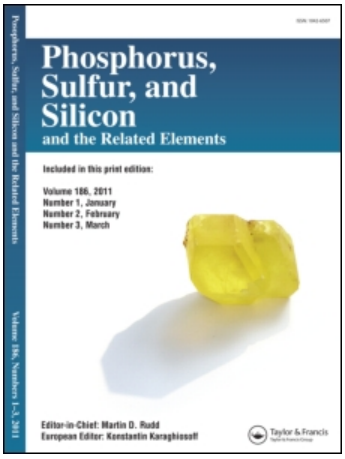

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PHOSPHORYLATION OF ALCOHOLS BY CYCLIC PHOSPHODIESTERS IN APROTIC SOLVENTS

Fausto Ramirez[a]; James F. Marecek[a]; Hikotada Tsuboi[a]; Yufen Chaw[a]
[a] Department of Chemistry, State University of New York at Stony Brook, Stony Brook, N.Y.

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PHOSPHORYLATION OF ALCOHOLS BY CYCLIC PHOSPHODIESTERS IN APROTIC SOLVENTS

FAUSTO RAMIREZ*, JAMES F. MARECEK, HIKOTADA TSUBOI and YUFEN CHAW

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, N.Y. 11794

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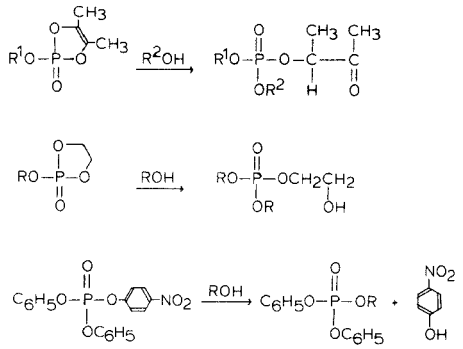
The reactions of alcohols with 4,5-dimethyl-2-hydroxy-2-oxo-2H-1,3,2-dioxaphosphole and 4,5-dimethyl-2-alkoxy-2-oxo-2H-1,3,2-dioxaphosphole have been studied in 0.2 M CD_2Cl_2 solutions at 25°. The data show that, the phosphorylation of alcohols in aprotic solvents of relatively low polarity are faster with a cyclic enediol *phosphodiester* than with the corresponding *phosphotriester*. The alcohol-phosphotriester reactions are catalyzed by trifluoroacetic and acetic acids, and the acid-catalyzed rates are still somewhat slower than the acid-autocatalyzed rates of the alcohol-phosphodiester reactions. It is suggested that both types of phosphorylation involve protonation of the phosphoryl-oxygen and formation of an intermediate with pentacoordinate phosphorus ("oxyphosphorane" or "addition-elimination" mechanism). Steric effects in the alcohol and in the phosphorylating reagents play an important role in this mechanism. The conjugate base of the cyclic enediol phosphodiester fails to react with alcohols under comparable conditions.

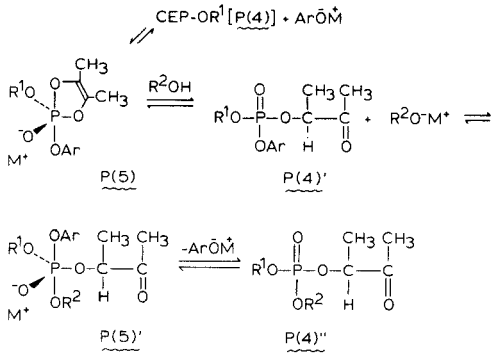
INTRODUCTION

The phosphorylation of alcohols by cyclic and acyclic *phosphotriesters* in aprotic solvents of relatively low polarity has been extensively investigated in this Laboratory (Scheme 1), and it has been shown that the reactions are susceptible to effective nucleophilic catalysis in $CDCl_3$, CD_3CN and acetone-d_6 solutions.[1–4] The following nucleophiles are known to increase the rate of reaction of alkyl cyclic enediol phosphates[5,6] (CEP-OR^1) and alkyl ethylene phosphates: imidazole, certain tertiary amines like triethylamine and quinuclidine, p-nitrophenoxide ion and acetate ion. The reactions of *p*-nitrophenyldiphenyl phosphate have been studied only in the presence of *p*-nitrophenoxide ion, since the relatively strong acid *p*-nitrophenol (p*K*a = 7.15 in water) is a by-product of the phosphorylation, and the introduction of additional basic nucleophiles would complicate the interpretation of the results due to the existence of equilibria of the type: $ArOH + R_3N \rightleftharpoons ArO^-R_3NH^+$.

Two alternate mechanisms have been considered[1–4] to account for the nucleophilic catalysis of phosphorylation. Mechanism 1 can be abbreviated[5] as **P(4)** ⇌ **P(5)** ⇌ **P(4)′** ⇌ **P(5)′** ⇌ **P(4)″**, and is illustrated in Scheme 2 for the reaction CEP-OR^1 + R^2OH catalyzed by ArO^-M^+. The first step is the addition of phenoxide to the phosphate, **P(4)** = CEP-OR^1, to form the oxyphosphorane intermediate[7–11], **P(5)**. The **P(5)** intermediate collapses to a new phosphate, **P(4)′**, which in the presence of



