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NUCLEOPHILIC CATALYSIS OF PHOSPHORYLATIONS BY p-NITROPHENYLDIPHENYL PHOSPHATE AND BY ALKYL ETHYLENE PHOSPHATES IN APROTIC SOLVENTS

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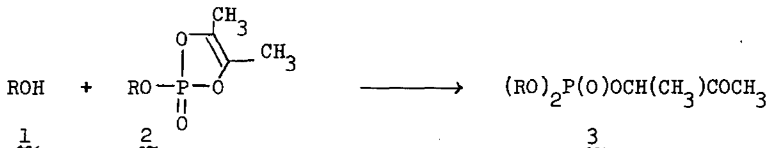
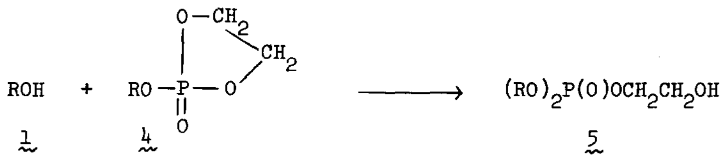
A novel mechanism[1-5] to account for the nucleophilic catalysis of phosphorylation of alcohols by alkyl cyclic enediol phosphates[6] in aprotic solvents, **1** + **2** ⟶ **3**, has been proposed.



1 2 3

One purpose of this Communication is to show that nucleophilic catalysis in aprotic solvents can also be detected in the less reactive alkyl ethylene phosphates (**4**) and p-nitrophenyldiphenyl phosphate (**6**), which have been extensively studied in aqueous solutions[7-11]. The results are summarized in Table I.



1 4 5

$$ROH + (p\text{-}NO_2.C_6H_4O)P(O)(OC_6H_5)_2 \longrightarrow (RO)P(O)(OC_6H_5)_2 + p\text{-}NO_2.C_6H_4OH$$

1 6 7 8

A second purpose of the Communication is to show that the behavior of phosphate **6** provides strong support for the new phosphorylation mechanism[1-5]. These results are deemed important since they could contribute to an understanding of the role played by tyrosine, aspartic and glutamic acids, histidine, arginine and lysine residues in the hydrophobic active sites of enzymes that catalyze certain reactions of phosphates[12].

Table I. Half-times[a] of the Reactions of Alcohols, ROH, with p-Nitrophenyldiphenyl Phosphate (PDP), Ethylene Phosphates (EP-OR) and Alkyl 1,2-Dimethylethenylene Phosphates (CEP-OR), in 0.2M Solutions at 25°.

		R = CH_3	R = CH_3		R = $(CH_3)_2CHCH_2$		R = c-C_5H_9
Catalyst	Solvent	PDP	EP-OR	CEP-OR	EP-OR	CEP-OR	CEP-OR
None	$CDCl_3$	N.R.[b]	9 hr	25 min	ca. 21 days	4 hr	28 hr
	CD_3CN	N.R.	96 hr	1.25 hr	N.R.	7 hr	32 hr
$p\text{-}NO_2\text{-}C_6H_4O^-$	$CDCl_3$	4 hr	40 min	Fast[c]	...[d]	10 min	1.5 hr
$(n\text{-}C_4H_9)_4N^+$	CD_3CN	45 min	1.5 hr	Fast	N.R.	3 min	20 min
$p\text{-}NO_2\text{-}C_6H_4O^-$	$CDCl_3$	30 hr	4 min	Fast	7.5 hr	2 min	15 min
$(C_2H_5)_3NH^+$	CD_3CN	24 hr	30 min	Fast	N.R.	3 min	20 min
CH_3COO^-	$CDCl_3$	...[e]	...[d]	~1 min	...[d]	1 hr	4.5 hr
$(n\text{-}C_4H_9)_4N^+$	CD_3CN			Fast	N.R.	5 min	20 min
CH_3COO^-	$CDCl_3$	...[e]	1.5 hr	~1 min	ca. 10 days	1 hr	7.5 hr
$(C_2H_5)_3NH^+$	CD_3CN		6 hr	~1 min	N.R.	35 min	4 hr
Imidazole	$CDCl_3$	...[e]	20 min	Fast	20 hr	2 min	15 min
	CD_3CN		30 hr	2.5 min	N.R.	12 min	2 hr
$(C_2H_5)_3N$	$CDCl_3$	...[e]	25 min	~20 sec	ca. 21 days	40 min[f]	30 hr[g]
	CD_3CN		12 hr	~40 sec	N.R.	1 hr	17 hr
CH_3COOH	$CDCl_3$	N.R.	2 hr	5 min	28 hr	20 min	1.5 hr
	CD_3CN	N.R.	48 hr	40 min	N.R.	3 hr	8.5 hr

[a] Figures are the times at which [Reactant] = [Product] when the reagents and the catalysts are mixed in equimolar amounts. Analyses were performed by ^1H nmr spectrometry. Product composition was verified by ^{31}P nmr spectrometry (at 40.5 MHz).

[b] N.R. = no reaction detectable in 14 days.

[c] Too fast to measure under the present conditions.

[d] The catalyst competitively dealkylates EP-OR.

