Methods of Phosphorylation by Means of Organic Dehydrating Reagents

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The use of organic dehydrating reagents in the synthesis of pyrophosphates and the selective phosphorylation of alcohols has been investigated. The reaction of pyridinium phenyl hydrogen phosphate with ketene dimer gave *sym*-diphenyl pyrophosphate, acetone, and carbon dioxide. Tetraethyl pyrophosphate was prepared in excellent yields by the reactions of diethyl hydrogen phosphate with either ethyl vinyl ether, diethyl phosphorochloridite, or with tetraethyl pyrophosphite. In the model experiment on the synthesis of nucleotides, triethyl phosphate was prepared. When aluminum ethoxide was added to the ether solution of tetraethyl hypophosphate, followed by ethanol, only triethyl phosphate was obtained in a high yield.

Intramolecular dehydration of primary nitroparaffins, aldoximes, and hydroxamic acids by means of organic reagents—*i.e.* isocyanates, carbodiimides, ethoxy acetylene, vinyl ethers, ketene acetals, ketene dimer, and esters of phosphoric acid—have been described in preceding papers.[1–6]

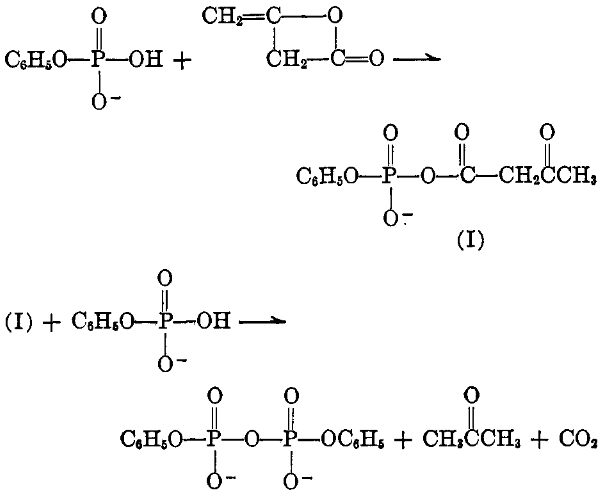
In the present study, intermolecular dehydration of various phosphates, with the formation of pyrophosphates, has been brought about by the use of such substances as ketene dimer, ethyl vinyl ether, diethyl phosphorochloridite, and tetraethyl pyrophosphite.

When one mole of ketene dimer reacted with two moles of diethyl hydrogen phosphate, tetraethyl pyrophosphate could not be obtained; only a red-colored tar was produced. Since it is known that ketene dimer does not react with an acid, such as acetic acid, it is desirable to react ketene dimer with a phosphoric acid derivative with a pK value of about 6, as has been used in the reaction of triethylammonium phenyl hydrogen phosphate with an isocyanate.[7]

When one mole of ketene dimer was added to a solution of two moles of pyridinium phenyl hydrogen phosphate in acetonitrile at 80°, carbon dioxide was evolved for one hour. *sym*-Diphenyl pyrophosphate was isolated as a barium salt in 72% yield from the reaction mixture by the usual method and identified by elementary analysis and paper chromatography.

Similarly, *sym*-di-*p*-chlorophenyl pyrophosphate was obtained in 70% yield by the reaction of one mole of ketene dimer with two moles of pyridinium *p*-chlorophenyl hydrogen phosphate in acetonitrile at 80°.

The reaction is thought to proceed through the initial formation of an additional compound of ketene dimer and phosphate, which in turn reacts with another phosphate to yield pyrophosphate, acetone, and carbon dioxide.



$$C_6H_5O-\overset{O}{\underset{O^-}{\overset{\|}{P}}}-OH + \begin{matrix} CH_2=C-O \\ | \quad\;\; | \\ CH_2-C=O \end{matrix} \longrightarrow C_6H_5O-\overset{O}{\underset{O^-}{\overset{\|}{P}}}-O-\overset{O}{\overset{\|}{C}}-CH_2\overset{O}{\overset{\|}{C}}CH_3 \quad \text{(I)}$$

$$\text{(I)} + C_6H_5O-\overset{O}{\underset{O^-}{\overset{\|}{P}}}-OH \longrightarrow C_6H_5O-\overset{O}{\underset{O^-}{\overset{\|}{P}}}-O-\overset{O}{\underset{O^-}{\overset{\|}{P}}}-OC_6H_5 + CH_3\overset{O}{\overset{\|}{C}}CH_3 + CO_2$$

Of various organic reagents used for the formation of pyrophosphates from phosphates, ketene dimer is of superior character, since it gives acetone and carbon dioxide which can be readily removed from the products.

