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Aminolysis and Ammonolysis Polymerizations of Spiro(acylpentaoxy)phosphoranes to Polyphosphate Derivatives

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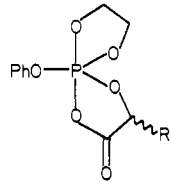
ABSTRACT: Polymerization of spiro(acylpentaoxy)phosphoranes (**1**) has been induced at room temperature by reaction of **1** with *N*-nucleophiles of amines and ammonia to give polyphosphate derivatives (**4** and **9**) having amine and ammonia components, respectively ("aminolysis and ammonolysis polymerizations"). Amines employed were primary and secondary ones. Product polymers contained an amide–phosphate type unit (**4a** or **9a**) as the major component. A possible mechanism is proposed in which amine attacks the phosphorus atom of **1** to produce a spiro(acyloxyamino)phosphorane (**12**) as a predominant intermediate. Phenol is eliminated during the reaction. Then **12** rearranges to a cyclic phosphate (**11**), leading to unit **4a**. Acute toxicities of the product phosphate derivatives were examined to investigate the derivatives' suitability as carrier polymers of drug amine components.

Spiro(acyloxy)phosphoranes are a new group of pentacovalent phosphorus species originally prepared and isolated by us via the reactions of cyclic phosphorus(III) compounds with α-keto acids[1,2] or glyoxylic acid[3] and with acrylic acid or β-propiolactone.[2,4] These phosphoranes are quite reactive monomers and produce various types of phosphorus-containing polymers.[5] Among them, spiro(acylpentaoxy)phosphoranes (**1**) have been studied most



1a, R = Me
b, R = Ph

extensively.[5-7] Hitherto, we have found that **1** is a reactive amphiphile; i.e., **1** reacts with various nucleophiles and electrophiles.[8] **1** has been reacted with *O*-nucleophiles of primary and secondary alcohols to give poly(phosphoric acid triesters) **2** ("alcoholysis polymerization")[7] and also with *O*-nucleophiles of water ("hydrolysis polymerization")[8] and tertiary alcohols[7] to produce poly(phosphoric acids) consisting of diester (**3a**) and triester (**3b**) units. The

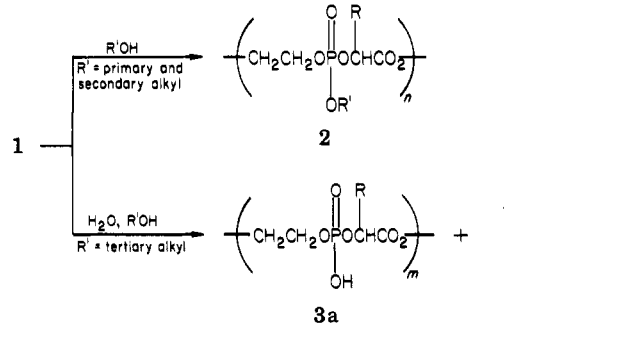


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Table I
Aminolysis Polymerization of 1 under Various Reaction Conditions[a]

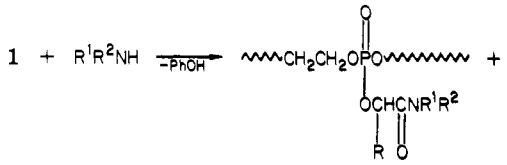
no.	phosphorane	amine	reaction		polymer		
			solvent	time, h	yield, %	mol wt	appearance
1	1a	n-$BuNH_2$	MeCN	384	50	1800	pale brown paste
2	1a	sec-$BuNH_2$	MeCN	384	53	800	pale yellow paste
3	1a	t-$BuNH_2$	MeCN	336	44	6500	white powder
4	1a	$PhNH_2$	MeCN	63[b]	50	4000	orange powder
5	1a		MeCN	168	49	1200	reddish paste
6	1a		MeCN	336	83	3300	white powder
7	1a		MeCN	504[c]	83	2600	white powder
8	1a	Et_2NH	MeCN	336	75	3300	brownish paste
9	1b	Et_2NH	MeCN	336	54	900	pale yellow powder
10	1a	$(i\text{-}Pr)_2NH$[d]	$CHCl_3$[e]	60[b]	31	1800	pale brown powder

[a] [Phosphorane (1)] = [amine] = 3.0 mmol in 1.0 mL of solvent under nitrogen at room temperature unless otherwise noted. [b] Reaction at 90 °C. [c] Reaction at 6 °C. [d] 3.6 mmol of the amine was used. [e] 3.0 mL of $CHCl_3$.

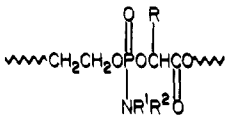
present paper deals with reactions of **1** with N-nucleophiles having an N–H bond, namely, primary and secondary amines and ammonia, to produce polyphosphate derivatives having incorporated N-nucleophile components ("aminolysis and ammonolysis polymerizations").

