Tetrahedron Letters No. 42, pp 3791 - 3794, 1976. Pergamon Press. Printed in Great Britain.

ACETATE ION CATALYSIS OF PHOSPHORYLATIONS IN APROTIC SOLVENTS

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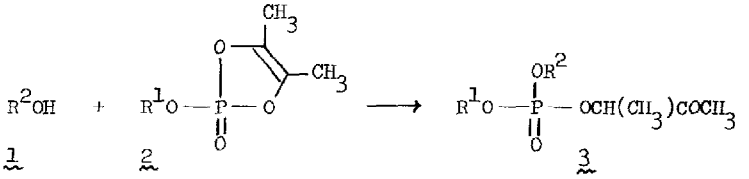
(Received in UK 29 June 1976; received in UK for publication 7 September 1976)

Alkyl cyclic enediol phosphates[1], 2, have been utilized to probe into the catalysis of the phosphorylation of alcohols, 1, by amines[2] and by phenoxide ions[3] in aprotic solvents. This type of reaction could provide information on the role of histidine, arginine, lysine and tyrosine residues in the hydrophobic active sites of the enzymes that catalyze the reactions of phosphates and pyrophosphates[4], to the extent that those reactions may involve additions of nucleophiles to tetracoordinate phosphorus. The catalysis of the reaction: 1 + 2 → 3 has been explained in terms of intermediates with penta- and hexacoordinate phosphorus[2,3].



1 2 3

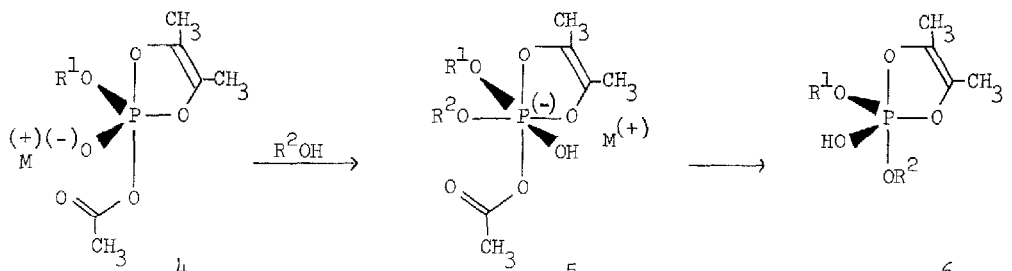
This Communication discloses the effective catalysis of the reaction 1 + 2 → 3 by acetate salts[5] (Table 1), which may be regarded as a model for a possible role of aspartic and glutamic acid residues[4,6] in enzymatic phosphorylations. New data from a more extensive study of the catalysis by phenoxide salts are also presented. For comparison, the earlier results[2] using imidazole and tertiary amines as catalysts are quoted. Since in aprotic solvents the dissociations: $CH_3COO^-(C_2H_5)_3NH^+ \rightleftharpoons CH_3COOH + (C_2H_5)_3N$, and $p\text{-}NO_2\cdot C_6H_4O^-(C_2H_5)_3NH^+ \rightleftharpoons p\text{-}NO_2\cdot C_6H_4OH + (C_2H_5)_3N$ must be taken into account, the effect of acetic acid on the reaction rates is included; p-nitrophenol has no detectable effect under comparable conditions. The values in Table 1 are the times at which $[CEP\text{-}OR^1] = [(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3]$, from ^1H nmr spectra, when the reagents and the catalysts are mixed in equimolar amounts.

Table 1. Half-times of the reaction: $R^2OH + CEP\text{-}OR^1 \longrightarrow (R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$ in 0.2 M Solutions at 25°.

Catalyst	Solvent	$R^2 = (CH_3)_2CHCH_2$ $R^1 = \underline{c}\text{-}C_5H_9$	$R^2 = \underline{c}\text{-}C_5H_9$ $R^1 = \underline{c}\text{-}C_5H_9$	$R^2 = (CH_3)_2CHCH_2$ $R^1 = [(CH_3)_2CH]_2CH$
None	$CDCl_3$	7.5 hr	28 hr	22 hr
	CD_3CN	12 hr	32 hr	22 hr
CH_3COO^- $(n\text{-}C_4H_9)_4N^+$	$CDCl_3$	1 hr	4.5 hr	10 hr
	CD_3CN	3 min[a]	20 min[a]	30 min[a]
CH_3COO^- $(C_2H_5)_3NH^+$	$CDCl_3$	1.5 hr	7.5 hr	10 hr
	CD_3CN	1 hr	4 hr	6 hr
$p\text{-}NO_2\cdot C_6H_4O^-$ $(n\text{-}C_4H_9)_4N^+$	$CDCl_3$	15 min	1.5 hr	4.5 hr
	CD_3CN	3 min	20 min	30 min
$p\text{-}NO_2\cdot C_6H_4O^-$ $(C_2H_5)_3NH^+$	$CDCl_3$	4 min	15 min	25 min
	CD_3CN	4 min	20 min	25 min
Imidazole	$CDCl_3$	3 min	15 min	10 min
	CD_3CN	25 min	2 hr	2 hr
$(C_2H_5)_3N$	$CDCl_3$	1.5 hr	30 hr	15 hr
	CD_3CN	2.5 hr	17 hr	12 hr
Quinuclidine	$CDCl_3$	3 min	40 min	20 min
	CD_3CN	6 min	1 hr	35 min
CH_3COOH	$CDCl_3$	20 min	1.5 hr	2.5 hr
	CD_3CN	4 hr	8.5 hr	6 hr

[a] Same values in acetone-d_6.