In the second reaction one mole of ethyl vinyl ether reacted with one mole of diethyl hydrogen phosphate; tetraethyl pyrophosphate was obtained in 92% yield together with acetaldehyde and acetal.

The formation of tetraethyl pyrophosphate by the interaction of ethyl vinyl ether and diethyl hydrogen phosphate is considered to proceed through the addition compound (II) of diethyl hydrogen phosphate and ethyl vinyl ether, which in turn decomposes into tetraethyl pyrophosphate and hemiacetal by the attack of the other phosphate. The hemiacetal decomposes easily to ethanol and acetaldehyde, and the ethanol reacts further with the vinyl ether to form acetal.

Finally, reactions of phosphates with diethyl phosphorochloridite or with tetraethyl pyrophosphite, both of which can be used as excellent intramolecular dehydrating reagents, were tried.

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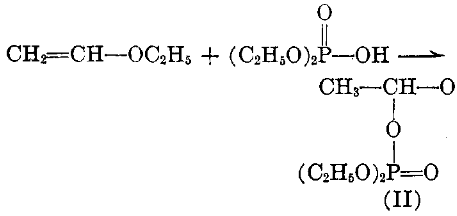
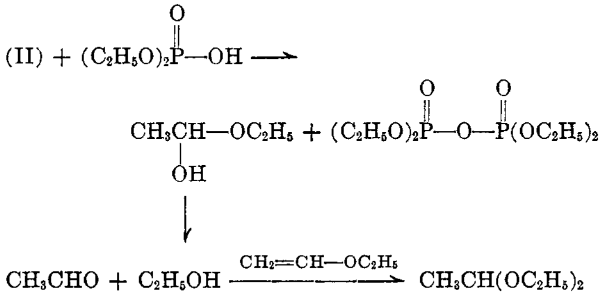


$$\mathrm{CH_2{=}CH{-}OC_2H_5 + (C_2H_5O)_2\overset{\overset{O}{\|}}{P}{-}OH \longrightarrow \underset{\underset{\underset{\textstyle (II)}{(C_2H_5O)_2P{=}O}}{|}}{\underset{|}{\underset{\textstyle O}{CH_3{-}CH{-}OC_2H_5}}}}$$

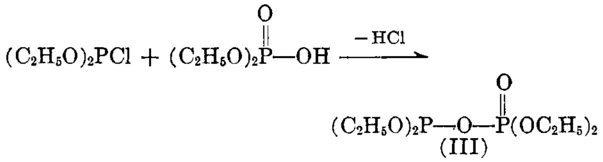


$$\mathrm{(II) + (C_2H_5O)_2\overset{\overset{O}{\|}}{P}{-}OH \longrightarrow CH_3\underset{\underset{OH}{|}}{C}H{-}OC_2H_5 + (C_2H_5O)_2\overset{\overset{O}{\|}}{P}{-}O{-}\overset{\overset{O}{\|}}{P}(OC_2H_5)_2}$$

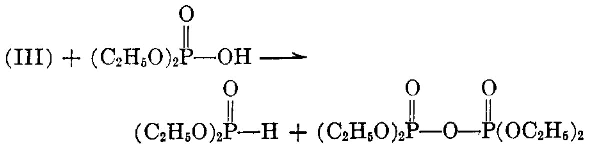
$$\mathrm{\downarrow}$$

$$\mathrm{CH_3CHO + C_2H_5OH \xrightarrow{CH_2{=}CH{-}OC_2H_5} CH_3CH(OC_2H_5)_2}$$

The reaction of one mole of diethyl phosphorochloridite with two moles of diethyl hydrogen phosphate or phenyl dihydrogen phosphate in the presence of basic medium afforded tetraethyl pyrophosphate or *sym*-diphenyl pyrophosphate in high yields.