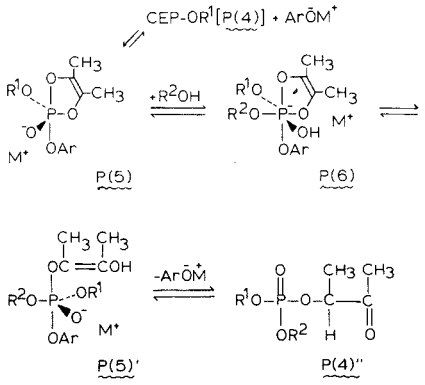
SCHEME 1



SCHEME 2

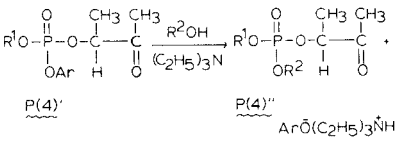
alcohol R^2OH can exist as an equilibrium mixture of several species, including the keto-tautomer shown. Phosphate **P(4)′** is still a reactive intermediate and adds alkoxide ion to yield a new oxyphosphorane, **P(5)′**, which collapses to the observed phosphate, **P(4)″**. This mechanism, whose distinct feature is the reactive phosphate intermediate **P(4)′**, is of a type widely accepted at the present time.[1,2–22]

Mechanism 2 is conveniently described as **P(4)** ⇌ **P(5)** ⇌ **P(6)** ⇌ **P(5)′** ⇌ **P(4)″**, and is depicted in Scheme 3. The first step is identical with that postulated in Mechanism 1; however, now the oxyphosphorane **P(5)** reacts with the alcohol R^2OH and forms the hexacoordinate intermediate, **P(6)**. Collapse of **P(6)** generates **P(5)′**, which loses phenoxide ion to yield the observed phosphate ester.[1–4]



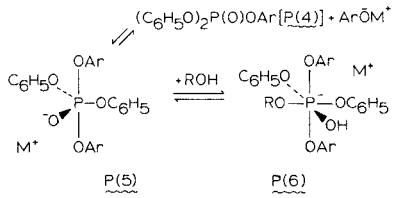
SCHEME 3

Mechanism 2 includes a bimolecular reaction occurring during the lifetime of a high energy intermediate: **P(5)** + ROH ⇌ **P(6)**, and we were led to it in an attempt to rationalize the following observations.[1–4] (1) The transient phosphate, **P(4)′**, that should have resulted from the operation of Mechanism 1 was independently synthesized, and was allowed to react with a given alcohol as shown in Scheme 4 (R^1 = *c*-C_5H_9, Ar = *p*-$NO_2 \cdot C_6H_4$, R^2 = $(CH_3)_2CHCH_2$). The reaction proceeded with t1/2 ~ 15 hr (at 25° in 0.2 M $CDCl_3$, employing equimolar amounts of reactants and catalyst). This value proved to be much larger than the figure t1/2 ~ 3 min found for the corresponding reaction: R^2OH + CEP-OR^1 + [$ArO^-(C_5H_5)_3NH^+$] → (R^2O)(R^1O)P(O)OAcn, performed under comparable conditions. Therefore, the cyclic triester **P(4)** is not converted into the acyclic triester, **P(4)″**, *via* the transient acyclic intermediate **P(4)′**. Mechanism 2 proceeding *via* intermediate **P(6)** can explain these results. The rate of the catalyzed reaction R^2OH + CEP-OR^1 is strongly affected by the structure of R^2OH and of R^1 in CEP-OR^1. It is therefore conceivable that step **P(5)** + R^2OH ⇌ **P(6)** may be rate-limiting in Mechanism 2.[23]



SCHEME 4

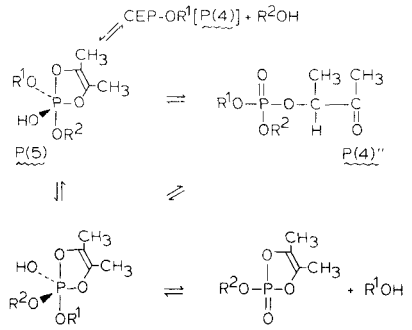
(2) The reaction of *p*-nitrophenyldiphenyl phosphate with alcohols (*cf.* Scheme 1) is effectively catalyzed by the *p*-nitrophenoxide anion, both as its triethylammonium and tetra-*n*-butylammonium salts, in the solvents $CDCl_3$ and CD_3CN. The **P(5)** intermediate that is common to Mechanisms 1 and 2 is shown in Scheme 5. It is evident that in this case the transient phosphate, **P(4)′**, of Mechanism 1 is identical with the starting phosphate, **P(4)**, and therefore the effect of the catalyst would remain unexplained. Mechanism 2, on the other hand, accounts for the catalysis in terms of the **P(6)** intermediate formed from the alcohol and **P(5)**.



