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Spontaneous Alternating Copolymerization of Six-Membered Cyclic Phosphonites with Lipoic Acid

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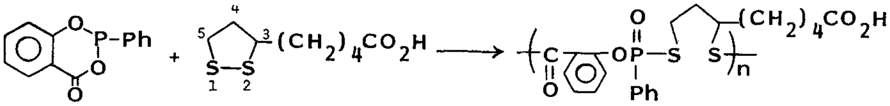
SUMMARY

Alternating copolymerizations of six-membered cyclic phosphonites as M_N with lipoic acid as M_E are described. The phosphonites employed were salicylyl phenyl phosphonite(SPO) and 2-phenyl-1,3,2-dioxaphosphorinane (trimethylene phenylphosphonite, TPO). The copolymerization took place without catalyst at 0°C or room temperature. The reaction of SPO with lipoic acid gave alternating copolymer **1**, which was formed directly from a genetic zwitterion **4**. On the other hand, the reaction of TPO with lipoic acid gave alternating copolymer **2**, which was produced after a proton transfer as well as an *O-S* scrambling giving rise to units **2A** and **2B**, respectively. Both copolymers 1 and 2 have a lipoic acid component in the main chain.

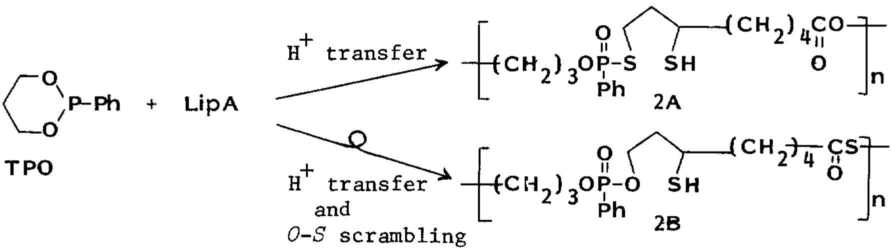
INTRODUCTION

Polymerizations involving a proton-transfer step are well known in "no-catalyst copolymerizations via zwitterion intermediates"(1). One of such examples using a nucleophilic phosphorus monomer has recently been published by us(2). It is known that disulfide bond is cleaved by trivalent phosphorus compound giving rise to a phosphonium-thiolate zwitterion(3). The thiolate anion is capable of accepting a proton to give a thiol group. Namely, a disulfide group is an electrophilic reagent as well as a "proton-acceptor"(3). 5-(1,2-Dithiolane-3-yl)pentanoic acid (lipoic acid, LipA), which has both a cyclic disulfide bond and a carboxylic acid group in a single molecule, would be expected to be an electrophilic monomer(M_E) when LipA is combined with a nucleophilic monomer(M_N) in our "no-catalyst copolymerizations". It is to be mentioned that LipA is an important coenzyme for the acyl transfer and oxidation-reduction reactions in the biological systems.

Here, we report a new alternating copolymerization of two six-membered cyclic phosphonites(M_N) with LipA(M_E). The phosphorus monomers used are salicylyl phenyl phosphonite(SPO) and 2-phenyl-1,3,2-dioxaphosphorinane (trimethylene phenylphosphonite, TPO). Copolymers(1 and 2) have a chain consisting of phosphorus monomer and LipA in 1:1 composition. When this study was under progress, the polymerization of LipA using tributylphosphine as a deoxygenating agent has been reported(4). In this case the trivalent



SPO LipA 1



phosphine abstracted an oxygen atom from LipA to produce tributylphosphine oxide and the residual part of LipA gave poly(thio-1-oxo-6-mercaptooctamethylene). In the present copolymerization, however, SPO and TPO behave as comonomer of LipA and constitute the main chain of the resulting copolymers.

RESULTS AND DISCUSSION

Copolymerization

An equimolar mixture of SPO and LipA in $CHCl_3$ without added initiator was kept at room temperature and the copolymerization took place to give copolymer 1. Similarly, the copolymerization of TPO with LipA occured at room temperature or 0°C without initiator to yield copolymer 2. These results are shown in Table 1. Copolymer 1 is a white powdery material and 2 is a gummy substance. They are hygroscopic and soluble in common polar organic solvents such as $CHCl_3$, CH_2Cl_2, DMSO, DMF, but insoluble in less polar solvents like diethyl ether or hexane and in water.

