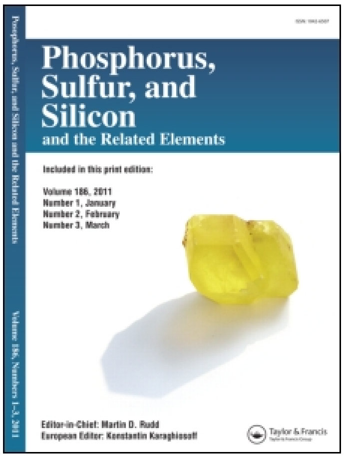

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STRUCTURE AND REACTIVITY OF CYCLIC ENEDIOL *N*-PHOSPHORYLAZOLES AND *N*-PHOSPHORYLTETRAMETHYLGUANIDINE

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STRUCTURE AND REACTIVITY OF CYCLIC ENEDIOL *N*-PHOSPHORYLAZOLES AND *N*-PHOSPHORYLTETRAMETHYLGUANIDINE

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A series of cyclic enediol phosphorylazoles (CEP-azoles) derived from the 4,5-dimethyl-2-oxo-1,3,2-dioxaphosphole ring system and pyrrole, imidazole, pyrazole, 1,2,4-triazole and tetrazole have been prepared. The structures of CEP-triazole and of the related phosphoramidate CEP-tetramethylguanidine (CEP-TMG) have been determined by X-ray crystallographic analysis and compared with the known structure of CEP-imidazole. The reactions of CEP-azoles and CEP-TMG with alcohols have been studied and compared with the reactions of CEP-esters, CEP-OR^1, with alcohols, R^{2}OH, under catalysis by the azoles or tetramethylguanidine. Relative rates of reactions and differences in product composition are discussed in terms of the formation of an oxyphosphorane intermediate in nucleophilic substitutions at 4-coordinate phosphorus. Differences in reactivities among the CEP-derivatives have been determined from the occurrence and direction of the following reactions:

$$\text{CEP-Azole}^1 + \text{Azole}^2 \rightarrow \text{CEP-Azole}^2 + \text{Azole}^1$$
$$\text{CEP-Azole} + \text{TMG} \rightarrow \text{CEP-TMG} + \text{Azole}$$

INTRODUCTION

The reaction of 4,5-dimethyl-2-(1′-pyrrolyl)-2-oxo-1,3,2-dioxaphosphole (Scheme 1) with alcohols in aprotic solvents proceeds with *ring opening* and yields exclusively an alkyl (3-oxo-2-butyl)-*N*-phosphorylpyrrole.[2,3] In striking contrast, the reaction of the imidazole analogue with alcohols under comparable conditions proceeds with *ring retention* and yields exclusively 4,5-dimethyl-2-alkoxy-2-oxo-1,3,2-dioxaphosphole.[4–6] The reason for this sharp difference in the behavior of the two types of CEP-azoles[7] is not known.

In its reactions with alcohols, CEP-pyrrole resembles the cyclic triester, CEP-OR^1, where the main kinetically controlled product is formed by ring-opening. When the attacking alcohol, R^{2}OH, is different from the alkoxy group in CEP-OR^1, some transesterification to CEP-OR^2 and R^{1}OH takes place. Transesterification, which represents substitution at phosphorus with ring retention, increases in importance when the alkyl group of the attacking alcohol, R^2, is more sterically hindered than the alkyl group in CEP-OR^1.

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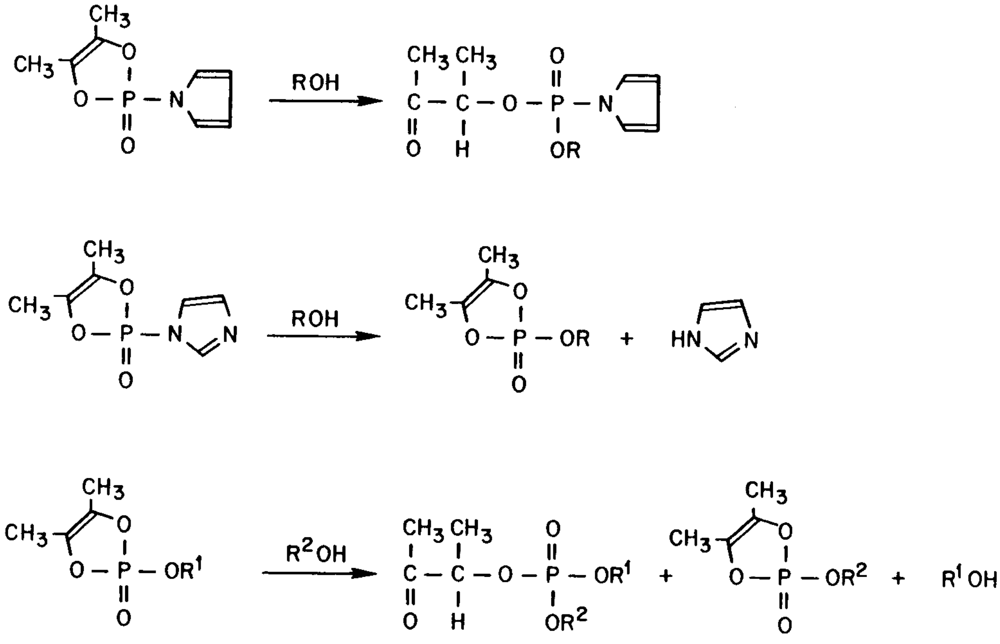
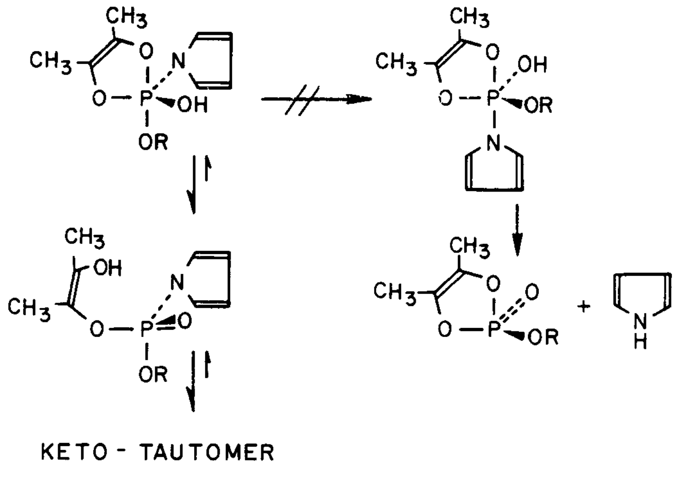
*Author to whom all correspondence should be addressed.

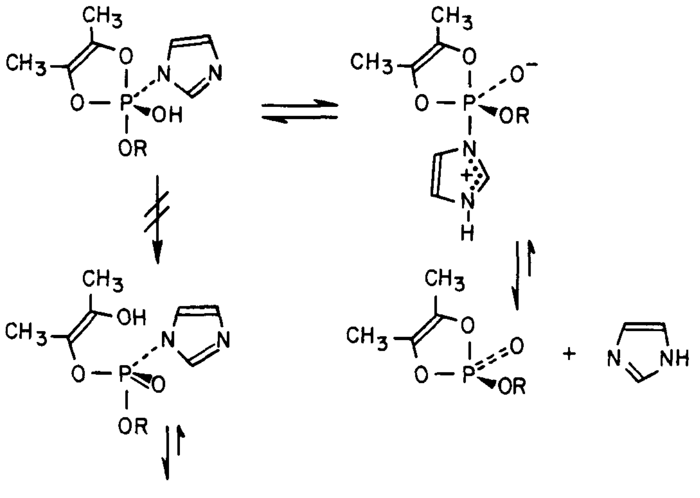


SCHEME 1

A rationalization[2] for the differences between CEP-pyrrole and CEP-imidazole in nucleophilic substitutions by alcohols is provided by the hypothesis (Schemes 2 and 3) that oxyphosphoranes[8-18] are formed as *intermediates* in these reactions, and that pyrrole is apicophobic, while imidazole is apicophilic when covalently bonded to trigonal bipyramidal pentacovalent phosphorus.[9-23] The term apicophobic describes the assumed reluctance of the *N*-pyrrolyl ligand to move from the equatorial to the apical skeletal position in the oxyphosphorane.[2]



SCHEME 2

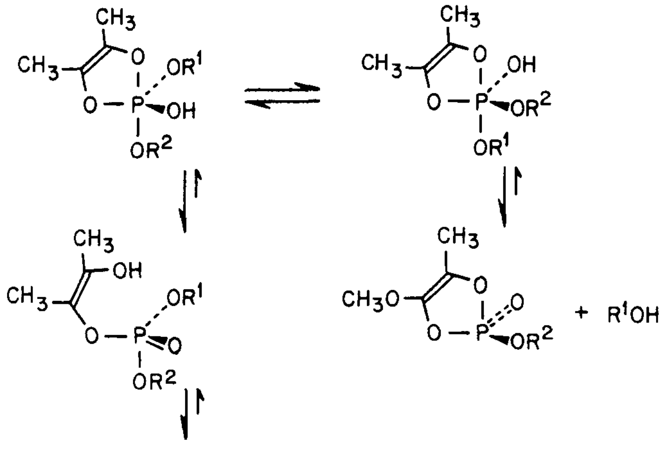


SCHEME 3

In Scheme 2, it is assumed that pyrrole apicophobicity favors the ring-opening mechanism in which the enolate anion is the nucleofugic group (in this and subsequent schemes, proton transfer among oxygen and nitrogen ligands is represented as being virtually instantaneous).

