Science Foundation under Grant No. 78-11955.

**Registry No.** I, 88392-12-5; II, 88392-13-6; X, 88392-14-7; i, 6289-83-4; iii, 35236-42-1; (*trans*-1,4-cyclohexanediol)·(*trans*-1,4-cyclohexanedicarbonyl chloride) (copolymer), 88392-15-8; poly(oxy-*trans*-1,4-cyclohexyleneoxycarbonyl-*trans*-1,4-cyclohexylenecarbonyl), 88392-10-3; (2-methylresorcinol)·(terephthaloyl chloride) (copolymer), 88392-16-9; poly(oxy-2-methyl-1,3-phenyleneoxyterephthaloyl), 88392-11-4; (*cis*-1,4-cyclohexanediol)·(*trans*-1,4-cyclohexanedicarbonyl chloride) (copolymer), 88392-17-0; poly(oxy-*cis*,*trans*-1,4-cyclohexyleneoxycarbonyl-*trans*-1,4-cyclohexylenecarbonyl), 88424-59-3.

## References and Notes

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# Hydrolysis Polymerization of Spiro(acylpentaoxy)phosphoranes to Polyphosphates

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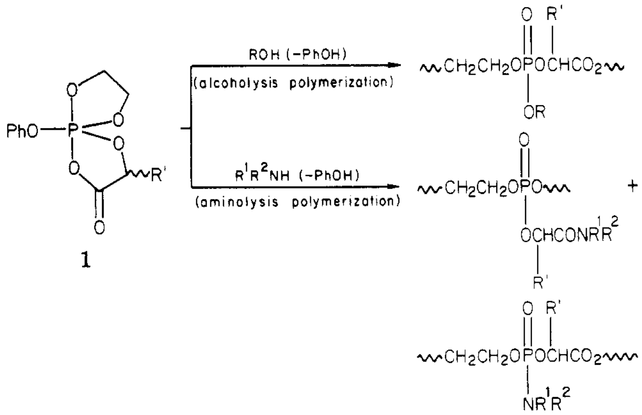
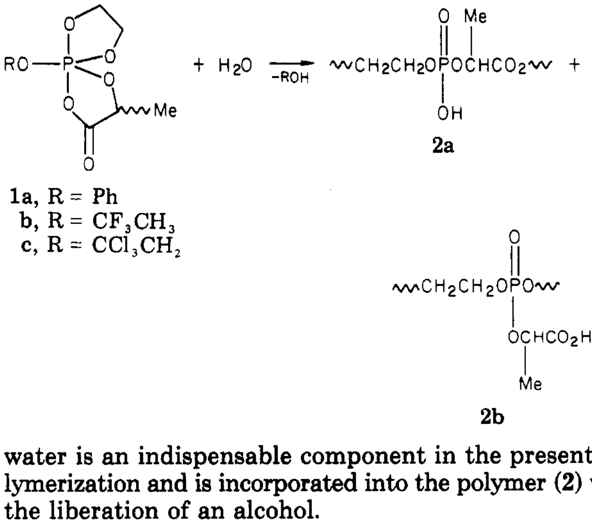
ABSTRACT: Reaction of spiro(acylpentaoxy)phosphoranes **1a–c** induced by an *O*-nucleophile of water gave polyphosphate **2** made of phosphate diester unit **2a** and phosphate triester unit **2b** ("hydrolysis polymerization" of **1**). The content of **2a** and **2b** was determined by two methods: the $^{31}$P NMR method on the benzoylated polymer and the IR method on the polymer salts with triethylamine. The mechanism of the hydrolysis polymerization is outlined as follows. The reaction of **1** with water rapidly forms acyclic and cyclic phoshate triester intermediates (**7** and **8**, respectively). **7** and **8** are still reactive, and subsequent reactions between these species slowly take place to yield polyphosphate **2** via two modes of reaction: a polycondensation and a ring-opening addition polymerization.

