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AMINE CATALYSIS IN PHOSPHORYL TRANSFER FROM 2,4-DINITROPHENYL PHOSPHATE IN APROTIC AND PROTIC SOLVENTS

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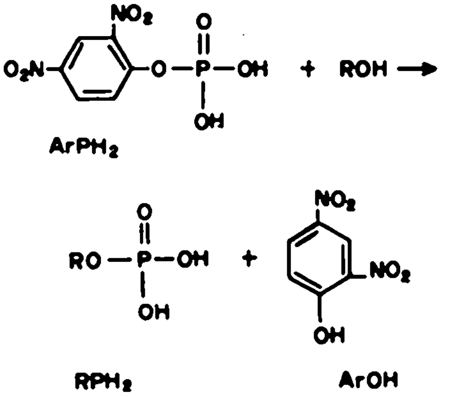
Abstract—Reactions of tetra-n-butylammonium 2,4-dinitrophenyl hydrogen phosphate, $(ArPH)^-(R_4N)^+$, in aprotic and protic solvents, in the absence and in the presence of alcohols or water, ROH, are compared with analogous reactions of the salt in the presence of hindered and unhindered amines, e.g. diisopropylethyl amine and quinuclidine. Similar studies are performed with the acid, $ArPH_2$, in the presence of variable amounts of amines. The release of phenol and the fate of the phosphorus compounds are followed by ^1H and ^{31}P NMR spectrometry. In the absence of free unhindered amine, reactions of the monoanion are relatively slow, sensitive to steric hindrance in the alcohol, and incapable of producing t-butyl phosphate from t-butanol; reactions of the dianion are relatively fast, insensitive to steric hindrance in the alcohol, and produce t-butyl phosphate. In the presence of free unhindered amine, reactions of the monoanion are relatively fast but still sensitive to steric hindrance in the alcohol, and hence do not produce t-butyl phosphate. The intermediate $CH(CH_2CH_2)_3\overset{+}{N}P(0)(OH)O^-$ is detected in the presence of quinuclidine. Reactions of the dianion in the presence of unhindered amines are analogous to those observed in the presence of hindered amines. The uncatalyzed and the nucleophilic amine-catalyzed reactions of the monoanion are assumed to proceed via oxyphosphorane, P(5), intermediates. The dianion reactions, which are not susceptible to nucleophilic catalysis, are assumed to proceed via the monomeric metaphosphate ion intermediate, PO_3^-. Significant effects related to solvent properties are observed in these reactions.

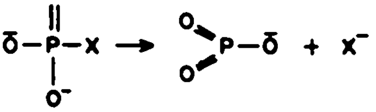
This investigation is concerned with the effect of amines on phosphoryl transfer reactions; eqn (1).[2]



(1)

We studied the reactions of $ArPH_2$ in aprotic and protic solvents, in the absence and in the presence of alcohols or water, ROH, with and without added diisopropylethyl amine (PrEN) or quinuclidine (QuiN). The sterically hindered and unhindered amines were introduced in various molar proportions relative to $ArPH_2$ and the results were compared with those obtained from the preformed salt, $(ArPH)^-(R_4N)^+$, in the absence and in the presence of the same amines. The course of the reactions was followed by ^1H and ^{31}P NMR spectrometry to ascertain the approximate rate of formation of ArOH and of the phosphorus-containing products. These experiments have led to the conclusion that, in the absence of free unhindered amine, the reactions of $ArPH_2$ can take place via oxyphosphorane intermediates, P(5), or via a monomeric metaphosphate ion intermediate, PO_3^-, depending on the experimental conditions, and that the course of these reactions is markedly affected by direct interactions between unhindered amines and the phosphate-phosphorus. This intrusion of nucleophilic catalysis via P(5) intermediates appears to be limited to the monoanion species, $(ArPH)^-$, and is most apparent in non-aqueous media.

Kirby[3,5] has investigated the hydrolysis of $ArPH_2$ in buffered aqueous media in the absence and in the presence of various amines. In the absence of nucleophilic amines, the pH-rate profile shows maximum rate at the pH which corresponds to a maximum concentration of dianion, $(ArP)^{2-}$. Kirby[4,5] proposed that this type of phosphate undergoes hydrolysis via a PO_3^- intermediate, which is generated from dianion by the mechanism shown in eqn (2), and from monoanion by the mechanism shown in eqn (3), with the former mechanism resulting in a faster reaction rate.