SCHEME 5

(3) The **P(6)** Mechanism 2 is consistent also with the observation that the proportion of unsymmetrical *vs.* symmetrical triesters, (R^1O)(R^2O)-P(O)OAcn *vs* (R^1O)$_2$P(O)OAcn and (R^2O)$_2$P(O)-OAcn, formed in the reaction CEP—OR^1 + R^2OH, varies significantly in the presence and in the absence of the nucleophilic catalysts. The *uncatalyzed* reaction R^2OH + CEP—OR^1 can be pictured as involving the initial formation of an oxyphosphorane, **P(5)**, formed by direct addition of the alcohol R^2OH to **P(4)** (Scheme 6). The collapse of **P(5)** produces acyclic triester **P(4)″**. However, permutational isomerization of **P(5)** prior to its collapse generates an isomer of **P(5)** which can decompose either with ring-opening to **P(4)″** or with ring-retention to the new cyclic phosphate, CEP—OR^2. The latter reaction is a transesterifica-

tion, which may result in the formation of symmetrical phosphotriesters according to the following equations: $R^2OH + CEP{-}OR^1 \rightarrow CEP{-}OR^2 + R^1OH$, $R^2OH + CEP{-}OR^2 \rightarrow (R^2O)_2P(O)OAcn$ and $R^1OH + CEP{-}OR^1 \rightarrow (R^1O)_2P(O)OAcn$. The presence of nucleophilic catalysts could alter the proportion of unsymmetrical *vs.* symmetrical triesters by interfering with the formation of the two **P(5)** isomers in Scheme 6. This can be accomplished by collapse of the **P(6)** intermediate in the previous Scheme 3 to the acyclic oxyphosphorane, **P(5)'**. (Evidently, the **P(6)** intermediate in Scheme 3 could also decompose with ring-retention to give one or both **P(5)** isomers, in which case transesterification would again be possible.)



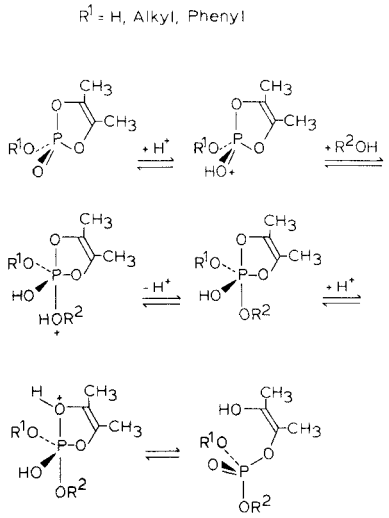
SCHEME 6

(4) Finally, the existence of relatively stable **P(5)**[24] and **P(6)**[25] compounds analogous to those postulated in the previous Schemes has been amply documented, and the direct observation of a *hydroxyphosphorane* in equilibrium with a phosphate ester, in aprotic solvents, has been recently reported.[26] These facts strengthen the mechanistic postulations.

The investigations of nucleophilic catalysis of displacements at the **P(4)** center of phosphotriesters in aprotic solvents,[1–4] complement other research dealing with related processes in alcoholic[12] and in aqueous[13–15] solutions.

The phosphorylation of alcohols by phosphodiesters in aprotic solvents has not received the same degree of attention as the phosphorylation by neutral triesters. However, there is a relatively large literature dealing with displacements at the phosphorus of phosphodiesters in aqueous solution.[27–36] The present investigation is concerned with the behavior of the cyclic enediol phosphodiester[37] (CEP–OH, $R^1 = H$ in Scheme 7) toward alcohols in aprotic solvents. Since phosphodiesters are relatively strong acids[27,38,39] ($pKa \sim 1.3 \pm 0.2$ in water), it is apparent that a comparison of reactivities among diesters and triesters requires information on the effect of acids on the rate of the reaction: $CEP{-}OR + ROH \rightarrow (RO)_2P(O)OAcn$, under comparable conditions. These data are included in the present paper. Data are also given for the behavior of alcohols towards the salts $CEPO^-M^+$, where M^+ = alkali metal, R_4N^+ and R_3NH^+ ions, in order to correlate relative reactivities in the series CEP–OR, CEP–OH and $CEPO^-$ in comparable aprotic solvents.

Studies on acid-catalyzed displacements at **P(4)** of phosphotriesters in aqueous solutions have been described.[40,41] More recently, the simultaneous effect of imidazolium and metal ions on the hydrolysis of catechol cyclophosphate in limited amounts of water has been discussed.[42]

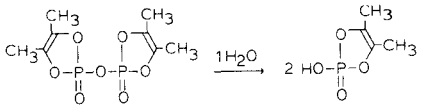


SCHEME 7

RESULTS AND DISCUSSION

Reactions of Cyclic Diesters and Triesters with Alcohols

The diester, CEP–OH, is prepared by the controlled hydrolysis of bis(1,2-dimethylethenylene) pyrophosphate[43] (Scheme 8).



SCHEME 8

The diester, CEP–OH, is an effective phosphorylating reagent for alcohols, as disclosed by the data

TABLE I

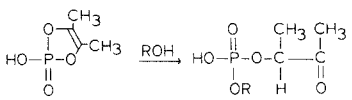
Half-Times of the Reaction of Cyclic Phosphodiesters (R^1 = H) and Phosphotriesters (R^1 = Alkyl or Phenyl) with Alcohols and Phenols (R^2OH) in 0.2 M CD_2Cl_2 at 25°C[a]: CEP–OR^1 + R^2OH → $(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$

R^1	R^2	Catalyst	
		None	CF_3COOH
H	CH_3	2 min	—
CH_3	CH_3	25 min	4 min
H	$(CH_3)_2CHCH_2$	15 min	—
$(CH_3)_2CHCH_2$	$(CH_3)_2CHCH_2$	4 hr	35 min
H	*c*-C_5H_9	1 hr	—
c-C_5H_9	*c*-C_5H_9	20 hr	2 hr
H	$(C_2H_5)_2CH$	3 hr	—
$(C_2H_5)_2CH$	$(C_2H_5)_2CH$	*ca.* 50 hr	7 hr
H	$[(CH_3)_2CH]_2CH$	15 hr	—
$[(CH_3)_2CH]_2CH$	$[(CH_3)_2CH]_2CH$	N.R.[b]	7 days
H	C_6H_5	7 hr	—
C_6H_5	C_6H_5	N.R.[b]	12 hr

[a] Figures are the times at which [Reactant] = [Product] when the reagents and the catalyst 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), with the aid of authentic samples of the compounds.

