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Reactions between β-Propiolactone and Dialkyl Dimethylphosphoramidite-Ambident Character of β-Propiolactone and of Dialkyl Dimethylphosphoramidite

Jugo KOKETSU,*[1] Seiji Kojima and Yoshio ISHII

Department of Synthetic Chemistry, Faculty of Engineering, Nagoya University, Nagoya

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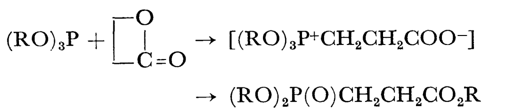
The reactions between dialkyl dimethylphosphoramidite, $Me_2NP(OR)_2$, and β-propiolactone were carried out in various solvents at 80°C. Two kinds of reaction products were separated on a silica gel by elution with benzene-ethanol (4 : 1 v/v). The first species eluted was *N,N*-dimethyl-*O*-alkyl 2-alkoxycarbonylethylphosphoramidate, $(RO)P(O)(NMe_2)CH_2CH_2CO_2R$. The fraction having lower R_f value contained dialkyl 2-*N,N*-dimethylcarbamoylethylphosphonate, $(RO)_2P(O)CH_2CH_2CONMe_2$. The reaction mechanism is discussed from kinetic study.

During the course of studies on the reactions of aminophosphines, we found that aminophosphines showed an ambident nature in their reactions with various kinds of electrophilic reagents, such as phenyl cyanate,[1] alkyl benzenesulfonate,[2] dialkyl sulfates,[2] acetic anhydride,[3] and cyclic carbonate esters.[4] On the other hand, β-propiolactone is well known to be cleaved through either alkyl-oxygen bond or acyl-oxygen bond in the reactions with various nucleophilic reagents. The mode of ring-opening of β-propiolactone depends upon the nature of nucleophiles. Therefore, in the reaction between aminophosphine and β-propiolactone, several reaction products would be obtained.

McConnell and Coover[5] reported that β-propiolactone reacted with trialkyl phosphite to give dialkyl 2-alkoxycarbonylethylphosphonate. This results from the attack of the trivalent phosphorus atom on the β-carbon atom of β-propiolactone followed by Arbuzove-like rearrangement, as shown by the following equation.



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*[1] Present address: Department of Synthetic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya.

1) J. Koketsu, S. Sakai and Y. Ishii, *Kogyo Kagaku Zasshi*, **72**, 2503 (1969).

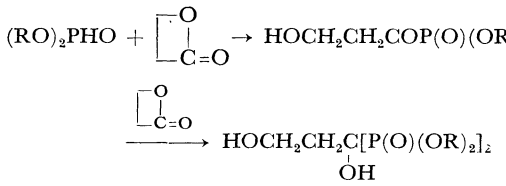
2) J. Koketsu and Y. Ishii, This Bulletin, **34**, 2527 (1970).

3) J. Koketsu, S. Sakai and Y. Ishii, *Kogyo Kagaku Zasshi*, **73**, 205 (1970).

4) J. Koketsu, S. Sakai and Y. Ishii, *ibid.*, **73**, 201 (1970).

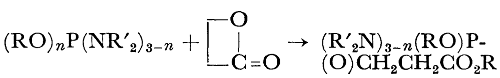
5) R. L. McConnell and H. W. Coover, Jr., *J. Amer. Chem. Soc.*, **78**, 4453 (1956).

They also found[6] that acyl-oxygen bond fission occured in the reaction with dialkylphosphite:



(2)

As regards the reaction of β-propiolactone with dialkyl dialkylphosphoramidite and alkyl tetraalkylphosphorodiamidite, they disclosed in U. S. Patent[7] that the products obtained were *N,N*-dialkyl-*O*-alkyl 2-alkoxycarbonylethylphosphoramidate ($n=2$ in Eq. (3)) and *N,N,N′,N′*-tetraalkyl 2-alkoxycarbonylethylphosphonic diamide ($n=1$ in Eq. (3)), respectively, and that the P–N bond was not cleaved at all.



(n=1 or 2) (n=1 or 2) (3)

However, we found that diphenyl dimethylphosphoramidite reacted with β-propiolactone to give *N,N*-dimethylacrylamide and undistillable polymer containing P(O), P–O–Ph, and P–O–P groups, and that in the reaction of β-propiolactone with *N,N*-dimethyl diphenylphosphinous amide, poly-β-propiolactone was obtained quantitatively.[8]

6) R. L. McConnell and H. W. Coover, Jr., *ibid.*, **78**, 4450 (1956).

