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PHOSPHORYL TRANSFER FROM PHENYL AND 4-NITROPHENYL PHOSPHATES IN APROTIC AND PROTIC SOLVENTS

AMINE CATALYSIS AND FORMATION OF OXYPHOSPHORANE AND METAPHOSPHATE INTERMEDIATES

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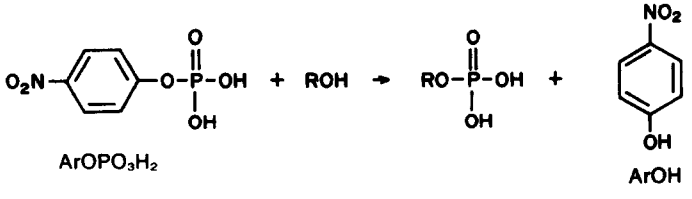
Abstract—The behavior of 4-nitrophenyl dihydrogen phosphate, $ArOPO_3H_2$, and of its tetra-n-butylammonium and tetramethylammonium salts, $ArOPO_3H^-R_4N^+$, $ArOPO_3^{2-}2(R_4N^+)$, was studied in aprotic solvents, in the absence and in the presence of increasing amounts of alcohols or water. The reactions were investigated in the absence of amines, and in the presence of hindered and unhindered amines, diisopropylethylamine and quinuclidine. The course of the reactions was followed at 35° or at 70° by ^{31}P and ^1H NMR spectrometry. Values for the approximate half-times of the reactions were estimated (±25%) from the times at which reactant signal intensity becomes equal to product signal intensity. The mononitrophenyl ester transfers its phosphoryl group to alcohols and water from the diprotonated acid by the addition–elimination mechanism via oxyphosphorane intermediates, and from the monoanion and dianion by the elimination–addition mechanism via the monomeric metaphosphate intermediate, PO_3^-. Formation of PO_3^- is faster from dianion than from monoanion in acetonitrile and in alcohol solutions. Conversely, PO_3^- is generated at a faster rate from monoanion than from dianion in aqueous solution. This effect results from a decrease in the rate of formation of PO_3^- in the solvent series: acetonitrile > alcohols > water. The rate depression as a function of the medium is greater for the dianion than for the monoanion, and is attributed to greater solvation of the more polar phosphate ground state than of the less polar transition state in the more polar protic solvents. Unhindered amines add to 4-nitrophenyl phosphate monoanion, but not to the dianion. The oxyphosphorane intermediate thus formed collapses to aroxide ion and a protonated dipolar phosphoramide which is rapidly deprotonated by the relatively basic 4-nitrophenoxide: $ArOPO_3H^- + CH(CH_2CH_2)_3N$(acetonitrile $\rightleftharpoons CH(CH_2CH_2)_3N^+P(O)(OH)O^- + ArO^- \rightleftharpoons CH(CH_2CH_2)_3N^+PO_3^{2-} + ArOH \rightarrow CH(CH_2CH_2)_3N + PO_3^-$. The postulated formation of PO_3^- by this route explains why the addition of quinuclidine to an acetonitrile solution containing the monoanion salt, $ArOPO_3H^-R_4N^+$, and t-BuOH produces t-butyl phosphate at a faster rate than the addition of diisopropylethylamine to the same solution. 2,4-Dinitrophenyl phosphate, which was previously studied by the same techniques, reacts via oxyphosphorane intermediates from the diprotonated and the monoanion forms, and via monomeric metaphosphate, from the dianion form.

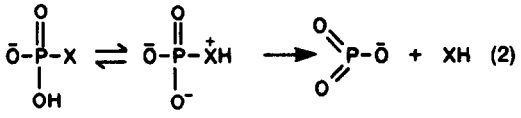
The behavior of 2,4-dinitrophenyl phosphate, and of its quaternary ammonium salts, has been studied in aprotic solvents in the absence and in the presence of alcohols or water.[2] The reactions were investigated in the absence of amines, and in the presence of variable amounts of the sterically hindered and unhindered amines, diisopropylethylamine and quinuclidine, respectively.[3] From these experiments it was concluded that, in the absence of free quinuclidine, the dinitrophenyl phosphate, in its diprotonated form or as its monoanion, undergoes nucleophilic displacements by an addition–elimination mechanism which involves an oxyphosphorane intermediate. On the other hand, the dinitrophenyl phosphate dianion appears to react by an elimination–addition mechanism which involves a monomeric metaphosphate anion intermediate, PO_3^-. One of the criteria employed to arrive at these conclusions is the rapid formation of t-butyl phosphate from reactions of the aryl phosphate in the presence of t-butyl alcohol under certain experimental conditions. These studies also led to the conclusion that sterically unhindered amines are capable of adding to the monoanion, but not to the dianion, of the dinitrophenyl phosphate, and that the resulting oxyphosphorane decomposes into a protonated dipolar phosphoramide intermediate. The phosphoramide derived from quinuclidine, $CH(CH_2CH_2)_3N^+P(O)(OH)O^-$, was assumed to be responsible for the transient ^{31}P NMR signal that could be detected in some of the systems investigated.

The present work is a qualitative study of the reactions by which 4-nitrophenyl phosphate and its salts, e.g. $ArOPO_3H^-$ $(n\text{-}C_4H_9)_4N^+$ and $ArOPO_3^{2-}2[(n\text{-}C_4H_9)_4N^+]$, transfer their phosphoryl group to nucleophiles (eqn 1) in nonaqueous media under conditions similar to those previously employed for 2,4-dinitrophenyl phosphate. A more limited study of the behavior of phenyl phosphate is also included.