Table 1

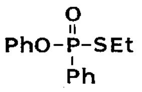
Spontaneous Alternating Copolymerization of SPO and TPO with LipA[a]

No	P(III) Monomer	Reaction		Copolymer	
		Temp.	Time(day)	Yield(%)	Mol.wt.[b]
1	SPO	r.t.	11	88	1500
2	SPO	r.t.	7	30	2600
3	TPO	r.t.	10	82	16100[c]
4	TPO	0°C	4	70	10300[c]

a) P(III) monomer=LipA=3 mmol in 3 ml of $CHCl_3$.
b) Determined by VPO in $CHCl_3$ at 35°C.
c) Measured with acetylated sample polymer.

Copolymer Structures

The IR spectrum of copolymer from the SPO-LipA system showed characteristic stretching bands at 1665 cm^{-1} (ArC(=O)S), 1230 cm^{-1} (P=O), and 1720 as well as 2500-3300 cm^{-1} (CO_2H). The ^{31}P NMR of the copolymer in $CHCl_3$ showed two peaks at +44.4 and +43.0 ppm(lower magnetic field relative to external H_3PO_4 standard) in a ratio of 69% and 31%. The peaks at this area are ascribed to the structure like -OP(Ar)(=O)S- (5). To confirm this assignment a model compound of *S*-ethyl phenyl phenylphosphonothiolate (3) as a unit of the copolymer was prepared, which showed a single peak at +43.3 ppm in $CHCl_3$. The splitting into two peaks is due to whether S1 or S2 atom of LipA is linked to the phosphorus. The form of the P-S1 linkage is probably more than that of P-S2 and is illustrated in copolymer structure 1. ^1H NMR and elemental analysis data(Table 2) supported the 1:1 composition of the two monomers. ^{13}C NMR spectrum of the copolymer showed two peaks of carbonyl carbons at +174.8 and 190.4 ppm, which were assigned to the pendant carboxylic acid and the thiolester carbonyl carbon, respectively(6). All these data support the structure of


$PhO-\overset{\overset{O}{\|}}{\underset{\underset{Ph}{|}}{P}}-SEt$

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the copolymer given by **1**.

Table 2
Elemental Analysis of Copolymers

Sample No	Formula[a]		C(%)	H(%)	P(%)
1	$[(C_{21}H_{23}O_5PS_2)(H_2O)_{0.5}]_n$	Calcd	54.89	5.26	6.74
		Found	54.90	5.36	5.60
2	$[(C_{21}H_{23}O_5PS_2)(H_2O)_{0.5}]_n$	Calcd	54.89	5.26	6.74
		Found	54.99	5.28	6.22
3	$[(C_{19}H_{27}O_5PS_2)(H_2O)_{0.5}]_n^b$	Calcd	51.92	6.42	7.05
		Found	51.91	6.56	6.84
4	$[(C_{19}H_{27}O_5PS_2)(H_2O)_{0.5}]_n^b$	Calcd	51.92	6.42	7.05
		Found	52.22	6.44	6.34

a) Calculated for the 1:1 composition with taking the water due to incomplete drying into account.
b) Obtained for the acetylated polymer sample.

The presence of the pendant carboxylic acid group was confirmed by IR spectroscopy. Namely, the copolymer solution was treated with triethylamine, and then, the characteristic stretching bands due to the carboxylic acid group shifted from 1720 to 1620 cm^{-1} due to the formation of carboxylate anion ($\sim CO_2^-$) and from 2500-3300 to 2100-2600 cm^{-1} due to the formation of ammonium ion (Et_3N^+H)(7).

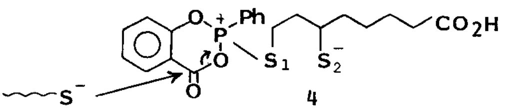
The IR spectrum of copolymer from the TPO-LipA system, on the other hand, showed characteristic stretching bands at 2530 cm^{-1} (-SH), 1730 cm^{-1} (ester, $-CO_2-$), 1690 cm^{-1} (thiolester, -COS-), and 1230 cm^{-1} (P=O). No peak due to free carboxylic acid groups was detected. The ^{31}P NMR of the copolymer showed three main peaks at +44.4(relative intensity, 49%), +43.0(19%) and +20.0 ppm(25%). Other small unidentified peaks were also observed. The peaks of +44.4 and +43.0 ppm are ascribed to the structure of unit **2A** whereas the peak of +20.0 ppm is assigned to a phosphonic acid ester of unit **2B**. In **2A** the major unit is the form having P-S1 bond and the minor is that having P-S2 bond which is not given in **2A** for the sake of brevity. ^1H NMR and elemental analysis data(Table 2) are in accord with the 1:1 composition of TPO and LipA.

