Cyclic Organophosphorus Compounds, V*

**Cyclic Esters of Phosphorous – Phosphoric Anhydride as a Tool for Studying the “Abnormal” Biphilic Reactivity of P\textsuperscript{III}-P\textsuperscript{V} Anhydride System**

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Phosphorus, Hudson’s concept, cyclic esters, anhydrides

A series of esters of phosphorous-phosphoric anhydride containing cyclic ester groups at one or both phosphorus atoms were prepared. The typical biphilic character of these compounds has been found. Unexpectedly observed lack of reactivity of anhydrides containing cyclic ester groups at trivalent phosphorus atom with respect to diethylphosphoric and acetic acids is the starting point for discussion on the mechanism of acidolysis. Unusual inertness of P\textsuperscript{III} cyclic esters of phosphorous-phosphoric anhydride towards protic acids is discussed in terms of Hudson’s concept of steric retardation on quaternisation.

Although tetraalkyl esters of phosphorous-phosphoric anhydride (1) have been recognized as fairly good phosphorylating agents for acids\textsuperscript{1,2}, the mechanism of acidolysis of an anhydride bond is so far contradictory and controversial\textsuperscript{2,5}.

\[
\begin{array}{c}
\text{RO} & \text{OR'} \\
\downarrow & \downarrow \\
P-\oslash-\oslash-\oslash & R = R'; R \neq R'. \\
\end{array}
\]

\[
\begin{array}{c}
\text{RO} & \text{OR'} \\
\downarrow & \downarrow \\
P-\oslash-\oslash-\oslash & R = R'; R \neq R'. \\
\end{array}
\]

The pronounced biphilic reactivity of acyclic P\textsuperscript{III}-P\textsuperscript{V} anhydride systems renders any detailed studies on the mechanism of phosphorylation practically impossible.

The present work is an attempt to use less reactive cyclic esters of phosphorous-phosphoric anhydride as more convenient models for studying the biphilic reactivity of P\textsuperscript{III}-P\textsuperscript{V} anhydride systems.

**Results**

Cyclic esters of phosphorous-phosphoric anhydride (1a-e) containing both tri- and tetracovalent phosphorus atoms incorporated in five- or six-membered rings were obtained by the action of suitable chlorophosphites on pyridinium salts of diethyl hydrogen phosphate (compounds: 1a) or 2-hydroxy-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan (compounds: 1d and 1e).

\[
\begin{array}{c}
\text{O} & \text{P-}\text{O} & \text{P-}\text{O} \\
\downarrow & \downarrow & \downarrow \\
\text{EtO} & \text{EtO} & \text{EtO} \\
\hline
\text{1a} & \text{1b} & \text{1c} \\
\end{array}
\]

\[
\begin{array}{c}
\text{O} & \text{P-}\text{O} & \text{P-}\text{Et} \\
\downarrow & \downarrow & \downarrow \\
\text{EtO} & \text{EtO} & \text{EtO} \\
\hline
\text{1d} & \text{1e} \\
\end{array}
\]

According to expectations the mixed anhydrides (1a-e) were found to be active electrophilic reagents. They reacted with typical nucleophiles, like water, alcohols and amines, readily and in one way only, the attack of the nucleophilic reagent being directed exclusively to the trivalent phosphorus atom.

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Typical reactions of anhydrides (1a, b and d) with nucleophiles were discussed in our earlier publication. Contrary to the expectations it was found that anhydrides 1a-c do not react with diethyl hydrogen phosphate as well as acetic-acid even when mixtures of the substrates are heated for several hours at 100 °C. Unchanged starting materials could be recovered almost quantitatively from such mixtures. The observed resistance of anhydrides (1a-c) containing trivalent phosphorus atom in a cyclic dioxaphospholan or diaxaphosphorinan system to the action of acids indicates that their nucleophilicity is lower than that of analogous acyclic compounds 1.

The behaviour of anhydrides 1d and 1e (containing tetracovalent phosphorus or both phosphorus atoms in the cyclic diaxaphosphorinan system) in the reactions with diethyl hydrogen phosphate and acetic acid was different. In the case of diethyl hydrogen phosphate the reaction led to the equilibrium and 2-hydroxy-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan (2) and the corresponding new mixed anhydride 3 could be isolated from the reaction mixtures in addition to the unchanged substrates. All the above described reactions of anhydrides 1d and 1e were taking place very readily at room temperature, which was not previously observed in the case of the acyclic analogues 1.

The products were unambiguously characterised by comparison with authentic samples of standard preparations. The structure of 2-acetoxy-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan (4) inferred from the spectral data was confirmed by aminolysis with aniline, affording anilinium salt of 2-hydroxy-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan (6) and acetanilide (7).