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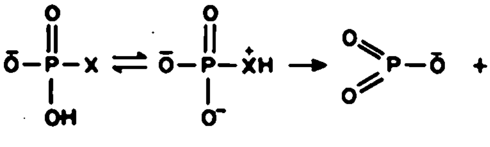
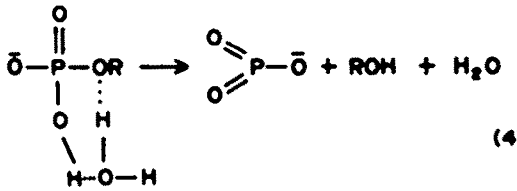


(3)

For the hydrolysis in the presence of a large excess of nucleophilic amines relative to $ArPH_2$, Kirby[5] proposed a bimolecular mechanism *from both monoanion and dianion*, with the amine participating in the rate limiting step. The details of this bimolecular mechanism were not explicitly given.

The formation of PO_3^- intermediate was first proposed[6-9] in connection with the hydrolysis of alkyl phosphates to account for a maximum reaction rate at the pH which corresponds to a maximum concentration of monoanion, $(RPH)^-$. The formation of PO_3^- from this type of monoanion was pictured[6,7] as shown in Eqn (4). Aryl phosphates, $XP(0)(OH)_2$ derived from phenols, XH, with $pKa > 5.5$ (in water), e.g. 4-nitrophenyl phosphate, have pH-rate profiles similar to those of alkyl phosphates.[3-5] For this type of phosphate, Kirby has also proposed a non-catalyzed mechanism in which the PO_3^- intermediate is generated from dianion (eqn 2) and from monoanion (eqn 3), this time with the latter mechanism resulting in a faster reaction rate. The amine-catalyzed bimolecular mechanism for this type of phosphate could not be detected in reactions of the monoanion, but was proposed for reactions of the dianion.[5]



(4)

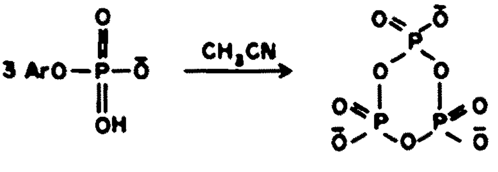
A number of investigators[10-22] have invoked the formation of PO_3^- intermediate from dianions (eqn 2) to explain the reactions of several types of phosphomonoester analogs. The PO_3^- hypothesis has recently been discussed in theoretical papers.[23,24] There is also a growing literature[25-31] dealing with transformations of structures XP(A)(Y)(ZH) into YP(=A)(=Z). Monomeric alkyl metaphosphates, $ROPO_2$, have been proposed as intermediates in pyrolyses[32,33] and in mass spectrometry.[34]

The participation of P(5) intermediates in reactions of phosphotriesters[35-37] and phosphodiesters[38] is now widely accepted.[39-43] A hydroxyphosphorane has recently been observed in solutions in dynamic equilibrium with a phosphotriester.[44,45] The tendency for the formation of hydroxyphosphoranes from certain acyl phosphotriesters[46] and phosphinate esters[47] has also been demonstrated.

RESULTS

Acid–base equilibria in reactions of $ArPH_2$. The pKa values in water of the acids which are relevant to this study are as follows: $ArPH_2$,[48] 1.0 and 4.6; RPH_2,[49] 1.5 and 6.6; H_3PO_4, 2.1, 7.2 and 12.0; ArOH, 4.1; and the aminium ions, $PrENH^+$, $QuiNH^+$, 11.0. These acids should become significantly weaker in non-aqueous solvents[50-52] on the basis of data given for acetic and hydrochloric acids, whose pK_a's are, respectively: 4.8 and −6.3 (water), 9.6 and 1.0 (methanol), 22.3 and 8.9 (acetonitrile). This effect is not so marked for aminium acids, e.g. pK_a's for $C_5H_5NH^+$ are: 5.2 (water), 5.0 (methanol), 12.3 (acetonitrile).[53] We assume that the solutions prepared from $ArPH_2$ and one mol equiv. of PrEN or QuiN in non-aqueous solvents consist of equilibrium mixtures of $ArPH_2$ and $(ArPH)^-$, with the monoanion predominating to approximately the same extent with both amines. The reference system with respect to the behavior of monoanion is, therefore, the preformed salt, $(ArPH)^-(R_4N)^+$, in the same solvent. A similar reasoning suggests that solutions prepared from $ArPH_2$ and two mol equiv. of the amines in non-aqueous solvents should contain relatively more $(ArPH)^-$ than $(ArP)^{2-}$. Moreover, the amount of dianion present at equilibrium with monoanion should be significantly lower in these solutions than in those prepared from the salt $(ArPH)^-(R_4N)^+$ and one mol equiv. of the corresponding amine in the same medium.