Results and Discussion

Aminolysis Polymerization of 1. Stoichiometric reactions of **1** with primary and secondary amines took place at room temperature and gave polyphosphate derivatives consisting of a phosphate ester unit **4a**, a phosphoramidate ester unit **4b**, or both units ("aminolysis polymerization").

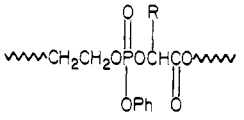


4a



4b

The ratio of the two units in the polymer was mainly dependent upon the nature of the amine employed, **4a** always being the major unit. During the reaction phenol was eliminated. In addition to **4a** and **4b**, another phosphate unit, **4c**, was present in the polymer in some cases. **4c** is a unit derived directly from **1**.[7]



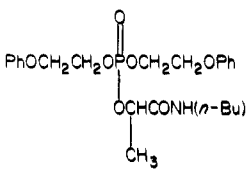
4c

An equimolar mixture of **1a** and n-butylamine (3.0 mmol of each) in 1.0 mL of acetonitrile was kept at room temperature for 16 days under nitrogen in a sealed tube. The tube was opened and the reaction mixture was poured into a large amount of diethyl ether to precipitate a polymeric material. The precipitation procedure was repeated three times. After the precipitate was dried, 0.36 g of polymer was obtained (50% yield). The polymer (sample no. 1) was a very hygroscopic, pale brown paste soluble in polar organic solvents such as DMF, Me_2SO, $CHCl_3$, and methanol and also in water (Table I).

The structure of the polymer was determined by ^1H and ^{31}P NMR spectroscopy, IR spectroscopy, and elemental analysis. The ^1H NMR spectrum of the polymer showed that it is composed of a 1:1 molar ratio of **1a** and n-butylamine, with elimination of phenol. Six kinds of proton signals were observed and assigned as follows. A signal at δ 0.9 is due to the methyl protons of CH_2CH_3. A signal centered at δ 1.4 is assigned as $OCHCH_3$ and $NCH_2CH_2CH_2CH_3$. A broad peak (δ 2.6–3.3) is due to the two methylene protons of NCH_2. A large, broad signal (δ 3.5–4.4) is ascribed to the two methylene protons of OCH_2CH_2O. A broad signal (δ 4.5–5.0) is due to the methine proton of $OCHCH_3$. A small signal (δ 7.6–8.1) is ascribed to NHCO. The relative ratio of these signals was 3:7:2:4:1:1, indicating the 1:1 molar ratio of **1a** and n-butylamine. A broad small signal at δ 7.2–7.6 is ascribed to the hydroxy protons of the polymer end groups and of water included in the polymer due to its very hygroscopic nature. This assignment was confirmed by the fact that the signal disappeared when the sample solution was treated with D_2O.

In the IR spectrum two characteristic stretchings of the carbonyl group were observed at 1645 (strong) and 1715 cm^{-1} (weak), which are ascribable, respectively, to the amide and ester groups. From these observations the unit structures **4a** and **4b** were proposed. Furthermore, two kinds of stretchings due to P=O at 1215 cm^{-1} and due to P–O–alkyl at 1030 cm^{-1} were observed. In accordance with the IR data, the ^{31}P NMR spectrum of the polymer showed two peaks at −1.8 and +9.6 ppm,[9] which were assigned to units **4a** and **4b**, respectively. The content of **4a** and **4b** in the polymer was determined as 85% and 15%, respectively, by the integral ratio of the two peaks (Table II).

The ^{31}P NMR signal was assigned by comparison with that of two model compounds: **5** as a model for the phosphate triester unit **4a** and **6** for the phosphoramidate ester unit **4b**. Since the phosphorus atom of **5** has two



5

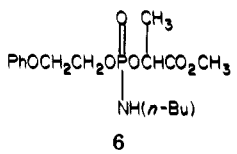


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Table II
IR and ^{31}P NMR Data of Polymers Obtained by Aminolysis Polymerization

no. of polymer sample	IR (ν (cm^{-1}), neat)				^{31}P NMR[a]		
	C=O(ester)	C=O(amide)	P=O	P—O—alkyl	4a (%)	4b (%)	4c (%)
1	1715	1650	1215	1030	−1.8 (85)	+9.6 (15)	n.o.[b]
2	1720	1640	1235	1050	−1.4 (96)	+9.3 (4)	n.o.
3	1740	1645	1200	1070	−1.9 (85)	n.o.[b]	−6.9 (15)
4	n.o.[b]	1680	1250	1030	−1.9 (98)	n.o.[b]	−6.8 (2)
5	1715	1630	1250	1000	−1.5 (93)	+7.6 (7)	n.o.[b]
6	n.o.[b]	1640	1240	1030	−1.3 (97)	+7.5 (1)	−7.6 (2)
7	1720	1660	1250	1040	−1.5 (95)	+7.8 (2)	−7.5 (3)
8	1740	1640	1210	1040	−1.7 (94)	n.o.[b]	−6.7 (14)
9	1750	1630	1220	1040	−1.4 (72)	+8.9 (1)	−6.4 (27)
10	1760	1620	1220	1060	−1.7 (82)	n.o.[b]	−6.7 (18)