[b] No reaction detectable in several days.

summarized in Table I. The reaction produces alkyl(3-oxo-2-butyl) phosphates (Scheme 9) with both primary and secondary alcohols, including some fairly hindered ones. The cyclic diester also phosphorylates phenol, although at a relatively slow rate.



SCHEME 9

Table I includes data for the reaction of the triesters, CEP–OR, with the same series of alcohols. It is apparent that the diester is a more effective phosphorylating reagent than the triesters; however, the difference in reactivity almost vanishes when trifluoroacetic acid is introduced into the triester reaction. It is therefore quite probable that the reaction of CEP–OH with alcohols is autocatalytic. The mechanism shown in the previous Scheme 7 is suggested to account for the acid catalysis of the reactions of CEP–OH and CEP–OR. The mechanism involves protonation of the phosphoryl-oxygen and formation of an oxyphosphorane or **P(5)** intermediate; presumably, the step CEP–OH_2^+ + ROH → **P(5)** is rate-limiting in this mechanism.

Table II discloses that the catalytic efficiencies of trifluoroacetic and acetic acids are comparable in the reaction CEP–OR + ROH, although the two acids differ significantly in acidity (pK_a's in water are 0.2 and 4.8, respectively). The interpretation of this observation is not unequivocal, in the absence of data on acidities in chlorocarbon solvents, but the effect is consistent with the assumption that the addition of alcohol to the protonated phosphotriester is rate-limiting, and that the concentrations of the protonated species in the low polarity solvents are not very different in the two cases.

Table II also discloses that the rate acceleration of the reaction CEP–OR + ROH by acids is less significant than the acceleration caused by nucleophilic catalysts, e.g., the acetate and *p*-nitrophenoxide ions. It is noteworthy that an increase in solvent polarity results in a modest decrease in reaction-rate in both the uncatalyzed and the acid-catalyzed reactions. However, an increase in solvent polarity is accompanied by a moderate increase in

TABLE II

Solvent Effect on Acid and Nucleophilic Catalysis of Phosphorylation of Alcohols by Cyclic Phosphotriesters at 25°C[a]: CEP–OR + ROH → $(RO)^2P(O)OCH(CH_3)COCH_3$

Catalyst	None		CH_3COOH		CH_3COO^- $(n\text{-}C_4H_9)_4N^+$		*p*-$NO_2.C_6H_4O^-$ $(n\text{-}C_4H_9)_4N^+$	
Solvent								
R	$CDCl_3$[b]	CD_3CN	$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN
CH_3	25 min	1.25 hr	5 min	40 min	1 min	1 min	1 min	1 min
$(CH_3)_2CHCH_2$	4 hr	7 hr	20 min	3 hr	1 hr	5 min	10 min	3 min
c-C_5H_9	28 hr	32 hr	1.5 hr	8.5 hr	4.5 hr	20 min	1.5 hr	20 min

[a] Figures are the times at which [Reactant] = [Product], from Ref. 4. Dielectric constants of solvents (ε at 20°) = $CHCl_3$, 4.8; CH_2Cl_2, 9.0; CN_3CN, 38.8

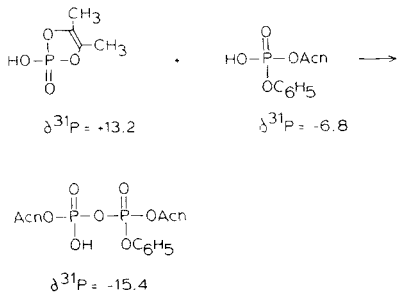
[b] Differences in t1/2 for the uncatalyzed reactions in $CDCl_3$ and CD_2Cl_2 are negligible within the accuracy of these measurements.

reaction-rate when the catalyst is a quaternary ammonium salt of the acetate or the *p*-nitrophenoxide ions, i.e., in the reactions subject to nucleophilic catalysis. These effects reflect, presumably, significant differences of charge types in the respective transition states *vs.* ground states for the acid- and nucleophile-catalyzed phosphorylations, as suggested in the corresponding intermediates depicted in Schemes 7 and 3, respectively.

The significant difference in the phosphorylation of alcohols by the cyclic triesters, CEP—OR, under catalysis by acetate and phenoxide ions, on the one hand, and by acids, on the other hand, relates to the proportion of unsymmetrical *vs.* symmetrical acyclic triesters produced in the reaction CEP—OR^1 + R^2OH. For example the reaction CEP—OCH_3 + $(CH_3)_2CHCH_2OH$ generates unsymmetrical and symmetrical triesters in the proportion 54:46%, which increases to 72:28% and 78:22% in the presence of CH_3COO^- $(n\text{-}C_4H_9)_4N^+$ and *p*-$NO_2\cdot C_6H_4O^-(n\text{-}C_4H_9)_4N^+$, respectively (all in 0.2 M $CDCl_3$ at 25°); the catalytic amines also have a pronounced effect in this respect. In contrast, acids do not affect the proportion of unsymmetrical to symmetrical triesters to any appreciable extent. These differences are rationalized by the different mechanisms proposed in Schemes 3 and 7 for nucleophilic and acid catalysis of phosphorylation, respectively.