Reactions of $ArPH_2$ *in the presence of one mol equiv. of amines.*[54,55] The data in Table 1 show that, in pure acetonitrile, the solutions made from preformed salt, $(ArPH)^-(R_4N)^+$, and by addition of one mol equiv. of either PrEN or QuiN to the acid $ArPH_2$, behave in a similar manner; the only observable products are cyclic trimetaphosphate, $(CP_3)^{3-}$, and the phenol (eqn 5). This reaction is somewhat slower with PrEN vs QuiN or the $(R_4N)^+$-salt, but such small rate differences are not regarded as significant in the present qualitative study.[56,57]



$(ArPH)^-$ $(CP_3)^{3-}$

+ 3 ArOH (5)

Acetonitrile solutions of the monoanion, $(ArPH)^-$, containing one mol equiv. of alcohols or water yield only $(CP_3)^{3-}$, but no detectable alkyl or inorganic phosphate, $(RPH)^-$ (eqn 6). However, mixtures of $(CP_3)^{3-}$ and $(RPH)^-$ are obtained when several mol equiv. of ROH (excepting t-butanol) are added to the acetonitrile solution; the amount of $(RPH)^-$ increases with increasing ROH concentration.

$$(ArPH)^- + ROH\ (1\ \text{mol equiv.} \xrightarrow{CH_3CN} 1/3(CP_3)^{3-} + ArOH \tag{6}$$

R = 1°, 2°, 3° Alkyl or H.

It should be noted that an increase in the ROH/phosphate ratio inevitably alters the nature of the medium and, hence, the degree of dissociation of the acids. In addition, there seems to be a retardation of the reaction $(ArPH)^- \rightarrow (CP_3)^{3-}$, as the medium becomes poorer in acetonitrile and richer in alcohol.

Data not shown in Table 1 disclose that the rate of phosphorylation of ROH by $(ArPH)^-$ is quite sensitive to the size of ROH. Phosphorylation of ROH is no longer competitive with formation of $(CP_3)^{3-}$ in mixtures of acetonitrile and alcohol when the latter is larger than methanol. However, 1° and 2° alcohols can be phosphorylated by $(ArPH)^-$ in dilute solutions in the pure alcohol (eqn 7). No phosphoryl transfer to t-butanol has been observed from $(ArPH)^-$ under any set of conditions. Independent experiments also show that the alkyl phosphates in Table 1 are not generated from preformed $(CP_3)^{3-}$.

$$2(ArPH)^- + ROH \xrightarrow{ROH} 1/3(CP_3)^{3-} + (RPH)^- + 2ArOH \tag{7}$$

R = 1°, 2° Alkyl or H.

Table 1. Reactions of 2,4-dinitrophenyl phosphate, $ArPH_2$, and one mol equiv. of diisopropylethyl amine (PrEN) or quinuclidine (QuiN) in 1.0 M solutions at 35°. $(RPH)^-$ = alkyl phosphate; $(CP_3)^{3-}$ = cyclic trimetaphosphate; $(R_4N)^+ = [(n\text{-}C_4H_9)_4N]^+$

Solvent	Reagent (mol equiv)[a]	t 1/2 [b]	Results[c,d]
$(ArPH)^-(R_4N)^+$			
CD_3CN	None	2 days	$(CP_3)^{3-}$
CD_3CN	CH_3OH(1)	3 days	$(CP_3)^{3-}$
$CD_3CN:CH_3OH$, 60:40[e]	CH_3OH(10)	6 days	$(CP_3)^{3-} + (RPH)^-$; 1:1[f]
$CD_3CN:CH_3OH$, 30:70	CH_3OH(17)	6 days	$(CP_3)3- + (RPH)^-$; 1:3
CD_3CN	H_2O(1)	2 days	$(CP_3)^{3-}$
$CD_3CN:H_2O$, 60:40	H_2O(22)	6 days	$(CP_3)^{3-} + H_2PO_4^-$; 1:4
$CD_3CN:H_2O$, 30:70	H_2O(39)	6 days	$(CP_3)^{3-} + H_2PO_4^-$; 1:10
$ArPH_2 + PrEN \rightleftharpoons (ArPH)^-(PrENH)^+$			
CD_3CN	None	6 days	$(CP_3)^{3-}$
CD_3CN	CH_3OH(1)	7 days	$(CP_3)^{3-}$
$CD_3CN:CH_3OH$, 60:40	CH_3OH(10)	10 days	$(CP_3)^{3-} + (RPH)^-$; 4:3
$CD_3CN:CH_3OH$, 30:70	CH_3OH(17)	10 days	$(CP_3)^{3-} + (RPH)^-$; 1:4
CD_3CN	H_2O(1)	7 days	$(CP_3)^{3-}$
$CD_3CN:H_2O$, 60:40	H_2O(22)	8 days	$(CP_3)^{3-} + H_2PO_4^-$; 1:4
$CD_3CN;H_2O$, 30:70	H_2O(39)	8 days	$(CP_3)^{3-} + H_2PO_4^-$; 1:10
$ArPH_2 + QuiN \rightleftharpoons (ArPH)^- (QuiNH)^+$			
CD_3CN	None	3 days	$(CP_3)^{3-}$
CD_3CN	CH_3OH(1)	2 days	$(CP_3)^{3-}$
$CD_3CN:CH_3OH$, 60:40	CH_3OH(10)	4 days	$(CP_3)^{3-} + (RPH)^-$; 1:1
$CD_3CN:CH_3OH$, 30:70	CH_3OH(17)	5 days	$(CP_3)^{3-} + (RPH)^-$; 1:3
CD_3CN	H_2O(1)	...[g]	$(CP_3)^{3-}$
$CD_3CN:H_2O$, 60:40	H_2O(22)	8 days	$(CP_3)^{3-} + H_2PO_4^-$; 1:4
$CD_3CN:H_2O$, 30:70	H_2O(39)	6 days	$(CP_3)^{3-} + H_2PO_4^-$; 1:10