Our recent investigations have disclosed that spiro(acyloxy)phosphoranes are quite reactive pentacovalent phosphorus species and can be used as starting monomers to give various phosphorus-containing polymers,[1] e.g., polyphosphates,[2–6] polyphosphonates,[5,7] and polyphosphinates.[6–8] All these polymerizations have been considered to proceed via phosphonium zwitterion intermediates.[1] During the course of these studies we have found that spiro(acyloxy)phosphoranes are good amphiphiles; they react with both nucleophiles and electrophiles.[9,10] Recently, we reported the reaction of spiro(acylpentaoxy)phosphoranes **1**, containing a PhO group with alcohols acting as an *O*-nucleophile to give polyphosphate triesters having alcohol components incorporated ("alcoholysis polymerization" of **1**).[3] Polymerization of **1** has also been induced by the reaction of **1** with *N*-nucleophiles of amines and ammonia to give polyphosphate derivatives possessing the amine and ammonia components, respectively ("aminolysis and ammonolysis polymerizations").[11] The present paper describes the polymerization of spiro(acylpentaoxy)phosphoranes **1a–c** induced by the reaction of **1** with an another *O-nucleophile of water*, which gives rise to polyphosphate **2** containing both open-chain phosphate diester unit **2a** and phosphate triester unit with pendant carboxylic acid group **2b** ("hydrolysis polymerization").



**1**

The present water-induced polymerization (reaction 1) is unique from the standpoint that in ionic polymerization water is normally an undesirable impurity and hence should be removed from the reaction system. In contrast, water is an indispensable component in the present polymerization and is incorporated into the polymer (**2**) with the liberation of an alcohol.



**2a**

**1a**, R = Ph
**b**, R = $CF_3CH_2$
**c**, R = $CCl_3CH_2$

**2b** (1)

## Results and Discussion

**Hydrolysis Polymerization of Spiro(acylpentaoxy)phosphorane 1 Induced by Water.** The polymerization of **1** with water was carried out at room temperature by using a stoichiometric or a small excess amount of water for **1**. Solvents employed were acetonitrile, chloroform,

Table I
Hydrolysis Polymerization of 1[a]

| entry no. | R of 1 | mmol of $H_2O$ | solvent | temp[b] | time, h | yield, % polymer | yield, % ROH | mol wt[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | Ph | 3.3 | $CH_3CN$ | rt | 5 | 49 | 78 | 960 |
| 2 | Ph | 3.3 | $CH_3CN$ | rt | 24 | 74 | 80 | 1500 |
| 3 | Ph | 3.3 | $CH_3CN$ | rt | 120 | 78 | 80 | 2300 |
| 4 | Ph | 3.0 | $CH_3CN$ | 90 °C | 18 | 74 | 61 | 2300 |
| 5 | Ph | 3.9 | $CHCl_3$ | rt | 24 | 80 | 80 | 1100 |
| 6 | Ph | 3.6 | DMF | rt | 96 | 66 | 83 | 2000 |
| 7 | $CF_3CH_2$ | 3.0 | $CH_3CN$ | rt | 72 | 76 | 72 | 1800 |
| 8 | $CCl_3CH_2$ | 3.3 | $CH_3CN$ | rt | 72 | 74 | 82 | 2000 |

[a] [Phosphorane 1] = 3.0 mmol in 3 mL of solvent. [b] rt = room temperature. [c] Determined by vapor pressure osmometry in DMF at 55 °C.

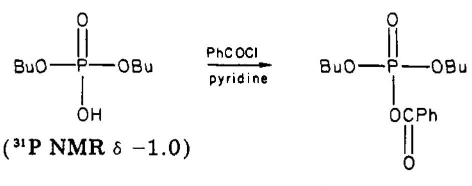
and DMF. In DMF solvent the reaction was homogeneous throughout the polymerization, whereas in acetonitrile or chloroform the reaction mixture formed two layers with the progress of the reaction. After the reaction, the mixture was poured into dry diethyl ether to precipitate polymeric materials. The polymer obtained was a viscous oil or powdery solid, depending on the molecular weight. The polymer was soluble in aprotic polar solvents such as DMF and $Me_2SO$ and in protic solvents such as methanol, trifluoroethanol, and water. During the reaction, a hydroxyl compound, e.g., phenol in entry no. 1–6 of Table I, trifluoroethanol in no. 7, and trichloroethanol in no. 8, was liberated and the amount of the alcohol was determined by the GLC analysis of the diethyl ether layer. These results are given in Table I.

Reaction 1 is a new polymerization of 1 induced by water and, hence, can be termed the "hydrolysis polymerization" of phosphorane 1.