Discussion

The observation that five-membered cyclic phosphate esters are more electrophilic than their acyclic analogues was recently supplemented by Greenhalgh and Hudson who found that they are also considerably less prone to quaternization and offered a plausible explanation of this phenomenon.

The application of the “steric retardation” hypothesis to the reactions of cyclic phosphites with electrophilic reagents leads to definite mechanistic implications regarding the proved lack of reactivity of anhydrides (1a-e) in acidolysis reactions. Since three different nucleophilic centres are present in the molecules of cyclic anhydrides 1a-e at least four different acidolysis paths (A–D) could be considered:

A. Protonation of tervalent phosphorus atom and subsequent attack of the anion $\text{A}^-$ on the tetracovalent phosphorus atom:

$$\text{(EtO)}_2\text{P-O-} \text{CH}_2\text{O} + \text{EtOH} \rightarrow \text{Et}_2\text{P(OEt)}_2\text{O} + \text{CH}_3\text{C(OH)Ph}$$

Only 2-hydroxy-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan (2) could be, however, isolated in 27% yield from the mixture of products formed in the reaction of anhydride 1e with acetic acid.

All the above described reactions of anhydrides 1d and 1e were taking place very readily at room temperature, which was not previously observed in the case of the acyclic analogues 1.
B. Protonation of the anhydride-bridge oxygen atom followed by the attack of anion $A^-$ on the tetracovalent phosphorus atom:

$$\text{(EtO)}_2P=O\text{(CH}_2\text{n)} + H^+ = A^-$$

\[ \text{(EtO)}_2P-A + HO-P\text{(CH}_2\text{n)} \rightleftharpoons H^0 - P^+ \text{(CH}_2\text{n)} \]

C. Protonation of the anhydride-bridge oxygen atom followed by the attack of anion $A^-$ on the tervalent phosphorus atom:

$$\text{(EtO)}_2P=O\text{(CH}_2\text{n)} + H^+ = A^- [\text{(EtO)}_2P\text{(OEt)}_2]$$

\[ \text{(CH}_2\text{n)} \rightleftharpoons P-A + HO-P\text{(OEt)}_2 \]

D. Protonation of the phosphoryl oxygen atom followed by the attack of anion $A^-$ on the tervalent phosphorus atom:

$$\text{(EtO)}_2P=O\text{(CH}_2\text{n)} + H^+ = A^- [\text{(EtO)}_2P\text{(OEt)}_2]$$

\[ \text{(CH}_2\text{n)} \rightleftharpoons P-A + O=P\text{(OEt)}_2 \]

Paths C and D of acidolysis of cyclic anhydrides 1a-c seem to be improbable and ineffective, since in both cases the position of the equilibrium is unfavourable. This is undoubtedly due to the fact that diethyl hydrogen phosphate is a poor leaving group. Moreover, if acidolysis could take place according to these paths we should not observe any significant differences between the reactivities of cyclic anhydrides 1a-c and their acyclic analogues 1 since in this case none of the reaction stages involves the quaternisation of the ring phosphorus atom.

Since it has been found that cyclic anhydrides 1a-c are not sensitive to acids, it appears that this is due to steric factors. Paths A and B of acidolysis of cyclic anhydrides 1a-c are unfavourable from the thermodynamical point of view, and consequently these compounds do not react with diethyl hydrogen phosphate and acetic acid.

The sensitivity of anhydrides 1d and 1e to acids becomes readily understandable when it is assumed that acidolysis can take place according to paths C or D. In all cases the position of equilibrium in these reactions is favourable as a result of separation of 2-hydroxy-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan 2 from the reaction mixture in the form of a crystalline, practically insoluble precipitate. The formation of new mixed anhydrides 3 in the reactions of 1d and 1e with diethyl hydrogen phosphate additionally confirms the possibility of a direct attack of acid anion $A^-$ on tervalent phosphorus atom.

The formation of acetylphosphate 4 and diethyl phosphite 5 in the reaction of cyclic anhydride 1d with acetic acid is a result of the consecutive reaction between the primarily formed (according to Scheme C or D) diethyl acetylphosphite 9 and 2-hydroxy-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan 2.

$$\text{(EtO)}_2P=O\text{(CH}_2\text{n)} + CH_3-C-O-P\text{(OEt)}_2 \rightleftharpoons \text{(CH}_2\text{n)} \rightleftharpoons P-A + HO-P\text{(OEt)}_2 \rightleftharpoons \text{(CH}_2\text{n)} \rightleftharpoons P-A + O=P\text{(OEt)}_2$$

This course of the reaction is also indicated by the fact that a crystalline precipitate of 2 separates from the solution in the initial stage of the reaction.

**Conclusions**

The results of the present investigation are insufficient for deciding which one of the proposed paths of acidolysis of phosphorous-phosphoric anhydride esters 1 is the most effective.