[a] The content of each unit was obtained by the integral ratio of the respective peak. Solvent of $CDCl_3$ was used for measurement in all cases except for no. 2, where Me_2SO-d_6 was used. [b] n.o. means "not observed".

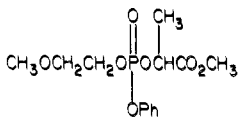
Table III
Ammonolysis Polymerization of 1[a]

no.	phosphorane	amt of NH_3, mmol	reaction		polymer		
			solvent (mL)	time, h	yield, mg	mol wt	appearance
11	1a	30	CH_2Cl_2 (1)	216	306	5000	white powder
12	1a	30	CH_2Cl_2 (1) + C_6H_6 (1)	216	375		white powder
13	1a	3.6	CH_2Cl_2 (3)	216	325		pale yellow powder
14	1b	30	CH_2Cl_2 (1)	96	387	2300	pale yellow powder

[a] [Phosphorane (1)] = 3.0 mmol in solvent at room temperature in a sealed tube.

2-phenoxyethoxy groups, it is not a chiral atom, and hence **5** showed a singlet at −2.2 ppm. On the other hand, **6** showed two singlets, at +9.7 and +8.9 ppm, with almost equal intensity due to the presence of the two diastereomers. These chemical shifts are very close to those of the polymer, and hence, the result was taken to support the unit structures, **4a** and **4b**, respectively.

As to the ^{31}P NMR chemical shift of phosphate triester unit **4c** having the POPh group, model compound **7** was prepared. **7** also showed two signals at −6.9 and −7.4 ppm with equal intensity because of the two diastereomers.



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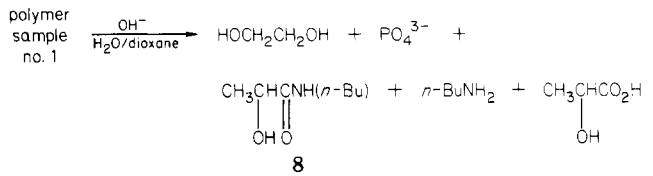
To obtain further information on the polymer structure the polymer was subjected to alkaline hydrolysis. For-



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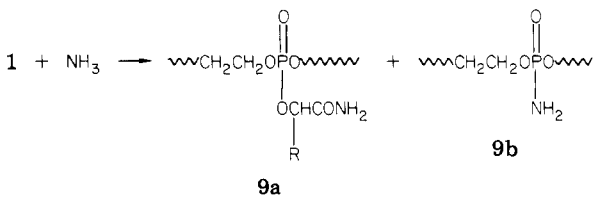
mation of five products is expected with the reaction. From the reaction mixture *N*-*n*-butyllactamide (**8**) was obtained in 19% yield for the molar percent of unit **4a**, which is not high. It should be noted, however, that an authentic sample of **7** was treated under similar hydrolysis and workup procedures and was recovered in 39% yield. These results indicate that **4a** is contained as the major unit in polymer sample no. 1, which is compatible with the findings of the ^{31}P NMR analysis. Anal. Calcd for $(C_9H_{18}NO_5P)_n$: P, 12.33. Found: P, 12.08.

IR and ^{31}P NMR spectroscopic data are given in Table II for all polymer samples. Besides *n*-butylamine, several primary and secondary amines such as *sec*-butylamine, *tert*-butylamine, aniline, pyrrolidine, morpholine, diethylamine, and diisopropylamine were found to induce the reactions with **1a** above 6 °C. Diethylamine also reacted with **1b** at room temperature to give a polymer (Table I). Among the three kinds of units **4a**, **4b**, and **4c**, **4a** was always the major unit in the polymer. Unit **4c**, produced directly from **1a** without incorporation of the amine, was found in the cases of amines that were bulky and less reactive toward **1**, e.g., nos. 3 and 8–10, since the reaction of **1** with an amine to produce units **4a** and **4b** and the formation of unit **4c** are competitive processes. In addition to these three units, a small ^{31}P NMR signal was observed around +17 ppm in less than several percent for the total unit. This signal was assigned to a cyclic phosphate species probably due to an end group.

