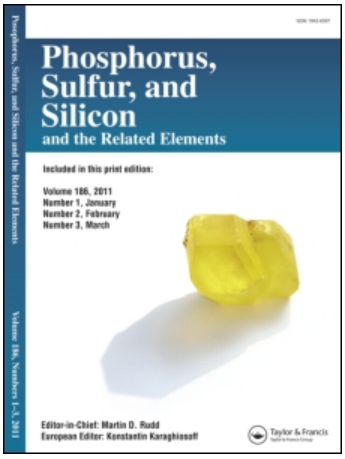


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# NEW SYNTHESES OF UNSYMMETRICAL PHOSPHODIESTERS BASED ON THE OXYPHOSPHORANE CONCEPT

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# NEW SYNTHESES OF UNSYMMETRICAL PHOSPHODIESTERS BASED ON THE OXYPHOSPHORANE CONCEPT †

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Reagents for the phosphorylative coupling of two different alcohols are obtained from five-membered cyclic enediolphosphates and acyl phosphates. The primary alcohol of a diol is selectively phosphorylated in the presence of an unprotected secondary alcohol. The acetoinyl group (Ac.Me.CH) is used to block the phosphate function in the synthesis of unsymmetrical phosphodiesters. Phosphomonoesters can also be made by the proper choice of one of the two alcohols. The method has been applied to the synthesis of oligonucleotide models.



## INTRODUCTION

Phosphodiesters, (RO)(R'O)P(O)(OH), play a key role in biochemistry in the form of nucleic acids, phospholipids, coenzymes, etc., and it is not surprising that much attention has been paid to the development of reagents for the phosphorylation of alcohols.[1-8] The field of oligonucleotide synthesis in particular has been the subject of numerous investigations which have led to outstanding achievements in recent years.[9-18] This paper presents new approaches to the synthesis of unsymmetrical phosphodiesters, with emphasis on the development of phosphorylating reagents that might be suitable for oligonucleotide synthesis. The development of these reagents has been based on the *oxyphosphorane concept*, which assumes that P(5)-intermediates[19] having one or more P—O bonds are formed in nucleophilic displacements of P(4)-compounds.[19] The oxyphosphorane concept gives rules for the formation, the decomposition, and the stereochemistry of the P(5)-intermediates. The development of these rules has been discussed in a recent review.[20] and various aspects of the problem have been treated by several investigators.[21-28] One of the main questions in the oxyphosphorane concept pertains to the mechanisms by which the regular and irregular[29] PI[19] of oxyphosphoranes take place. The view that the regular PI of cyclic oxyphosphoranes proceeds by the TR[19] mechanisms has been advanced by the present authors.[30-32]

This investigation is an outcome of earlier observations to the effect that the hydrolyses of certain 5-membered cyclic saturated oxyphosphoranes give exclusively or predominantly the corresponding cyclic saturated phosphotriesters, when the reactions are carried out by one mol equivalent of water in aprotic solvents.[33-40] Likewise, the hydrolyses of certain 5-membered cyclic saturated phosphotriesters proceed with 100% retention of the ring and give the corresponding cyclic saturated phosphodiesters, if the solvent is aprotic and the amount of water is limited to one mol equivalent.[41] These observations, taken together with the results of extensive research by Westheimer and his coworkers,[42-47,24] and by Aksnes et al.,[48,49] on the hydrolyses of 5-membered cyclic saturated phosphotriesters and phosphonates in aqueous solution, disclose an important effect of the medium on the course of nucleophilic displacement on these cyclic saturated phosphorus rings.