In Scheme 3, imidazole apicophilicity would favor the ring-retention mechanism in which uncharged imidazole is the nucleofugic group. This rationalization does not address the question of what factors determine the assumed apicophilicity or apicophobicity of the azole ligands.

A possible mechanism for substitutions at the CEP-triesters, CEP-OR^1, is shown in Scheme 4. Facile permutational isomerization[24,25] among pentaoxyphosphoranes

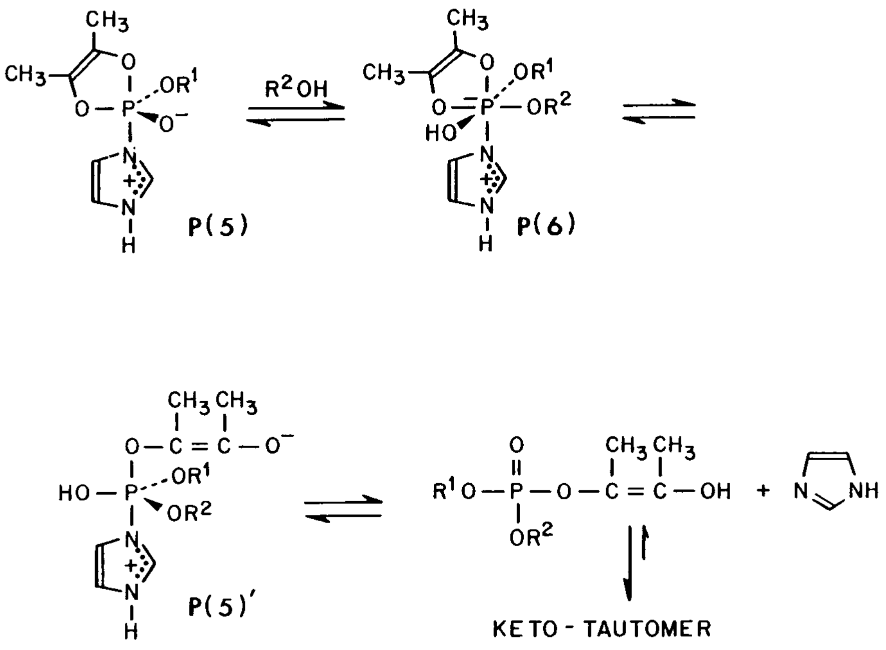


SCHEME 4

is possible, and both pathways, ring-opening and ring-retention, are operative. The apical skeletal position of the bipyramid is more sterically demanding than the equatorial position, and the oxyphosphorane with the less sterically hindered ligand in an apical position should be favored. In this picture, the relative stabilities of acyclic versus cyclic phosphotriesters and phosphoramidates also play a role in the thermodynamic control of the products.

Two significant observations have been made pertaining to the reaction of a cyclic ester, CEP-OR^1, with an alcohol, R^{2}OH. (i) The rate of the reaction is increased by certain nucleophiles such as imidazole[5], quinuclidine, triethylamine, the aroxide ion[26,27] and acetate ion.[28] (ii). The proportion of ring-opening: ring-retention is significantly different in the catalyzed versus the uncatalyzed reaction. The magnitude of this effect varies with the catalyst, and with some catalysts it is affected by the polarity of the aprotic solvent, e.g., chloroform versus acetonitrile.[5,26-28]

The rate enhancement seems to involve nucleophilic rather than acid–base catalysis, on the basis of the following catalytic efficiencies (pK_B in water in parenthesis): imidazole (7.0) ~ quinuclidine (3.5) > triethylamine (3.5) in chloroform; imidazole $\geqslant$ $ArO^-M^+ > CH_3COO^-M^+$ in chloroform, and $CH_3CO_2^-M^+ \sim ArO^-M^+ \geqslant$ quinuclidine in acetonitrile, $[M^+ = (n\text{-}C_4H_9)_4N^+]$. To account for the observations in (i) and (ii), the mechanism shown in Scheme 5, for the specific case of imidazole catalysis, has been suggested.[5] Note that the oxyphosphorane, P(5), is identical to one of the oxyphosphoranes involved in the reaction of CEP-imidazole with alcohols (Scheme 3). It is assumed that P(5) adds the second alcohol to form an intermediate with hexacoordinate phosphorus, P(6). Ring rupture can occur at the P(6) stage to

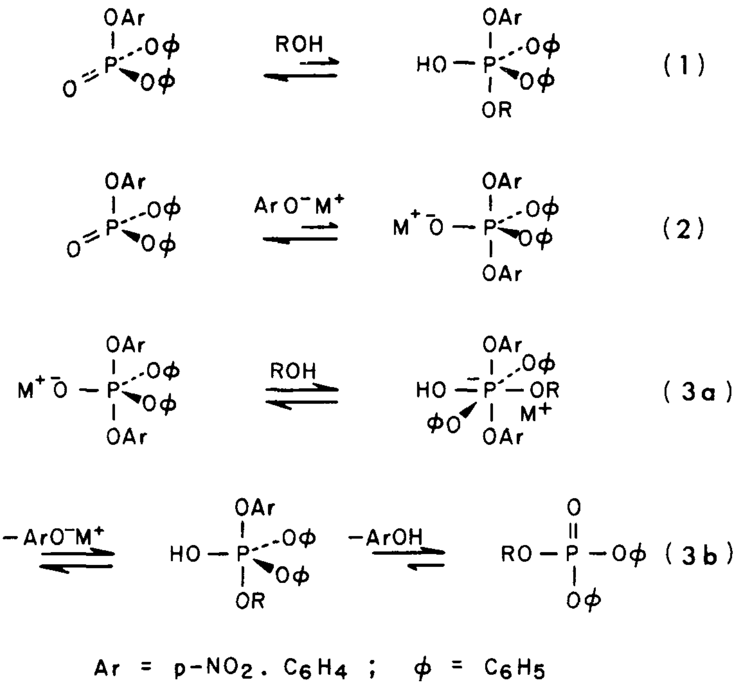


SCHEME 5

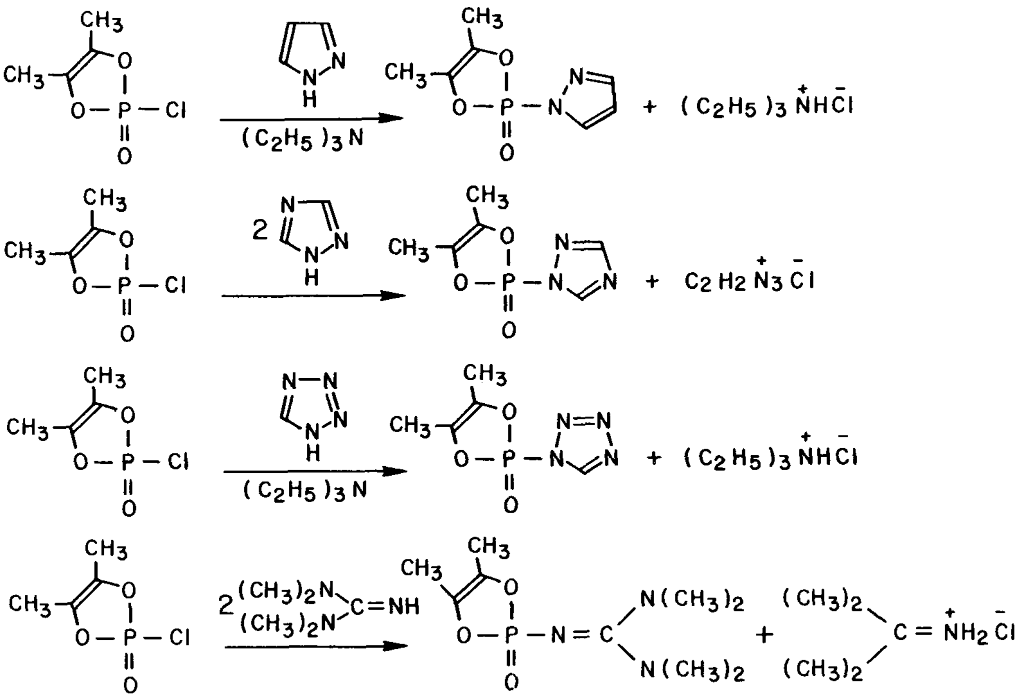
yield another oxyphosphorane, P(5)′, on the way to the observed products. This picture is supported by the discovery that relatively stable hexacoordinate phosphorus compounds related to those postulated in Scheme 5 can be isolated from reactions of pentaoxyphosphoranes with tertiary amines or aroxide ions.[29]