Ammonolysis Polymerization of 1. In addition to the aliphatic and aromatic amines examined above, ammonia was chosen as an *N*-nucleophile. Ammonia induced the reactions with **1a** and **1b** at room temperature to give polymers consisting of two units, **9a** and **9b** ("ammonolysis polymerization") (Table III). These polymers are not completely soluble in dipolar aprotic solvents such as DMF but are readily soluble in water.



9a 9b

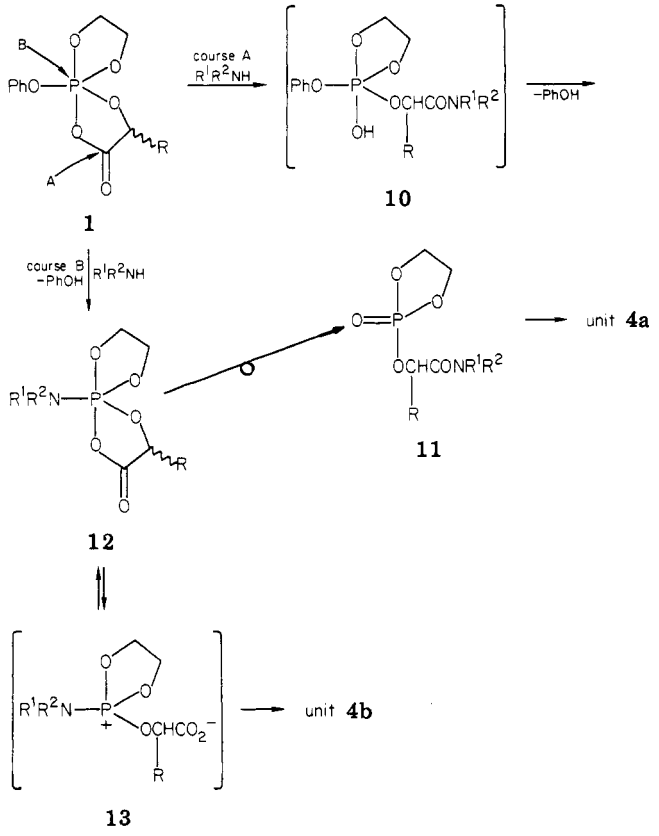
The ^{31}P NMR spectrum of the polymer (sample no. 11 in Me_2SO) showed two signals at −1.7 (66%) and +11.4 ppm (34%), which were assigned, respectively, to phosphate triester unit **9a**[7] and phosphoramidate ester unit **9b**.[10] The IR spectrum of the polymer showed characteristic stretching bands at 1685 (amide C=O), 1250 (P=O), and 1025 cm^{-1} (P–O–alkyl), supporting the presence of unit **9a**. It should be noted that the α-ester component was eliminated, to give unit **9b** having a PNH_2 group. Anal. Calcd for $[(C_5H_{10}O_5NP)_{0.66}(C_2H_6O_3NP)_{0.34}]_n$:

Table IV
IR and ^{31}P NMR Data of Polymers Obtained by Ammonolysis Polymerization

no. of polymer sample	IR (ν (cm^{-1}), neat)[a]			^{31}P NMR[b] (Me_2SO-d_6)	
	C=O(amide)	P=O	P—O—alkyl	9a (%)	9b (%)
11	1685	1250	1025	−1.7 (66)	+11.4 (34)
12	1690	1240	1030	−1.4 (54)	+11.8 (46)
13	1680	1220	1040	−1.6 (91)	+11.7 (9)
14	1690	1250	1030	−2.2 (58)	+11.7 (42)

[a] No stretching band due to the ester carbonyl group was observed. [b] No signal due to unit 4c was detected.

Scheme I



C, 26.95; H, 5.09. Found: C, 26.41; H, 5.66.

9a was a major unit in the polymers. A tenfold excess of ammonia over 1 yielded unit **9b** in large quantities (34–46 molar percent) whereas the use of only a small excess of ammonia gave a polymer having unit **9b** in only 9 molar percent (Tables III and IV).

Reaction Mechanism. Spiro(acylpentaoxy)phosphorane 1 is a mixed acid anhydride derivative of phosphoric and carboxylic acids. Aminolysis-type polymerizations of 1 with amines having an N–H bond, therefore, may involve two possible reaction sites, i.e., the carbonyl carbon atom (course A) and the central phosphorus atom (course B) (Scheme I). An amine nucleophile could attack the carbonyl carbon atom of 1 to yield hydroxyphosphorane **10**, which is quite unstable under the reaction conditions and could give cyclic phosphate **11** with the liberation of phenol. It is possible that 11 opens spontaneously since cyclic phosphates are known to be polymerized via ring opening with initiators such as an amine.[11] On the other hand, the attack of an amine on the phosphorus atom yields spiro(acyloxyamino)phosphorane **12** with the liberation of phenol, probably through a hexacoordinated intermediate.[12] **12** is in equilibrium with zwitterion **13**, whose ring-opening reactions (Arbuzov-type reaction) by nucleophilic attack of the carboxylate anion of another zwitterion such as **13** and macrozwitterions or