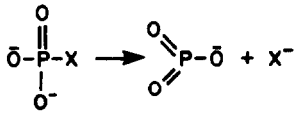


$ArOPO_3H_2$ ArOH (1)

The hydrolysis of 2,4-dinitrophenyl phosphate[4–7] and of 4-nitrophenyl phosphate[6,8–12] has been extensively studied in aqueous solution. In the absence of nucleophilic amines, the pH-rate profile of the dinitro-ester shows maximum rate at the pH which corresponds to a maximum concentration of dianion, $XP(O)O_2^{2-}$. This behavior is typical of other aryl phosphates derived from phenols, XH, with pKa < 5.5 (in water). The pH-rate profile of the mononitro-ester shows a maximum rate at the pH which corresponds to a maximum concentration of monoanion, $XP(O)(OH)O^-$. This behavior is also found in other aryl phosphates derived from phenols with pKa > 5.5, and in alkyl phosphates[13–16], where XH is an alcohol. It has been suggested[4–6] that the dinitro- and mononitro-esters undergo hydrolysis via the PO_3^- intermediate, which is generated from the monoanion by the mechanism[5,6] shown in eqn (2), and from the dianion by the mechanism[5–30] given in eqn (3). In view of the observed pH-rate profiles, it must be concluded that the monoanion mechanism results in slower reaction rates than the dianion mechanism in the dinitro-ester, but that the opposite is the case in the mononitro-ester.

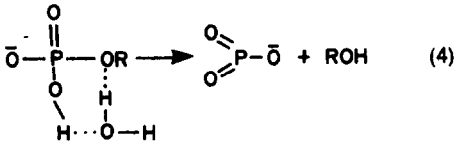


(2)



(3)

The formation of PO_3^- from monoanion has also been pictured[13,14] as shown in eqn (4); this mechanism is kinetically indistinguishable from that shown in eqn (2).



(4)

For the hydrolysis of aryl phosphates in the presence of nucleophilic amines, Kirby[5,6] has suggested a bimolecular mechanism, with the amine participating in the rate limiting step, in both the dinitro- and mononitroesters, and from both the monoanion and dianion forms of the phosphate.

The operation of the oxyphosphorane mechanism in reactions of phosphotriesters[31–33] and diesters[34] is now widely accepted.[35–39] A hydroxyphosphorane has recently been observed in solutions in equilibrium with a phosphotriester.[40,41] Certain acyl phosphotriesters[42] and phosphinate esters[43] also display a tendency to form hydroxyphosphoranes in solution.

RESULTS AND DISCUSSION

Acid-base equilibria in solutions of aryl phosphates. Acids become progressively weaker when water is replaced by alcohol and by aprotic solvents.[44–47] Data in acetonitrile pertinent to this work are given in Table 1. The decrease in acidity of aminium cations, R_3NH^+, is not nearly as large as that of carboxylic acids. Among carboxylic acids, the maximum decrease in acidity is observed in the weakest acids. A similar trend is observed among phenols.

Table 1. Acid dissociation constants of brönsted acids in water and in acetonitrile (data from Ref. 46)

Acid	pK_a Water	pK_a Acetonitrile	ΔpK_a
Acetic	4.8	22.3	17.5
Benzoic	4.2	20.7	16.5
4-Nitrobenzoic	3.4	18.7	15.3
3,5-Dinitrobenzoic	2.8	16.9	14.1
Phenol	10.0	26.6	16.6
4-Nitrophenol	7.1	20.7	13.5
2,4-Dinitrophenol	4.1	16.0	11.9
Piperidine	11.2	18.9	7.7
Diethylamine	11.0	18.7	7.7
Triethylamine	10.7	18.5	7.8
Ethylamine	10.6	18.4	7.7
Ammonia	9.2	16.5	7.3
Pyridine	5.2	12.3	7.1

From the data in Table 1, and on the assumption that the effects of aprotic solvents vs water on the acidity of phosphoric and carboxylic acids are of comparable magnitude, the following inferences can be drawn. The weakly acidic function of the aryl phosphate should be affected to a greater extent than the strongly acidic function when the medium is changed from water to acetonitrile. In water, the separation between pK_{a2} (5.5) and pK_{a1} (1.2) in 4-nitrophenyl phosphates is 4.3 pK units, while in acetonitrile this separation should be about 9 pK units, using the values $\Delta pK_a \sim 17$ and 13 for the decrease in acidity of the weak and strong acids, respectively. In other words, a study of the behavior of the aryl phosphate in acetonitrile should facilitate the task of ascertaining the type of mechanism which is operative in the monoanion and the dianion forms of the phosphate.

An acetonitrile solution containing the phosphate dianion salt plus several mol equiv of alcohol or water should not contain a significant concentration of monoanion salt and alkoxide (or hydroxide) ion: $ArOPO_3^{2-}2R_4N^+ + ROH \rightleftharpoons ArOPO_3H^- + RO^- + 2R_4N^+$. Data on alcohol or water acidity in acetonitrile as solvent is not available. However, from the phenol data it is reasonable to expect a decrease in acidity of at least 16 pK units for acids of type ROH. Hence, the decrease in $ArOPO_3H^-$ acidity in acetonitrile is compensated by a decrease in ROH acidity. In other words, in acetonitrile, ROH is too weak an acid to protonate even the relatively strong base $ArOPO_3^{2-}$.