**Polymer Structure.** The IR spectrum of the polymer (no. 4, neat) showed characteristic absorptions at 3350 (br, $\nu_{\mathrm{O-H}}$), 1740 ($\nu_{\mathrm{C=O}}$), and 1210 (br, $\nu_{\mathrm{P=O}}$) cm$^{-1}$. The $^1$H NMR spectrum of the polymer ($Me_2SO$-$d_6$, $Me_4Si$) showed broad signals at $\delta$ 1.2–1.6 (3.0 H, $CH_3$), 3.7–4.4 (4.0 H, $OCH_2CH_2O$), and 4.4–5.0 (1.0 H, OCH). In addition to these signals, a peak at $\delta$ 7.0–7.3 ascribable to phenyl protons (0.34 H) was observed, indicating the presence of phenoxy group in the polymer. The $^{31}$P NMR spectrum of the polymer ($Me_2SO$-$d_6$) showed a signal at $\delta$ −2.2 (relative to 85% $H_3PO_4$ external standard). Anal. Calcd for $(C_5H_9O_6P)_n$: C, 30.62; H, 4.63; P, 15.79. Found: C, 30.88; H, 5.04; P, 15.66.

All the above data indicate that the polymer is constructed from phosphate diester **2a**, phosphate triester **2b**, or both units. It is not possible from the above data to distinguish the unit structure of **2a** and **2b**. To determine the polymer structure in an unambiguous way, polymers were examined according to the following two methods.

**$^{31}$P NMR Method.** As mentioned above $^{31}$P NMR signals of the phosphate diester and triester appear in the same region around −2 ppm. Therefore, the polymer was modified by a chemical reaction. It is known that a phosphate diester reacts with carboxylic acid chloride to give an acyl phosphate.[12] First, a model reaction was carried out. Di-*n*-butyl phosphate (**3**) was subjected to the reaction with benzoyl chloride in the presence of pyridine. Then di-*n*-butyl benzoyl phosphate (**4**) was quantitatively formed, which was confirmed by the complete disappearance of the $^{31}$P NMR signal at $\delta$ −1.0 due to **3** accompanied by the appearance of a new signal at $\delta$ −8.4 due to **4**.



$$\mathrm{BuO{-}P(=O)(OH){-}OBu} \xrightarrow[\text{pyridine}]{\text{PhCOCl}} \mathrm{BuO{-}P(=O)(OC(=O)Ph){-}OBu}$$

3 ($^{31}$P NMR $\delta$ −1.0)

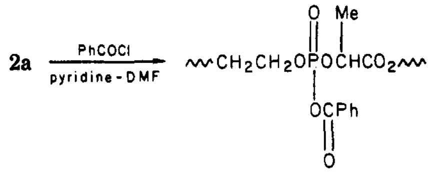
4 ($^{31}$P NMR $\delta$ −8.4)

Table II
Content of Units 2a and 2b in Polymer 2

| sample polymer no. | $^{31}$P NMR method 2a, % | $^{31}$P NMR method 2b, % | IR method log $(T_0/T)_{1740}$ 6a | IR method log $(T_0/T)_{1600}$ 6b |
|---|---|---|---|---|
| 1 | 25 | 75 | 0.02 | 0.10 |
| 2 | 82 | 18 | 0.13 | 0.09 |
| 3 | 80 | 20 | 0.12 | 0.04 |
| 4 | 71 | 29 | 0.11 | 0.04 |
| 5 | 87 | 13 | 0.15 | 0.07 |
| 6 | 54 | 46 | 0.09 | 0.08 |
| 7 | 40 | 60 | | |
| 8 | 30 | 70 | | |

Under similar reaction conditions the $^{31}$P NMR signal of tri-*n*-butyl phosphate (−0.8 ppm) as a model of unit **2b** remained unchanged. Therefore, the benzoylation will not affect the phosphate triester moiety of unit **2b**.

The benzoylation of polymer **2** should give unit **5a** from unit **2a**. Indeed, **5a**, the benzoylated unit, exhibited a $^{31}$P NMR signal at $\delta$ −8.5. Under the benzoylation conditions of the polymer, the carboxylic acid group of unit **2b** might partially be benzoylated to give carboxylic anhydride. However, the $^{31}$P NMR signal of such a compound still appeared at $\delta$ −2.3, indicating that the chemical shift of unit **2b** is not changed upon treatment with benzoyl chloride. Thus, the benzoylated polymer exhibited two $^{31}$P NMR signals, one at $\delta$ −8.5 and another at −2.3, respectively. From the integration ratio of these signals the unit content of **2a** and **2b** could be determined. As shown in Table II all polymers consisted of both units. Polymer (sample no. 1) obtained with a shorter reaction time, e.g., 5 h, contained more triester unit **2b** than diester unit **2a**. With a longer reaction time or at a higher reaction temperature of 90 °C, **2a** became a major unit. In the reaction in DMF, the content of **2a** was almost comparable to the content of **2b**.