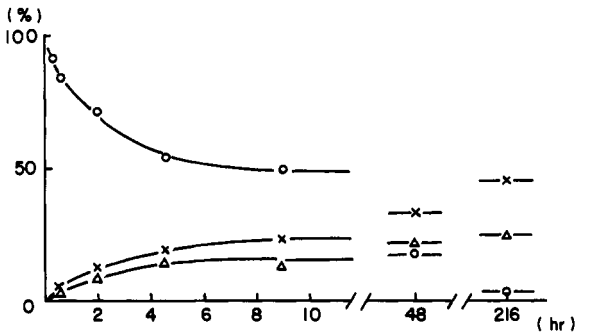
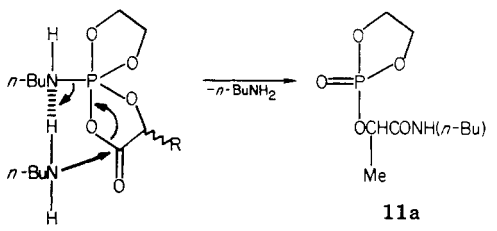


Figure 1. Reaction of **1a** (3.0 mmol) with *n*-butylamine (3.6 mmol) in 3.0 mL of $CHCl_3$ at room temperature as followed by ^{31}P NMR: phosphorane **12a** (R = Me, R^1 = *n*-Bu, R^2 = H) (○); unit **4a** (×); unit **4b** (△).

such as the propagating end group from 11 give rise to the production of unit **4b**.[5,13]

In order to shed more light on the above scheme, we monitored the reaction of **1a** with *n*-butylamine by ^{31}P NMR spectroscopy. Under the reaction conditions of **1a**/*n*-butylamine (1.0/1.2 molar ratio) at room temperature in $CHCl_3$, the signal of the starting phosphorane **1a** (−39.9 and −39.4 ppm) disappeared within 10 min and a new signal appeared at −36.1 ppm as a major peak, which was assigned as a new spiro(acyloxyamino)phosphorane, **12a** (R = Me, R^1 = *n*-Bu, R^2 = H).[14] Then the signal for **12a** diminished gradually, and instead, signals due to units **4a** (−2.4 ppm) and **4b** (+9.3 ppm) increased (Figure 1). After 216 h, **12a** disappeared almost completely, and units **4a** and **4b** resulted in yields of 45% and 26%, respectively. From these observations it is clear that **12a** is primarily formed as a major product at an early stage of polymerization and that **12a** leads to the production of both units **4a** and **4b**. Therefore, the major unit **4a** should be derived from the isomerized intermediate **11a** from **12a**. Actually, a small peak at 16 ppm ascribable to **11a** was observed during the reaction. The isomerization of **12a** to **11a** may be explained, for example, by nucleophilic attack of the amine on the carbonyl carbon as follows.



As a whole the major course of the polymerization is the route 1 → 12 → 11 → unit **4a**.

Applications of Aminolysis Polymerization. The present study has offered a polymerization producing polyphosphate derivatives having an amine component introduced as a carboxylic acid amide unit **4a** and/or a phosphoramidate unit **4b**. One possible application of the

aminolysis polymerization is the fixation of amine components into polyphosphate derivatives. There are many drugs having amino groups and therefore it is possible to introduce these drug components into polyphosphate derivatives. For the preparation of such polymeric drugs, the parent polymer should be of very low toxicity. Therefore, the acute toxicity was tested. The LD_{50} values of four polymer samples of no. 4, 6, 8, and 12 were >500, >2000, ~500, and >1000 mg/kg of mouse, respectively. These results indicate the low toxicity of these polymers and hence suggest their possible utilization as carrier polymers of polymer drugs.

Experimental Section

Materials. All solvents were dried by conventional methods, distilled, and stored under nitrogen. All amines were obtained from commercial sources, dried over CaH_2, and distilled before use. Ammonia was taken from a cylinder and used without further purification. 2-Phenoxy-1,3,2-dioxaphospholane was prepared according to the literature.[15] Pyruvic acid was a commercial reagent and was purified by repeated distillations under reduced pressure. Phenylglyoxylic acid was prepared according to the previous method.[16] Spiro(acylpentaoxy)phosphoranes **1a** and **1b** were prepared by reactions of 2-phenoxy-1,3,2-dioxaphospholane with pyruvic acid and with phenylglyoxylic acid, respectively, according to procedures recently reported.[1,12] Phosphorus oxychloride, methyl lactate, 2-methoxyethanol, and 2-phenoxyethanol were distilled before use. Phenyl phosphorodichloridate was used as supplied.