7) R. L. McConnell, H. W. Coover, Jr., and K. Tenn, U.S. 3121105 (1964).

8) J. Koketsu, S. Sakai and Y. Ishii, Preprint of Autumn Meeting of the Chem. Soc. of Japan, (Nagoya, 1969), p. 136.

$$(PhO)_2PNMe_2 + \begin{matrix} -O \\ | \\ -C=O \end{matrix} \rightarrow [(PhO)_2POCH_2CH_2\text{-}CONMe_2]$$

$$\rightarrow Me_2NCOCH{=}CH_2 + \text{"polymer"} \quad (4)$$

$$Ph_2PNMe_2 + \begin{matrix} -O \\ | \\ -C=O \end{matrix} \rightarrow [Ph_2P^+(NMe_2)CH_2CH_2CO_2^-]$$

$$\rightarrow -(CH_2\ CH_2CO_2)-n \quad (5)$$

It seemed worthwhile to reinvestigate the reaction between β-propiolactone and dialkyl dimethylphosphoramidite in order to elucidate the discrepancies between the above results.

Experimental

Commercial β-propiolactone was distilled before use. All the solvent were thoroughly dried over calcium hydride and distilled before use. The reactions and measurements of physical constants of the products were carried out under dry nitrogen. Infrared and NMR spectra were measured on a Nippon Bunko IR 403G Spectrometer and a Japan Electron Minimer spectrometer. Thin-layer chromatography was carried out on 250 mμ thick silica gel layer by using benzene - ethanol (4 : 1 v/v). Column chromatography was performed in a column 50 cm long (ratio of column length to diameter=20 : 1). Into the column filled with 40 g of 100 mesh silica gel (Mallinckrodt Chemical Works) was put 1—2 g of samples by the wet method and eluted by benzene - ethanol (4 : 1 v/v).

Synthesis of Dialkyl Dimethylphosphoramidites. To a solution of lithium alkoxide, prepared from the corresponding alcohol and *n*-butyllithium in petroleum ether, an equimolar amount of Me_2NPCl_2 was added slowly with ice-cooling. After stirring for 30 min at room temperature, the mixture was refluxed for 1 hr. Separation of lithium chloride and removal of the solvent gave crude phosphoramidite which was purified by column-distillation. Boiling points and the yields of the phosphoramidites are shown in Table 1.

Table 1. Dialkyl dimethylphosphoramidites

Compound	Bp (°C/mmHg)	Yield (%)
$(i\text{-PrO})_2PNMe_2$	Ia 62—65/7.0	75.5
$(s\text{-Bu})_2PNMe_2$	Ib 47—52/3.5	78.4
$(n\text{-PrO})_2PNMe_2$	Ic 75—84/5.4	73.0
$(EtO)_2PNMe_2$	Id 40—48/12.0	55.6

Reaction of $(i\text{-PrO})_2PNMe_2$ (Ia) with β-Propiolactone. β-Propiolactone (1.5 g, 21 mmol) was added to a solution of Ia (40 g, 20.9 mmol) in 40 m*l* of benzene, and the mixture was allowed to stand for 30 hr at 80°C. Completion of the reaction was confirmed by means of IR absorption spectrum. After removal of the solvent, a fraction having boiling point range of 50—100°C/0.007 mmHg was obtained in 75% yield (4.28 g). The fraction showed two spots on thin-layer chromtography at R_f=0.62 and 0.50. By column chromatographic treatment on silica gel, two species II and III were obtained. The first species II was identified as *N,N*-dimethyl-*O*-isopropyl 2-isoproxycarbonylethylphosphoramidate, yield 2.60 g (45% based on Ia), and the other III as diisopropyl 2-*N,N*-dimethylcarbamoylethylphosphonate, yield 1.67 g (29% based on Ia), by their NMR and IR spectra, respectively, shown in Tables 2 and 3, and by their elemental analyses.

II: Found: C, 49.26; H, 9.30; P, 11.53%. Calcd for $C_{11}H_{24}NO_4P$: C, 49.80; H, 9.12; P, 11.67%. III: Found: C, 49.74; H, 9.38; P, 11.59%. Calcd for $C_{11}H_{24}NO_4P$: C, 49.80; H, 9.12; P, 11.67%.