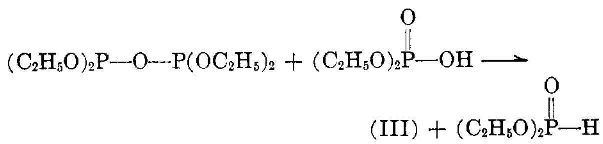


$$\mathrm{(C_2H_5O)_2PCl + (C_2H_5O)_2\overset{\overset{O}{\|}}{P}{-}OH \xrightarrow{-HCl} \underset{\textstyle (III)}{(C_2H_5O)_2P{-}O{-}\overset{\overset{O}{\|}}{P}(OC_2H_5)_2}}$$



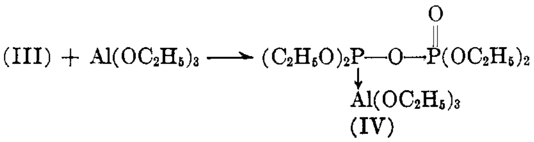
$$\mathrm{(III) + (C_2H_5O)_2\overset{\overset{O}{\|}}{P}{-}OH \longrightarrow (C_2H_5O)_2\overset{\overset{O}{\|}}{P}{-}H + (C_2H_5O)_2\overset{\overset{O}{\|}}{P}{-}O{-}\overset{\overset{O}{\|}}{P}(OC_2H_5)_2}$$

Since tetraethyl hypophosphate, which is assumed to be the intermediate (III) in the above reaction, could be obtained by the reaction of tetraethyl pyrophosphite with diethyl hydrogen phosphate, tetraethyl pyrophosphite can also be used as an excellent dehydrating agent of phosphate.

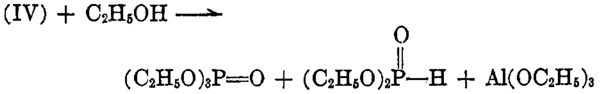


$$\mathrm{(C_2H_5O)_2P{-}O{-}P(OC_2H_5)_2 + (C_2H_5O)_2\overset{\overset{O}{\|}}{P}{-}OH \longrightarrow (III) + (C_2H_5O)_2\overset{\overset{O}{\|}}{P}{-}H}$$

The intermediate III of these reactions was reported to afford, by the reaction with ethanol, triethyl phosphite in 75% yield and triethyl phosphate in 25% yield.[8] In the recent experiment, only triethyl phosphate was obtained in high yield when ethanol was added to the ether solution of complex IV, formed by the reaction of tetraethyl hypophosphate with aluminum ethoxide.



$$\mathrm{(III) + Al(OC_2H_5)_3 \longrightarrow (C_2H_5O)_2\underset{\underset{\underset{\textstyle (IV)}{Al(OC_2H_5)_3}}{\downarrow}}{P}{-}O{-}\overset{\overset{O}{\|}}{P}(OC_2H_5)_2}$$



$$\mathrm{(IV) + C_2H_5OH \longrightarrow (C_2H_5O)_3P{=}O + (C_2H_5O)_2\overset{\overset{O}{\|}}{P}{-}H + Al(OC_2H_5)_3}$$

The fact that triethyl phosphate alone has been obtained in a high yield can be explained by assuming the existence of a complex (IV). This complex is considered to have been formed as the result of the coordination of aluminum ethoxide to an electron pair on the trivalent phosphorus atom of the hypophosphate. Presumably alkoxy anion may attack the pentavalent phosphorus more readily than trivalent phosphorus, thereby causing cleavage of pentavalent phosphorus-oxygen linkage and triethyl phosphate has been obtained, exclusively.

In view of these results, the successful use of organic dehydrating agents in formation of pyrophosphates from various phosphates suggests that such intermediates as I, II, or III are useful, if isolated, as selective phosphorylating reagents.

Experimental

All boiling points are uncorrected.