[a] Per mole of phosphate, in this and in subsequent Tables. [b] Values are approximate half-times of reaction, defined as [Phosphate Reactant] = [Phosphate Products], in this and in subsequent Tables. [c] Phosphate analyses by ^{31}P and ^1H NMR spectrometry, with reference to authentic compounds. Phenol analyses by ^1H NMR. [d] Phosphate products observed at t 1/2. Only these products are observed upon completion of the reaction. [e] All mixed solvents are v/v. [f] Under these conditions, $(CP_3)^{3-}$ is not converted into $(RPH)^-$ by reaction with the alcohol. [g] The salt is only partially soluble.

Reactions of $ArPH_2$ *in the presence of two mol equiv. of amines.* The hindered and the unhindered amines exert dramatically different effects when added, to the extent of two mol equiv., to acetonitrile solutions of $ArPH_2$; Table 2. In the absence of alcohols or water, this difference between PrEN and QuiN manifests itself only in the rate of formation of the same product, $(CP_3)^{3-}$ (eqn 8). This reaction is significantly faster with QuiN vs PrEN.

$$ArPH_2 + 2PrEN \quad \text{or} \quad 2QuiN \xrightarrow{CH_3CN} 1/3(CP_3)^{3-} + ArO^-. \tag{8}$$

In the presence of one mol equiv. of alcohols or water, the difference in the effect of PrEN and QuiN is reflected in the nature of the products, as well as in the rates at which they are formed (eqns 9 and 10). The hindered amine causes phosphoryl transfer to 1°, 2° and 3° alcohols and to water at comparable rates, while the unhindered amine results in the formation of $(CP_3)^{3-}$ in all these cases. The formation of $(CP_3)^{3-}$ is faster than that of $(RPH)^-$.

$$ArPH_2 + 2PrEN + ROH \text{ (1 mol equiv.)} \xrightarrow{CH_3CN} (RPH)^- + ArO^- \tag{9}$$

$$R = 1°, 2°, 3° \text{ Alkyl or H}$$

$$ArPH_2 + 2QuiN + ROH \text{ (1mol equiv.)} \xrightarrow{CH_3CN} 1/3(CP_3)^{3-} + ArO^- \tag{10}$$

$$R = 1°, 2°, 3° \text{ Alkyl or H.}$$

Both hindered and unhindered amines promote exclusive phosphoryl transfer to ROH when added to solutions of $ArPH_2$ in methanol or in water (eqn 11).

$$ArPH_2 + 2PrEN \quad or \quad 2QuiN \xrightarrow{ROH} (RPH)^- + ArO^- \tag{11}$$

$$R = CH_3 \text{ or H.}$$

A striking medium effect in the formation of $(RPH)^-$ is

Table 2. Reactions of $ArPH_2$ and two mol equiv. of PrEN or QuiN in 1.0 M solutions at 35°

Solvent	Reagent (mol equiv)	t 1/2	Results[a]
$ArPH_2 + PrEN \rightleftharpoons (ArPH)^-(PrENH)^+$; $(ArPH)^-(PrENH)^+ + PrEN \rightleftharpoons (ArP)^{2-}\ 2(PrENH)^+$			
CD_3CN	None	40 min	$(CP_3)^{3-}$
CD_3CN	$CH_3OH(1)$	30 min	$(RPH)^-$
CD_3CN	$(CH_3)_3COH(1)$	35 min	$(RPH)^-$
CD_3CN	$H_2O(1)$	20 min	$H_2PO_4^-$
CH_3OH	$CH_3OH(25)$	3.5 hr	$(RPH)^-$
H_2O	$H_2O(55)$	2.5 hr	$H_2PO_4^-$
$CD_3CN:(CH_3)_2CHOH$, 10:90	$(CH_3)_2CHOH(12)$	2.0 hr	$(RPH)^-$
$CD_3CN:(CH_3)_3COH$, 10:90	$(CH_3)_3COH(10)$	3.5 hr	$(RPH)^-$
CH_2Cl_2	$CH_3OH(1)$	4 hr	$(RPH)^-$
$ArPH_2 + QuiN \rightleftharpoons (ArPH)^-(QuiNH)^+$; $(ArPH)^-(QuiNH)^+ + QuiN \rightleftharpoons (ArP)^{2-}\ 2(QuiNH)^+$			
CD_3CN	None	1 min	$(CP_3)^{3-}$
CD_3CN	$CH_3OH(1)$	1 min	$(CP_3)^{3-}$
CD_3CN	$(CH_3)_3COH(1)$	1 min	$(CP_3)^{3-}$
CD_3CN	$H_2O(1)$	1 min	$(CP_3)^{3-}$
CH_3OH	$CH_3OH(25)$	3 hr	$(RPH)^-$ [b]
H_2O	$H_2O(55)$	2.5 hr	$H_2PO_4^-$
$CD_3CN:(CH_3)_2CHOH$, 10:90	$(CH_3)_2CHOH(12)$	... [c]	$(CP_3)^{3-} + (RPH)^-$; 5:1
$CD_3CN:(CH_3)_3COH$, 10:90	$(CH_3)_3COH(10)$	10 min	$(CP_3)^{3-}$
CH_2Cl_2	$CH_3OH(1)$	4 min	$(CP_3)^{3-}$