$$\mathbf{2a} \xrightarrow[\text{pyridine-DMF}]{\text{PhCOCl}} \sim\mathrm{CH_2CH_2OP(=O)(OC(=O)Ph)OCH(Me)CO_2}\sim$$

5a ($^{31}$P NMR $\delta$ −8.5)

**IR Method.** The second way to obtain information on the polymer structure was IR spectroscopy, with special attention paid to the carbonyl stretching band. Acidic

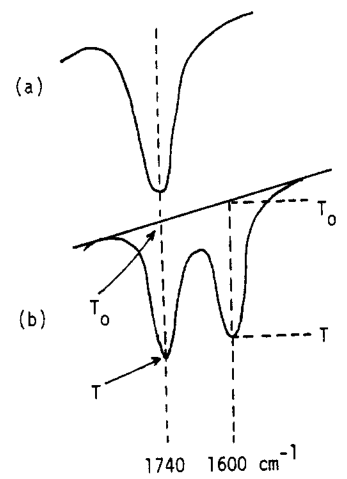
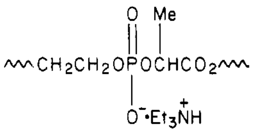
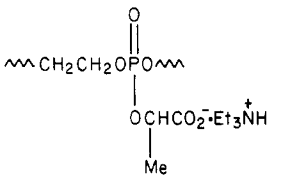


**Figure 1.** IR spectra of (a) polymer sample no. 6 and (b) polymer sample no. 6 and triethylamine; $T_0$ and $T$ denote the transmittance at the point indicated in the figure.

hydrogens of both **2a** and **2b** protonate triethylamine to form salts **6a** and **6b**, respectively. With the addition of triethylamine to the polymer solution, the $\nu_{C=O}$ band of carboxylic acid ester unit **6a** was not affected and appeared in the same region as **2a** i.e., at 1740 $cm^{-1}$. However the $\nu_{C=O}$ band of carboxylate anion **6b** appeared at 1600 $cm^{-1}$ (Figure 1). Thus, the values of log ($T_0/T$) at 1740 and 1600 $cm^{-1}$ were obtained with a base-line method (Figure 1b) and were taken as a measure of the content of units **2a** and **2b**, respectively (Table II). These values of log ($T_0/T$) are in accord with those obtained by the $^{31}P$ NMR method, and these results strongly support the presence of both units **2a** and **2b** in the polymers obtained by the hydrolysis polymerization.

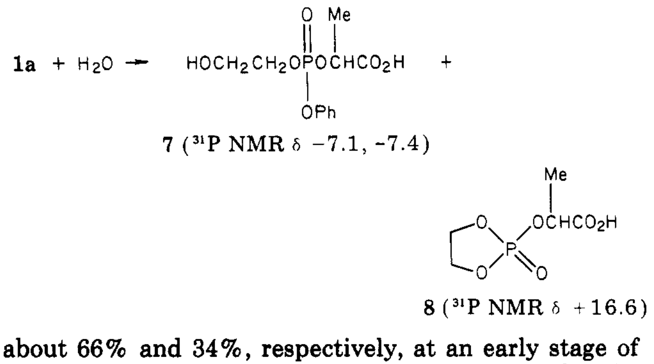

$\sim CH_2CH_2OP(=O)(O^-\cdot Et_3\overset{+}{N}H)OCHCO_2\sim$ (with Me on CH)