The complex mechanism shown in Scheme 5 accounts for the observed effect of the catalyst on the proportion of ring-opening: ring-retention in the reaction CEP-OR^1 + R^{2}OH. The mechanism also explains[30] the observed catalysis by the *p*-nitrophenoxide ion of the reaction of *p*-nitrophenyldiphenyl phosphate with alcohols: $(C_6H_5O)_2P(O)OAr + ROH \rightarrow (C_6H_5O)_2P(O)OR + ArOH$. Scheme 6 depicts the assumed oxyphosphorane intermediate in the uncatalyzed reaction [Eq. (1)]. The oxyphosphorane intermediate in the catalyzed reaction is shown in Eq. (2); if this intermediate were to decompose directly into a tetracoordinate phosphorus intermediate, the catalysis by *p*-nitrophenoxide ion would not be accounted for. However, the mechanism shown in Eqs. (3a) and (3b), proceeding via the P(6) intermediate, would explain the catalytic effect.[30]

The purpose of this investigation was threefold. (a) To prepare a series of CEP-azoles (Scheme 7) derived from pyrazole, 1,2,4-triazole, and tetrazole for comparison with CEP-pyrrole and CEP-tetramethylguanidine (CEP-TMG), where nitrogen is not part of an aromatic ring. (2) To determine the molecular structure of as many of these compounds as possible by X-ray crystallographic analysis in order to uncover possible differences in their molecular structure. The structure of CEP-



SCHEME 6



SCHEME 7

imidazole is known.[6] CEP-pyrrole has not furnished single crystals of the quality needed for X-ray work; however, the structures of CEP-triazole and CEP-TMG have been solved and are described here. (3) To compare the behavior of these compounds toward alcohols, and to explore the catalytic effect of the various azoles and of tetramethylguanidine in these reactions. We have also studied possible interconversions among the compounds, i.e., the behavior of the systems: CEP-Azole^1 + Azole^2; CEP-Azole^2 + Azole^1; CEP-Azole + TMG and have obtained information on kinetic and thermodynamic factors operating in CEP-azoles, CEP-TMG and CEP-OR reactions.

DISCUSSION OF RESULTS

Structure of CEP-Derivatives

Figure 1 depicts the molecule of CEP-triazole. The triazole ring and the phosphoryl group, PO, are in the plane of a crystallographic mirror which bisects the dioxaphosphole ring. The triazole ring is oriented with a methine carbon, C(4) vicinal to the phosphoryl oxygen at a nonbonded distance of 3.038(2) Å. The separation between one of the nitrogens, N(2), and the endocyclic oxygen, O(1), is 3.072(2) Å (numbers in parentheses are estimated standard deviations in the least-significant digits).

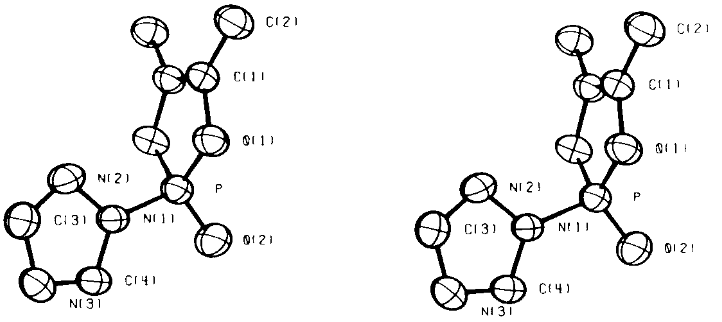


FIGURE 1 Stereoscopic drawing of one molecule of CEP-triazole. $C_6H_8O_3NP$. The 50% probability ellipsoids are shown.

The molecule of CEP-TMG is illustrated in Figure 2. Four of the guanidine atoms, N(1), N(2), N(3), C(5) are in one of the best least-squares planes; another of these planes contains atoms C(5), N(1), P, O(3).

The dioxaphosphole rings in both CEP-triazole and CEP-TMG are planar and have nearly identical geometry, which is that of a highly irregular pentagon virtually identical to that in CEP-imidiazole.[6] The phosphoramidate groups, PO_3N in these three CEP-derivatives also have very similar geometry, which is a highly distorted tetrahedron. This is shown in Table I, where the least-significant digits are not shown. Note the small endocyclic O(1)—P—O(2) angles and the relatively large O(1)-P—O(3) and O(2)—P—O(3) angles. It has already been noted[6,20,31] that the formation of a trigonal bipyramidal oxyphosphorane intermediate, with its 90° and

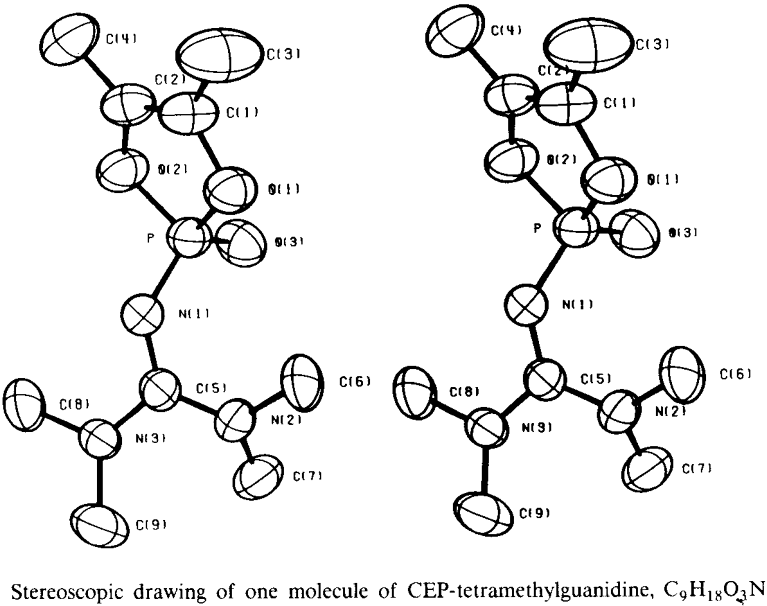
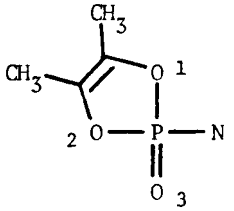


FIGURE 2 Stereoscopic drawing of one molecule of CEP-tetramethylguanidine, $C_9H_{18}O_3N_3P$. The 50% probability ellipsoids are shown.

TABLE I

Bond distances and angles in the PO_3N Group of CEP-azoles and CEP-tetramethylguanidine (CEP-TMG)[a]



Atoms[b]	CEP-Imidazole[c]	CEP-Triazole	CEP-TMG
P—O(1)	1.58	1.58	1.61
P—O(2)	1.59	1.58	1.61
P—O(3)	1.44	1.44	1.46
P—N	1.66	1.68	1.59
O(1)—P—O(2)	97.5	97.6	94.7
O(1)—P—O(3)	117.8	118.7	113.1
O(2)—P—O(3)	118.3	118.7	112.5
O(1)—P—N	106.4	105.8	108.9
O(2)—P—N	104.3	105.8	104.9
O(3)—P—N	110.8	108.9	119.6

[a] The least significant digits (estimated standard deviations .002 Å) have been omitted in the bond distances. The estimated standard deviations in the bond angles are 0.1°. The numbers in this partial formula do not correspond to the numbering systems for the individual formulas (Figures 1, 2).

[b] Pure single bond distances: P—O = 1.76 Å, P—N = 1.78 Å.

[c] Data from Ref. 6.

120° bond angles, from these CEP derivatives involves relatively small additional bond angle deformations beyond those already present in the CEP-derivatives.

The most interesting feature in Table I is the relatively short P—N bond distances: CEP-imidazole[6] = 1.659(3), CEP-triazole = 1.680(2) and CEP-TMG = 1.591(2) Å. The pure single P—N bond is given[32,33] as 1.78 Å, and the shorter bonds in CEP-derivatives possibly reflect some p—d bonding. The P—N bond in CEP-TMG is particularly short, which would be consistent with the enhanced double bond character implied in the resonance structures shown in Scheme 16. Other features of the structures are unexceptional.

