Preparation of Alkyl Dihydrogenphosphates with Monomeric Metaphosphate Anion Generated by Photochemical C–P Bond Cleavage of *p*-Nitrobenzylphosphonic Acid

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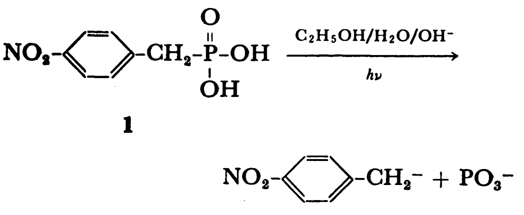
Alkyl dihydrogenphosphates were prepared by a procedure that probably involves a monomeric metaphosphate anion as an intermediate. The monomeric metaphosphate anions used in this reaction were generated by a photochemical C–P bond cleavage of the *p*-nitrobenzylphosphonate dianion. The photolysis of a 1:2 molar mixture of *p*-nitrobenzylphosphonic acid and 1,8-diazabicyclo[5.4.0]undec-7-ene (or 2,2,6,6-tetramethylpiperidine) in excess alcohol gave alkyl dihydrogenphosphate in fairly good yield.

In our previous study of the photolysis of *p*-nitrobenzylphosphonic acid (**1**) in an alkaline 80% ethanol solution, we observed the heterolytic cleavage of the C–P bond and the generation of monomeric metaphosphate anions (**2**) with a high efficiency (Eq. 1—4).[1]

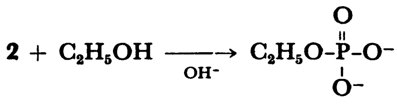
For almost 30 years, metaphosphate (**2**) has been postulated as an intermediate in the hydrolysis of phosphate esters and has been suggested as an essential phosphorylating agent in reactions involving intermediary metabolism.[2] Excellent evidence that **2** acts as a phosphorylating agent in solution has been accumulating.[3—9] Recently, Ramirez et al. reported that alkyl dihydrogenphosphates were conveniently prepared by a procedure involving **2** as an intermediate: An acetonitrile solution of 2,4-dinitrophenyl dihydrogenphosphate, or (*erythro*-1-phenyl-1,2-dibromopropyl)phosphonic acid containing 2 molar equivalents of the hindered tertiary amine behaves thermally as a source of **2** at ambient temperature. By this method, sensitive and valuable alcohols can be converted into alkyl dihydrogenphosphates.[10]

Kirby reported the photochemical phosphorylation of methanol with 3,5-dinitrophenyl dihydrogenphosphate.[11] When a 70% methanol solution of cyclohexylammonium 3,5-dinitrophenyl hydrogenphosphate (2.8 mmol dm^{-3}) at pH 9 was irradiated at room temperature, methyl dihydrogenphosphate was obtained in 58—68% yield.

We have now established a novel procedure for the photochemical phosphorylation of alcohol using **2** generated by the photolysis of **1** in the presence of an organic base. The acid **1** was readily made available through the nitration of benzylphosphonic acid.

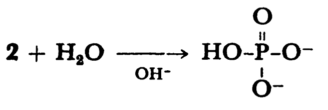


1 **2** (1)



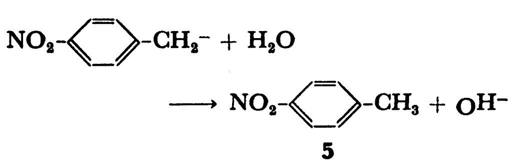
$$2 + C_2H_5OH \xrightarrow[OH^-]{} C_2H_5O\text{-}\overset{O}{\overset{\|}{P}}\text{-}O^- \atop \quad\quad\quad\quad\quad\quad\quad O^- \quad (2)$$

3b



$$2 + H_2O \xrightarrow[OH^-]{} HO\text{-}\overset{O}{\overset{\|}{P}}\text{-}O^- \atop \quad\quad\quad\quad\quad O^- \quad (3)$$

4



(4)

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Results and Discussion

An 80% ethanol solution of **1** (50 mmol dm^{-3}) at pH 12, was adjusted with sodium hydroxide in a Pyrex tube. Upon irradiation by a high-pressure mercury lamp at ambient temperature, a highly efficient C—P bond cleavage of **1** occurred. The course of the reaction was followed by a GLC analysis of 4-nitrotoluene (**5**). The quantum yield was 0.86, which was larger than that of the photolysis of sodium 3-nitrophenyl hydrogenphosphate (ϕ= 0.05—0.24).[12] The phosphorus compounds were analyzed by ^{31}P NMR spectrometry. The photolysis was completed within about 30 min, and dianions of ethyl dihydrogenphosphate $C_2H_5OPO_3^{2-}$ (**3b**), ^{31}P NMR (80% C_2H_5OH, pH 12) δ=3.6 (t, J_{PH}=5.6 Hz), and orthophosphoric acid $HOPO_3^{2-}$ (**4**), δ=2.6 (s) were formed in 28 and 72% yields, respectively.