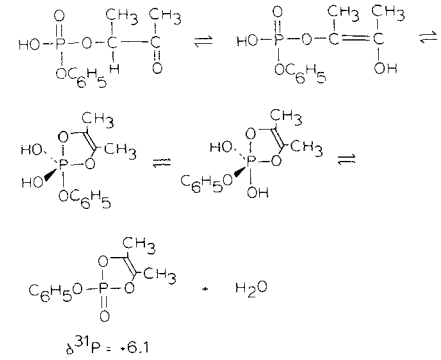
The reaction of phenol with CEP—OH is not as simple as it appears in Scheme 9 (R = C_6H_5). Conditions can be found (e.g., equimolar amounts of these reactants in 1.7 M CH_2Cl_2 solution at 25° for 20 hr) under which the main product is indeed the expected phenyl-3-oxo-2-butyl phosphate. However, when equimolar amounts of phenol and CEP—OH are kept for *ca.* 20 hr at 25° in 0.2 M CD_2Cl_2 solution additional products are formed in relatively small amounts. The ^{31}P nmr spectrum suggests that the structure of the major additional product is 1-phenyl-1,2-di(3-oxo-2-butyl) pyrophosphate since there are overlapping multiplets centered at −15.4 ppm (Scheme 10).

In separate experiment, equimolar amounts of CEP—OH and phenyl-3-oxo-2-butyl phosphate were allowed to react in 4 M CH_2Cl_2 solution at 35°. The signals at −15.4 attributed to the pyrophosphate (*cf.* Scheme 10) were indeed observed, but the reaction slowly (*ca.* 11 days) produced two additional substances, with ^{31}P nmr signals at +6.1 (singlet) and *ca.* 0 (doublet), respectively. A possible interpretation of these results is shown in Scheme 11. In this interpretation, the enol form of phenyl-3-



SCHEME 10 Acn = $-CH(CH_3)COCH_3$

oxo-2-butyl phosphate cyclizes to CEP—OC_6H_5, and the water generated in this cyclization reacts with the remaining CEP—OH, to give 3-oxo-2-butyl phosphate: CEP—OH + H_2O → $(HO)_2P(O)OCH(CH_3)COCH_3$($\delta^{31}P$ ~O, doublet).



SCHEME 11

The reaction of phenol with the phenyl cyclic enediol phosphotriester CEPO—C_6H_5 is particularly interesting because it discloses the operation of *three*

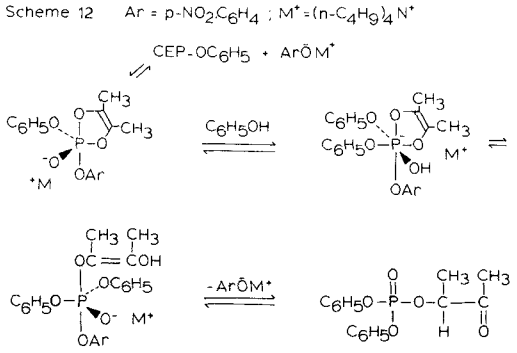
TABLE III

p-Nitrophenoxide[a] and Amine[b] Catalysis of the Reaction of the Phenyl Cyclic Enediol Phosphotriester with Phenol in 0.2 M $CDCl_3$ Solution at 25°C: CEP—OC_6H_5 + C_6H_5OH → $(C_6H_5O)_2P(O)OCH(CH_3)COCH_3$.

Catalyst	$pK_B(H_2O)$	t1/2
None	None	N.R.
p-$NO_2.C_6H_4O^-(n\text{-}C_4H_9)_4N^+$	6.8	1.5 hr
Tetramethylguanidine	0.4	2 min
Diisopropylethylamine	2.0	35 min
Triethylamine	3.0	45 min
γ-Collidine	6.7	36 hr
Imidazole	6.9	1.5 hr
Pyridine	8.7	N.R.

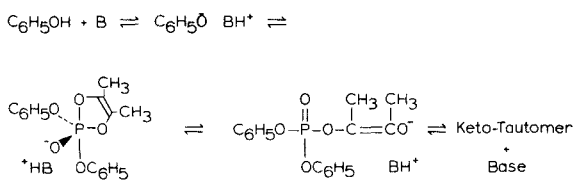
[a] Present work.
[b] Data from Ref. 2.

types of catalysis in phosphorylations in aprotic solvents. Catalysis by acid is shown in Table I, and is interpreted by the mechanism shown in Scheme 7. Nucleophilic catalysis by the *p*-nitrophenoxide ion is shown in Table III; the reaction occurs cleanly without incorporation of the nitrophenoxide into the product, and is interpreted by the mechanism of Scheme 12.