**6a**


$\sim CH_2CH_2OP(=O)(OCH(Me)CO_2^-\cdot Et_3\overset{+}{N}H)O\sim$

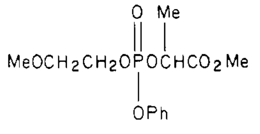
**6b**

**Polymerization Mechanism.** In order to shed light on the mechanism of hydrolysis polymerization, the early stage of the reaction of 1 with water was followed by $^{31}P$ NMR spectroscopy. It was found that the reaction of **1a** with water (1:1 molar) was very rapid; i.e., the $^{31}P$ NMR signals of **1a** ($\delta$ −39.0 and −39.3 ppm in acetonitrile) disappeared completely within 10 min at 0 °C, and new signals appeared at $\delta$ −7.1 and −7.4 and at $\delta$ +16.6. These two groups of signals were assigned respectively to an open-chain phosphate triester **7** and a cyclic triester **8**, both having a carboxylic group. The fractions of **7** and **8** were about 66% and 34%, respectively, at an early stage of reaction. Since **7** and **8** were very unstable under the reaction conditions, model compounds **9** and **10** were independently prepared, isolated, and characterized for the confirmation of the structure. The $^{31}P$ NMR ($CDCl_3$) signals were as follows: **9**; $\delta$ −6.9 and −7.4; **10**, $\delta$ +17.0. These data were taken to support the structures of **7** and **8**. Two peaks of **7** and **9** with equal intensity are due to the presence of two diastereomers arising from the asymmetric carbon atom of POCH(Me).

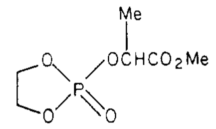


7 ($^{31}P$ NMR $\delta$ −7.1, −7.4)

8 ($^{31}P$ NMR $\delta$ +16.6)

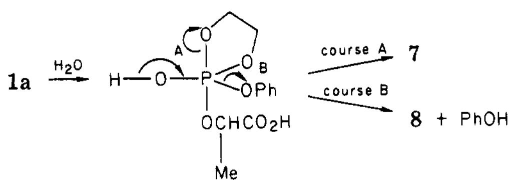

$MeOCH_2CH_2OP(=O)(OPh)OCH(Me)CO_2Me$

9 ($^{31}P$ NMR $\delta$ −6.9, −7.4)



10 ($^{31}P$ NMR $\delta$ +17.0)

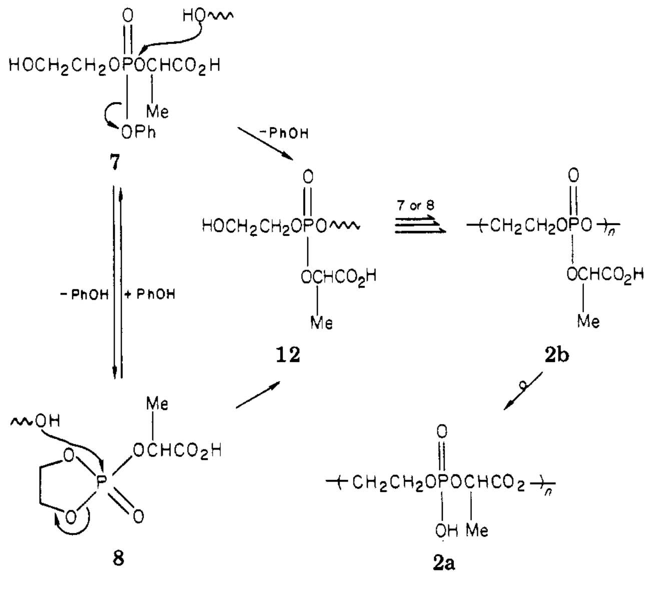
Formation of **7** and **8** was explained in the following manner. A nucleophilic attack of water on the central phosphorus atom of **1a** gives hydroxyphosphorane **11** via a hexacoordinate intermediate.[9] **11** is a very unstable species and further causes ring opening to give **7** via course A or eliminates phenol to yield **8** via course B.



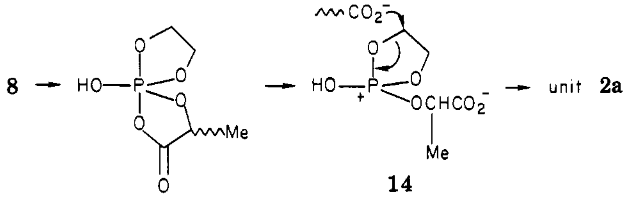
**11**

**7** and **8** are unstable and still reactive. They were consumed slowly, and in turn polymer formation was observed by $^{31}P$ NMR. As mentioned above, the polymer obtained in a shorter reaction time contained unit **2b** predominantly whereas the polymer obtained with longer reaction time contained **2a** as the major unit. This result would suggest that unit **2b** is formed at the early stage of polymerization and is isomerized later to unit **2a**.[13] Elucidation of this point, however, requires further studies.