Instrumentation. ^1H NMR spectra were determined on a Hitachi R-20B NMR spectrometer operating at 60 MHz. ^{31}P NMR spectra were recorded on a Hitachi R-900 Fourier transform spectrometer equipped with a ^{31}P unit operating at 36.4 MHz; the field was stabilized with an external field lock and all spectra were obtained with wide-band proton decoupling. IR spectra were recorded on a Hitachi 260-20 spectrometer. Molecular weights of polymers were measured by a vapor pressure osmometer (Hitachi Perkin-Elmer Model 115) in DMF at 55 °C.

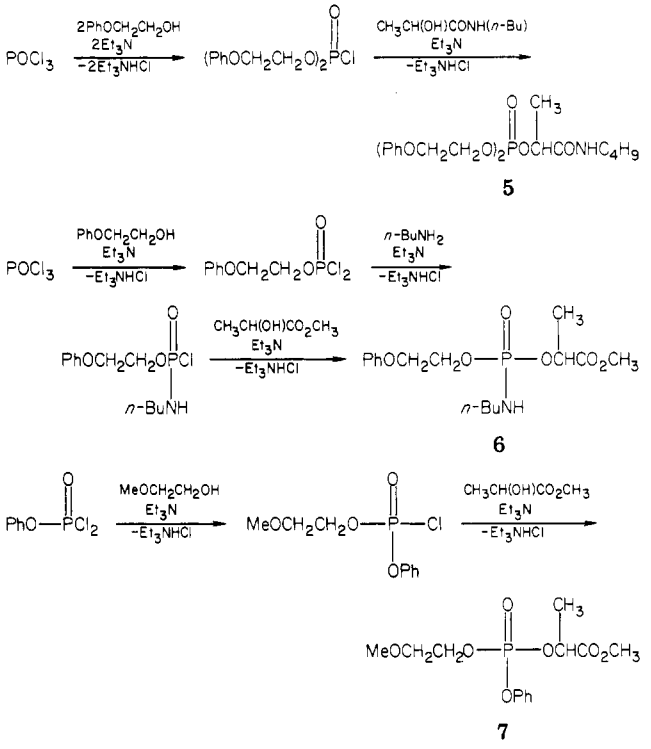
Polymerization Procedure. A typical run for the aminolysis polymerization is as follows. To a solution of freshly prepared **1a** (3.0 mmol) in 1.0 mL of acetonitrile in a test tube was added *n*-butylamine (3.0 mmol) at 0 °C under nitrogen. The tube was sealed and kept at room temperature for 16 days. During the polymerization, the reaction mixture became viscous and brown. The tube was opened and the mixture was poured into a large amount (ca. 70 mL) of diethyl ether to precipitate a polymeric material. This precipitation procedure was repeated three times, using chloroform (good solvent) and diethyl ether (poor solvent). Drying of the material in vacuo gave 362 mg of a pale yellow, pasty polymer (50% yield).

Ammonolysis polymerization using excess ammonia was carried out as follows. Into a test tube was introduced 510 mg (30 mmol) of liquid ammonia at −78 °C from a cylinder, and to this system was added a solution of freshly prepared **1a** (3.0 mmol) in 1 mL of dichloromethane. The mixture was warmed to room temperature and allowed to stand for 213 h. Repeated precipitation of the product gave 306 mg of a white powdery polymer.

Ammonolysis polymerization using a slight excess of ammonia was performed as follows. A solution of **1a** (3.0 mmol) in 3.0 mL of dichloromethane was cooled to −78 °C. Into this was introduced 81 mL (3.6 mmol) of gaseous ammonia with an airtight syringe through a septum cap. The mixture was vigorously shaken, kept at −20 °C for 1 h, and then kept at room temperature for 213 h. The usual isolation procedure gave 325 mg of polymer as a pale yellow powder.

Preparation of Model Compounds. *N*-*n*-Butyllactamide (8). A mixture of ethyl lactate (11.8 g, 0.10 mol) and *n*-butylamine (30 mL, 0.30 mol) was refluxed for 3 h. After evaporation of the excess amine and the ethanol was liberated, the residue was distilled to afford 10.83 g (75%) of the lactamide **8**: bp 114 °C (0.9 mm) [lit.[17] bp 116 °C (0.9 mm)]; ^1H NMR ($CDCl_3$) δ 0.72–1.61 (m, 7 H, $CH_3CH_2CH_2$), 1.33 (d, J = 7 Hz, 3 H, CH_3), 3.16 (br q, J = 7 Hz, 2 H, CH_2N), 4.11 (q, J = 7 Hz, 1 H, CH), 4.93 (br s, 1 H, OH), 7.04 (br s, 1 H, CONH); IR (neat) 3300 (HN, OH), 1640 (C=O), 1535, 1125 cm^{-1}.