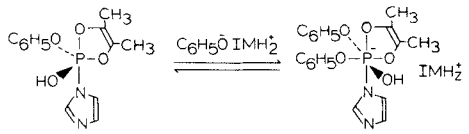
SCHEME 12 $Ar = p\text{-}NO_2 \cdot C_6H_4$; $M^+ = (n\text{-}C_4H_9)_4N^+$

Catalysis by amines is summarized in Table III. The amines fall into two categories: (1) The hindered diisopropylethylamine and γ-collidine (2,4,6-trimethylpyridine) presumably exert their catalytic effect by generating phenoxide ion which is a better nucleophile than phenol (Scheme 13). The penoxide ion adds to the phosphate to form the **P(5)** intermediate which generates the product after ring-opening. In this general-base catalysis mechanism there is no need to invoke intermediacy of a **P(6)** structure formed by addition of undissociated phenol to **P(5)**. The hindered diisopropylethylamine and γ-collidine do not increase the rate of the reaction CEP—OR + ROH (alcohols) and this supports their role as general-base catalysts in the reaction $CEP\text{—}OC_6H_5 + C_6H_5OH$. Pyridine also fails to catalyze the alcohol phosphorylation, and its failure to catalyze the phenol phosphorylation is attributed to a relatively weak basicity, as well as to a poor nucleophilicity toward phosphates.



SCHEME 13

(2) The second category of amines is illustrated by tetramethylguanidine, triethylamine and imidazole. These relatively efficient nucleophiles are also catalysis for the reaction CEP—OR + ROH as discussed above. In the phenol-phosphorylation they may operate in two different ways: (i) by converting the phenol into the more nucleophilic phenoxide ion; (ii) by adding to the **P(4)** to form a **P(5)** intermediate (Scheme 14, nucleophilic catalysis).

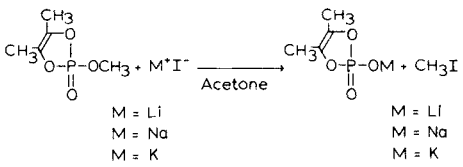


SCHEME 14

These considerations help to explain the surprising effect of tetrabutylammonium *p*-nitrophenoxide on the reaction of the cyclic phosphodiester with alcohols in aprotic solvents: CEP—OH + ROH + $ArO^-M^+ \not\rightarrow$ No Reaction. The pK_a's (in water) of CEP—OH and ArOH (*p*-nitrophenol) are *ca.* 1.0 and 7.1 respectively; hence, the equilibrium: $CEPOH + ArO^-H^+ \rightleftharpoons CEPO^-M^+ + ArOH$ lies far to the right, in both water and CD_2Cl_2. Since the $CEPO^-$ anion is unreactive toward alcohols (see below) the alcohol phosphorylation by CEP—OH does not occur in the presence of ArO^-M^+.

Behavior of the Cyclic Phosphodiester Anion, $CEPO^-$, Toward Alcohols and Water

Alkali metal salts of the $CEPO^-$ anion are readily prepared from the reaction of the methyl ester with an appropriate metal halide in an aprotic solvent (Scheme 15). The properties of three of these salts are given in Table IV.



SCHEME 15

The *N*-methylpyridinium salt of $CEPO^-$, made from the reaction of $CEP\text{—}OCH_3$ with pyridine has already been described.[37] Likewise, several salts of the type $CEPO^-BH^+$, where B = triethylamine, imidazole and γ-collidine (2,4,6-trimethylpyridine), are known.[1,37] Neither these salts nor the alkali metal salts show appreciable reactions when dissol-

ved in an excess of methanol, at least after 1 week at 25° (Scheme 16). As expected, the addition of methanol to $CDCl_3$ solutions of the ammonium salts has no significant effect.

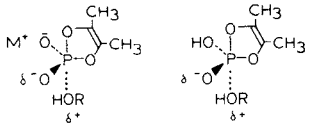
$$CEPO\bar{M}^{+} + ROH \not\longrightarrow \text{N.R.}$$

$M = Li, Na, K, C_5H_5NCH_3$

$M = (C_2H_5)_3NH, C_3H_3N_2H_2, 2,4,6\text{-}(CH_3)_3C_5H_2NH$

SCHEME 16

The lack of reactivity of the anion in the aprotic solvents is in marked contrast to the fast reaction of the conjugate acid, CEP—OH, with alcohols under comparable conditions (Table I). These differences are attributed mainly to the high energy of the negatively charged oxyphosphorane intermediate that would result from the addition of alcohol to the diester *anion*, relative to the uncharged oxyphosphorane obtained from the diester acid (or more accurately to the energies of the corresponding transition states; Scheme 17). In the aprotic solvents, differences between ground-state solvation of $CEPO^{-}M^{+}$ *vs.* CEP—OH are probably not crucial and, hence, the differences between rates in steps: $CEPO^{-}M^{+}$ + ROH ⇌ **P(5)**$^{-}M^{+}$ *vs.* CEP—OH + ROH ⇌ **P(5)**H are probably due mainly to the respective transition state energy differences.



SCHEME 17

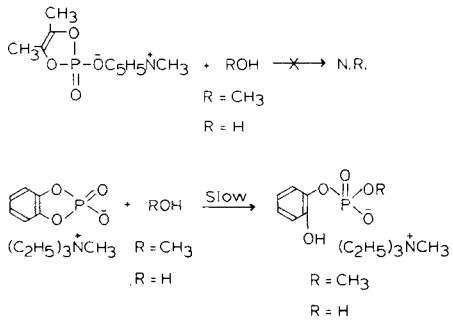
Pyridine is a relatively weak base (pK_B in water = 8.7); therefore, the pyridinium salt of $CEPO^{-}$ is in equilibrium with a significant concentration of the free acid, CEP—OH in aprotic solvents. The addition of alcohols to a CH_2Cl_2 solution of this salt generates the alkyl(3-oxo-2-butyl) phosphate at a rate which is satisfactory for preparative purposes. Scheme 18 illustrates some of the compounds prepared and isolated in pure form by this procedure, which consists in adding equimolar amounts of the alcohol and pyridine to a CH_2Cl_2 solution of CEP—OH.