Reactivity of CEP-Azoles and CEP-TMG toward Azoles and TMG

A scale of reactivity can be established for the five CEP-azoles and CEP-TMG by determining whether or not the phosphorus atom in these compounds undergoes substitution by a given *nitrogen-containing* nucleophile. These relationships are expressed by the forward and backward reaction of the equations:

$$\text{CEP-Azole}^1 + \text{Azole}^2 \rightarrow \text{CEP-Azole}^2 + \text{Azole}^1$$
$$\text{CEP-Azole} + \text{TMG} \rightarrow \text{CEP-TMG} + \text{Azole}$$

The results of these experiments are summarized in Table II. All five CEP-azoles react with some of the nucleophiles, however, CEP-TMG does not react with any of

TABLE II

Scale of decreasing reactivity of CEP-azoles and CEP-TMG in their reactions with TMG and azoles[a]

1. CEP-Tetrazole
2. CEP-Triazole
3. CEP-Imidazole
4. CEP-Pyrazole
5. CEP-Pyrrole
6. CEP-TMG

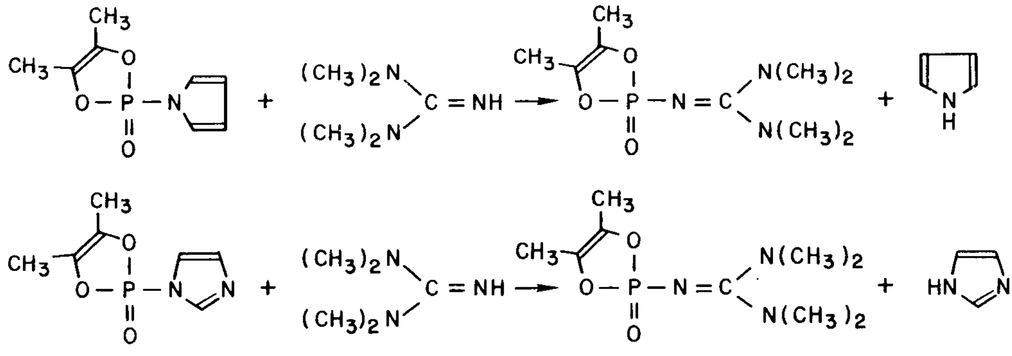
[a] The corresponding azoles are triazole, imidazole, pyrazole, tetrazole and pyrrole.

these nucleophiles. With respect to the nucleophiles, one finds that TMG and three of the azoles react with one or more of the CEP-azoles, but tetrazole and pyrrole do not react with any of the five reactive CEP-azoles.

From these relationships it follows that CEP-TMG can be prepared from the reaction of TMG with the five reactive CEP-azoles because: (a) TMG is an excellent nucleophile towards the phosphorus atom of CEP-derivatives, and (b) the five CEP-azoles are above CEP-TMG in the reactivity scale. CEP-pyrrole cannot be prepared from any of the CEP-derivatives listed in Table II mainly because pyrrole is not sufficiently nucleophilic. In general, utilizing TMG or a *reactive* azole one can prepare any CEP-derivative in Table II from all those CEP-derivatives that are above it in the Table, but not from those below it in the table; e.g., CEP-imidazole is obtained from the reaction of imidazole with CEP-tetrazole or CEP-triazole.

The phosphorochloridate, CEP-Cl[4] is of a higher order of reactivity than the CEP-azoles and, hence, all the CEP-azoles and CEP-TMG are readily prepared from CEP-Cl. However, the potassium salt of pyrrole, not pyrrole itself, must be employed in the preparation of CEP-pyrrole[2] utilizing CEP-Cl.

The most interesting of the reactions between CEP-derivatives and the nucleophiles listed in Table II are shown in Scheme 8. Note that CEP-pyrrole reacts with TMG *with complete ring retention* to give CEP-TMG and pyrrole, which is in sharp contrast to the reaction of CEP-pyrrole with alcohols (c.f., Scheme 1). The reaction



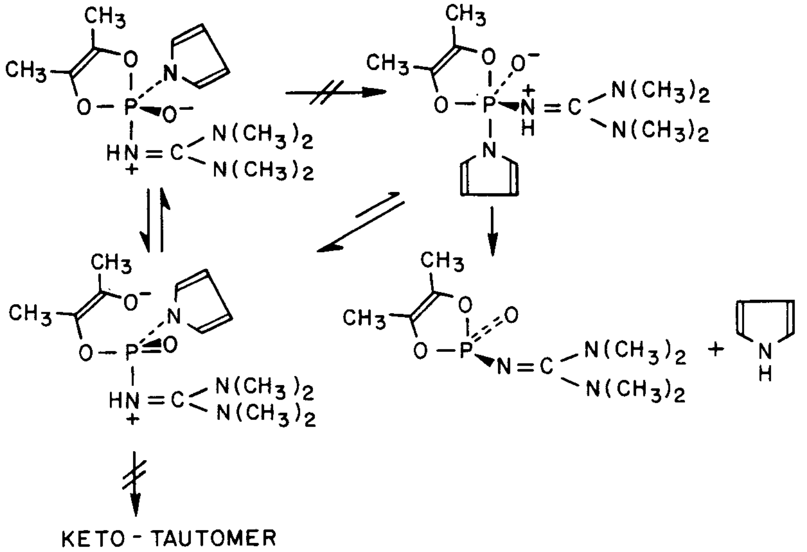
SCHEME 8

of CEP-imidazole with TMG is a ring-retention reaction as was the reaction of CEP-imidazole with alcohols.[4–6]

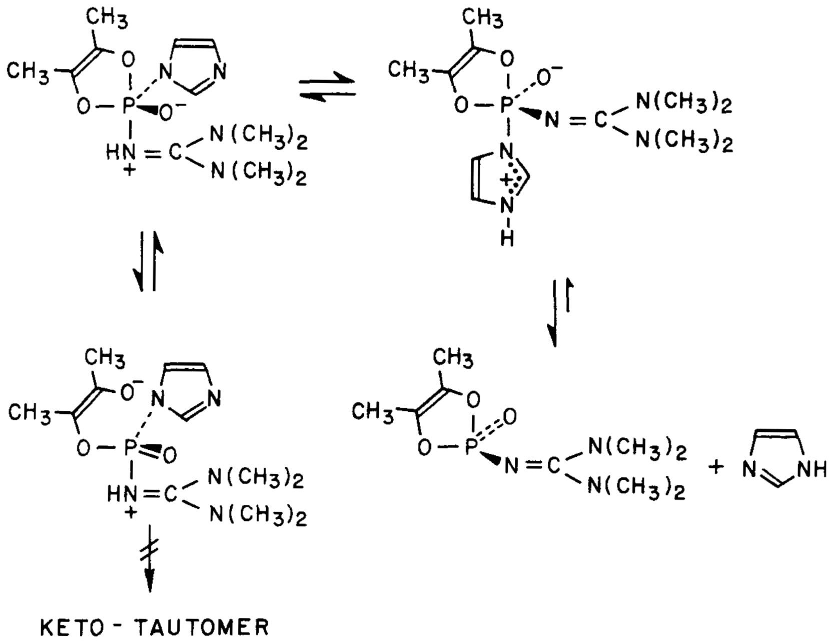
A possible interpretation of this interesting phenomenon is offered in Scheme 9. The oxyphosphorane derived from CEP-pyrrole and TMG should have a relatively high, or a prohibitive, barrier for the "regular" or "bond-deformation," permutational isomerization,[25,34,35] as a result of the assumed pyrrole apicophobicity. Therefore, the only option for this oxyphosphorane is ring-opening; however, if the very strong basicity of TMG (pK_B 0.4 in water) prevents the proton from being added to the carbon atom of the enolate anion in the aprotic solvent, the ring-opening reaction cannot be driven to completion by the enol keto tautomerization step. Under these circumstances, the alternative mechanism of an "irregular" or "bond-rupture" permutational isomerization[25,34,35] (see Scheme 9) may still be capable of leading to the observed substitution with ring-retention. In this interpretation, the pyrrole ligand can, under certain circumstances, occupy the apical position, but to do so a path with a significantly higher energy barrier must be followed.

The formation of CEP-TMG from CEP-imidazole and TMG can be rationalized as shown in Scheme 10. The other reactions among the CEP-derivatives and the nucleophiles listed in Table II can also be explained by the mechanism shown in Scheme 10, with suitable changes in the appropriate ligands to phosphorus, since in all cases they lead to substitution with exclusive ring-retention.

