile products were evaporated under vacuum and the resulting poly-**7** was dissolved in benzene and evaporated on a vacuum line. This procedure was repeated several times in order to remove the remaining acetic acid and diethylacetamide. Poly-**7** was purified by precipitation into cyclohexane from benzene or dioxane solution, giving yellow or slightly yellow semisolid product; $[\alpha]^{25}_D$ + 2.94° in DMF. It was difficult to remove completely the diethylacetamide from poly-**7**. Thus after subtraction of the known amount of diethylacetamide in the polymer (calculations were based on the nitrogen content) we obtained the following elemental analysis results: Anal. Calcd: C, 37.11; H, 5.67; P, 15.97. Found: C, 36.93; H, 5.87; P, 15.21.

Oxidation. Poly-**7** was oxidized by using different oxidizing agents, i.e., peracetic acid, nitrogen tetraoxide, or ozone. The best results were obtained by passing ozone (~0.75 g/h for 2.5 g of poly-**7** in 40 mL of CH_2Cl_2 at −15 °C) through a solution of polymer. The oxidation was complete within a few hours. The progress of the reaction was followed by ^{31}P NMR analysis of the reaction mixture. The resulting polyacid poly-**8** was further purified by precipitation into dioxane from a CH_2Cl_2 solution. We avoided using water and alcohols in further workup of the polymer in order to avoid losing the acetal methoxy group from poly-**8**. Indeed, after dissolving poly-**8** in water, we found that only a few hours was needed to completely remove the blocking methoxy groups, yielding poly-**9**.

Esterification. To the aqueous ethanol solution of polyacid poly-**9** was added CH_2N_2 in ether solution at 0 °C until the yellow color of the mixture did not disappear. After partial evaporation of solvent, the polyester poly-**11** was purified by precipitation to dioxane from aqueous solution ($\bar{M}_n$ = 4300).

Spectra and Molecular Weight Determination. ^1H NMR spectra were determined with a 60-MHz Perkin-Elmer Model R12B.

$^{13}C\{^1H\}$ and ^{31}P NMR spectra were measured with a 60-MHz JEOL JNM-FX-60 with Fourier transformation and with a 90-MHz Bruker HX-72 apparatus. ^{31}P chemical shifts are positive downfield from the standard (85% H_3PO_4).

Polymerization degrees were determined with a Hewlett-Packard vapor pressure osmometer Model 302B in benzene, CH_2Cl_2, or DMF solutions.

Registry No. α-**1**, 51255-17-5; β-**1**, 51255-18-6; **2**, 2283-11-6; α-**3**, 83831-44-1; β-**3**, 83831-45-2; α-poly-**3**, 83831-46-3; β-poly-**3**, 83831-47-4; α-poly-**7**, 83831-49-6; β-poly-**7**, 83831-51-0; α-poly-**8**,

83831-53-2; β-poly-8, 83831-55-4; α-poly-9, 83831-57-6; β-poly-9, 83831-59-8; α-poly-11, 83831-61-2; β-poly-11, 83831-63-4.

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Helix Initiation and Propagation by (Hydroxyethyl)-L-glutaminyl Residues in Water

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ABSTRACT: Random copolypeptides composed of (hydroxyethyl)-L-glutaminyl and (hydroxybutyl)-L-glutaminyl residues have been synthesized by aminolysis of high molecular weight poly(γ-benzyl L-glutamate). The mole fraction of (hydroxyethyl)-L-glutaminyl residues in the copolypeptides ranged from 0.37 to 0.81. Circular dichroism spectra measured in water from 4 to 64 °C had the shapes and intensities expected for partially helical polypeptides. Zimm–Bragg statistical weights for the (hydroxyethyl)-L-glutaminyl residue in water were deduced by matrix methods and the σ,s reported by von Dreele et al. (*Macromolecules* **1971**, *4*, 408–417) for the (hydroxybutyl)-L-glutaminyl residue. Ability of theory to reproduce experimental helicities is not sensitive to the value assigned to σ for the (hydroxyethyl)-L-glutaminyl residue so long as that value is small. With $\sigma = 1 \times 10^{-5}$, s for the (hydroxyethyl)-L-glutaminyl residue is found to decrease from 0.945 to 0.928 as the temperature rises from 4 to 64 °C. The observed behavior of the (hydroxyethyl)-L-glutaminyl residue in water is in harmony with the trend established by (hydroxypropyl)-L-glutaminyl and (hydroxybutyl)-L-glutaminyl residues.

The series of homopolypeptides based on (hydroxyalkyl)-L-glutamine has been studied extensively. The three most prominent members of this series are the poly[(hydroxyalkyl)-L-glutamines] with alkyl = ethyl, propyl, and butyl. These three nonionic homopolypeptides exhibit a wide range of conformational properties in aqueous solution. Hydrodynamic[1] and optical[1-3] properties of poly[(hydroxyethyl)-L-glutamine] in water are those expected for a disordered homopolypeptide bearing a CH_2R side chain. In contrast, at low temperatures in water, poly[(hydroxypropyl)-L-glutamine] is partially helical and poly[(hydroxybutyl)-L-glutamine] is predominantly helical.[2,4-8] Poly[bis(hydroxyethyl)-L-glutamine] shows behavior similar to that exhibited by poly[(hydroxypropyl)-L-glutamine].[9] Helical content of these three polypeptides is reduced by an elevation in temperature. Helicity of poly[(hydroxyalkyl)-L-glutamines] can also be modified by changes in solvent composition. Inorganic salts[4,8,10] and organic cosolvents[2,4,5,7,11-16] are effective in this regard.

Zimm–Bragg[17] statistical weights, σ and s, have been determined for (hydroxypropyl)-L-glutaminyl[5-7] and (hydroxybutyl)-L-glutaminyl[6] residues in water by study of the homopolypeptides and also via the "host–guest" technique. While poly[(hydroxyethyl)-L-glutamine] does not present solubility problems in water, its values for σ and s still cannot be determined by study of the homopolypeptide because the observed helicity is vanishingly small. We report here σ and s for the (hydroxyethyl)-L-glutaminyl residue which were determined by the "host–guest" technique, with (hydroxybutyl)-L-glutaminyl residues playing the role of host. These statistical weights are obtained by examining the manner in which helicity declines when (hydroxyethyl)-L-glutaminyl residues are randomly incorporated into poly[(hydroxybutyl)-L-glutamine]. The results provide insight into the conformational consequences of addition of methylene groups to the periphery of an amino acid residue bearing a long nonionic side chain.

Experimental Section

Copolypeptides were prepared in dioxane by aminolysis of poly(γ-benzyl L-glutamate) using a mixture of hydroxyethanolamine and hydroxybutanolamine. Reaction conditions were a slight modification of the procedure by which poly[(hydroxybutyl)-L-glutamine] was prepared from poly(γ-benzyl L-glutamate).[18] Copolypeptide compositions were determined from a quantitative ninhydrin analysis of the hydroxyethanolamine and hydroxybutanolamine in the acid hydrolysate, using a Beckman 119 amino acid analyzer, and also from proton magnetic resonance spectra.[6] Similar results were obtained by both

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