[a] Phosphate products observed after completion of the reaction. [b] In a 0.2 M solution in 50:50 $CD_3CN:CH_3OH$, the product consists of $(CP_3)^{3-}$ and $(RPH)^-$ in 2:3 proportion upon completion of the reaction. [c] The salt is only partially soluble.

observed when two mol equiv. of PrEN are added to $ArPH_2$ in: (a) acetonitrile containing one mol equiv. of methanol or water, and (b) pure methanol or water. In (b), the concentration of nucleophile, ROH, is significantly higher than in (a), and yet $(RPH)^-$ is formed at a slower rate in (b) than in (a). This is understandable if the rate limiting step in the formation of $(RPH)^-$ is decelerated by changing the medium from aprotic to protic.

Reactions of the salt, $(ArPH)^-(R_4N)^+$, *in the presence of one mol equiv. of amines*. The results of this study are given in Table 3. PrEN-promoted reactions in Table 3 are faster than the corresponding reactions in Table 2, except when the solvent is pure methanol or water. It is reasonable to expect that in these two protic solvents of relatively high dielectric constant, the concentration of dianion relative to that of monoanion should be at a maximum compared to alcohols of lower dielectric constant and to acetonitrile. Therefore, the data in Tables 2 and 3 suggest that the observed products stem from the dianion which is present in the respective solutions.

The data on QuiN-promoted reactions in Table 3 suggest that the observed $(CP_3)^{3-}$ is formed mainly or exclusively from the amine-catalyzed reaction of monoanion, while the observed $(RPH)^-$ stems from the uncatalyzed reaction of monoanion, since in pure methanol or water, where maximum dianion concentration is expected, only $(RPH)^-$ is observed.

From Tables 1–3 we infer that:

(1) Hindered and unhindered amines, when added to the extent of one mol equiv. to $ArPH_2$, act simply as proton-acceptors and give rise only to monoanion, since the three systems of Table 1 give comparable results.

(2) Hindered amines, when added to the extent of two mol equiv. to $ArPH_2$, act also as proton acceptors and generate the monoanion and small amounts of dianion, with the dianion reacting at a much faster rate than the monoanion. This follows from the rapid formation of t-butyl phosphate which is not observed in reactions of monoanion.

Table 3. Reactions of monoanion, $(ArPH)^-(R_4N)^+$, and one mol equiv. of PrEN or QuiN in 1.0 M solutions at 35°

Solvent	Reagent (mol equiv)	t 1/2	Results[a]
$(ArPH)^-(R_4N)^+ + PrEN \rightleftharpoons (ArP)^{2-}(R_4N)^+(PrENH)^+$			
CD_3CN	None	1 min	$(CP_3)^{3-}$
CD_3CN	CH_3OH(1)	1 min	$(RPH)^-$
CD_3CN	$(CH_3)_2CHOH$(1)	1 min	$(RPH)^-$
CD_3CN	$(CH_3)_3COH$(1)	1 min	$(RPH)^-$
CD_3CN	H_2O(1)	1 min	$H_2PO_4^-$
CH_3OH	CH_3OH(25)	1 hr	$(RPH)^-$
H_2O	H_2O(55)	2.5 hr	$H_2PO_4^-$
$CD_3CN:(CH_3)_2CHOH$, 10:90	$(CH_3)_2CHOH$(12)	12 min	$(RPH)^-$
$CD_3CN:(CH_3)_3COH$, 10:90	$(CH_3)_3COH$(10)	20 min	$(RPH)^-$
CH_2Cl_2	None	5 min	$(CP_3)^{3-}$
$(ArPH)^-(R_4N)^+ + QuiN \rightleftharpoons (ArP)^{2-}(R_4N)^+(QuiNH)^+$			
CD_3CN	None	<1 min	$(CP_3)^{3-}$
CD_3CN	CH_3OH(1)	<1 min	$(CP_3)^{3-} + (RPH)^-$; 1:4
CD_3CN	$(CH_3)_2CHOH$(1)	<1 min	$(CP_3)^{3-} + (RPH)^-$; 1:4
CD_3CN	$(CH_3)_3COH$(1)	<1 min	$(CP_3)^{3-} + (RPH)^-$; 1:4
CD_3CN	H_2O(1)	<1 min	$(CP_3)^{3-} + H_2PO_4^-$; 1:5
CH_3OH	CH_3OH(25)	1 hr	$(RPH)^-$
H_2O	H_2O(55)	2.5 hr	$H_2PO_4^-$
$CD_3CN:(CH_3)_2CHOH$, 10:90	$(CH_3)_2CHOH$(12)	10 min	$(RPH)^-$
$CD_3CN:(CH_3)_2COH$, 10:90	$(CH_3)_3COH$(10)	1 min	$(RPH)^-$
CH_2Cl_2	None	1 min	$(CP_3)^{3-}$