The disodium salt of **1** is only slightly soluble in anhydrous alcohol, but its amine salts are soluble. The anhydrous ethanol solutions of **1** (30 mmol dm^{-3}) containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, pK_a 11.5) were irradiated to give **3b**. The yield of **3b** reached a maximum upon the addition of 2 molar equivalents of DBU and decreased upon a further excess addition of the base (Fig. 1). This was explained by the inner filter effect of the DBU itself and its photoproducts.[13] The quantum yield of the C–P bond cleavage of **1** under the best conditions was 0.57. The use of 2,2,6,6-tetramethylpiperidine (pK_a 11.1) also gave good results. However, the quantum yield of the C–P bond cleavage was low (ϕ=0.13). The yield of **3b** was not reduced even though an excess amount of the base was used. A large excess amount of triethylamine (pK_a 10.65) was required for obtaining **3b** in 50—60% yield, and the quantum yield of C–P bond cleavage was lower (ϕ=0.025). With pyridine (pK_a 5.17), the C–P bond cleavage did not occur. The photochemical C–P bond cleavage of **1** occurred only during its dianion.[1] The effect of the organic base can be explained by the degree of dissociation of **1**; with a weak base, triethylamine or pyridine, the acid **1** did not completely ionize into dianion. Thus, **2** was not generated.

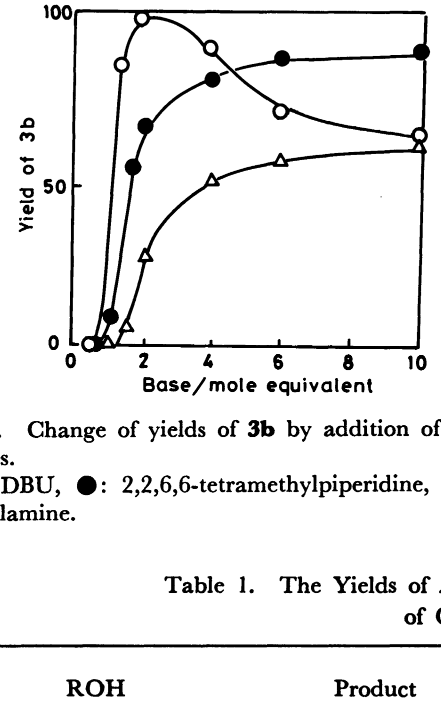


Fig. 1. Change of yields of **3b** by addition of organic bases.
○: DBU, ●: 2,2,6,6-tetramethylpiperidine, △: triethylamine.

Various alcohols were phosphorylated by a method in which a large excess amount of alcohol containing 2 molar equivalents of DBU were used. The phosphorylation proceeded without any detectable amount of a by-product. The yields and ^{31}P NMR chemical shifts of dianion of alkyl dihydrogenphosphates **3**, and the quantum yields of a C–P bond cleavage of **1** are summarized in Table 1. The quantum yields decreased in the order CH_3OH=C_2H_5OH>*i*-C_3H_7OH>*n*-C_4H_9OH>*n*-$C_5H_{11}OH$=*s*-C_4H_9OH>*t*-C_4H_9OH. This order is essentially the same as that for the polarity of alcohol used in these reactions. With increasing alcohol polarity, the acid **1** dissociated more completely and underwent highly efficient C–P bond cleavage.

Reactions using one molar equivalent of alcohol were performed in dichloromethane. The dichloromethane solutions of **1** (50 mmol dm^{-3}) containing a molar equivalent of alcohol and 2 molar equivalents of DBU were irradiated for 1 h. When cholesterol, borneol, and 1-dodecanol were used, the dianions of cholesteryl (**3j**), bornyl (**3k**), and dodecyl dihydrogenphosphate (**3l**) were obtained in 25, 35, and 27% yields, respectively. However, 72—78% of **1** were consumed during the irradiation. It was revealed by a ^{31}P NMR investigation that the greater part of **2** generated by irradiation was consumed during the formation of pyrophosphate ions (**8** or **9**) and a metastable intermediate (**10**) by a reaction with DBU.[4]