Reaction of $(s\text{-BuO})_2PNMe_2$ (Ib) with β-Propiolactone. The reaction betwene Ib (3.60 g, 16.2 mmol) and β-propiolactone (1.17 g, 16.2 mmol) was carried out in a similar way by refluxing their mixture in 30 m*l* of benzene for 46 hr. After the reaction was over, the reaction mixture was distilled under reduced pressure to give a fraction having the boiling point range of 39—110 °C/0.01 mmHg. By column chromatographic treatment on silica gel, two species IV and V were obtained. The first species IV eluted was proved to be *N,N*-dimethyl-*O*-*s*-butyl 2-*s*-butoxycarbonylethylphosphoramidate, yield 2.41 g (49% based on Ib), and the other V to be di-*s*-butyl 2-*N,N*-dimethylcarbamoylethylphosphonate, yield 1.52 g (31% based on Ib), by their spectral data shown in Tables II and III, and by elemental analyses.

IV: Found: C, 52.64; H, 10.19%. Calcd for $C_{13}H_{28}NO_4P$: C, 53.23; H, 9.62%. V: Found: C, 52.43; H, 9.82; P, 10.49%. Calcd for $C_{13}H_{28}NO_4P$: C, 53.23; H, 9.62; P, 10.91%.

Reactions of $(n\text{-PrO})_2PNMe_2$ (Ic) and $(EtO)_2PNMe_2$ (Id) with β-Propiolactone. The reaction between Ic (4.00 g, 21 mmol) and β-propiolactone (1.50 g, 20 mmol) was carried out by refluxing the benzene solution (40 m*l*) for 51 hr. Distillation of the reaction mixture gave a fraction which had a boiling point range of 39—119°C/0.02 mmHg (4. 91 g, 85% based on Ic). This distillate exhibited strong IR absorption at 1740 and 1658 cm^{-1} in equal intensity, which could be assigned to the stretching frequencies of an ester carbonyl and an amide carbonyl group, respectively. Other strong absorption bands appeared at 1245 (P=O) and 990 cm^{-1} (P–O–C). In the NMR spectrum, there were a doublet at τ 7.50 (J=10 Hz) which could be ascribed to P–NMe_2 protons, and two singlets at τ 7.45 and τ 7.60 assignable to –$CONMe_2$. However, when the reaction product was chromatographed on silica gel, it decomposed to various species such as di-*n*-propyl phosphite, a polymer which contained phosphoryl group and unidentified substances.

The same phenomenon as that of the above experiment was observed in the reaction of $(EtO)_2PNMe_2$ (Id) with β-propiolactone, and no identified product was obtained.

Reaction of II, III, IV and V with Elementary Sulfur. Equimolar amounts of elementary sulfur were added to a solution of II in ethyl ether. Even after refluxing this solution for two days, sulfur did not react, and phosphonamidate II was recovered quantitatively. In the cases of III, IV and V also, sulfur addition reaction did not occur at all.

Kinetic Study on the Reaction between Ib and β-Propiolactone. A solution containing 0.1807 mol/*l* of Ib and 0.2070 mol/*l* of β-propiolactone was prepared and divided into several ampoules filled with nitrogen and then sealed. The sealed ampoules were heated in a bath kept at 80±0.5°C. At an appropriate time interval, an ampoule was broken and the concentrations

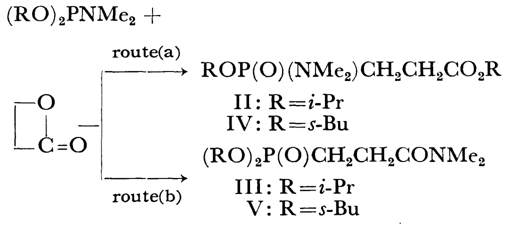
of IV and V were determined from the intensity of the absorptions at 1743 and 1658 cm^{-1}, respectively.

Results and Discussion

Contrary to the results of McConnell *et al.*,[7] two kinds of products were obtained in the reaction between dialkyl dimethylphosphoramidite and β-propiolactone. The two products were identified to be *N,N*-dimethyl-*O*-alkyl 2-alkoxycarbonylethylphosphoramidate (II and IV) and dialkyl 2-*N,N*-dimethylcarbamoylethylphosphonate (III and V) by their chemical behavior and spectral data. None of them reacted with elementary sulfur. Thus, it is likely that they have a quinquevalent phosphorus atom rather than the trivalent phosphorus atom. In the NMR spectrum of II, shown in Table 2, the methyl protons of isopropyl group of II showed two doublets at τ 8.73 and 8.42, and in the case of IV, those of *s*-butyl group showed complex multiplets at τ 8.50—9.45. The results indicate that each of the two alkoxy groups attaches itself to different sites of the molecules. In addition, the β-substituted ethyl protons were observed over the range of τ 7.20—8.40 as a complex multiplet, which could be explained by the fact that the ethyl group attaches itself to the phosphorus atom.