[a] Phosphate product after completion of the reaction.

Table 4. Intermediate from $ArPH_2$ and two mol equiv. of QuiN in 1.0 M solutions at 35°

Solvent	ROH[a]	Time of Observations	^{31}P, ppm[b]
CH_2Cl_2	None	20 sec	+10.2[c] ; −0.7[d]
		1.5 min	+10.2 ↑ ; −0.7 ↓
	$(CH_3)_3COH$	2.5 min[e]	+10.2 ↓ ; −20.5 [f]
		5 min	+10.2 ↓ ; −20.5 ↑
		t→∞	−20.5
CH_2Cl_2	CH_3OH	2.5 min	+10.2 ; −20.5
		t→∞	−20.5
CD_3CN	$(CH_3)_3COH$	2 min	+10.2 ; −20.5
		10 min	−20.5

[a] One mol equiv of ROH used.

[b] Positive values are down-field from 85% H_3PO_4 = 0.

[c] Attributed to intermediate $CH(CH_2CH_2)_3\overset{+}{N}P(O)(OH)O^-$.

[d] Starting material.

[e] One mol equiv of ROH introduced at this time.

[f] Cyclic trimetaphosphate.

(3) Unhindered amines, when added to the extent of two mol equiv. to $ArPH_2$, act as both proton acceptors and nucleophilic catalysts. The amine generates both monoanion and dianion, with the monoanion reacting at a faster rate via nucleophilic catalysis. Thus, in alcohol-rich media, e.g. $CD_3CN:(CH_3)_2CHOH$, 10:90, where a relatively large dianion concentration is expected, one sees a mixture of $(CP_3)^{3-}$ and $(RPH)^-$ (5:1) with QuiN, but only $(RPH)^-$ with PrEN. In acetonitrile with one mol equiv. of ROH, where a relatively low dianion concentration is expected, $(CP_3)^{3-}$ is produced in the presence of QuiN, while $(RPH)^-$ is produced in the presence of PrEN. The inference is that $(CP_3)^{3-}$ is formed from the QuiN-catalyzed reaction of monoanion, and $(RPH)^-$ from dianion.

Metastable intermediate in the reactions of $ArPH_2$ *with two mol equiv. of* QuiN. Table 4 shows that a metastable intermediate is rapidly generated from $ArPH_2$ and two mol equiv. of QuiN.[38] The amount of intermediate increases at the expense of the starting material during the first few seconds of the reaction, and then decreases as its is being replaced by $(CP_3)^{3-}$, which is the final and sole phosphorus-containing product of the reaction under the specified conditions. Analogous results are observed in different aprotic solvents, in the absence and in the presence of limited amounts of different alcohols. The transformation of the intermediate into $(CP_3)^{3-}$ occurs, not only while there is still starting material present in the solution, but also after the starting material is no longer observable.

A structure for the metastable intermediate consistent with its behavior and the value of its ^{31}P NMR shift is shown in eqn (12). It is clear that at least some of the final product, $(CP_3)^{3-}$, is formed by further reactions of the intermediate with itself, although the formation of some $(CP_3)^{3-}$ by reaction of the intermediate with the monoanion, $(ArPH)^-$, is not ruled out.

We have been unable to observe the formation of $(RPH)^-$ by reaction of alcohol with the dipolar ion intermediate. When one–three mol equiv. of alcohol is introduced into a solution which contains the maximum build-up of the +10 ppm signal, the product is $(CP_3)^{3-}$ rather than $(RPH)^-$. No intermediate can be detected in reactions induced by the addition of PrEN.