Reagents.—Phenyl dihydrogen phosphate was prepared by hydrolysis of phenyl phosphorodichloridate. Phenyl phosphorodichloridate was prepared by improved procedures, of which an example is given below. A mixture of 1 mole of phenol, 1.5 moles of phosphorus oxychloride, and 0.2 mole of sodium chloride was heated at 180° for 6 hr. After removal of hydrogen chloride and excess phosphorus oxychloride, 158 g. (75%) of phenyl phosphorodichloridate, b.p. 118–120°/12 mm., was obtained. *p*-Chlorophenyl dihydrogen phosphate was prepared according to the procedure of Cramer.[7] Diethyl hydrogen phosphate was prepared according to a method described previously.[9] Diethyl phosphorochloridite, tetraethyl pyrophosphite, and tetraethyl hypophosphate were prepared by literature procedures.[8,10,11]

Reaction of Ketene Dimer with Phenyl Dihydrogen Phosphate.—A solution of ketene dimer (1.0 g.) in 5 ml. acetonitrile was added dropwise over a period of 5 min. to a refluxing solution of phenyl dihydrogen phosphate (3.48 g., 0.02 mole) and pyridine (1.58 g., 0.02 mole) in 5 ml. acetonitrile. The mixture was refluxed for an additional 1 hr. and carbon dioxide was evolved during this period. A solution of barium chloride ($BaCl_2.2H_2O$, 0.45 g.) in 15 ml. water and pyridine (5 ml.) was added to the cold reaction mixture and allowed to stand in a refrigerator for about 30 min. The white precipitate was washed twice with acetone, dried, and then washed with 50 ml.of water thoroughly. The undissolved precipitate was filtered and dried *in vacuo* over phosphorus pentoxide at room temperature; 3.62 g. (72%) of barium diphenyl pyrophosphate was obtained.

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[9] T. Mukaiyama and T. Fujisawa, *Bull. Chem. Soc. Japan*, **34**, 812 (1961).

[10] H. G. Cook, J. D. Ilett, B. C. Saunders, G. J. Stacey, H. G. Watson, I. J. E. Wilding, and S. J. Woodcock, *J. Chem. Soc.*, 2921 (1949).

[11] G. W. Anderson, J. Blodinger, and A. D. Welcher, *J. Am. Chem. Soc.*, **74**, 5309 (1952).

Anal. Calcd. for $C_{12}H_{10}P_2O_7Ba \cdot 2H_2O$; P, 12.4. Found: P, 12.3. R_f 0.51 (propyl alcohol–concd. ammonia–water, 6:3:1).

A 1.1-g. sample *i.e.* 18% of barium phenyl hydrogen phosphate was recovered by adding 10 ml. of pyridine and 20 ml. of acetonitrile to the latter filtrate.

Anal. Calcd. for $C_6H_5PO_4Ba \cdot H_2O$; P, 9.45. Found: P, 9.31. R_f 0.51 (propyl alcohol–concd. ammonia–water, 6:3:1).

Reaction of Ketene Dimer with *p*-Chlorophenyl Dihydrogen Phosphate.—By the same procedure barium di-*p*-chlorophenyl pyrophosphate was obtained in 70% yield.

Anal. Calcd. for $C_{12}H_8Cl_2P_2O_7Ba \cdot 2H_2O$: P, 10.9. Found: P, 11.1.

Reaction of Ethyl Vinyl Ether with Diethyl Hydrogen Phosphate.—To a solution of ethyl vinyl ether (2.4 g., 0.03 mole) in 10 ml. of dry ether, a solution of diethyl hydrogen phosphate (5.1 g., 0.03 mole) in 5 ml. of dry ether was added dropwise with continuous stirring. Stirring was continued for 3 hr. at room temperature. After removal of ether and diethyl acetal which contains acetaldehyde, the residue was distilled under reduced pressure and 4.5 g. (92%) of tetraethyl pyrophosphate, b.p. 148–149°/1.5 mm., was obtained.

Reaction of Diethyl Phosphorochloridite with Diethyl Hydrogen Phosphate.—To a solution of diethyl hydrogen phosphate (3.1 g., 0.02 mole) in 15 ml. of dry benzene, a solution of diethyl phosphorochloridite (1.6 g., 0.01 mole) and diethylaniline (1.5 g., 0.01 mole) in 10 ml. of dry benzene was added dropwise over a period of 8 min. with vigorous stirring at room temperature. Stirring was continued for an additional 20 min. The mixture was cooled to 0° and the precipitate of diethylanilinium chloride was removed from the filtrate. Benzene was removed from the filtrate under reduced pressure and the residual materials fractionated. One gram (72%) of diethyl phosphite, b.p. 72–74/14 mm. and 2.8 g. (97%) of tetraethyl pyrophosphate, b.p. 124–130°/0.5 mm. were obtained.