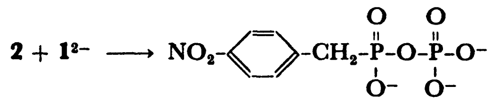
In the presence of a large excess of alcohol, metaphosphate (**2**) can react predominantly with the alcohol to give **3** in a quantitative yield (Eq. 2). When a comparable amount of alcohol was used, metaphosphate (**2**) reacted with alcohol (Eq. 2), its source (**1**) (Eq. 5), itself (**2**) (Eq. 6), **3** (Eq. 7), and

Table 1. The Yields of Alkyl Phosphates Ions (**3**) and Quantum Yields of C–P Bond Cleavage of **1**[a)]

ROH	Product	Yield/%[b)] of **3**	^{31}P NMR[c)] δ ppm	Quantum yield[d)] of C–P bond cleavage
CH_3OH	**3a**	94	4.4	0.72
C_2H_5OH	**3b**	97	2.6	0.72
i-C_3H_7OH	**3c**	77	0.5	0.49
n-C_4H_9OH	**3d**	80	3.0	0.40
s-C_4H_9OH	**3e**	55	0.2	0.30
t-C_4H_9OH	**3f**	32	−3.9	0.11
n-$C_5H_{11}OH$	**3g**	81	2.4	0.30
$HOCH_2CH_2OH$	**3h**	85	4.7	—
$C_6H_5CH_2OH$	**3i**	81	3.6	—

a) Five ml alcohol solutions of **1** (50 mmol dm^{-3}) containing 2 molar equivalent of DBU were irradiated by a high-pressure mercury lamp at ambient temperature for 1 h. b) Yields were determined by ^{31}P NMR spectrometry, based on **1** used. c) ^{31}P NMR chemical shifts of **3** were determined in the reaction mixtures (pH 12), which agreed with the values of authentic samples. d) These quantum yields were determined from the yield of **5**. The photolyses were carried out with no more than 20% decomposition. (see Experimental).

DBU (Eq. 8). When the amount of alcohol was reduced, the yield of **3** decreased remarkably, and other products were given through other reactions (Eqs. 5, 6, 7, and 8).



(5)

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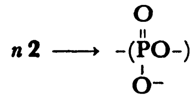
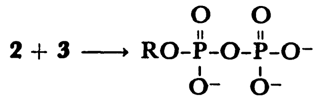


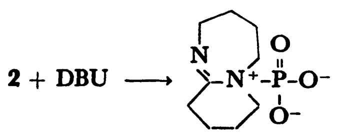
$$n\mathbf{2} \longrightarrow -(\underset{\underset{\mathrm{O^-}}{|}}{\overset{\overset{\mathrm{O}}{\|}}{\mathrm{P}}}\mathrm{O}-)_n \qquad (6)$$

8



$$\mathbf{2}+\mathbf{3} \longrightarrow \mathrm{RO}-\underset{\underset{\mathrm{O^-}}{|}}{\overset{\overset{\mathrm{O}}{\|}}{\mathrm{P}}}-\mathrm{O}-\underset{\underset{\mathrm{O^-}}{|}}{\overset{\overset{\mathrm{O}}{\|}}{\mathrm{P}}}-\mathrm{O^-} \qquad (7)$$

9



(8)

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R=Alkyl-

The same experiment with 2,2,6,6-tetramethylpiperidine was unsuccessfully carried out since the piperidinium salt of **1** is only slightly soluble in dichloromethane or acetonitrile. In another preparative experiment, **31** was isolated in 32% yield.

Experimental

All the melting points are uncorrected. ^{31}P NMR spectra were recorded at 40.25 MHz on a JNM FX 100 using triphenylphosphine as an external standard (δ=−5.6 ppm) for measurements of their chemical shifts, and diethyl methylphosphonate as an internal standard (δ=29.7 ppm) for quantitative analysis, respectively. Chemical shifts are expressed in ppm from 85% H_3PO_4, higher positive values indicated lower shieldings. Quantitative measurements were carried out under the conditions of proton decoupling while taking into account the differences in T_1 and nuclear Overhauser effects.[14] GLC analyses were performed on a Shimadzu GC-7A using a 1-m glass column packed with Silicone OV 17 (2%) on Chromosorb W AW DMCS.

Materials. Dichloromethane and other solvents were dried and distilled by the usual method. Cholesterol, borneol, and 1-dodecanol were of reagent grade and used without further purification. Other alcohols and amines were used after distillation. *p*-Nitrobenzylphosphonic acid (**1**) was prepared by the nitration of benzylphosphonic acid and recrystallized from 50% ethanol, mp 228—229 °C; ^{1}H NMR (D_2O, DSS, pH 12), δ=2.98 (2H d, J_{HH}=20 Hz, CH_2), 7.2—8.2 (5H, m, arom.); ^{31}P NMR (80% C_2H_5OH, pH 12) δ=15.2 (t, J_{HP}=20 Hz); Dissociation constant (80% C_2H_5OH) pK^1_a 3.9; pK^2_a 9.3; UV$_{max}$ (80% C_2H_5OH, pH 12) 305 nm (ε 10,500).