An acetonitrile solution of monoanion salt plus one mol equiv of diisopropylethylamine or quinuclidine should contain a relatively low concentration of dianion: $ArOPO_3H^- + R_3N \rightleftharpoons ArOPO_3^{2-} + R_3NH^+ + R_4N^+$. Note that replacing water by acetonitrile decreases the acidity of phosphate monoanion to a much greater extent than it decreases the acidity of aminium ion. Therefore, the amine should be too weak a base in acetonitrile to deprotonate the monoanion to a significant extent. The amine, however, should appreciably deprotonate the neutral acid, $ArOPO_3H_2$.

These inferences concerning acid-base equilibria of 4-nitrophenyl phosphate in acetonitrile, based on data for carboxylic acids, phenols and aminium acids (Table 1), are in line with the results of phosphoryl transfer from the mononitro-ester to alcohols and water in the same solvent, as described in the next Sections.

Reactions of 4-nitrophenyl dihydrogen phosphate. The anhydrous diprotonated acid was prepared as described[48] and was studied in anhydrous dioxane. The results are summarized in Table 2. The acid is quite stable even at 70° (Expt 1). At these temperatures, anhydrous acetonitrile, which is the solvent of choice in our investigations,[2,3] is unsatisfactory as reaction medium for the acid, although this solvent can be used with the phosphate salts (see below). The technique utilized to obtain half-times of reaction is described in the Experimental. The values of t 1/2 are taken as accurate to within 25% of the times indicated, and only differences by factors of three or more are regarded as significant.[49]

Phosphorylation of limited amounts of methanol occurs in dioxane at a relatively slow rate (Expt 2); eqn (5).

$$ArOPO_3H_2 + 1\,ROH \xrightarrow{\text{Dioxane}} ROPO_3H_2 + ArOH \quad (5)$$

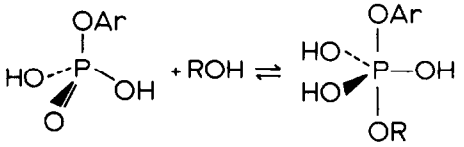
$$R = CH_3 \text{ or } H$$

The solvolysis of the acid is only slightly faster in pure methanol (Expt 3); eqn (6). The reaction is sensitive to the size of the alcohol, and is no longer observed with 2-propanol (Expt 4).

$$ArOPO_3H_2 + ROH \xrightarrow{ROH} ROPO_3H_2 + ArOH \quad (6)$$

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

The reactions of the acid with water (Expts 5, 6) are comparable to the reactions with methanol under analogous conditions. There is little doubt that all of these phosphoryl transfers occur via an oxyphosphorane intermediate; Scheme 1.



Scheme 1

Reactions of tetra-n-butylammonium 4-nitrophenyl phosphate. The results are summarized in Table 3. A solution of the monoanion salt in anhydrous acetonitrile decomposes into cyclic trimetaphosphate at a much faster rate than a solution of the neutral acid (Expt 1); eqn (7). Cyclic trimetaphosphate was characterized as described.[50]

$$ArOPO_3H^-R'_4N^+ \xrightarrow{CH_3CN} 1/3(P_3O_9)^{3-} + ArOH. \quad (7)$$

Table 2. Reactions of 4-nitrophenyl dihydrogen phosphate in 1.0 M solutions at 70°

Expt. No.	Solvent	Reagent (Mol Equiv)	t 1/2	Results
1	Dioxane	None	N.R.[a]	N.R.
2	Dioxane	CH_3OH(1)	6 days	$ROPO_3H_2$
3	CH_3OH	CH_3OH(25)	2 days	$ROPO_3H_2$
4	$(CH_3)_2CHOH$	$(CH_3)_2CHOH$(13)	N.R.[a]	N.R.
5	Dioxane	H_2O(1)	3.5 days	H_3PO_4
6	H_2O	H_2O(55)	6 hr	H_3PO_4
7	1 M HCl(H_2O)	H_2O	3 hr	H_3PO_4

[a] No reaction after 7 days.

Table 3. Reactions of tetra-n-butylammonium 4-nitrophenyl phosphate in 1.0 M solutions at 70°, $P_3O_9^{3-}$ = cyclic trimetaphosphate

Expt. No.	Solvent	Reagent (Mol Equiv)[a]	t 1/2	Results[b]
1	CD_3CN	None	5 hr	$P_3O_9^{3-}$
2	CD_3CN	CH_3OH(1)	8 hr	$ROPO_3H^-$ + $RP_2O_7H^{2-}$ + $P_3O_9^{3-}$; 6:3:1
3	CD_3CN	$(CH_3)_2CHOH$(1)	8 hr	$ROPO_3H^-$ + $RP_2O_7H^{2-}$ + $P_3O_9^{3-}$; 6:3:1
4	CD_3CN	$(CH_3)_3COH$(1)	7 hr	$ROPO_3H^-$ + $RP_2O_7H^{2-}$ + $P_3O_9^{3-}$; 4:1.5:1
5	CD_3CN	H_2O(1)	7 hr	$H_2PO_4^-$ + $H_2P_2O_7^{2-}$; 4:3
6	CH_3OH	CH_3OH(25)	30 hr	$ROPO_3H^-$
7	$(CH_3)_2CHOH$	$(CH_3)_2CHOH$(13)	36 hr	$ROPO_3H^-$
8	CD_3CN:$(CH_3)_3COH$, 10:90[d]	$(CH_3)_3COH$(10)	30 hr	$ROPO_3H^-$
9	H_2O[e]	H_2O(55)	6 hr	$H_2PO_4^-$
10	$CDCl_3$	None	30 hr	$P_3O_9^{3-}$[c]
11	$CDCl_3$	$(CH_3)_3CHOH$(1)	35 hr	$ROPO_3H^-$

[a] Per mol of phosphate. [b] The products indicated are those observed upon completion of the reaction. [c] Aryl pyrophosphate, observed as intermediate. [d] The salt is insufficiently soluble in pure t-butanol. All mixed solvents are v/v. [e] $(CH_3)_4N^+$ salt used to attain water solubility.