From all of these observatons the following reaction course is postulated. **7**, first formed from **1a** and water, possesses an alcoholic OH group. It is well-known that an alcohol induces a nucleophilic attack on the phosphorus atom of phosphate triesters such as **7** and **8**.[14] The alcoholic hydroxyl group of **7** attacks the phosphorus atom of another **7** to produce unit **12** with the elimination of phenol. The nucleophilic attack of the hydroxyl group of **7** also takes place on the phosphorus of **8**, leading also to the formation of unit **12**. Repetition of these reactions



of **7** or **8** with **12** will ultimately produce polymer **2b**. It is also reasonable to envisage an interconversion between **7** and **8**. If the proposed course is right, a phenoxy group could be present at the polymer end. This was actually confirmed by $^1$H NMR of polymer sample no. 4. On the assumption that one phenoxy group is present at the polymer end an attempt was made to calculate the degree of polymerization (DP) from the $^1$H NMR data, leading to DP = 15 (molecular weight = 3000). This value is not inconsistent with the value of 2300 obtained by vapor pressure osmometry. The mode of polymerization of phenyl phosphate **7** with **12** is a polycondensation while that of cyclic phosphate **8** with **12** is a ring-opening addition polymerization. The intermediacy of hydroxyphosphorane **13** or hydroxyphosphonium zwitterion **14** from **8** is at present less likely.



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## Experimental Section

**Materials.** Spiro(acylpentaoxy)phosphorane **1a** was prepared according to our method from 2-phenoxy-1,3,2-dioxaphospholane and pyruvic acid.[15] **1b** was obtained by the reaction of 2-(2,2,2-trifluoroethoxy)-1,3,2-dioxaphospholane with pyruvic acid: $^{31}$P NMR ($CDCl_3$) δ −38.2, −38.7; $^1$H NMR ($CDCl_3$) δ 1.45 (d, $J$ = 7 Hz, 3 H, $CH_3$), 3.63–5.00 (m, 7 H, $OCH_2CH_2O$, OCH, $OCH_2CF_3$). **1c** was prepared analogously from 2-(2,2,2-trichloroethoxy)-1,3,2-dioxaphospholane and pyruvic acid: $^{31}$P NMR ($CDCl_3$) δ −38.4, −38.8; $^1$H NMR ($CDCl_3$) δ 1.63 (d, $J$ = 7 Hz, 3 H, $CH_3$), 3.95–5.00 (m, 7 H, $OCH_2CH_2O$, OCH, $OCH_2CCl_3$). Tri-*n*-butyl phosphate and di-*n*-butyl phosphate were obtained from Tokyo Kasei Co. (Tokyo, Japan) and used without further purification. Benzoyl chloride and methyl lactate were distilled before use. All solvents employed were reagent grade, dried by a conventional method, and distilled under nitrogen prior to use. Dinitrogen tetraoxide, obtained from Seitetsu Kagaku Co. (Osaka), was taken from a cylinder and dried over phosphorus pentaoxide before use.

**Measurement.** $^{31}$P NMR spectra were recorded on a Hitachi R-900 FT-NMR instrument operated at 36.4 MHz with wide-band proton decoupling. $^{31}$P chemical shifts are given in parts per million from 85% $H_3PO_4$ external standard; positive chemical shifts are downfield from the standard. $^1$H NMR spectra were recorded on a Hitachi R-20B spectrometer with $SiMe_4$ as an internal standard. IR spectra were obtained on a Hitachi 260-50 spectrophotometer. Molecular weight of the polymers was determined by vapor pressure osmometry in DMF at 55 °C on a Hitachi Perkin-Elmer Model 115 instrument. Gas chromatographic analyses were carried out on a Schimadzu GC-6A chromatograph.

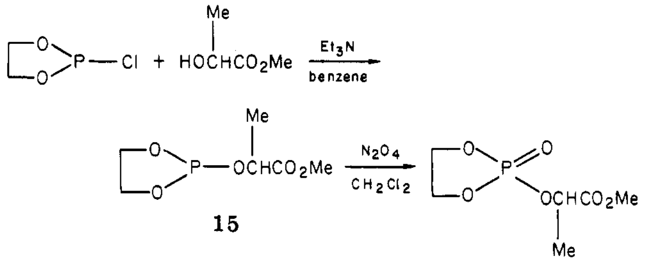
**General Procedure of Polymerization.** A typical procedure of hydrolysis polymerizations of **1a–c** is as follows, where **1a** is used as an example (entry no. 3 in Table I). To a stirred, 0 °C solution of freshly prepared **1a** (3.0 mmol) in 3 mL of acetonitrile was added under nitrogen 59 mg of distilled water (3.3 mmol) with a microsyringe. The mixture was gradually warmed to room temperature and allowed to stand for 5 days with stirring. During the reaction, a colorless paste was separated from the solution. After the polymerization, the paste was dissolved by adding 1 mL of DMF, and the solution was poured into 70 mL of dry diethyl ether to precipitate the polymeric materials. The precipitated product was separated, and the supernatant liquid was analyzed by GLC using *trans*-decalin as an internal standard to give the yield of phenol as 80% on the basis of reaction 1. The crude polymeric material was purified by repeated reprecipitation (twice from DMF solution to diethyl ether and once from trifluoroethanol solution to diethyl ether) to give 459 mg (78% yield) of the product as a white powdery material.