In principle, the reaction 1 + 2 → 3 can give rise to symmetrical as well as unsymmetrical triesters, as follows: $R^2OH + CEP\text{-}OR^1 \rightarrow CEP\text{-}OR^2 + R^1OH$, $R^2OH + CEP\text{-}OR^2 \longrightarrow (R^2O)_2P(O)OCH(CH_3)COCH_3$ and $R^1OH + CEP\text{-}OR^1 \longrightarrow (R^1O)_2P(O)OCH(CH_3)COCH_3$. The proportion of unsymmetrical to symmetrical triesters varies with the size of R^1 and R^2; the systems in Table 1 produce less than 2% of symmetrical triesters in the absence or in the presence of catalysts. However, the reaction, $(CH_3)_2CHCH_2OH + CEP\text{-}OCH_3$ gives 54:46% unsymmetrical:symmetrical triesters in the absence of catalysts; this proportion changes to: 72:28 $[CH_3COO^-(n\text{-}C_4H_9)_4N^+]$, 79:29 $[CH_3COO^-(C_2H_5)_3NH^+]$, 78:22 $[p\text{-}NO_2\cdot C_6H_4O^-(n\text{-}C_4H_9)_4N^+]$, 84:16 $[p\text{-}NO_2\cdot C_6H_4O^-(C_2H_5)_3NH^+]$, 70:30 [Imidazole], 75:25 $[(C_2H_5)_3N]$. (All in 0.2 M $CDCl_3$ at 25°). Acetic acid has little effect on this proportion (57:43). These results are not consistent with a simple general acid-base catalysis for this reaction. Moreover, although phenoxide is not incorporated into the product when it is used as catalyst for the reaction 1 + 2 → 3, phenylalkyl(1-methylacetonyl) phosphates are formed in the amine catalyzed reaction ArOH + CEP-OR. Furthermore, imidazole is a weaker base than triethylamine but is a better catalyst; quinuclidine and triethylamine are equally basic but the former is a better catalyst; p-nitrophenoxide is a relatively weak base but an excellent catalyst. For these reasons the present observations are considered to be consistent with the hypothesis[2,3] that the catalysis of the phosphorylation involves intermediates with penta- and hexacoordinate[7] phosphorus, 4 and 5, the former being involved in the rate-controlling step. Decomposition of the latter produces the intermediate 6 of the uncatalyzed reaction. The effect of the catalysts on the proportion of unsymmetrical to symmetrical might result from ring-opening in 5.



4 5 6

A comparison of the catalytic efficiencies of acetate and phenoxide salts with that of the most effective of the amines so far encountered[2] leads to the following sequence. (a) in $CDCl_3$: Imidazole $\sim ArO^-R_3NH^+ > ArO^-R_4N^+ > CH_3COO^-R_4N^+ > CH_3COO^-R_3NH^+$. (b) In CD_3CN: $CH_3COO^-R_4N^+ \sim ArO^-R_4N^+ \sim ArO^-R_3NH^+ \gtrsim$ quinuclidine $> CH_3COO^-R_3NH^+$.

A comparison of the relative rates in $CDCl_3$ vs CD_3CN discloses the following effects. (i) While the efficiency of imidazole is markedly decreased (a factor of $\sim$8), that of $CH_3COO^-R_4N^+$ is strongly increased ($\sim$18-20), and that of $p\text{-}NO_2.C_6H_4O^-R_4N^+$ is increased moderately ($\sim$5). (ii) The uncatalyzed and the quinuclidine-catalyzed reactions are not sensitive to the solvent change (slight deceleration $\sim$2). (iii) The solvent effect on the triethylamine-catalyzed reactions is complicated by the circumstance that this amine is selective for primary (vs secondary) alcohols, R^2OH, and that this selectivity is manifested mainly in $CDCl_3$[2].

A comparison of relative rates using $(n\text{-}C_4H_9)_4N^+$ vs $(C_2H_5)_3NH^+$ as the cation of the salt shows these effects. (iv) In $CDCl_3$, the efficiency of the CH_3COO^- ion is slightly decreased ($\sim$2), while that of the $p\text{-}NO_2.C_6H_4O^-$ ion is somewhat increased ($\sim$4-6). (v) In CD_3CN, the efficiency of the CH_3COO^- ion is strongly decreased ($\sim$12-20), while that of the $p\text{-}NO_2.C_6H_4O^-$ ion is virtually unaffected.

Acknowledgment. This work was supported by Grant GM 20672 from the National Institute of General Medical Sciences.

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1. Abbreviated CEP-OR = 4,5-dimethyl-2-alkoxy-2-oxo-2H,1,3,2-dioxaphosphole.

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