For reasons discussed below, the reaction of eqn (7) is assumed to proceed via the monomeric metaphosphate anion, as suggested for the hydrolysis of the same species in aqueous solution.[6,8-12] The formation of PO_3^- is assumed to occur as follows:[6]

$$ArO-\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{P}}-OH \rightleftharpoons ArO^+-\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{P}}-O^- \rightarrow ArOH + PO_3^-.$$

The next step is a relatively fast reaction of the strongly electrophilic[5,1] PO_3^- with the original aryl phosphate monoanion to give 4-nitrophenyl pyrophosphate. The pyrophosphate is detected by its characteristic ^{31}P NMR spectrum: $PO_3^- + ArOPO_3H^- \rightarrow ArP_2O_7H^{2-}$. Further reaction of PO_3^- with the aryl pyrophosphate yields the aryl tripolyphosphate. A reasonable alternative to this step is the addition of the aryl phosphate monoanion to the highly reactive Pα-atom of the aryl pyrophosphate to form first an oxyphosphorane, and then the aryl tripolyphosphate:[2,3] $PO_3^- + ArP_2O_7H^{2-} \rightarrow ArP_3O_{10}H^{3-}$ or $ArOPO_3H^- + ArP_2O_7H^{2-} \rightarrow ArP_3O_{10}H^{3-} + ArOH$. The intramolecular reaction of the aryl tripolyphosphate to cyclic trimetaphosphate has already been discussed.[2,3]

***Note Added in Proof.** In this pathway to cyclic trimetaphosphate, the formation of monomeric metaphosphate anion is required only in the first step which leads to 4-nitrophenyl pyrophosphate. This aryl pyrophosphate, and the linear aryl tripolyphosphate formed at a later stage, have highly electrophilic P_α atoms capable of being transformed into oxyphosphorane intermediates in route ton cyclic trimetaphosphate (*cf.* Ref. 2 and 3). For a discussion of cyclic polymetaphosphate formation from activated phosphoric acid and inorganic pyrophosphate and linear polyphosphates see: T. Glonek, J. R. Van Wazer, M. Mudgett and T. C. Myers, *Inorg. Chem.* **11**, 567 (1972); T. Glonek, J. R. Van Wazer, R. Kleps and T. C. Myers, *Ibid* **13**, 2337 (1974); T. Glonek, J. R. Van Wazer and T. C. Myers, *Ibid* **14**, 1597 (1975); T. Glonek, R. A. Kleps, J. R. Van Wazer and T. C. Myers, *Bioinorganic Chemistry* **5**, 283 (1976).

It should be noted that the decomposition of 2,4-dinitrophenyl phosphate monoanion in acetonitrile does not proceed via monomeric metaphosphte but occurs via an oxyphosphorane intermediate.[2,3] Presumably, the more basic ester–oxygen of the mononitro–monoanion, but not the less basic ester–oxygen of the dinitro–monoanion,[52] can accept the proton, and thus can form the intermediate,

$$ArO^+-\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{P}}-O^- \quad (H \text{ on } O^-)$$

which seems to be required for decomposition to PO_3^-. The structural features in the phosphate which lead to a decrease in basicity of the ester-oxygen also lead to an increase in electrophilicity of the phosphorus, which favors oxyphosphorane formation.

The 4-nitrophenyl phosphate monoanion transfers its phosphoryl group to one mol equiv of alcohols in aprotic solvents (Expts 2–4); eqn (8). Note that reaction rates and product composition do not change much as the steric hindrance in the alcohol is increased. The main product of the reaction is the alkyl phosphate, even when the nucleophile is t-butyl alcohol. Significant amounts of alkyl pyrophosphate are also produced. Only traces of cyclic trimetaphosphate are detected among the products.

$$ArOPO_3H^-R'_4N^+ + 1\,ROH \xrightarrow{CH_3CN} ROPO_3H^- + RP_2O_7H^{2-} + 1/3(P_3O_9)^{3-} + ArOH \quad (8)$$

R = 1°, 2°, 3° Alkyl or H

These observations are reasonable if the mononitro–monoanion decomposes into PO_3^- in a rate-limiting step, as was the case in the absence of alcohol (*cf* Expt. 1); in fact, rates of reaction are very similar in the presence and in the absence of alcohols. However, now the alcohol intercepts the monomeric metaphosphate: $PO_3^- + ROH \rightarrow ROPO_3H^-$. The resulting alkyl phosphate also captures metaphosphate and generates alkyl pyrophosphate: $PO_3^- + ROPO_3H^- \rightarrow RP_2O_7H^{2-}$.

As shown in Expt 5, the reactions of the monoanion salt with water and with alcohols have the same characteristics in the aprotic medium. All of these reactions undoubtedly represent the behavior of the monoanion, since the rates of reactions and the composition of the products are substantially different from those observed when the starting material is the mononitroester *dianion* salt (Table 4).

The rates of phosphorylation by the mononitro-monoanion decrease when the reactions are carried out in pure, or nearly pure, alcohols, in spite of the fact that the ratio of alcohol to phosphate increases significantly (Expts. 6–8); eqn (9).

$$ArOPO_3H^-R'_4N^+ + ROH \xrightarrow{ROH} ROPO_3H^- + ArOH \quad (9)$$

R = 1°, 2°, 3° Alkyl or H.