However, the pronounced steric retardation effect observed in the case of cyclic anhydrides 1a-c and considered in the light of the Hudson's hypothesis makes it possible to give preference to paths A and B limiting the remaining possibilities to
Experimental

Solvents and reagents were purified by conventional methods. All solutions were evaporated under reduced pressure. Boiling points and melting points (taken in capillaries) are uncorrected. IR spectra were recorded for liquid films or Nujol mulls using an UR-10 spectrophotometer (C. Zeiss, Jena) or Perkin-Elmer Infracord 137 spectrophotometer.

Preparation of the anhydrides 1a, 1b and 1e as well as the compound 1e6 was described previously. P-Diethoxyphosphoryl-P'-(5,5-dimethyl-1,2,3-dioxaphosphorinan)oxide (1e).

To the solution of diethyl hydrogen phosphate (30.8 g, 0.2 mole) and pyridine (15.8 g, 0.2 mole) in benzene (100 ml) 2-chloro-5,5-dimethyl-1,2,3-dioxaphosphorinan (33.7 g, 0.2 mole) was added dropwise with stirring and efficient cooling. The reacting mixture was stirred for 1 hour at room temperature. Pyridine hydrochloride was then filtered off and washed with benzene (100 ml).

After evaporation of solvent the residue was distilled in vacuo to give pure cyclic ester 1e, b.p. 90 °C/0.01 mm Hg, n^20 1.4254 (Lit.10: b.p. 74 °C/0.01 mm Hg, n^20 1.4254). With 2 m equivalents of aniline in ether (1, R = Et) gave anilinium salt of diethyl hydrogen phosphate in 69% yield. M.p. (from ether) and m. m.p. - 69-70 °C (Lit.11: m.p. 69-70 °C). The residue left in the distillation flask was found to contain the unreacted cyclic ester 1d, which afforded the acid 12 on hydrolysis with water.

Cyclic ester 1e (5.96 g) reacted with diethyl hydrogen phosphate (3.1 g) in benzene (40 ml) at 40 °C for 6 hours. 2-Hydroxy-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan (2), which crystallized on cooling, was filtered off and washed with benzene (20 ml).

Yield: 0.93 g (28%), m.p. and m.m.p. - 170-172 °C (Lit.12: m.p. 174-176 °C). After removal of solvent the residue was distilled in vacuo to give the fraction boiled at 92 °C/0.01 mm Hg, n^20 1.4450, yield: 1.6 g (28%), identified (IR) as cyclic ester 1e.

The residue left in the distillation flask contained the unreacted ester 1e. It afforded quantitatively the acid 2 when hydrolyzed with water.

Reactions of cyclic esters of phosphorus-phosphoric anhydride 1a-e with acetic acid. General procedure.

The mixture of the corresponding cyclic ester 1a-e (0.02 mole) and acetic acid (1.2 g, 0.02 mole) was protected against moisture and heated for 2 hours at 50 °C. Liquid products were separated and purified by distillation in vacuo. Solid compounds were isolated by filtration and purified by crystallization.

Cyclic esters (1a-e) did not react when heated with acetic acid at 100 °C for several hours. In all cases only unchanged starting materials could be recovered quantitatively from the reaction mixture by distillation in vacuo.

Cyclic ester (1d) (5.72 g) reacted with acetic acid (1.2 g) at room temperature. When equinolar amounts of starting materials were mixed together in benzene (15 ml) a white, crystalline precipitate was formed during the initial stage of the reaction. A sample of this precipitate was taken off from the reaction mixture and identified (IR, m.p. and m.m.p. - 171-173 °C) as 2-hydroxy-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan (2). The reaction mixture was maintained at room temperature for 48 hours Crystalline precipitate filtered off and washed with benzene (20 ml) was identified as 2-acetoxy-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan (4), m.p. 116-118 °C, yield: 2.91 g (70%).

C_3H_8O_3P
Calcd.: C 40.4 H 6.3 P 14.9,
Found: C 39.9 H 6.2 P 15.5.

IR spectrum: (Nujol) C = 0 1760 cm^-1, P = 0 1305 cm^-1. The anhydride (4) reacted with 2 m equivalents of aniline in benzene (50 ml) at room temperature to give acetanilide (7) in 70% yield;
When treated with water. The reaction of cyclic ester 1e (5.96 g) with acetic acid (1.2 g) was carried out in benzene (40 ml) at 40 °C for 6 hours. Crystalline precipitate which separated on cooling was filtered off and washed with benzene (20 ml). It was identified as the acid 2, yield = 0.9 g (27%), m.p. and m.m.p. = 170-172 °C (Lit12: m.p. 174-176 °C). No pure identifiable compounds could be, however, isolated by high-vacuum distillation of the filtrate.