**Treatment of Di-*n*-butyl Phosphate and Tri-*n*-butyl Phosphate with Benzoyl Chloride.** To a stirred ice-cooled solution of 0.1 mL (0.5 mmol) of di-*n*-butyl phosphate in 1 mL of pyridine was added under nitrogen 0.2 mL (1.7 mmol) of benzoyl chloride. A part of the mixture was immediately placed into an NMR sample tube. Its $^{31}$P NMR spectrum showed quantitative formation of benzoyl phosphate **4** (δ −8.4). Treatment of tri-*n*-butyl phosphate with benzoyl chloride under similar reaction conditions caused no change in its $^{31}$P NMR signal at δ −0.9 even after 1 day at room temperature.

**Benzoylation of Polymer Samples for the $^{31}$P NMR Method.** A polymer sample (ca. 0.1 g, 0.5 unit mmol) was dissolved in 0.5 mL of DMF. The solution was cooled to 0 °C with an ice bath, and to this were added 0.3 mL (4 mmol) of pyridine and 0.3 mL (2.6 mmol) of benzoyl chloride successively. A part of the mixture was immediately placed into an NMR sample tube that had been dried and filled with nitrogen, and this sample was subjected to $^{31}$P NMR measurement.

**Polymer Salts of Triethylamine for the IR Method.** First, an IR sample of the product polymer was obtained as follows. About 20 mg of the polymer was dissolved in 1 mL of methanol and a few drops of this solution was placed on a KBr plate. The solvent was evaporated, and the IR spectrum was recorded. Then, to the remaining methanol solution was added a sufficient amount of triethylamine. The second IR sample was prepared from the solution, and the spectrum was recorded. Triethylamine was added again to the remaining methanol solution, and the third IR spectrum was recorded concerning this mixture. The quantitative formation of the salts **6a** and **6b** was confirmed by comparing the second and the third IR measurement, no increase in strength of the band at 1600 cm$^{-1}$ being observed from the second to third measurement.

**Preparation of Model Compounds.** Phenyl phosphate **9** was prepared previously.[11] Cyclic phosphate **10** was obtained by two-step reactions as follows.



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10

**2-(1-(Methoxycarbonyl)ethoxy)-1,3,2-dioxaphospholane (15).**[16] To an ice-cooled solution of methyl lactate (2.70 g, 25.9 mmol) and triethylamine (2.61 g, 25.8 mmol) in 30 mL of benzene was added dropwise with stirring a solution of 2-chloro-1,3,2-dioxaphospholane[17] (3.22 g, 25.5 mmol) in 10 mL of benzene during 25 min. Stirring was continued at room temperature for an additional 50 min. The precipitate of the ammonium salt was removed by filtration, and the filtrate was concentrated to give a pale yellow oil, which was distilled to afford 3.73 g (75%) of **15** as a colorless liquid: bp 63 °C (0.3 mmHg); $^1$H NMR ($CDCl_3$) δ 1.38 (d, $J$ = 7 Hz, 3 H, $CH_3$), 3.61 (s, 3 H, $CH_3OCO$), 3.73–4.23 (m, 4 H, $OCH_2CH_2O$), 4.50 (two q, $J_{HCCH}$ = 7.1 Hz, $J_{HCOP}$ = 8.6 Hz, 1 H, POCH); $^{31}$P NMR ($CDCl_3$) δ 135.4; IR (neat) 1740 (C=O), 1450, 1210, 1120, 1010, 920, 880, 735 cm$^{-1}$. Anal. Calcd for $C_6H_{11}O_5P$: C, 37.12; H, 5.71; P, 15.96. Found: C, 37.09; H, 5.51; P, 15.69.