A possible explanation of this effect is that the protic solvents solvate the more polar phosphate monoanion ground state to a greater extent than the less polar transition state which generates monomeric metaphosphate. This preferential solvation of ground state vs transition state, which results in rate depression,[53] overcomes the effect of the increase in alcohol/phosphate ratio. The preferential solvation effect is also noted in reactions with water, since the rate in Expts 5 and 9 remain about the same although the mol equiv of water vs phosphate has been increased from 1 to 55.

The reactions of the acid given in Table 2 (Expts 2 vs 3 and 5 vs 6) also disclose the rate depression which we attribute to preferential solvation of ground state vs transition state. In that case, the transition state corresponds to the formation of oxyphosphorane from the acid, $ArOPO_3H_2$, in the production of alkyl phosphate or phosphoric acid.

Reactions of bis(tetra-n-butylammonium) 4-nitrophenyl phosphate. This dianion salt could not be isolated in the pure anhydrous state. However, the monohydrate of the salt was prepared by the procedure given in the Experimental. Expts 1–4 in Table 4 summarize the reactions of acetonitrile solutions of the dianion salt monohydrate with limited amounts of alcohols and water. These reactions are extremely rapid and had to be studied at 35° instead of at 70°, which is a convenient temperature to study comparable reactions of the monoanion salt. The dianion transfers its phosphoryl group to both alcohols and water at comparable rates; eqn (10). The

Table 4. Reactions of *bis*-tetra-n-butylammonium 4-nitrophenyl phosphate in 1.0 M solutions

Expt. No.	Solvent	T°C	Reagent (Mol Equiv)	t 1/2	Results
1	CD_3CN	35[a]	$CH_3OH(2) + H_2O(1)$	5 min	$ROPO_3H^- + H_2PO_4^-$; 1:1
2	CD_3CN	35	$(CH_3)_2CHOH(2) + H_2O(1)$	4 min	$ROPO_3H^- + H_2PO_4^-$; 2:1
3	CD_3CN	35	$(CH_3)_3COH(2) + H_2O(1)$	4 min	$ROPO_3H^- + H_2PO_4^-$; 1:1
4	CD_3CN	35	$H_2O(3)$	5 min	$H_2PO_4^-$
5	CH_3OH	35	$CH_3OH(25)$	N.R.[b]	N.R.
6	CH_3OH	70	$CH_3OH(25)$	6 hr	$ROPO_3H^-$
7	$(CH_3)_2CHOH$	35	$(CH_3)_2CHOH(13)$	24 hr	$ROPO_3H^-$
8	$(CH_3)_2CHOH$	70	$(CH_3)_2CHOH(13)$	3 min	$ROPO_3H^-$
9	$(CH_3)_3COH$	35	$(CH_3)_3COH(10)$	5 hr	$ROPO_3H^-$
10	$(CH_3)_3COH$	70	$(CH_3)_3COH(10)$	1 min	$ROPO_3H^-$
11	H_2O[c]	35	$H_2O(55)$	N.R.[b]	N.R.
12	H_2O	70	$H_2O(55)$	3.5 days	$H_2PO_4^-$

[a] At 70°C, the reaction is too fast for measurements by the present technique.

[b] No reaction after 12 days. [c] $(CH_3)_4N^+$ salt used to attain water solubility.

reaction rates are very similar with alcohols of different steric hindrance, including t-butyl alcohol. Only alkyl phosphate and inorganic phosphate are observed as products.

$$ArOPO_3^{2-}2R'_4N^+ + ROH \xrightarrow{CH_3CN} ROPO_3^{2-} + ArOH \qquad (10)$$

R = 1°, 2°, 3° Alkyl or H

The reactions of the dianion are reasonably explained by a very fast decomposition of dianion into monomeric metaphosphate in the aprotic solvent: $ArOPO_3^{2-} \rightarrow ArO^- + PO_3^-$.

The reactions of the dianion salt in pure or nearly pure alcohols or water show an interesting effect (Expts 5–10); eqn (11). To detect these trends measurements were carried out at both 35° and 70°. As the aprotic solvent is replaced by alcohols or water, rates of reaction decrease in the sequence: acetonitrile > t-butyl alcohol > 2-propanol > methanol > water.

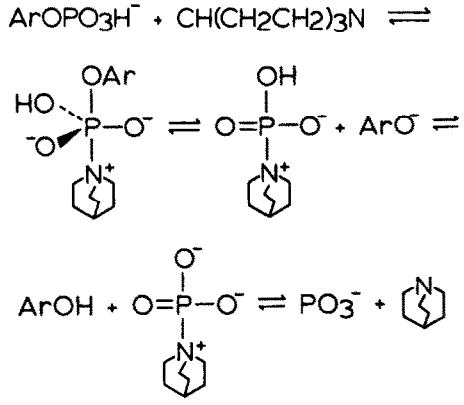
$$ArOPO_3^{2-}2R'_4N^+ + ROH \xrightarrow{ROH} ROPO_3^{2-} + ArOH \qquad (11)$$

R = 1°, 2°, 3° Alkyl or H

A comparison among Expts in Tables 3 and 4 discloses that while the formation of PO_3^- is *faster from dianion than from monoanion in acetonitrile and alcohol solutions*, the PO_3^- is generated at a faster rate from monoanion than from dianion in aqueous solution. Apparently, there is an inherently greater tendency for the dianion to decompose to PO_3^-, relative to the monoanion. However, the dianion seems to be more susceptible to rate depression due to preferential solvation of ground state vs transition state, in comparison to the monoanion. Consequently a reversal of reactivity in phosphoryl transfer from dianion vs monoanion by the monomeric metaphosphate mechanism is noted when the aprotic solvent or the alcohols are replaced by water.