The relatively high reactivity of CEP-tetrazole implied in Table II is manifested in the reaction shown in Scheme 11. CEP-tetrazole converts the free acid, CEP-OH[36] into *bis*(1,2-dimethylethenylene) pyrophosphate[4] in $CDCl_3$ solution at 35°C. Under comparable conditions the salt, $CEPO^-(n\text{-}C_4H_9)_4N^+$ does not react with CEP-tetrazole, illustrating the importance of the nucleofugic group in this type of reaction.

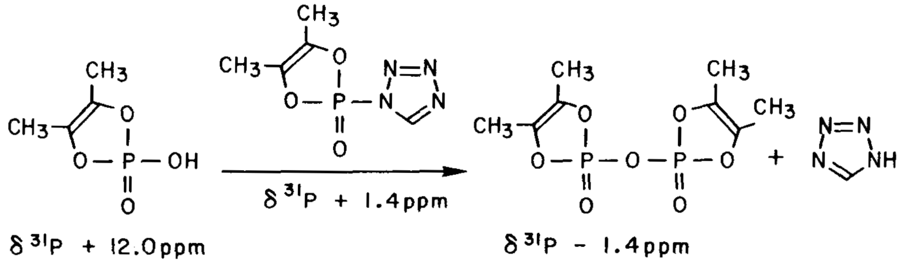


SCHEME 9

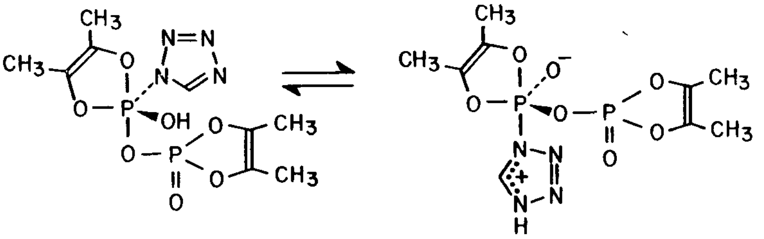


SCHEME 10

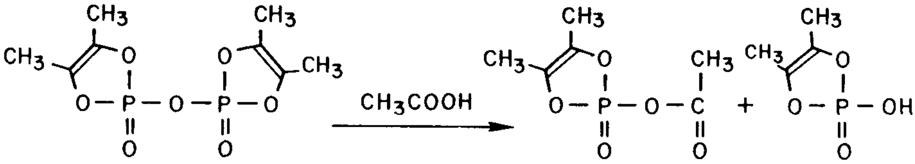
The hypothetical oxyphosphoranes involved in this reaction are shown in Scheme 12. An entirely analogous reaction is observed between CEP-triazole and the free acid, CEP-OH, with formation of the pyrophosphate and triazole: CEP-OH + CEP-triazole → CEP-OCEP + Triazole. *In striking contrast, CEP-imidazole does not convert CEP-OH into the pyrophosphate, CEP-OCEP.* In this case, the reverse reaction is favored: CEP-OCEP + Imidazole → CEP-OH + CEP-imidazole. The direction of these reactions is consistent with the reactivity scale given in Table II. It should be emphasized that imidazole (pK_{B} 7.0) is a stronger base than triazole[37] (pH_{B} 11.7) and tetrazole[37,38] (pK_{B} 17.0), and this factor probably contributes to the observed differences in the course of these reactions.



SCHEME 11



SCHEME 12



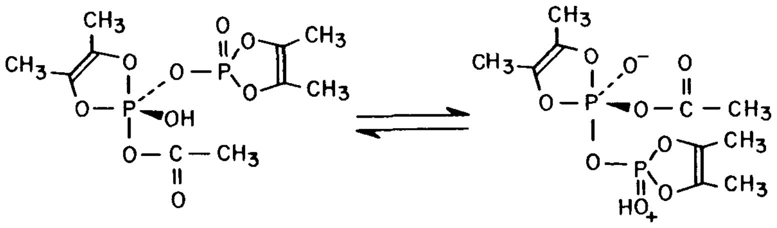
SCHEME 13

The strong phosphorylating power of the pyrophosphate, CEP-OCEP is illustrated by its conversion of acetic acid into the mixed anhydride. CEP-OCOCH$_3$, with elimination of the free acid, CEP-OH, in CDCl$_3$ solution at 35°C; Scheme 13. It is, therefore, noteworthy that the reaction of Scheme 11 proceeds in favor of the pyrophosphate, CEP-OCEP, i.e., that this pyrophosphate is not able to phosphorylate tetrazole under the conditions of our experiments, presumably because tetrazole is not sufficiently nucleophilic and/or CEP-tetrazole has a higher energy content than CEP-OCEP. A similar argument can be advanced in the case of the more basic and nucleophilic triazole. As the basicity and nucleophilicity of the azole increase, as in imidazole, and the relative energy content of the CEP-azole decreases (cf. Table II), the direction of these reactions is reversed.

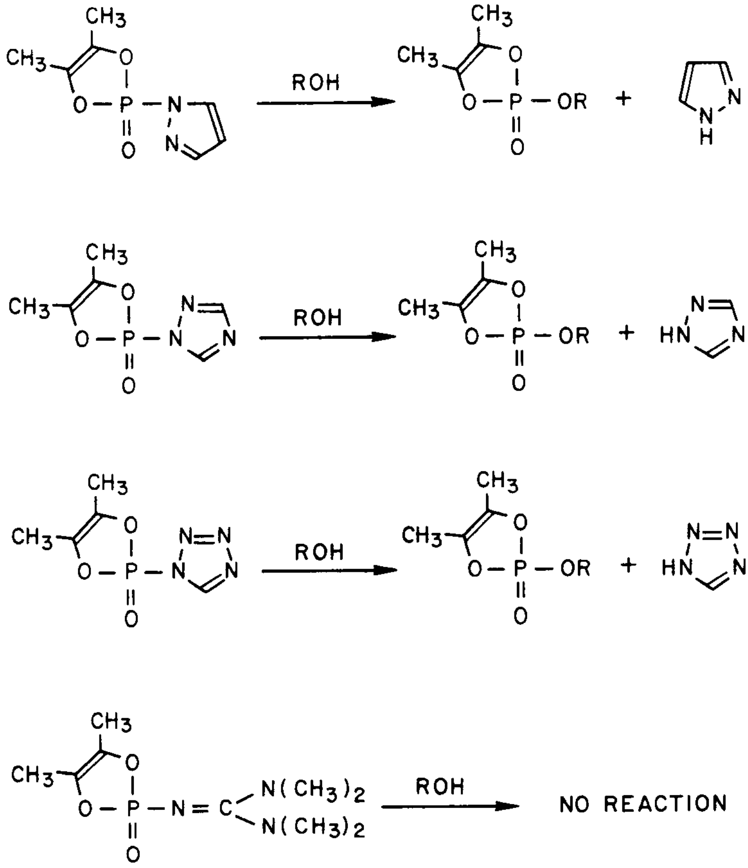
Scheme 14 illustrates oxyphosphorane intermediates that account for the formation of CEP-OCOCH$_3$. As expected, acetic anhydride is formed in the presence of an excess of acetic acid: CEP-OCOCH$_3$ + CH$_3$CO$_2$H → CEP-OH + (CH$_3$CO)$_2$O.

Reactions of CEP-Azoles and CEP-TMG with Alcohols

Scheme 15 shows that the three new CEP-azoles described in this paper react with alcohols with *ring-retention* and yield exclusively the CEP-ester, CEP-OR. In terms



SCHEME 14



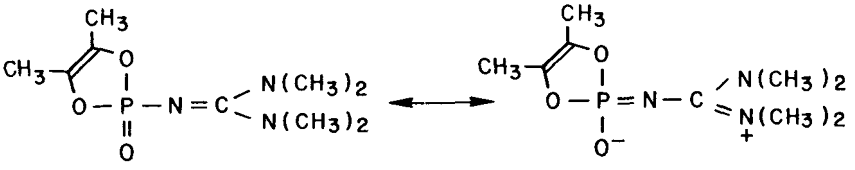
SCHEME 15

of the oxyphosphorane-intermediate hypothesis, these reactions follow the same mechanism outlined in Scheme 3 for the reaction of CEP-imidazole with alcohols. CEP-pyrrole, therefore, remains as the only "abnormal" CEP-azole in the sense that it reacts with alcohols to give exclusively the product of ring-opening (cf. Scheme 2).[39]

In this context it should be noted that an intermediate analogous to the acyclic phosphoramidate shown in Scheme 2 has been proposed for the imidazole catalyzed hydrolysis of a cyclic unsaturated phosphonate.[40]

CEP-TMG fails to react with alcohols under the conditions of these experiments (chloroform solution at 25°C for periods of up to several days). The lack of reactivity of CEP-TMG toward alcohols is attributable partly to its relatively low reactivity, which is possibly related to the resonance structures depicted in Scheme 16 to justify the relatively short P—N bond distance in the CEP-TMG ground state.