Scheme II



Preparations of model compounds **5**–**7** are outlined in Scheme II.

Bis(2-phenoxyethyl) 1-(*N*-*n*-Butylcarbamoyl)ethyl Phosphate (5). To an ice-cooled solution of phosphorus oxychloride (813 mg, 5.30 mmol) in 10 mL of benzene was added dropwise with stirring a solution of 2-phenoxyethanol (1.44 g, 10.4 mmol) and triethylamine (1.05 g, 10.4 mmol) in 10 mL of benzene. After the addition, the mixture was stirred at room temperature for 3 h. To this was added a solution of *N*-*n*-butyllactamide (**8**) (1.17 g, 8.08 mmol) and triethylamine (502 mg, 4.96 mmol) in 10 mL of benzene, and the mixture was allowed to stand at room temperature for 4 days with occasional stirring. The precipitate of the ammonium salt was removed by filtration and the filtrate was washed with aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated to give a yellow oil, which was chromatographed on silica gel using ether–ethyl acetate (first 2:1 and then 1:1) to afford 1.06 g (43%) of **5** as a liquid: ^1H NMR ($CDCl_3$) δ 0.73–1.48 (m, 7 H, $CH_3CH_2CH_2$), 1.58 (d, J = 7 Hz, 3 H, CH_3), 2.98–3.43 (q, J = 7 Hz, 2 H, CH_2N), 4.08–4.63 (m, 8 H, OCH_2CH_2O), 4.90 (q, J = 7 Hz, 1 H, POCH), 6.63 (br, 1 H, NHCO), 6.80–7.55 (m, 10 H, aromatic); ^{31}P NMR ($CDCl_3$) δ −2.2; IR (neat) 3300 (N–H), 2950, 2920 (C–H), 1670 (C=O), 1245 (P=O), 1040 (P–OC), 750 cm^{-1}. Anal. Calcd for $C_{23}H_{32}NO_7P$: C, 59.34; H, 6.93; N, 3.01; P, 6.65. Found: C, 59.58; H, 7.13; N, 3.05; P, 6.43.

1-(Methoxycarbonyl)ethyl 2-Phenoxyethyl *N*-*n*-Butylphosphoramidate (6). To an ice-cooled solution of phosphorus oxychloride (517 mg, 3.37 mmol) in 20 mL of benzene was added dropwise with stirring a solution of 2-phenoxyethanol (467 mg, 3.38 mmol) and triethylamine (370 mg, 3.66 mmol) in 10 mL of benzene. The addition was performed in 45 min. The resultant mixture was stirred at room temperature for 30 min and again cooled in an ice bath. To this was added dropwise over 50 min with stirring a solution of *n*-butylamine (248 mg, 3.39 mmol) and triethylamine (351 mg, 3.47 mmol) in 10 mL of benzene. After the solution was stirred at room temperature for 2 h, a white precipitate of triethylammonium salt was removed by filtration. To the filtrate was added a solution of methyl lactate (3.17 g, 30.5 mmol) and triethylamine (343 mg, 3.39 mmol) in 10 mL of benzene in one portion. The mixture was kept at room temperature for 2 days with occasional stirring. The resultant white precipitate was removed by filtration, and concentration of the filtrate in vacuo gave an oil which was chromatographed on silica gel using dichloromethane–triethylamine (100:1) to afford 1.06 g (87%) of

6: ^{1}H NMR ($CDCl_3$) δ 0.67–1.01 (m, 3 H, CH_3), 1.10–1.63 (m, 7 H, CH_2CH_2, CH_3), 2.54–3.24 (m, 3 H, CH_2NH), 3.63, 3.65 (2 s, 3 H, CH_3OCO), 4.00–4.48 (m, 4 H, OCH_2CH_2O), 4.56–5.28 (m, 1 H, CH), 6.70–7.40 (m, 5 H, C_6H_5); ^{31}P NMR ($CDCl_3$) δ 8.9 and 9.7 (relative intensity 45:55); IR (neat) 3220 (N–H), 1755 (C=O), 1240 (P=O), 1090, 1040, 980 cm^{-1}. Anal. Calcd for $C_{16}H_{26}NO_6P$: C, 53.47; H, 7.29; N, 3.90; P, 8.62. Found: C, 53.50; H, 7.29; N, 3.88; P, 8.60.