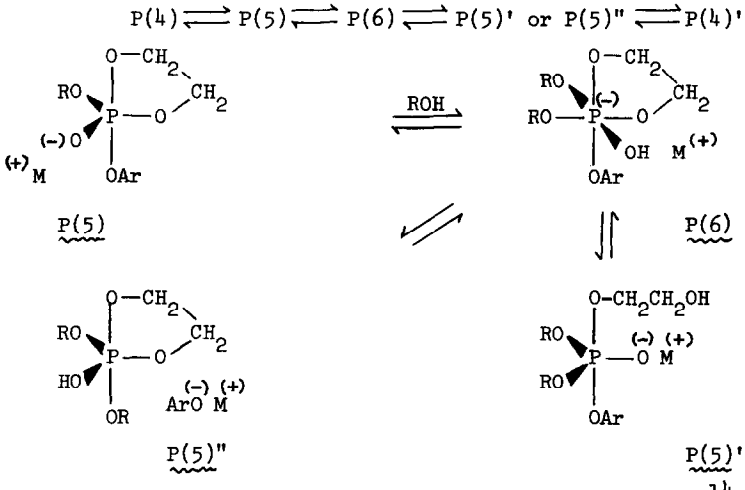
[e] No figures given because one of the products, $p\text{-}NO_2\text{-}C_6H_4O^-$, is also an effective catalyst.

[f] With quinuclidine, t 1/2 = 2 min ($CDCl_3$); 3 min (CD_3CN).

[g] With quinuclidine, t 1/2 = 40 min ($CDCl_3$); 1 hr (CD_3CN).

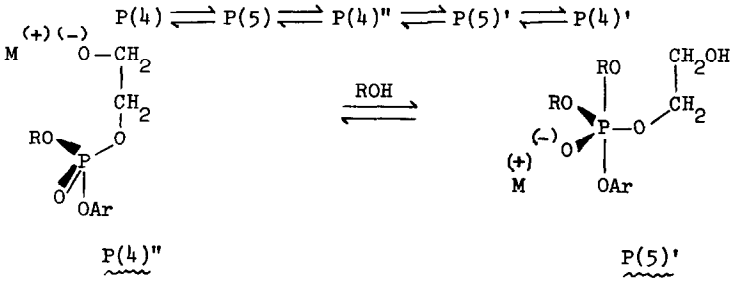
The new mechanism is represented by Scheme 1, where P(4) = 2 or 4, P(4)' = 3 or 5, and the catalyst is $ArO^{(-)}$ = p-NO_2.$C_6H_4O^{(-)}$, $M^{(+)} = (n\text{-}C_4H_9)_4N^{(+)}$. Ring opening can occur either at the P(6)[13] or P(5)" stages; however, the following observation is accommodated only by ring opening of P(6). The proportion of unsymmetrical to symmetrical triesters formed according to the following equations[1]: R^2OH + CEP-OR^1 $\longrightarrow$ $(R^1O)(R^2O)P(O)OAcn$, R^2OH + CEP-OR^1 $\longrightarrow$ CEP-OR^2 + R^1OH, R^2OH + CEP-OR^2 $\longrightarrow$ $(R^2O)_2P(O)OAcn$, and R^1OH + CEP-OR^1 $\longrightarrow$ $(R^1O)_2P(O)OAcn$, increases significantly in the catalyzed vs the uncatalyzed reactions of certain alcohols with some phosphates[3], e.g., when $R^2 = CH_2CH(CH_3)_2$ and $R^1 = CH_3$. Intermediate P(5)" can also be generated from P(4) and ROH in the absence of the nucleophilic catalyst; therefore, the effect of the latter on the proportion of unsymmetrical to symmetrical triesters is nicely explained by: P(6) $\longrightarrow$ P(5)' $\longrightarrow$ P(4)' [acetic acid has no effect on the proportion of triesters]. When the catalyst has no charge and carries no proton, (R_3N), P(5) becomes a zwitterion. If the catalyst has a transferable proton (imidazole), P(5) can become nonpolar. Solvent effects may be associated with those features, as well as with related differences in cation structure, $M^+ = R_4N^+$, R_3NH^+.

Scheme 1:

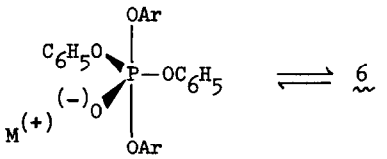


An alternate mechanism, of the type which is now widely accepted[14], is shown in Scheme 2. The first step is identical to that in Scheme 1, but now P(5) collapses to P(4)", which adds the alcohol to form a new P(5)' [analogous phosphoranes in these Schemes are interconvertible by appropriate sequences of intramolecular permutational isomerizations].

Scheme 2:



The mechanism in Scheme 2 obviates the postulation of P(6), i.e., of a bimolecular reaction occurring during the lifetime of a high energy intermediate. However, it should be noted that Scheme 1 adequately explains the p-nitrophenoxide catalysis of the reaction of p-nitrophenyldiphenyl phosphate, 1 + 6 ⟶ 7 + 8, while Scheme 2 is inapplicable in that case, since P(4)" is identical with P(4) = 6, and the need for p-nitrophenoxide catalysis of the reaction would remain unaccounted for. Hence, the P(6) route is suggested for the acyclic, and by analogy for the cyclic phosphate reactions.



⟹ 6

P(5)

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