If one assumes that an alcohol is capable of adding to CEP-TMG to form the oxyphosphorane shown in Scheme 17, collapse with ring-retention might be disfavored by apicophobicity of TMG, as in the case of CEP-pyrrole. Collapse with ring-opening could be disfavored by the very strong basicity of TMG. If no proton

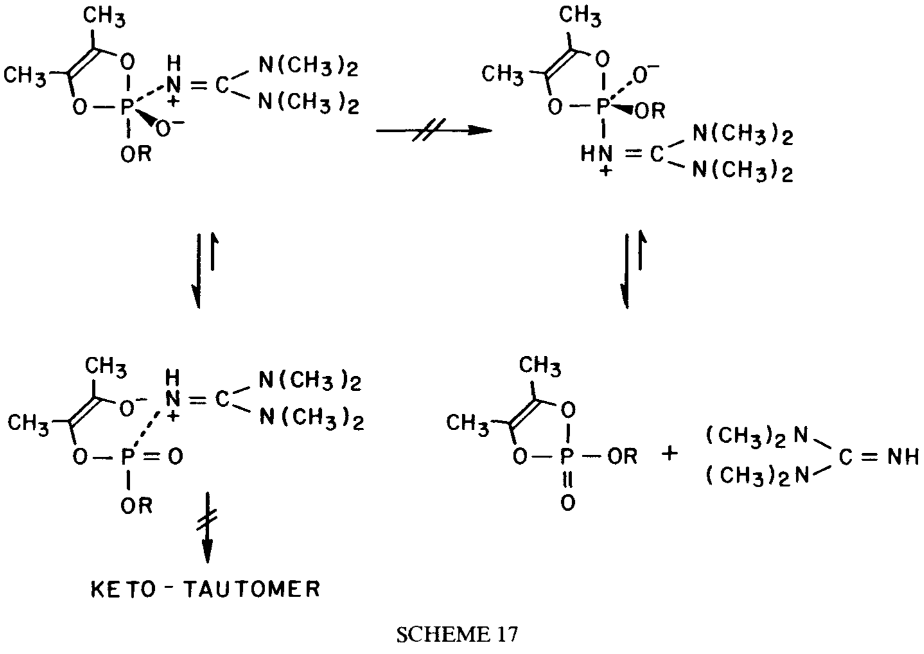


SCHEME 16

can be transferred to the carbon atom of the enolate anion, the overall ring-opening reaction will not be driven toward the more stable keto tautomer of the acyclic phosphoramidate, as is the case in the reaction of CEP-derivatives from much less basic nucleophiles.

Table III shows an interesting observation. Imidazole is an effective catalyst[41] for the ring-opening reaction of CEP-pyrrole, and for the ring-retention reaction of the other CEP-azoles. The imidazole catalysis cannot be demonstrated in the cases of CEP-triazole and CEP-tetrazole because these CEP-derivatives are rapidly converted into CEP-imidazole by imidazole. Imidazole fails to catalyze the reaction of CEP-TMG with alcohols. Pyrazole and triazole have little, if any, catalytic effect on these reactions.[41]

Neither pyrrole nor tetrazole has any effect on the reactions of Table III. Therefore, the fact that the reaction of CEP-tetrazole with alcohols is relatively fast even without assistance from tetrazole, is in accord with the relatively high degree of reactivity of CEP-tetrazole suggested by the scale shown in Table II.



SCHEME 17

TABLE III

Half-times of the reaction of CEP-derivatives with alcohols in 0.2 *M* $CDCl_3$ at 25°C[a]
CEP-pyrrole + ROH → $(C_4H_4N)(RO)P(O)OCH(CH_3)COCH_3$[b]
CEP-azole + ROH → CEP-OR + azole

CEP-Derivative	Catalyst: None	Catalyst: Imidazole
-Pyrrole	$R = CH_3$	$R = CH_3$
	6 min.	Fast[c]
	$R = c\text{-}C_5H_9$	$R = c\text{-}C_5H_9$
	1 hr	Fast
	$R = (C_2H_5)_2CH$	$R = (C_2H_5)_2CH$
	15 hr	3 min
	$R = (CH_3)_3C$	
-Imidazole	11 min	1 min
-Pyrazole	6 hr	6 min[d]
-Triazole	3 hr	...[e]
-Tetrazole	1 hr	...[e]

[a] Equimolar amounts of reactants and catalysts. The disappearance of CEP-derivative and the appearance of the product, $(C_4H_4N)(RO)P(O)OCH(CH_3)COCH_3$ or CEP-OR, were followed by ^1H NMR spectrometry; the figures are the times at which [CEP-derivative] = [Product].

[b] Pyrrole has no effect on this reaction.

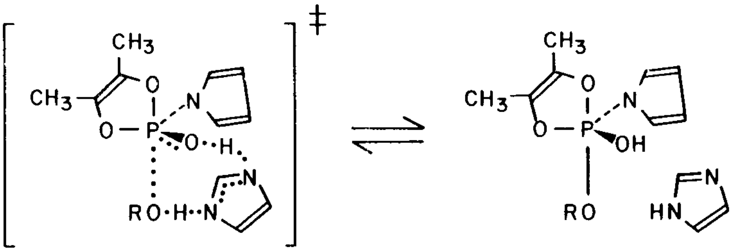
[c] Too fast to measure by the present technique.

[d] Pyrazole has no significant effect on this reaction $t_{1/2} = 4$ hr.

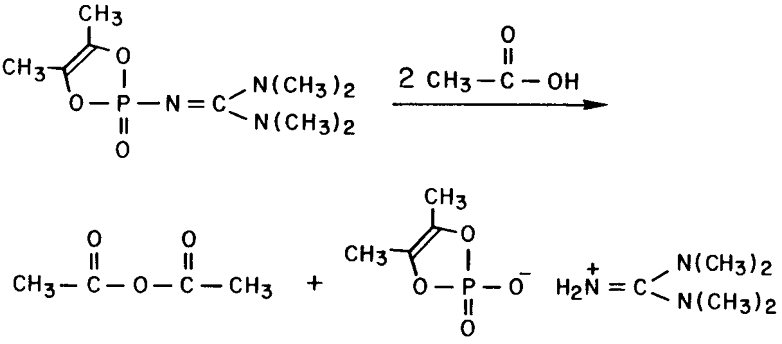
[e] Imidazole rapidly converts these CEP-derivatives into CEP-imidazole.

The simplest explanation for the catalytic effect exerted by imidazole on the ring-opening reaction of CEP-pyrrole and the ring-retention reaction of other CEP-azoles when treated with alcohols is illustrated in Scheme 18. This mechanism postulates that imidazole lowers the energy of the transition state for the formation of the oxyphosphorane by acting as a specific acid–base or biphilic catalyst. The resulting oxyphosphorane can then lead to the product of ring-opening as was shown previously in Scheme 2.

A mechanism analogous to that shown in Scheme 18 can be written for the reaction of the other CEP-azoles with alcohols under catalysis by imidazole. However, in these cases, the resulting oxyphosphorane leads to the product of ring-retention as shown in Scheme 3.