**2-(1-(Methoxycarbonyl)ethoxy)-1,3,2-dioxaphospholane 2-Oxide (10).**[18] Into a solution of **15** (1.27 g, 6.53 mmol) in 15 mL of dichloromethane was introduced dinitrogen tetraoxide at −78 °C until the blue color of the oxidant did not disappear. The mixture was then kept at room temperature overnight. Concentration of the mixture and distillaton using a high-vacuum oil diffusion pump gave 1.00 g (73%) of **10**: bp 57 °C (0.005 mmHg); $^1$H NMR ($CDCl_3$) δ 1.58, 1.60 (two d, $J$ = 7 Hz, 3 H, $CH_3$), 3.80 (s, 3 H, $CH_3OCO$), 4.15–4.80 (m, 4 H, $OCH_2CH_2O$), 5.00 (two q, $J_{HCCH}$ = 7 Hz, $J_{HCOP}$ = 8 Hz, 1 H, CHOP); $^{31}$P NMR ($CDCl_3$) δ 17.0; IR (neat) 1750 (C=O), 1450, 1280, 1220, 1100, 1030, 925, 850 cm$^{-1}$. Anal. Calcd for $C_6H_{11}O_6P$: C, 34.29; H, 5.28. Found: C, 34.22; H, 5.39.

**Registry No.** **1a**, 61356-97-6; **1b**, 77989-23-2; **1c**, 77989-24-3; **10**, 88229-79-2; **15**, 88229-80-5.

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# Conformational Study of the Dinucleotide dGpdCp–Tetrapeptide Ala$_4$ Complex[†]

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ABSTRACT: Conformational analysis of dinucleotide dGpdCp and tetrapeptide β-alanine (Ala$_4$), to the complex has been carried out with an empirical potential function by varying all the independent degrees of freedom of the nucleotide and peptide backbones. To understand the factors involved in the change of one conformation to another, we have estimated approximately the configurational entropies of the conformer and water molecules bound to it by using a potential surface analysis method. The total free energy changes for each conformational transition between dGpdCp, Ala$_4$, and their complex at room temperature were calculated and compared with each other. The free energy change of the free dGpdCp and Ala$_4$ to the free complex is −70.0 kcal/mol, in which the interaction energy change is −49.5 kcal/mol and the entropy change is 68.9 eu. Through the hydration, there have been large changes of free energies: −664.0 kcal/mol for dGpdCp, −72.0 kcal/mol for Ala$_4$, and −682.3 kcal/mol for the complex. The entropy changes corresponding to them are −28.1, −48.3, and −178.5 eu, respectively. The free energy change of the hydrated dGpdCp and Ala$_4$ to the hydrated complex is −16.2 kcal/mol, in which the energy change is −26.1 kcal/mol and the entropy change is −33.2 eu. It is found that this entropy change is mainly caused by the conformational entropy change of dGpdCp and Ala$_4$ through the complex formation and that the major contribution to the total interaction energy is ascribed to the hydrogen bond between the conformer and water molecules bound to it, whereas the hydration effect of counterions and bound water molecules is proved to play an important role in determining the conformational stabilities of dGpdCp, Ala$_4$, and their complex in the hydrated state.

## I. Introduction

The recognition between nucleic acids and proteins is one of the most fundamental processes and plays a central role in molecular communication in all living cells.[1-4] Examples of such interactions include complexes between histone and DNA, between repressor and DNA, between restriction endonuclease and DNA, and between transfer RNA and cognate synthetase.

The "structural recognition" between nucleic acids and proteins can be classified into two categories: nonspecific interaction and specific interaction. In the former case, protein recognizes some common structural features of nucleic acids and in the latter case, protein recognizes a particular base sequence of nucleic acids. Although ample experimental results[5-9] and model approaches[10-14] are available for these interactions, we know very little about the detailed mechanism of such interactions at the atomic or structural level. Carter and Kraut[10] proposed a model for a double-stranded RNA (ds RNA) and an antiparallel two-stranded β-sheet (β-ribbon), in which the 2′-hydroxyl of the ribose in RNA forms a hydrogen bond to the free carbonyl oxygen of the peptide backbone and the free NH group forms two hydrogen bonds through a water molecule with the ring oxygen and the 2′-hydroxyl oxygen of the next nucleotide on the narrow groove of ds RNA. They also pointed out that there is no room in the antiparallel β-ribbon for residues other than those with very small side-chain groups since the narrow groove of ds RNA is too shallow and ruled out the possibility of a similar model for ds DNA because DNA lacks a 2′-hydroxyl group and

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