Reactions of tetra-n-butylammonium 4-nitrophenyl phosphate and one mol equiv of hindered or unhindered amines. As shown in Expt 1 of Table 5 and Expt 1 of Table 3, an acetonitrile solution of 4-nitrophenyl phosphate monoanion salt plus one mol equiv of diisopropylethylamine behaves just like the solution of the salt without amine. Apparently, in the aprotic solvent, most of the monoanion remains protonated under these conditions, as discussed in the Section on acid-base equilibria. Quinuclidine and diisopropylethylamine have about the same basicity and, therefore, it is significant that the acetonitrile solution of the phosphate monoanion salt plus quinuclidine generates cyclic trimetaphosphate at a faster rate than the same solution without amine or with the sterically hindered amine.

A possible explanation for the effect of quinuclidine on the reaction of 4-nitrophenyl phosphate monoanion is given in Scheme 2. It is assumed that the increase in the rate of formation of cyclic trimetaphosphate is due to nucleophilic catalysis by the unhindered amine. The first step is the formation of an oxyphosphorane which decomposes to a protonated dipolar phosphoramide, or "phosphorylated-catalyst". This mechanism is analogous to that suggested for a similar effect of quinuclidine on 2,4-dinitrophenyl phosphate.[3,54] However, the 4-nitrophenoxide ion eliminated in the reaction of the mononitro-ester with the amine is a stronger base than the 2,4-dinitrophenoxide ion eliminated in the reaction of the dinitro-ester with the amine. Therefore, it is reasonable to expect significant deprotonation of the phosphoramide by 4-nitrophenoxide. The deprotonated phosphoramide should decompose rapidly into quinuclidine and monomeric metaphosphate. Scheme 2.



Scheme 2

In reactions of the dinitro-ester monoanion with quinuclidine we were able to detect a transient ^{31}P NMR signal at +10.2 ppm which was attributed to the protonated phosphoramide intermediate.[3] This signal was not detected in the comparable reactions of the mononitro-ester monoanion with quinuclidine, in line with the picture suggested in Scheme 2.

Table 5. Reactions of tetra-n-butylammonium 4-nitrophenyl phosphate and 1 mol equiv of diisopropylethylamine or quinuclidine in 1.0 M solutions at 70°. $(R_4N)^+ = [(n\text{-}C_4H_9)_4N]^+$

Expt. No.	Solvent	Reagent (Mol Equiv)	t 1/2	Results
$ArOPO_3H^-R_4N^+ + (i\text{-}C_3H_7)_2C_2H_5N \rightleftharpoons ArOPO_3^{2-}R_4N^+(i\text{-}C_3H_7)_2C_2H_5NH^+$				
1	CD_3CN	None	5 hr	$P_3O_9^{3-}$ [a]
2	CD_3CN	CH_3OH(1)	7 hr	$ROPO_3H^- + RP_2O_7H^{2-} + P_3O_9^{3-}$; 15:4:1
3	CD_3CN	$(CH_3)_2CHOH$(1)	7 hr	$ROPO_3H^- + RP_2O_7H^{2-} + P_3O_9^{3-}$; 13:6:1
4	CD_3CN	$(CH_3)_3COH$(1)	6 hr	$ROPO_3H^- + RP_2O_7H^{2-} + P_3O_9^{3-}$; 6:3:1
5	CD_3CN	H_2O(1)	5 hr	$H_2PO_4^- + H_2P_2O_7^{2-}$; 3:2
6	CH_3OH	CH_3OH(25)	36 hr	$ROPO_3H^-$
7	H_2O [b]	H_2O(55)	3 days	$H_2PO_4^-$
$ArOPO_3H^-R_4N^+ + CH(CH_2CH_2)_3N \rightleftharpoons ArOPO_3^{2-}R_4N^+CH(CH_2CH_2)_3NH^+$				
8	CD_3CN	None	30 min	$P_3O_9^{3-}$
9	CD_3CN	CH_3OH(1)	45 min	$ROPO_3H^- + P_3O_9^{3-}$; 3:1
10	CD_3CN	$(CH_3)_2CHOH$(1)	45 min	$ROPO_3H^- + P_3O_9^{3-}$; 2:1
11	CD_3CN	$(CH_3)_2COH$(1)	45 min [c]	$ROPO_3H^- + P_3O_9^{3-}$; 1:1
12	CD_3CN	H_2O(1)	30 min	$H_2PO_4^- + H_2P_2O_7^{2-}$; 3:2
13	H_2O [b]	H_2O(55)	3 days	$H_2PO_4^-$

[a] Aryl pyrophosphate observed as intermediate. [b] $(CH_3)_4N^+$ salt employed to achieve solubility in water. 4-Nitrophenol precipitates as the reaction proceeds.

[c] In the presence of two mol equiv of quinuclidine: t 1/2 = 30 min; $ROPO_3H^- + P_3O_9^{3-}$, 1:4 upon completion of reaction.