In IR spectra, shown in Table 3, there were strong absorptions at 1740 and 1240 cm^{-1} in both II and IV, which could be assigned to the carbonyl stretching frequency of ester group and to P=O group, respectively. Thus, the structures of II and IV were confirmed as phosphoramidate.

By similar chemical and spectral evidence as that of the above discussion, it could be assumed that III and V have phosphonate structures. Therefore, it would be reasonable to assume that there are two routes to give different reaction products as visualized in the following equation.



(6)

In order to elucidate the reaction mechanism, kinetic study on the reaction between Ib and β-propiolactone was carried out in various solvents by determining the absorbances of IR frequencies at 1743 and 1658 cm^{-1}, which are characteristic absorptions of IV and V, respectively. The rates of the formation of IV and V in the initial stage of the reaction satisfied typical first order kinetics. The first order rate constants [k_1(phosphoramidate) and k_1(phosphonate)] obtained in five solvents are sum-

Table 2. NMR spectra or the addition products; $(RO)P(O)(NMe_2)CH_2CH_2CO_2R$ (II, R=*i*-Pr; IV, R=*s*-Bu) and $(RO)_2P(O)CH_2CH_2CONMe_2$ (III, R=*i*-Pr; V, R=*s*-Bu)[a)]

Compound	assignment (τ)		POR and CO_2R
	NMe_2	$-CH_2CH_2-$	
II	7.60 (d, J=9.0 Hz)	7.20—8.50 (m)	5.26 (m), 8.35 (d), 8.42 (d).
III	7.32, 7.66	7.20—8.40 (m)	5.30 (m), 8.80 (d),
IV	7.55 (d, J=9.0 Hz)	7.20—8.40 (m)	5.10 (m), 5.54 (m), 8.75 (d), 9.15 (t)
V	7.31, 7.64	7.20—8.40 (m)	5.48 (m), 8.55 (m), 8.50—9.45 (m)

a) In 15% benzene solution.

Table 3. IR spectra of the addition products (II, III, IV and V) in 3% benzene solution

Compound	Absorptions
II	2990 (m), 2970 (m), 2870 (w), 1738 (vs), 1430 (m), 1383 (m), 1370 (m), 1240 (s), 1176 (s), 1139 (w), 1108 (s), 983 (vs), 886 (m), 812 (w), 772 (w), 672 (w).
III	2985 (m), 2920 (m), 2880 (w), 1650 (vs), 1500 (m), 1468 (m), 1455 (m), 1418 (m), 1403 (m), 1388 (m), 1377 (m), 1342 (s), 1242 (s), 1178 (m), 1108 (s), 985 (vs), 890 (m), 782 (m), 685 (m).
IV	2970 (m), 2800 (w), 1743 (vs), 1460 (m), 1420 (m), 1380 (m), 1243 (s), 1170 (m), 1122 (m), 1112 (m), 1092 (w), 1025 (m), 970 (vs), 810 (m).
V	2980 (w), 2900 (w), 1658 (vs), 1450 (m), 1394 (m), 1379 (m), 1325 (vs), 1242 (s), 1200 (m), 1170 (w), 1125 (m), 1100 (m), 1025 (m), 975 (vs), 955 (m), 850 (w), 810 (w), 760 (w).

Table 4. First order rate constants; k_1 (phosphoramidate), k_1 (phosphonate) for the formation of IV and V at 80±0.5°C[a]

Solvent	Dielectric constant (ε)	$10^5\,k_1$ (phosphoramidate) (sec^{-1})	$10^5 k_1$(phosphonate) (sec^{-1})
Acetonitrile	3.75	very fast[b]	very fast[b]
o-Dichlorobenzene	9.93	5.43	1.73
Tetrahydrofuran	7.93	3.57	2.11
Tetralin	2.76	1.07	0.74
Benzene	2.28	0.75	0.67

a) $[Ib]_0=0.1807$ mol/*l*, [*β*-Propiolactone]$_0=0.2070$ mol/*l*.
b) The reaction was completed within 30 min.

marized in Table 4.

A fairly good linear relationship exists between the logalithms of the rate constants and the Kirkwood parameter $(\varepsilon-1)/(2\varepsilon+1)$, as shown in Fig. 1.