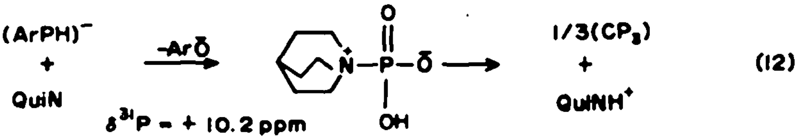
Effect of amines on dianion, $(ArP)^{2-}$ *in aqueous solutions.* The reactions summarized in Table 5 show that certain amines, e.g. pyridine, cause a slight acceleration of the hydrolysis of preformed salt, $(ArP)^{2-}2[(CH_3)_4N]^+$ in aqueous media. The effect of quinuclidine is in the same direction, but insignificant in the context of the present experiments. Similar observations are made in methanol solutions. It would appear from the previous data, that the effects shown in Table 5 cannot be attributed to nucleophilic catalysis by the amine upon the dianion $(ArP)^{2-}$.

DISCUSSION

This study provides a reasonable basis for the following hypotheses:

(1) *In the absence of nucleophilic amines.* (a) The monoanion, $(ArPH)^-$, reacts via P(5) intermediates. Perhaps the generation of PO_3^- by the mechanism of eqn (3) is not operative because X is not sufficiently basic[39] in strongly electronegative phosphomonoesters and related compounds, i.e. when the pK_a of XH (in water) is lower than 5.5 in structures of type $XP(O)(OH)_2$. (b) The dianion, $(ArP)^{2-}$, reacts via a PO_3^- intermediate. This conclusion is in agreement with those previously advanced by several investigators who interpreted their hydrolyses in terms of a PO_3^- intermediate generated as shown in eqn (2).[3–22]

(2) *In the presence of unhindered amines.* (a) The monoanion $(ArPH)^-$ is susceptible to effective nucleophilic catalysis with formation of a P(5) intermediate



(12)

Table 5. Effect of amines on dianion, $(ArP)^{2-}$ in 1.0 M solutions at 35°

Solvent	Amine[a]	t 1/2	Products[b]
$ArPH_2 + 2[(CH_3)_4N]^+ OH^- \longrightarrow (ArP)^{2-}\ 2[(CH_3)_4N]^+ + 2H_2O$			
H_2O	None	2.5 hr	$H_2PO_4^-$
H_2O	$(C_2H_5)_3N$	2.5 hr	$H_2PO_4^-$
H_2O	Pyridine	45 min	$H_2PO_4^-$
H_2O	QuiN	1.5 hr	$H_2PO_4^-$
$ArPH_2 + 2[(n\text{-}C_4H_9)_4N]^+ OH^- \longrightarrow (ArP)^{2-}\ 2[(n\text{-}C_4H_9)_4N]^+ + 2H_2O$			
CH_3OH	None	20 min	$(RPH)^- + H_2PO_4^-$ [c] ; 5:1
CH_3OH	PrHN	18 min	$(RPH)^- + H_2PO_4^-$; 4:1
CH_3OH	Pyridine	10 min	$(RPH)^- + H_2PO_4^-$; 5:1
CH_3OH	QuiN	10 min	$(RPH)^- + H_2PO_4^-$; 4:1

[a] One Mol Equiv.

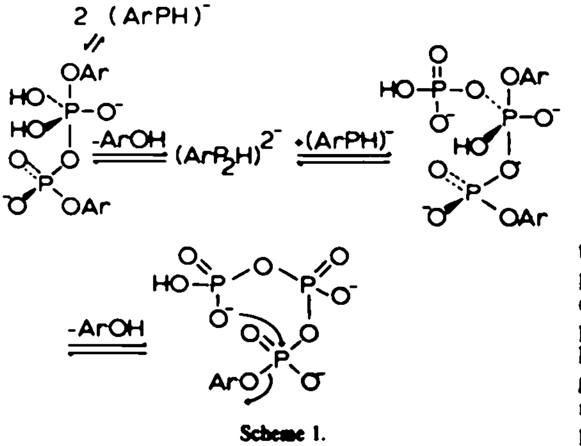
[b] Phosphate product upon completion of the reaction.

[c] From water generated in the neutralization.

which collapses to a new phosphorylated species. The latter gives the products via other P(5) intermediates. (b) The dianion, (ArP^{2-}), reacts via a PO_3^- intermediate. Presumably, the absence of nucleophilic catalysis is due to a loss of electrophilicity of the phosphorus associated with two negatively charged oxygens.

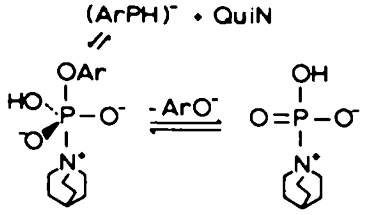
These various mechanistic pathways are associated with several characteristic experimental results. (i) Lower reaction rates are observed in the uncatalyzed P(5)-mechanisms than in the PO_3^--mechanisms. (ii) No t-butyl phosphate is generated via P(5), but the hindered phosphate is readily formed via PO_3^-. (iii) Rapid formation of $(CP_3)^{3-}$ is observed in the tertiary amine-catalyzed P(5)-mechanism from $(ArPH)^-$. However, no phosphoryl transfer to ROH has been demonstrated in this mechanism.