The route to PO_3^- by way of an oxyphosphorane and a phosphorylated-catalyst shown in Scheme 2 would explain the results when quinuclidine is added to an acetonitrile solution of the mononitro-ester monoanion salt containing limited amounts of alcohol or water; Expts 9–12 in Table 5. These reactions generate mixtures of alkyl phosphate and cyclic trimetaphosphate (or of inorganic phosphate and pyrophosphate, in the case of water); eqn (12).

$$ArOPO_3H^-R'_4N^+ + 1\,ROH + CH(CH_2CH_2)_3N \xrightarrow{CH_3CN} ROPO_3^{2-} + 1/3(P_3O_9)^{3-} + ArOH \qquad (12)$$

R = 1°, 2°, 3° Alkyl or H

In these reactions, alkyl phosphate is formed even from the t-butyl alcohol, which is consistent with the formation of PO_3^-. Reaction rates are similar for all alcohols and water, again in support of PO_3^- formation. In the hypothesis of Scheme 2, the rate of reaction increases as a result of catalysis by quinuclidine. The composition of the product is determined by the fast generation of PO_3^- and its rapid reaction with alcohol or water to give alkyl phosphate or inorganic phosphate, or with aryl phosphate to give cyclic trimetaphosphate as discussed above.

It should be noted that the introduction of diisopropylethylamine into the acetonitrile solution containing the monoanion salt and limited amounts of alcohol or water, does not alter the results of the same reaction in the absence of the hindered amine; *cf* Expts 2–5 in Table 5 and Expts 2–5 in Table 3. This observation is consistent with the conclusion that the *amine does not deprotonate the monoanion in acetonitrile to a significant extent.* Note that, in aqueous solution, the mixtures of mononitro-ester and the hindered or unhindered amines behave very much alike; *cf* Expts 7 and 13 in Table 5. This is reasonable, since in water one expects a nearly complete shift of the equilibrium from monoanion to dianion. Hence there is now little or no monoanion and free amine and no quinuclidine catalysis is observed.

A final point worth noting is that amines do not have a significant effect on the rates of hydrolysis of the mononitro-ester *dianion* salt in aqueous solution, at least in our qualitative measurements. Thus, when Expts 11 and 12 in Table 4 are carried out in the presence of one mol equiv of either triethylamine, quinuclidine or pyridine, reaction rates are virtually unchanged.[55] We have encountered an analogous

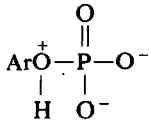
situation with the dinitroester–dianion,[3] and conclude that the dianion of aryl phosphates is not electrophilic enough to accept an amine at the phosphorus atom as in the mechanism of nucleophilic catalysis. Any slight rate enhancement by amines in reactions of dianions could be a medium effect of unknown origin.

Reactions of phenyl phosphate, $C_6H_5OPO_3H_2$. This acid is, as expected, even less reactive than 4-nitrophenyl phosphate. The reactions of the monoanion salt $C_6H_5OPO_3H^-R_4N^+$ and the dianion salt, $C_6H_5OPO_3^{2-}2R_4N^+$, seem to occur by the elimination–addition mechanism, and show the lower reaction rates expected from the weaker nucleofugic groups, phenol and phenoxide; *cf* Table 6.

CONCLUSIONS

From the results described in this and previous[2,3] papers we conclude that the type of mechanism operative in phosphoryl transfer from aryl phosphates depends on: (1) the structure of the phosphomonoester; (2) the state of ionization of the ester in a particular medium; and (3) the nature of the medium.

(1) The structure of the aryl group will determine: (a) the nucleofugicity of the leaving group, ArO^- from dianion, and ArOH from monoanion; (b) the strength of the acid, $ArOPO_3H_2$; (c) the basicity of the ester-oxygen, and hence the tendency for the formation of the metaphosphate precursor from monoanion:



(2) The diprotonated acid is capable only of reaction by the addition–elimination mechanism. The monoanion can react either by the addition–elimination or the elimination–addition mechanisms. The dianion can react only by the elimination–addition mechanism. Nucleophilic catalysis is operative only on the monoanion.

(3) The nature of the medium controls: (a) the degree of dissociation of the phosphomonoester; (b) the relative solvation of the more polar phosphate ground state vs the less polar transition states in both mechanisms, *i.e.* the transition states that lead to oxyphosphorane or to monomeric metaphosphate anion.

EXPERIMENTAL

The ^{31}P NMR spectra were measured in a Varian T 60 A NMR spectrometer. The signals are given in ppm *vs* 85% $H_3PO_4 = 0$ (positive values are downfield from the reference). Acetonitrile was dried and stored over 4 A molecular sieves. Quinuclidine was prepared from quinuclidine hydrochloride (Aldrich) and was purified by sublimation under reduced pressure.

4-Nitrophenyl dihydrogen phosphate ($ArOPO_3H_2$) was prepared as described;[54] $\delta^{31}P = -7.6$ ppm (CD_3CN).

Tetra-n-butylammonium 4-nitrophenyl hydrogen phosphate. An aliquot of 1.0 M methanolic tetra-n-butylammonium hydroxide containing 20.0 mmol of base was added to a soln of $ArOPO_3H_2$ (4.38 g, 20.0 mmol) in diethyl ether (50 mL). The soln was immediately evaporated at 20° (first at 30 mm, finally at 0.2 mm) to give the yellow crystalline *monohydrate* of the salt. A dichloromethane soln (30 mL) containing the monohydrate (3.0 g) and 4 A molecular sieves (10 g) was kept 4 days at 5°. Evaporation of the solution gave the *anhydrous salt*, which solidified after being kept at 30° (0.2 mm); m.p. 88–91°; $\delta^{31}P = -4.5$ ppm (CD_3CN). Calc. for

Table 6. Reactions of phenyl phosphate mono- and dianions, in 1.0 M solutions at 70°