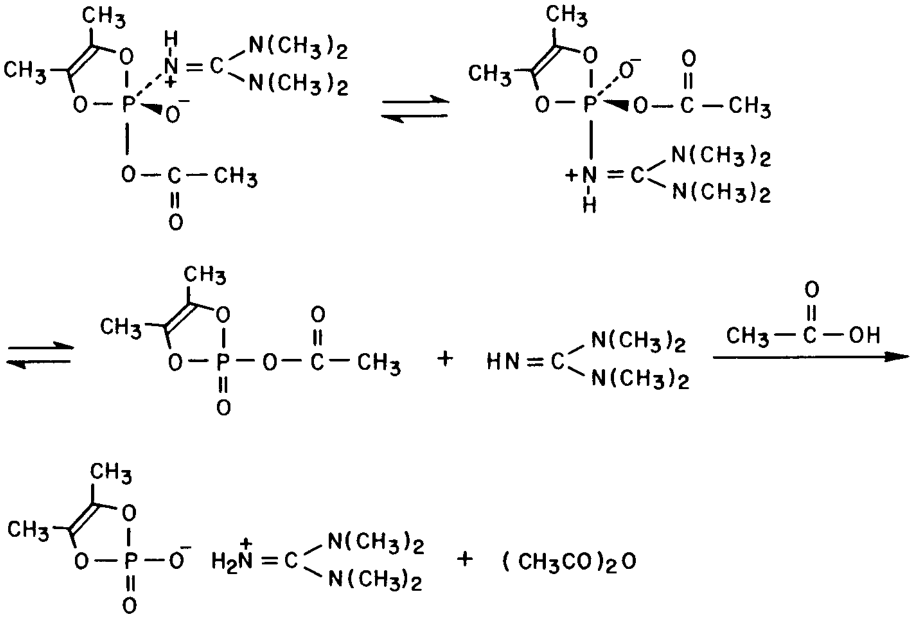


SCHEME 18



SCHEME 19

The hypothesis of biphilic acid–base imidazole catalysis of the reaction of CEP-pyrrole and other CEP-azoles with alcohols in aprotic solvents needs to be justified since in the Introduction it was suggested that the effect of imidazole on the reaction of CEP-esters, CEP-OR^1, with alcohols appeared to involve the azole as a nucleophilic catalyst (cf., Scheme 5). Note, however, that Scheme 5 is a mechanism for imidazole catalysis of the *ring-opening reaction* of the CEP-ester, CEP-OR^1. Scheme 18, on the other hand, accounts for the enhancement of the rate of formation of the oxyphosphorane, which in the case of CEP-azoles proceeds with ring-retention. In agreement with this proposed mechanism of biphilic catalysis it was observed that quinuclidine had only a slight effect on the rate of reaction of *t*-butyl alcohol with CEP-pyrazole ($t_{1/2}$ = 4 hr versus 6 hr without catalyst). Quinuclidine, a relatively



SCHEME 20

strong base (pK_B 3.0 in water), is an excellent nucleophile, but is obviously incapable of the biphilic catalysis exerted by imidazole.

An interesting property of CEP-TMG was discovered in an attempt to elicit some degree of reactivity in this particular CEP-derivative. We have seen that CEP-TMG fails to react with imidazole and other azoles, and with alcohols, under the conditions of the present study. However, when one molar equivalent of CEP-TMG and two molar equivalents of acetic acid are kept in $CDCl_3$ solution at 25°C for 24 hr, the products are acetic anhydride and the salt $CEPO^-TMGH^+$; Scheme 19.

A possible interpretation is given in Scheme 20. The oxyphosphorane derived from CEP-TMG and acetic acid could overcome the barrier for the regular or bond-deformation permutational isomerization to give a second oxyphosphorane capable of collapsing to the mixed anhydride CEP-$OCOCH_3$. This mechanism is analogous to that postulated in Scheme 14 for the formation of CEP-$OCOCH_3$ from the pyrophosphate, CEP-OCEP, and one molar equivalent of acetic acid. Alternatively, the second oxyphosphorane in Scheme 20 could be formed indirectly via the irregular or bond-rupture mechanism[34,35] for permutational isomerization previously depicted in Scheme 9. Acetic anhydride is formed as a result of nucleophilic attack by acetate ion on the acyl carbon activated by the CEPO-group in CEP-$OCOCH_3$.

Effect of Azoles and TMG on the Reaction of CEP-Esters, CEP-OR^1, with Alcohols, R^{2}OH

CEP imidazole is an excellent reagent for the synthesis of phosphodiesters[42-44] since it phosphorylates alcohols, rapidly and quantitatively: CEP-imidazole + $R^1OH \rightarrow$ CEP-OR^1 + Imidazole. The imidazole formed as by-product catalyzes the subsequent phosphorylation of a second alcohol by the CEP-ester: CEP-OR^1 + $R^2OH \rightarrow$ $(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$. Finally, the 3-oxo-2-butyl group which acts as a phosphorus protecting group is easily removed in an aqueous/aprotic solvent containing triethylamine to give the diester, $(R^1O)(R^2O)PO_2^-$. The three steps can be performed in one flask, and the success of the synthesis depends on the ability of imidazole to catalyze the second of the three steps and to enhance substitution with ring-opening in that step.[4] The mechanism of Scheme 5 was suggested to account for the imidazole effect. It was, therefore, of considerable interest to ascertain if other azoles also act as catalysts for the reaction of CEP-esters with alcohols in order to utilize the new CEP-azoles as reagents in the synthesis of phosphodiesters. Table IV discloses that pyrazole exerts only a small catalytic effect on this reaction, while triazole and tetrazole do not seem to affect the rate of reaction at all. Therefore, we conclude that of all the CEP-azoles, CEP-imidazole is the reagent of choice for synthetic purposes.

Table IV shows several effects that are relevant to the mechanism of catalysis suggested in Scheme 5. Quinuclidine and TMG exert a strong and comparable catalytic effect on the reaction, which supports the assumption of nucleophilic catalysis by the two compounds. Interestingly enough, 1-methylimidazole is virtually devoid of catalytic effect. Triethylamine is a fair catalyst but only when the alcohol R^2OH is primary. This inability of the more hindered tertiary amine to catalyze the reaction of a secondary alcohol with a CEP-ester has been previously documented.[4]

TABLE IV

Half-time of the reaction of CEP-esters with alcohols at 25°C:[a] CEP-OR^1 + R^{2}OH → (R^{1}O)(R^{2}O)P(O)OCH(CH$_3$)COCH$_3$[b]

Catalyst	$t_{1/2}$
R^1 = c-C$_5$H$_9$; R^2 = (CH$_3$)$_2$CHCH$_2$; 0.2 *M* CDCl$_3$	
None	7.5 hr
Imidazole	3 min
Quinuclidine	3 min
TMG	5 min
Triethylamine	1.5 hr
Pyrazole	1.5 hr
1-Methylimidazole	6 hr
R^1 = c-C$_5$H$_9$; R^2 = (CH$_3$)$_2$CHCH$_2$; 0.2 *M* CD$_3$CN	
None	12 hr
Imidazole	25 min
Quinuclidine	6 min
TMG	5 min
Triethylamine	2.5 hr
Pyrazole	6 hr
1-Methylimidazole	4 hr
R^1 = R^2 = c-C$_5$H$_9$; 0.2 *M* CDCl$_3$	
None	28 hr
Imidazole	15 min
Quinuclidine	40 min
TMG	50 min
Triethylamine	30 hr
Pyrazole	8 hr
1-Methylimidazole	30 hr

[a] Equimolar amounts of reactants and catalysts. The disappearance of CEP-OR^1 and the appearance of (R^{1}O)(R^{2}O)P(O)-OCH(CH$_3$)COCH$_3$ were followed by ^{1}H NMR spectrometry; the figures are the times at which both concentrations are equal. Pyrrole, triazole and tetrazole have no significant effect on these reactions.

[b] Less than 5% of substitution with ring-retention is observed in these reactions in the presence or absence of catalyst.

Summary

CEP-pyrrole differs from all other CEP-azoles in their reactions with alcohols. CEP-tetramethylguanidine fails to react with alcohols under comparable conditions. The hypothesis that oxyphosphoranes are formed as intermediates in nucleophilic substitutions at the phosphorus atom of CEP-derivatives accomodates these observations, if one introduces the further premise that pyrrole is "apicophobic." The observed significant departures from the regular pentagon bond angles in the 1,3,2-dioxaphosphole ring present in CEP-derivatives should facilitate the transformation of 4-coordinate into 5-coordinate phosphorus in the phosphoramidate → oxyphosphorane transformation. However, differences in some inherent property of

pyrrole and the other azoles must control the direction of the collapse of the hypothetical oxyphosphorane intermediate in these reactions. Imidazole proved to be vastly superior to all other azoles as catalyst for the reaction of alcohols with CEP-esters, and, therefore, CEP-imidazole represents the best reagent, among the CEP-azoles, for the conversion of two alcohols into a phosphodiester.

EXPERIMENTAL

Preparations. CEP-pyrrole and CEP-imidazole were prepared as previously described.[2,4]

4,5-Dimethyl-2-(1′-pyrazolyl)-2-oxo-1,3,2-dioxaphosphole (CEP-pyrazole). Pyrazole (1.88 g, 27.7 mmol) and triethylamine (2.80 g, 27.7 mmol) dissolved in diethyl ether (20 mL) were added dropwise with stirring to a solution of 4,5-dimethyl-2-chloro-2-oxo-1,3,2-dioxaphosphole[4] (4.66 g, 27.7 mmol) in ether (50 mL) at 25°C. Triethylammonium chloride was filtered off and the solvent was evaporated under reduced pressure. The CEP-pyrazole thus obtained (5.25 g, 95% yield) was virtually pure; recrystallization from ether–hexane gave CEP-pyrazole of m.p. 86–88°C (see Table V). Calcd. for $C_7H_9O_3N_2P$: C, 42.0; H, 4.5; N, 14.0; P, 15.5. Found: C, 41.8; H, 4.7; N, 13.8 P, 15.4.