The lack of reactivity of cyclic phosphodiester anions in aprotic solvents, which in the oxyphosphorane-intermediate hypothesis stems from the difficulties inherent in the development of negative charge on the oxygen atom of an oxyphosphorane that already carries a negative charge (*cf.* Scheme 17), is illustrated also by the behavior of a quaternary ammonium salt of catechol cyclophosphate[33] (Scheme 19). A 1.0 M solution of this salt in methanol produces the salt of methyl-*o*-hydroxyphenyl phosphate with t1/2 ~ 14 days (at 25°). Under identical conditions, no reaction is observed with an analogous salt of $CEPO^{-}$. Evidently the catechol cyclophosphate structure is more reactive than the corresponding cyclic enediol cyclophosphate analog.

$$CEPO\bar{C}_5H_5\overset{+}{N}H \rightleftharpoons CEP\text{—}OH + C_5H_5N \xrightarrow{ROH} CH_3COCH(CH_3)OP(O)(OR)\bar{O}C_5H_5NH^{+}$$

$R = (CH_3)_2CHCH_2$; $R = CH_2{=}C(CH_3)CH_2CH_2$;
$R = (CH_3)_2C{=}CHCH_2$; $R = c\text{-}C_5H_9$

SCHEME 18



SCHEME 19

A similar difference in reactivity between the catechol and the cyclic enediol cyclophosphates can be demonstrated toward hydrolysis of their salts in aqueous solution. While a 1 M solution of $CEPO^{-}M^{+}$ in D_2O is stable for several days at 25°, complete reaction is observed in 24 hr in an unbuffered 1 M solution of the catechol cyclophosphate salt.

EXPERIMENTAL

Analysis were performed by Galbraith Laboratories, Knoxville, Tenn. The analytical data for new compounds are listed in Table IV. All solvents were strictly anhydrous. The ^{31}P nmr measurements were made using a Varian XL-100 spectrometer at 40.5 MHz; chemical shifts are given in ppm *vs.* 85% H_3PO_4 = O; positive values are downfield from the reference signal.

4,5-Dimethyl-2-hydroxy-2-oxo-2H-1,3,2-dioxaphosphole

A solution of water (0.34 g, 19 mmol) in *anhydrous* acetone (10 ml) was added dropwise in 15 min to a solution of oxy*bis*(4,5-dimethyl-2-oxo-2H-1,3,2-dioxaphospholyl)[43] (or

TABLE IV

Elemental Analyses and Spectral data[a] of Salts of 4,5-Dimethyl-2-oxido-2-oxo-2H-1,3,2-dioxaphosphole (CEPOM) and Alkyl(3-oxo-2-butyl) Phosphates, (RO)[$CH_3COCH(CH_3)O$]P(O)$O^-[c\text{-}C_6H_{11})_2NH_s^+$]

Mp, °C	Molecular Formula	Calcd, %				Found, %			
		C	H	P	X	C	H	P	X
		CEPOM[a]							
—	$C_4H_6O_4PLi$	30.8	3.9	—	—	28.6	4.0	—	—
—	$C_4H_6O_4PNa$	27.9	3.5	18.0	13.4	27.9	3.6	18.1	13.1
—	$C_4H_6O_4PK$	25.5	3.2	—	—	24.7	3.4	—	—
	(RO)[$CH_3COCH(CH_3)O$]P(O)$O^-[(c\text{-}C_6H_{11})_2NH_2^+$][b]								
149–150[c]	$C_{20}H_{40}O_5PN$	59.2	9.9	7.6	3.4	59.3	9.9	7.6	3.4
167–169[c]	$C_{21}H_{40}O_5PN$	60.4	9.7	7.4	3.3	60.3	9.6	7.5	3.3
113–115[d]	$C_{21}H_{40}O_5PN$	60.4	9.7	7.4	3.3	60.3	9.8	7.5	3.3
99–101[d]	$C_{21}H_{40}O_5PN$	60.4	9.7	7.4	3.3	60.4	9.7	7.5	3.3

[a] $\partial^{31}P(ppm)$: $CEPO^-M^+$, +14.2 ± 0.2 (D_2O) and +12.0 ± 0.5 (CD_2Cl_2); CEP—OH, +13.2 (CD_2Cl_2); CEP—OR (alkyl), +11.7 ± 0.7 ($CDCl_3$); CEP—OC_6H_5, +6.1 ($CDCl_3$) (Positive values are downfield from the reference) τCH_3C (ppm): $CEPO^-M^+$, 8.17 ± 0.02 (D_2O or CD_2Cl_2); CEP—OR (alkyl, aryl), 8.08 ± 0.02 ($CDCl_3$).

[b] $\partial^{31}P = -2.0 \pm 1.0$ ($CDCl_3$); $\tau CD_3CO = 7.85 \pm 0.10$, $\tau CH_3CH = 8.60 \pm 0.05$ (doublet, J = 7.0 Hz).

[c] From cyclohexane.