When the gummy polymer sample was kept in air overnight, it became hardly soluble. This is thought to be due to crosslinking to form a disulfide bond by air-oxidation of thiol groups. Therefore, the copolymer was treated with an excess amount of acetic anhydride and pyridine. This procedure gave a acetylated copolymer which did not show a stretching band at 2530 cm^{-1} due to -SH anymore in the IR spectrum but instead the stretching band at 1690 cm^{-1} due to -C(=O)S- group became stronger. The copolymer showed a ^1H NMR signal at $\delta 2.3$ ascribable to acetyl protons. The acetylated sample remained soluble even after exposed to air overnight.

All the above data support the copolymer structure consisted of two units of **2A** and **2B**. The formation of unit **2A** involves a proton-transfer from $-CO_2H$ to -SH whereas that of unit **2B** involves a proton-transfer as well as a scrambling of oxygen and sulfur atoms.

Copolymerization Mechanism

The first step of the alternating copolymerization between SPO and LipA is the formation of a genetic zwitterion(4) in which only the structure



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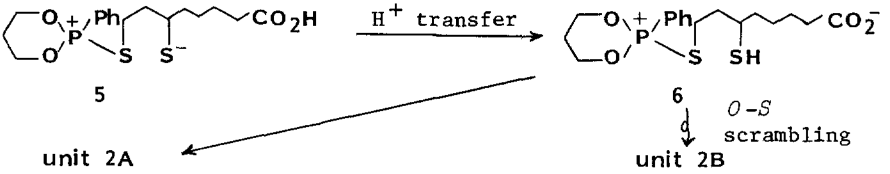
having P-S1 bond is indicated. Here, SPO acted as M_N and LipA behaved as M_E. Then, successive reactions between zwitterions via the attack of thiolate anion on the carbonyl carbon give rise to the formation of alternating copolymer **1**.

On the other hand, the copolymerization course of TPO with LipA is more complicated. The first formed zwitterion **5** does not react directly further. **5** undergoes a proton transfer to give **6** whose reaction leads to the production of unit **2A**. Unit **2B** is formed with involving an *O-S* scrambling from zwitterion **6**. The elucidation of the detailed mechanism of the scrambling, however, must await further studies.



EXPERIMENTAL PROCEDURES

Materials

LipA was a commercial reagent which was purified by recrystallization from cyclohexane (mp 59-61°C). SPO and TPO were obtained by reactions of dichlorophenylphosphine with salicylic acid and 1,3-propanediol, respectively; SPO (mp 40.5°C, ^{31}P NMR signal at +158.6 ppm) and TPO (78-80°C/1.0 mmHg, ^{31}P NMR signal at +151.6 ppm).

A model compound of *S*-Ethyl phenyl phenylphosphonothiolate(**3**) was obtained as follows. A mixture of phenol(30 mmol) and triethylamine(33 mmol) in 50 ml of benzene was slowly dropped with stirring into 30 ml of benzene solution of phenylphosphonic dichloride(30 mmol) at 0°C. After standing at room temperature for 2.5 hrs, the mixture was cooled down to 0°C, to which a benzene solution(30 ml) of ethanethiol(30 mmol) and triethylamine(30 mmol) was added for 30 min. The mixture was further allowed to react for 2 hrs at room temperature. After filtration and evaporation of solvent, **3** was isolated by thin layer chromatography in 38% yield; ^{31}P NMR at +43.3 ppm; ^{1}H NMR δ1.12(t, 3H, CH_3), 2.84(m, 2H, SCH_2), 7.0-8.0(m, 10H, aromatic protons); MS m/e=278.

Copolymerization

A typical copolymerization experiment was carried out as follows. A solution of LipA(3.0 mmol) in 1.5 ml of $CHCl_3$ was added dropwise into a solution of SPO(3.0 mmol) in 1.5 ml of $CHCl_3$ at -30°C under nitrogen. The tube was sealed and kept at room temperature for 11 days. Then, the tube was opened and polymeric materials was obtained by precipitation of the reaction mixture into a large amount of diethyl ether, which was separated and dried in vacuo to give 1.19 g of copolymer **1**(88% yield).

Acetylation of Copolymer 2

After the polymerization reaction, the sealed tube was opened and the reaction mixture(3.0 mmol scale) was immediately dropped into a mixture of acetic anhydride(6.4 mmol) and pyridine(6.2 mmol) under nitrogen. After stirring overnight at room temperature, the polymer solution was poured into an excess amount of diethyl ether to precipitate the acetylated polymer **2**.

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