4,5-Dimethyl-2-[1′-(1′2′,4′)-triazolyl]-2-oxo-1,3,2-dioxaphosphole (CEP-triazole). 4,5-dimethyl-2-chloro-2-oxo-1,3,2-dioxaphosphole (8.95 g, 53 mmol) dissolved in dichloromethane (10 mL) was added dropwise with stirring over 30 min to a suspension of 1,2,4-triazole (7.34 g, 110 mmol) in dichloromethane at 25°C. The mixture was stirred at 25°C for 6 hr. The precipitate was filtered off, the filtrate was kept at −20°C overnight and filtration was repeated. The filtrate was evaporated and the residue was redissolved in 80 mL of dichloromethane. The turbid solution was filtered and the clear solution was diluted with 80 mL of hexane to yield the CEP-triazole (8.0 g, 75% yield) mp 118–120°C (see Table V). Calcd for $C_6H_8O_3N_3P$: C, 35.8; H, 4.0; N, 20.9; P, 15.4. Found: C, 35.8; H, 4.11; N, 20.8; P, 15.5. Sample for X-ray: CEP-triazole (9.0 g) in dichloromethane (80 mL); diluted with hexane (80 mL); crystallized at 20°C.

4,5-Dimethyl-2-(1′-tetrazolyl)-2-oxo-1,3,2-dioxaphosphole (CEP-tetrazole). Freshly sublimed (80°, 0.1 mm) tetrazole (1.78 g, 25.4 mmol) was added at once to a solution of 4,5-dimethyl-2-chloro-2-oxo-1,3,2-dioxaphosphole (4.28 g, 25.4 mmol) and triethyl-amine (25.4 mmol) in diethyl ether (50 mL) at 25°C under N_2. The suspension was stirred 18 h at 25°C and filtered. The filtrate was concentrated to ca. 15 mL under a stream of N_2, diluted with hexane (10 mL) and then cooled to ca −80°C. The crystals thus obtained were filtered and dried in vacuum to give CEP-tetrazole (2.2 g, 41% yield), m.p. 78–80° (see Table V). Calcd for $C_5H_7O_3N_4P$: C, 29.7; H, 3.5; N, 27.7; P, 15.3. Found: C, 29.6; H, 3.7; N, 27.5; P. 15.4.

4,5-Dimethyl-2-[N-(N′, N′, N″, N″-tetramethyl)guanidyl]-2-oxo-1,3,2-dioxaphosphole (CEP-tetramethylguanidine). Tetramethylguanidine (0.67 g, 5.8 mmole) dissolved in 10 mL of diethyl ether was added dropwise over 5 min to a stirred solution of 4,5-dimethyl-2-chloro-2-oxo-1,3,2-dioxaphosphole (0.49 g, 2.9 mmole) in 20 mL of ether at 20°C. Stirring was continued a further 2h then the precipitated tetramethylguanidinium chloride was removed by filtration and washed with 10 mL of ether. The combined ether

TABLE V

Some N.M.R. signals of CEP-azoles and CEP-tetramethylguanidine

CEP-Derivative	$\delta\ ^{31}P$, ppm[a]	$\delta\ ^{1}H$, ppm[b]
-Pyrrole	+8.8	2.00
-Imidazole	+6.1	2.05
-Pyrazole	+6.8	2.00
-1,2,4-Triazole	+4.4	2.05
-Tetrazole	+1.4	2.15
-Tetramethylguanidine	+13.5	1.90

[a] In $CDCl_3$ solution; positive values are to low field from the reference, 85% H_3PO_4 = 0.

[b] $CH_3C = C$; in $CDCl_3$ solution from TMS = 0.

filtrates were evaporated under reduced pressure yielding 0.72 g (100%) of the crude product as a crystalline solid. Recrystallization from methylene chloride-ether afforded 0.69 g (94%) of CEP-TMG, m.p. 122–24°C (see Table V). Calcd for $C_9H_{18}O_3N_3P$: C, 43.7; H, 7.3; P, 12.5; N, 17.0. Found: C, 43.7; H, 7.4; P, 12.5; N, 17.0.

Crystal and Molecular Structures

Crystal Data for CEP-1,2,4-triazole. $C_6H_8O_3N_3P$: orthorhombic; Pnma; a = 7.703(1), b = 9.074(1), c = 12.830(1) Å; V = 896.8 Å^3 (λ_{CuK_α} = 1.5418 Å at 21°C); Z = 4; D_{calc} = 1.49 g cm^{-3}, D_{meas} = 1.49(1) g cm^{-3} (by flotation in CCl_4/hexane); μ(CuK_α = 25.90 cm^{-1}).

Crystal Data for CEP-tetramethylguanidine. $C_9H_{18}O_3N_3P$: monoclinic; C2/c; a = 14.621(4), b = 7.246(3), c = 24.054(9) Å; β = 91.62(2)°; V = 2547.5 Å^3 (λ_{CuK_α} = 1.5418 Å at 21°C); Z = 8; D_{calc} = 1.29 g cm^{-3}, D_{meas} (by flotation in aqueous $ZnCl_2$) = 1.27(1) g cm^{-3}; μ(CuK_α = 19.12 cm^{-1}).

Data collection and structure refinement. were performed by methods analogous to those already described in the paper on CEP-imidazole[6]. For CEP-triazole, the final values of $R_1 = \Sigma||Fo| - |Fc||/\Sigma|Fo|$ and $R_2 = \{[\Sigma w(|Fo| - |Fc|)^2]/\Sigma w|Fo|^2\}^{1/2}$ were 0.043 and 0.054, respectively and the error in an observation of unit weight was 1.74. The maximum density in a final difference electron density synthesis was 0.43 electron Å^{-3}, approximately ten percent of the height of a carbon atom peak. For CEP-tetramethylguanidine the corresponding values were for R_1, 0.047 and for R_2, 0.059 and the error in an observation of unit weight was 1.88. The maximum density in a final difference electron density synthesis was 0.29 electron Å^{-3}, approximately nine percent of the height of a carbon atom peak.

The data are presented in a set of tables (see paragraph on supplementary material at the end of this paper).

Reactions. Equimolar mixtures of CEP-azole^1 + azole^2, CEP-azole^2 + azole^1, CEP-azole + TMG, or CEP-TMG + azole in 1 M $CDCl_3$ solution at 35°C were examined by ^{31}P NMR spectroscopy.

Equimolar mixtures of CEP-azole + alcohol, or CEP-TMG + alcohol in 0.2 *M* $CDCl_3$ solution at 25°C were examined by ^1H NMR spectroscopy. The same experiments were repeated in the presence of one molar equivalent of an azole or TMG.

Equimolar mixtures of a cyclic triester, CEP-OR^1 + alcohol in 0.2 *M* $CDCl_3$ solution at 25°C were examined by ^1H NMR spectroscopy. The same experiments were repeated in the presence of one molar equivalent of azole, TMG, or certain tertiary amines.

SUPPLEMENTARY MATERIAL AVAILABLE

The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

The following data are deposited: Table VI: Positional and Anisotropic Thermal Parameters for 4,5-Dimethyl-2-[1′-(1′,2′,4′)-triazolyl]-2-oxo-1,3,2-dioxaphosphole; Table VII: Distances, Angles and Least-Squares Plane Involving Nonhydrogen Atoms in 4,5-Dimethyl-2-[1′-(1′,2′,4′)-triazolyl]-2-oxo-1,3,2-dioxaphosphole; Table VIII: Positional and Anisotropic Thermal Parameters ($\times 10^4$) for Nonhydrogen Atoms and Hydrogen Atom Positions ($\times 10^4$) in 4,5-Dimethyl-2-[N-(N′,N′,N″,N″-tetramethyl)guanidyl]-2-oxo-1,3,2-dioxaphosphole; Table IX: Distances and Angles Involving Nonhydrogen Atoms in 4,5-Dimethyl-2-[N-(N′,N′,N″,N″-tetramethyl)guanidyl]-2-oxo-1,3,2-dioxaphosphole.

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7. Abbreviations: CEP = 1,2-dimethylethenylenedioxyphosphoryl; TMG = tetramethylguanidine.
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39. The reactions of CEP-pyrrole with alcohols may be more complex than indicated here. While there is no question that the uncatalyzed and imidazole catalyzed reactions proceed with exclusive ring-opening, preliminary experiments indicate that the same reactions when catalyzed by triethylamine, quinuclidine, or salts of acetate or *p*-nitrophenoxide anions seem to yield either products of ring-opening, ring-retention or both of these in a manner which is not altogether clear at present.
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