[d] From *n*-hexane.

acetoinenediol cyclopyrophosphate; 5.32 g; 19 mmole) in anhydrous acetone (30 ml) at 0°. After 15 min at 0°, the solution was evaporated (25°C, 30 mm) and the residue was triturated with diethyl ether (15 ml), filtered and washed twice with 5-ml portions of ether. The CEP—OH (4.6 g; 80% yield) was virtually pure according to ^1H and ^{31}P nmr spectrometry in CD_2Cl_2; it can be recrystallized (m.p. 108–110°) from a mixture of dichloromethane and ether (2 ml and 5 ml, respectively for a 150 mg-sample); it is very sensitive to moisture and should be stored under dry N_2 or Ar.

Relative Rates of Reactions of Alcohols with Cyclic Phosphodiester, CEP—OH, and Phosphotriesters, CEP—OR

A weighted sample of CEP—OH or CEP—OR was dissolved in CD_2Cl_2, and the solution was allowed to reach a constant temperature of 25°C. An equimolar amount of the alcohol (and of catalyst when indicated) dissolved in CD_2Cl_2 was added, and the ^1H nmr spectrum was determined immediately and after various time intervals. The half-time of the reaction was taken as the time at which the concentration of starting cyclic phosphate was equal to the concentration of product. The solutions were 0.20 M in the cyclic phosphate. Product composition was confirmed by comparison with authentic samples.

The 4,5-dimethyl-2-alkoxy (or phenoxy)-2-oxo-2H-1,3,2-dioxaphospholes, and the dialkyl(3-oxo-2-butyl) phosphates involved in the experiments listed in Tables I–III, are known compounds.[1,37,44,45] The alkyl (3-oxo-2-butyl) phosphates obtained from the reactions of alcohols with CEP—OH (Table I) were isolated after evaporation of the solvent; the free acids were characterized by ^1H and ^{31}P nmr spectra; further characterization of the phosphodiesters was achieved by preparation of crystalline derivatives in relatively large scale reactions.

Preparative-Scale Reactions of CEP—OH with Alcohols in the Absence of Base

A solution of 2-methyl-1-propanol (0.932 g; 12.6 mmol) in dichloromethane (10 ml) was added, over a 15 min period, to a stirred dichloromethane suspension (20 ml) of CEP—OH (1.887 g; 12.6 mmol), at 0°C. After 30 min at 0°C and several hr at 25°C, the solution was evaporated, (2-methyl-1-proply) (3-oxo-2-butyl) phosphate was dissolved in ether (5 ml) and hexane (10 ml), and the solution was treated with dicyclohexylamine (2 molequiv) at 20°. The mixture was kept 12 hr at 0°C, and the crystalline salt (1.8 g, 94%, m.p. 145–148°C) was filtered; see Table IV. This procedure is suitable for the preparation of salts of other phosphodiesters derived from *acid-insensitive* alcohols. However, care must be exercised to avoid adventitious water which rapidly converts CEP—OH into the monoester 3-oxo-2-butyl phosphate, and results in contamination of the desired phosphodiester.

Preparative-Scale Reactions of CEP—OH with Alcohols in the Presence of Pyridine

3,3-Dimethylallyl alcohol (0.329 g; 3.82 mmol) was added to a mixture of CEP—OH (0.573 g. 3.82 mmol), pyridine (0.302 g; 3.82 mmol), and benzene (15 ml), at 25°C, with stirring. After 38 hr at 25°C, the solution was evaporated to yield pyridinium (3,3-dimethylallyl) (3-oxo-2-butyl) phosphate (1.0 g, 83% yield). This salt was converted into the dicyclohexylammonium salt

upon addition of this amine (1 molar equiv) to a benzene solution of the pyridinium salt at 25°C; *cf.* Table IV. This procedure is suitable for the preparation of salts of other phosphodiesters derived from *acid-sensitive* alcohols.

Preparation of Alkali Metal Salts of 2-Oxido-2-oxo-2H-1,3,2-dioxaphosphole

CEPO⁻LI⁺. Lithium iodide was dried for 30 hr at 125° C (0.7 mm). A solution of the ester, CEP—OCH_3 (5.08 g; 31 mmol) in anhydrous acetone (25 ml) was added at once to a solution of LiI (4.20 g; 31 mmol) in acetone (60 ml) at 25°C. The mixture was stirred for 2 hr, and the precipitate was filtered, washed with acetone and with ether, and dried at 20°C (0.1 mm). The $CEPO^-Li^+$ (3.7 g; 77% yield) was analyzed without further purification.

No changes were observed within 5 days in the ^1H spectra of 0.5 M D_2O solutions of $CEPO^-Li^+$ at 25°C, alone or in the presence of one molar equiv of LiBr.

CEPO⁻Na⁺. A solution of CEP—OCH_3 (5.361 g; 33 mmol) in acetone (25 ml) was added to NaI (4.55 g; 33 mmol) in acetone (25 ml). The mixture was stirred for 5 hr at 40°, and the salt was collected, and dried (5.0 g; 91% yield).

No ^1H nmr spectral changes were observed when 0.5 M D_2O or CD_3OD solutions of $CEPO^-Na^+$ were kept for 13 days at 25°.

CEPO⁻K⁺. A mixture of $CEPOCH_3$ (8.36 g; 51 mmol), KI (8.47 g; 51 mmol) and acetone (150 ml), was kept for 9 hr at 60°C. The salt was filtered, washed with acetone, and dried in vacuum to yield $CEPO^-K^+$ (5.6 g; 56% yield).

No changes in the ^1H nmr spectra of 0.08 M D_2O solutions, and 0.5 M CD_3OD solutions were observed after 5 days at 25°.

ACKNOWLEDGMENT

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