Reaction of Diethyl Phosphorochloridite with Phenyl Dihydrogen Phosphate.—To a solution of phenyl dihydrogen phosphate (1.74 g., 0.01 mole) and pyridine (1.58 g., 0.02 mole) in 15 ml. of dry acetonitrile, a solution of diethyl phosphorochloridite (1.57 g., 0.01 mole) in 10 ml. of dry acetonitrile was added with continuous stirring at room temperature. After 15 min., a further 1.74 g. of phenyl dihydrogen phosphate was poured into the solution. It was allowed to stand overnight at room temperature and excess pyridine was added. The solution was allowed to stand for 15 min. after which a solution of 2.5 g. of barium chloride was added. A large amount of white precipitate was filtered and was washed with two 80-ml. portions of cold water and dried *in vacuo* over phosphorus pentoxide at room temperature. Barium diphenyl pyrophosphate, 4.32 g. (86%), was obtained. The R_f of this compound was 0.80 in a mixture of propyl alcohol, concd. aqueous ammonia, and water (6:3:1).

Reaction of Tetraethyl Pyrophosphite with Diethyl Hydrogen Phosphate.—A solution of diethyl hydrogene phosphate (3.1 g., 0.02 mole) in 4 ml. of dry benzene was added to a solution of tetraethyl pyrophosphite (2.6 g., 0.01 mole) in 6 ml. of dry benzene with continuous stirring. Then the solution was kept at 45° for 1.5 hr. and allowed to stand overnight at room temperature. After removal of the benzene, diethyl phosphite, 1.2 g. (87%), b.p. 65°/5 mm., and 2.8 g. (97%) of tetraethyl pyrophosphate, b.p. 128–131°/0.6 mm., were obtained.

Reaction of Tetraethyl Hypophosphate with Ethanol in the Presence of Aluminum Ethoxide.—A solution of tetraethyl hypophosphate (III) (2.8 g., 0.01 mole) in 20 ml. of dry benzene was added to the suspension of aluminum ethoxide (1.6 g., 0.01 mole) in 10 ml. of dry benzene. The suspension soon became clear. The solution was stirred for an additional 20 min. after which a mixture of 0.5 g. of absolute ethanol and 5 ml. of dry benzene was added dropwise. It was then heated at 60° for 30 min.; the solution became gruelly. The thick mixture was allowed to stand overnight and then distilled under reduced pressure; 0.7 g. (51%) of diethyl phosphite, b.p. 70–72°/10 mm. and 1.0 g. (55%) of triethyl phosphate, b.p. 93–95°/10 mm., were obtained and 2.2 g. of white solid was left in the flask.

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Reactions of Phosphines with Cyclic Carbonate Esters

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Reactions of ethylene and substituted ethylene carbonates with secondary and tertiary phosphines result in oxidation of the phosphine and liberation of the olefin corresponding to the carbonate used. Secondary phosphines are converted to alkylenebis- or 2-hydroxyalkylphosphine oxides, depending upon the choice of carbonate. With higher-molecular weight ethylenic carbonates, phosphine oxidation and subsequent olefin synthesis occur only if a catalyst is used, or if the phosphine is sufficiently basic, or if there is a hydroxyl substituent on the carbonate. Large-ring carbonates (*e.g.*, tetramethylene carbonate) do not oxidize tertiary phosphines. Triphenyl phosphite reacts with ethylene carbonate in the presence of copper to yield tetraphenyl ethylenediphosphonate.

Under properly controlled reaction conditions, cyclic carbonates are excellent hydroxyalkylating agents. Ethylene carbonate and propylene carbonate react with compounds containing active hydrogen to yield 2-hydroxyethyl and 2-hydroxypropyl derivatives.[1–6] In an attempt to prepare 2-hydroxyethyl phosphines we therefore chose ethylene carbonate as a hydroxyethylating agent for secondary phosphines and from these reactions obtained some unexpected results.

Ethylene carbonate reacted with representative

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