Expt. No.	Solvent	Reagent (Mol Equiv)	t 1/2	Results
$C_6H_5OPO_3H^-(R_4N)^+$				
1	CD_3CN	None	[a]	$C_6H_5P_2O_7H^{2-}$
2	CD_3CN	CH_3OH(1)	4 days	$ROPO_3H^-$
3	CD_3CN	$(CH_3)_2CHOH$(1)	4 days	$ROPO_3H^-$
4	CD_3CN	$(CH_3)_3COH$(1)	4 days	$ROPO_3H^-$
5	CD_3CN	H_2O(1)	3 days	$H_2PO_4^-$ + $H_2P_2O_7^{2-}$; 3:2
6	H_2O	H_2O(55)	2 days	$H_2PO_4^-$
$C_6H_5OPO_3^{2-}2(R_4N)^+$				
7	CD_3CN	CH_3OH(2) + H_2O(1)	6 hr	$ROPO_3H^-$ + $H_2PO_4^-$; 2:1
8	CD_3CN	$(CH_3)_2CHOH$(2) + H_2O(1)	8 hr	$ROPO_3H^-$ + $H_2PO_4^-$; 2:1
9	CD_3CN	$(CH_3)_3COH$(2) + H_2O(1)	6 hr	$ROPO_3H^-$ + $H_2PO_4^-$; 1:1
10	CD_3CN	CH_3OH(1) + H_2O(2)	10 hr	$ROPO_3H^-$ + $H_2PO_4^-$; 1:2
11	H_2O	H_2O(55)	N.R.[b]	N.R.

[a] No value could be estimated. Significant amounts of phenyl pyrophosphate had formed after 23 hrs. [b] No reaction after 12 days.

$C_{22}H_{41}O_6N_2P$: C, 57.3; H, 8.9; N, 6.1; P, 6.7%). (Found: C, 57.2; H, 8.7; N, 6.0; P, 6.5.

An analogous procedure gave tetra-n-butylammonium phenyl hydrogen phosphate; $\delta^{31}P = -3.6$ ppm. Calc. for $C_{22}H_{42}O_4NP$: C, 63.6; H, 10.2; P, 7.5%). (Found: C, 63.4; H, 10.3; P, 7.3.

Bis quaternary ammonium salts of 4-nitrophenyl phosphate (*Table* 3)

(a) A 1.0 M *aqueous soln* of $ArOPO_3^{2-}2[(CH_3)_4N^+]$ was prepared by adding appropriate amounts of $(CH_3)_4N^+OH^-.5H_2O$ to an aqueous soln of $ArOPO_3H_2$. Aqueous solns of the corresponding salt of phenyl phosphate was made by the same procedure.

(b) 1.0 M *alcoholic solns of* dianion salt were prepared as follows. An aliquot of 1.0 M methanolic tetra-n-butylammonium hydroxide containing one mol equiv of base was added to $ArOPO_3H^-$ $(n\text{-}C_4H_9)_4N^+$ (one mol equiv) in an equal volume of MeOH. This gives a relatively stable 0.5 M methanolic soln of $ArOPO_3^{2-}2[(n\text{-}C_4H_9)_4N^+].H_2O$. The soln was diluted within equal volume of the desired alcohol, ROH, and evaporated in vacuum at 0° to attain an approximate concentration of 1 M. This procedure was repeated three more times, and the final volume was adjusted to give a 1.0 M alcoholic solution of the salt.

(c) 1.0 M *acetonitrile solns* of the dianion salt were prepared as follows. (1) To obtain solns of $ArOPO_3^{2-}2[(n\text{-}C_4H_9)_4N^+]$ $(H_2O)(CH_3OH)_2$, an aliquot of the 0.5 M methanolic soln of the salt prepared in (b) was mixed with an equal volume of anhyd acetonitrile, and evaporated in vacuum at 0° to an approximate concentration of 1 M. This procedure was repeated three more times, and the final volume was adjusted to give a 1.0 M acetonitrile soln of the salt. (2) To obtain acetonitrile solns of $ArOPO_3^{2-}2[(n\text{-}C_4H_9)_4N^+].(H_2O)(ROH)_2$, an aliquot of the 1.0 M alcoholic soln of the salt prepared in (b) was submitted to the acetonitrile evaporation described in (c-1). (3) to obtain acetonitrile solns of $ArOPO_3^{2-}2[(n\text{-}C_4H_9)_4N^+].(H_2O)_3$, 10 mol equiv of water were added to an aliquot of the 0.5 M methanolic soln of the salt prepared in (b). The soln was submitted to the acetonitrile evaporation described in (c-1).

Analogous procedures were employed to obtain the corresponding *aqueous* and *acetonitrile* solns of the phenyl dianion salts.

Determination of reaction half-times (t 1/2). The solns were prepared in a small volumetric flask and transferred to an NMR tube. The reactions were maintained at 70 ± 0.1° or 35 ± 0.5°, and the ^{31}P NMR spectra obtained at appropriate intervals. The values for the approximate half-times of the reactions were taken as the time at which the signal intensity of the reactants was equal to that of the products: t 1/2 ≡ [phosphate reactant] = [phosphate products]. The values are accurate to within 25% of the stated time. Phenol analyses are by ^1H NMR spectrometry.

^{31}P NMR *spectra.* 4-Nitrophenyl phosphate monoanion salt, $\delta^{31}P = -4.5$ ppm; 4-nitrophenyl pyrophosphate dianion salt, $\delta^{31}P = -10.4$ and -16.8 ($J = 16$ Hz) ppm; alkyl pyrophosphate dianion salt, $\delta^{31}P = -10.0$ and -12.5 (±1.5) ppm; cyclic trimetaphosphate trianion salt, $\delta^{31}P = -22.4$ ppm; all in acetonitrile solution.

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