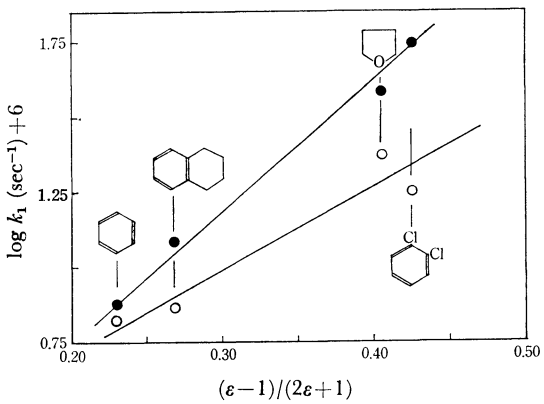


Fig. 1. Effect of solvent polarity on the rate constant; k_1 (phosphoramidate) —●— and k_1 (phosphonate) —○—.

Relative amounts of IV/V were determined in some solvents at the end point of the reaction by their IR absorption. The results are summarized in Table 5.

Table 5. Relative amount (IV/V) in various solvents at the termination of the reaction

Solvent	Dielectric constant (ε)	IV/V
Acetonitrile	37.5	5.77
o-Dichlorobenzene	9.93	2.31
Tetrahydrofuran	7.93	2.15
Benzene	2.28	1.58

It is clear from Fig. 1 and Table 5 that the overall rate of the reaction is more accelerated in polar solvent than in nonpolar solvent and that the relative amounts (IV/V) increase with increasing polarity of the solvent. This indicates that V was formed *via* the intermediate (VI) in which large charge-separation occurs. The mechanism of this reaction could be rationalized as follows: In the reaction of route(a) in Eq. (6), the sp^3 carbon of *β*-propiolactone is attacked by the phosphorus atom of the phosphoramidite to give betaine intermediate, and succeeding Arbuzov-like rearramgement of alkyl group gives phosphoramidate (II and IV) as shown in the following.

$$(RO)_2PNMe_2 + \underset{C=O}{\overset{O}{\square}} \rightarrow [(RO)_2P^+(NMe_2)CH_2CH_2COO^-] \quad \text{VI} \rightarrow (RO)P(O)(NMe_2)CH_2CH_2CO_2R \quad (7)$$

II: R=*i*-Pr
IV: R=*s*-Bu

On the other hand, in the reaction of route (6) in Eq. (6). the sp^2 carbon of *β*-propiolactone is attacked by the nitrogen atom of the phosphoramidite with synchronous interaction between the oxygen atom of the ester group and the phosphorus atom as visualized by the following equation.

$$(RO)_2PNMe_2 + \underset{C=O}{\overset{O}{\square}} \rightarrow \left[\begin{array}{l} O \\ \| \\ Me_2N\cdots C \\ \vdots \quad \vdots \\ (RO)_2P\cdots O \end{array} \right] \quad \text{VII} \rightarrow \left[Me_2NCOCH_2CH_2\cdots\overset{\cdots O\cdots}{P}(OR)_2 \right] \rightarrow Me_2NCOCH_2CH_2P(O)(OR)_2 \quad (8)$$

III: R=*i*-Pr
V: R=*s*-Bu

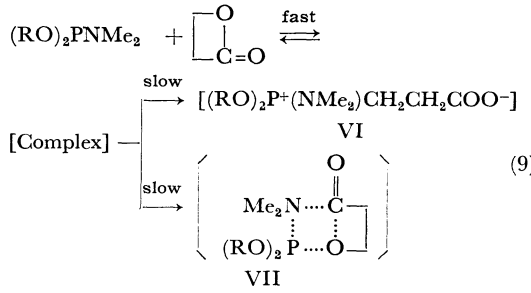
This four-centered mechanism explains the fact that the formation of V is less influenced than that of IV by solvent polarity.

In our former study on the reaction of aminophosphine with acetic anhydride[3] and cyclic carbonate esters,[4] the analogous four-centered mechanism was adopted.

According to Pearson, the sp^3 carbon atom may be a softer acid than the sp^2 carbon atom and also the phosphorus atom would be a softer base than the nitrogen atom. Therefore, it is relevant to as-

sume that in this reaction the softer phosphorus atom would attack preferably the sp^3 carbon atom of β-propiolactone, whereas the harder nitrogen atom interacts with the sp^2 carbon atom of β-propiolactone.

In this reaction, the rate determining step might be assumed from the solvent effect on the reaction to be the formation of betaine VI or four-centered intermediate VII. The fact that this reaction satisfied first order kinetics shows the existense of "complex" equilibrating quikly between phosphoramidite and β-propiolactone before the rate determing step:



(9)

Existence of this complex could not be identified spectroscopically or by other methods.