Irradiation of 1 in 80% Ethanol Solution. Five ml of an ethanol solution of **1** (50 mmol dm^{-3}) was adjusted at pH 12 with a 10% aqueous solution of sodium hydroxide. Nitrogen was bubbled through the solution before irradiation. The solution was irradiated in a Pyrex tube (ϕ) 10 mm) with a high-pressure mercury lamp (350 W) for 1 h under cooling with running water. The progress of the photolysis was monitored by a GLC analysis of **5**. After irradiation, a fixed amount of a chloroform-*d* solution of diethyl methylphosphonate was added to the mixture, which was submitted to a ^{31}P NMR analysis using triphenylphosphine as an external standard.

Preparation of 3. Irradiation of 1 in Excess Alcohol: A 5-ml alcohol solution of **1** (50 mmol dm^{-3}) containing DBU (100 mmol dm^{-3}) was irradiated in the same manner previously described. After the irradiation, the mixture was employed for a ^{31}P NMR analysis (Table 1).

Irradiation of 1 in Dichloromethane: A 5 ml dichloromethane solution of **1** (50 mmol dm^{-3}) containing alcohol (50 mmol dm^{-3}) and DBU (100 mmol dm^{-3}) was irradiated in the same manner previously described. After irradiation, the mixture was employed for a ^{31}P NMR analysis. In the case of 1-dodecanol, besides the signals of dianion of dodecyl dihydrogenphosphate (**31**, δ=1.50 ppm, yield 19%) and **4** (δ=1.98 ppm, 9%), two peaks were observed at δ=−11.22 (t, J_{PH}=16 Hz, yield 5.6%) and −8.97 (s, 19%). The former was assumed to be a metastable reaction intermediate (**10**), formed by the reaction of **2** with DBU[4] and the latter was pyrophosphate ion (**8**).[15] Fifty-three percent of the unreacted dianion of **1** remained.

Isolation of 31: The acid **1** (1.1 g, 5 mmol) was added to a 100 ml dichloromethane solution of 1-dodecanol (0.9 g, 0.5 mmol) and DBU (1.5 g, 10 mmol). The homogeneous solution was irradiated employing a Pyrex doughnut-type cell at 20 °C in a nitrogen atmosphere for 2 h. After the solvent was evaporated, the residue was triturated with ether to remove **5** and any unreacted alcohol. The residue was dried for a few minutes at 20 °C (0.1 mmHg).† The diammonium hydrogenphosphate was dissolved in a 2:1 V/V chloroform/ethanol mixture. The solution was treated with 3:48:47 V/V chloroform/methanol/1 mol dm^{-3} aqueous HCl reagent (15 ml) in order to liberate the free phosphoric acid under the mildest conditions. The two-phase system was stirred for a few minutes. The lower organic phase was separated and resubmitted to the same acidification procedure. Finally, this phase was washed with 3:48:47 V/V chloroform/methanol/water (10 ml). The organic phase was evaporated at 20 °C (0.1 mmHg), and the residue was triturated with ether (10 ml) to remove any unreacted 1-dodecanol that may have remained as a contaminant. The product **31** was dried at 20 °C for 3 h (0.1 mmHg). Yield 0.46 g (35%), mp 55—56 °C.[16]

Measurement of the Quantum Yield. The quantum yields were determined on the basis of generated **5** and chemical actinometry using 2-hexanone. The quantum yield of acetone formation was taken as 0.25 in 2,2,4-trimethylpentane at room temperature;[17] A 2 ml 2,2,4-trimethylpentane solution of 2-hexanone with the absorbance identical with that of the solution of **1** was

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† 1 mmHg=133.322 Pa.

irradiated for 1 h in a merry-go-round apparatus employing 313-nm monochromatic light using a filter solution of 0.1% K_2CrO_4–0.1% K_2CO_3. The yields of **5** and acetone were determined by a GLC analysis. The photolyses were carried out with no more than 20% decomposition.

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13) When the ethanol solution of DBU without **1** was irradiated, a broad absorption band (310—340 nm) also appeared. It is unkown what the absorption band resulted from.

14) Gated broadband decoupling and longer pulse intervals (50 s) were used. See, for example, A. D. Edward "Phosphorus-31 NMR of Phospholipids in Micelles" in "Phosphorus-31 NMR Principles and Applications," ed by D. G. Gorenstein, Academic Press, Inc. Orlando, Florida (1984), Chap. 14, p. 431.

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