1-(Methoxycarbonyl)ethyl 2-Methoxyethyl Phenyl Phosphate (7). To an ice-cooled solution of phenyl phosphorodichloridate (2.08 g, 9.87 mmol) in 20 mL of benzene was added dropwise over 30 min with stirring a solution of 2-methoxyethanol (758 mg, 9.96 mmol) and triethylamine (1.09 g, 10.8 mmol) in 10 mL of benzene. After an additional 30 min of stirring at room temperature, the reaction mixture was treated with a solution of methyl lactate (1.63 g, 15.6 mmol) and triethylamine (1.23 g, 12.2 mmol) in 10 mL of benzene. The mixture was kept at room temperature for 11 days. The resulting white precipitates of ammonium salt were removed by filtration, and the filtrate was washed with aqueous sodium bicarbonate solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford a yellow liquid, which was chromatographed on silica gel (diethyl ether–ethyl acetate 4:1) to give 1.86 g (59%) of **7** as a pale yellow liquid: ^{1}H NMR ($CDCl_3$) δ 1.48, 1.60 (2 d, J = 6 Hz, 3 H, CH_3), 3.35 (s, 3 H, CH_3O), 3.45–4.70 (m, 2 H, CH_2O), 3.70, 3.75 (2 s, 3 H, CH_3OCO), 4.10–4.53 (m, 2 H, CH_2O), 4.73–5.28 (m, 1 H, CH), 7.08–7.40 (m, 5 H, C_6H_5O); ^{31}P NMR ($CDCl_3$) δ −6.9 and −7.4 (relative intensity 10:9); IR (neat) 1755 (C=O), 1270 (P=O), 1040 (P–OC) cm^{-1}. Anal. Calcd for $C_{13}H_{19}O_7P$: C, 49.06; H, 6.02; P, 9.73. Found: C, 49.31; H, 6.09; P, 9.56.

Alkaline Hydrolysis of Polymer Sample No. 1. The polymer sample (255 mg, 1.02 unit mmol) prepared from **1a** and *n*-butylamine was dissolved in 5 mL of dioxane. To this was added 5 mL of 2 N NaOH aqueous solution, and the mixture was refluxed for 3 h. After the heating, the mixture was diluted with 30 mL of water and extracted with dichloromethane. The extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give 8 (23 mg, 0.16 mmol), which was identified by comparing its IR spectrum with that of an authentic sample. Treatment of the authentic lactamide 8 (515 mg) under similar hydrolysis and workup conditions gave 203 mg of the amide (the recovered yield was 39%). Assuming that the isolated yield of 8 in the hydrolysis of the polymer sample and the recovered yield of 8 in the treatment of the authentic sample 8 are the same, the content of **4a** in the polymer sample is assured to be at least 40%.

^{31}P NMR Monitoring of the Polymerization of 1a with *n*-Butylamine. Freshly prepared **1a** (3.0 mmol) in 3 mL of chloroform was mixed with *n*-butylamine (3.6 mmol) at 0 °C. A part of the mixture was transferred into an NMR sample tube with a syringe. The tube was sealed and kept at 25 °C during ^{31}P NMR monitoring. The amounts of products were determined by the integral ratio of the respective ^{31}P NMR peaks (Figure 1).

Acute Toxicity Examination. A polymer sample was dissolved in water, and the solution was intraperitoneally injected into 20 mice (10 male and 10 female) at a dose rate of 10 mL of solution/kg of mouse. The LD_{50} value was obtained from the number of surviving mice 14 days after the injection.

Acknowledgment. This work was partially supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan (No. 455335 and 443022). We are indebted to Sumitomo Chemical Co., Osaka, for the acute toxicity examination of the polymers.

Registry No. **5**, 85337-83-3; **6**, 85337-84-4; **7**, 85337-85-5; **8**, 3328-88-9; *n*-$BuNH_2$, 109-73-9; $POCl_3$, 10025-87-3; $PhOCH_2CH_2OH$, 122-99-6; $PhOP(O)Cl_2$, 770-12-7; $MeOCH_2CH_2OH$, 109-86-4; $CH_3CH(OH)CO_2CH_3$, 547-64-8; ethyl lactate, 97-64-3.

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(14) Reactions of **1a** (3 mmol) with the following three amines (3.6 mmol) in $CHCl_3$ at 0 °C for 1 h gave spiro(acyloxyamino)-phosphoranes (**12**) in the following yields (^{31}P NMR chemical shift): *n*-$BuNH_2$, **12a**, 84% (−36.1 ppm); *sec*-$BuNH_2$, **12b** (R = Me, R^1 = *sec*-Bu, R^2 = H), 83% (−36.1 ppm); $PhCH_2NH_2$, **12c** (R = Me, R^1 = $PhCH_2$, R^2 = H), 78% (−35.1 ppm). Under similar reaction conditions **1a** and ammonia yielded **12d** (R = Me, R^1 = R^2 = H) in 80% yield (−34.6 ppm). These spiro-(acyloxyamino)phosphoranes were not stable enough to be isolated.
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