The first step in the formation of $(CP_3)^{3-}$ from $(ArPH)^-$ in acetonitrile, when no free nucleophilic amine is present, is assumed to yield the P(5) intermediate shown in Scheme 1.[60] The second step is the collapse of P(5) with loss of ArO^- and formation of 2,4-dinitrophenyl pyrophosphate. $(ArP_2H)^{2-}$ should be more electrophilic than $(ArPH)^-$ due to the double activation of the phosphorus atom by electron-withdrawing groups. Therefore, the third step in the cyclization is relatively fast and yields a new P(5) intermediate. Collapse of this intermediate as before generates an aryl tripolyphosphate, where the reactive centers are well disposed to give a new P(5) intermediate, and the final $(CP_3)^{3-}$ at a relatively rapid rate.



Scheme 1.

The nucleophilic catalysis of the formation of $(CP_3)^{3-}$ in acetonitrile when $(ArPH)^-$ is generated in the presence of some free unhindered amine is depicted in Scheme 2. The first step is the formation of a P(5) intermediate which collapses with loss of ArO^- and formation of a dipolar structure.[58] We assume that this intermediate is the observed metastable species with the ^{31}P NMR signal at +10.2 ppm; its acid strength is probably weaker than that of ArOH, hence it should predominate in solution as the dipolar ion.



Scheme 2.

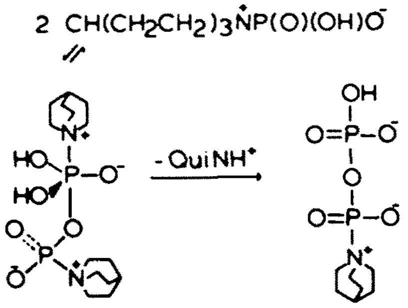
One of the pathways for the formation of $(CP_3)^{3-}$ from the dipolar intermediate is suggested in Scheme 3. It is possible that a dipole–dipole interaction facilitates the dimerization of this structure to a P(5) intermediate, in particular in aprotic media. The P(5) intermediate collapses to a quinuclidinium pyrophosphate which can generate $(CP_3)^{3-}$ by reaction with a third dipolar monomer, as in the cyclization of the aryl pyrophosphate. An additional cyclization mechanism involving the dipolar intermediate and $(ArPH)^-$ is not ruled out, but it should be emphasized that $(CP_3)^{3-}$ is known to form in solutions where $(ArPH)^-$ is no longer detectable by ^{31}P NMR spectrometry.

The uncatalyzed phosphoryl transfer to ROH from $(ArPH)^-$ is depicted in Scheme 4.

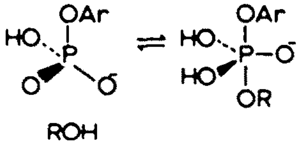
Scheme 5 depicts reactions of the strongly electrophilic hypothetical PO_3^- intermediate with monoanion, $(ArPH)^-$, and alcohols.

These mechanisms accommodate the observed medium effects. It is reasonable to expect higher degree of polarity in a ground-state phosphate than in a transition state which in an oxyphosphorane. Hence, preferential solvation[41] and hence stabilization of the more polar ground state by protic solvents (relative to aprotic solvents) could lead to rate depression[42] in the P(5) mechanism. This is observed in the uncatalyzed formation of $(CP_3)^{3-}$ and $(RPH)^-$, and in the QuiN-catalyzed formation of $(CP_3)^{3-}$ from monoanion. Likewise, a ground-state phosphate should be more polar than the transition state leading to PO_3^-, where there is incipient formation of three-coordinate phosphorus. Therefore a rate depression should be observed in protic vs aprotic media in the PO_3^- mechanism. Again, this is observed in the formation of $(CP_3)^{3-}$ and $(RPH)^-$ from dianion.

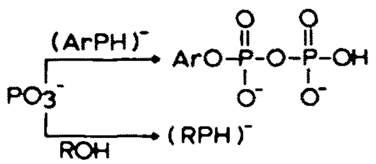
The very weak acceleration observed when the dianion is treated with certain amines in aqueous solution seems to be due to unknown medium effects rather than to nucleophilic catalysis.



Scheme 3.



Scheme 4.



Scheme 5.

EXPERIMENTAL

Anhydrous 2,4-dinitrophenyl phosphate and tetra-n-butylammonium 2,4-dinitrophenyl hydrogen phosphate were prepared as described.[40] The acid or the salt was dissolved in the appropriate solvent, the soln was treated as indicated in Tables 1–5, and the course of the reaction was followed as noted in the Tables. The characterization of the reaction products has been described.[40]

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