Even more striking is the observation that the reaction of a 5-membered cyclic *unsaturated* oxyphosphorane with one mol equivalent of water in aprotic solvents is capable of giving up to 30% of the product of ring-retention, namely, the enediol cyclic phosphotriester.[50,51] Moreover, the reaction of methyl acetoinenediol-cyclophosphate (Fig. 1) with one mol equivalent of water in aprotic solvent proceeds with some ring-retention,[52,53,20b] as shown by the direct observation of the cyclic unsaturated phosphodiester, and by the detection of the symmetric phosphotriester and phosphomonoester:

Major product: $H_2O + CEP{-}OCH_3 \rightarrow (CH_3O)(HO)P(O)(OAcn)$

† Plenary Lecture. Vth International Conference of Organic Phosphorus Chemistry, Gdansk, Poland, September 1974.

| | | | |
|---|---|---|---|
| Minor products: | $H_2O + CEP–OCH_3$ | → | $CH_3OH + CEP–OH$ |
| | $CH_3OH + CEP–OCH_3$ | → | $(CH_3O)_2P(O)(OAcn)$ |
| | $H_2O + CEP–OH$ | → | $(HO)_2P(O)(OAcn)$ |

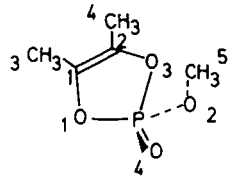


FIGURE 1 Methyl acetoinenediolcyclophosphate. A five-membered cyclic enediol phosphoryl derivative, or CEP–$OCH_3$. The numbering system is that of the x-ray crystallographic analysis (Ref. 51).

The alcoholyses, as well as the hydrolysis, of CEP–$OCH_3$ proceed with some ring retention, as shown by the results of the reaction with one mol equivalent of $CD_3OD$ in aprotic solvents:[52,53,20b]

| | | | |
|---|---|---|---|
| Major product: | $CD_3OD$ + | CEP–$OCH_3$ | $(CH_3O)(CD_3O)P(O)(OAcn)$ |
| Minor products: | $CD_3OD$ + | CEP–$OCH_3$ | $CH_3OD + CEP–OCD_3$ |
| | $CH_3OD$ + | CEP–$OCH_3$ | $(CH_3O)_2P(O)(OAcn)$ |
| | $CD_3OD$ + | CEP–$OCD_3$ | $(CD_3O)_2P(O)(OAcn)$ |

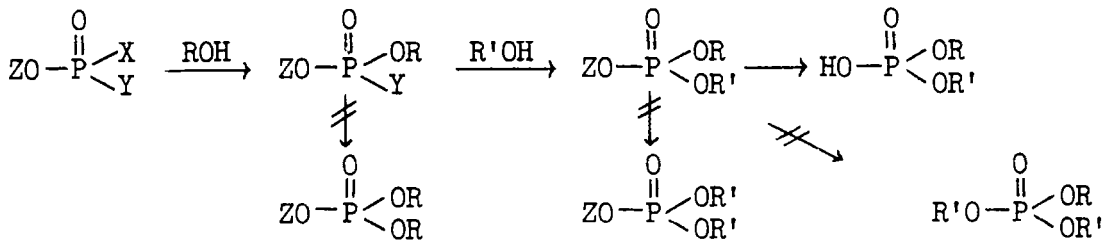
Transesterification is also observed in the reaction of primary, secondary and tertiary alcohols with CEP–$OCH_3$ in aprotic solvents,[52,53,20b] but one can surmise from these results that the extent of ring-retention vs. ring-opening in the alcoholyses of the cyclic unsaturated phosphotriesters is a sensitive function of the bulk of the alcohol. Evidently the bulk of the alkyl group present in the CEP-ester, or CEP–OR, should also exert its influence on ring-retention vs. ring-opening.

These observations, as well as others made in an investigation on the mechanism of hydrolysis of phosphate esters derived from α-hydroxyaldehydes and α-hydroxyketones,[54] provide the background for the present research. It was concluded that the rapid hydroxide-ion catalyzed removal of the acetoinyl group[19] from dimethylacetoinyl phosphate in aqueous solution at pH ca. 8 is due to the participation of a 5-membered cyclic saturated oxyphosphorane intermediate in the reaction;[54] there is very little loss of methanol (ca. 5%) in this hydrolysis.[23]



## A GENERAL SCHEME FOR THE SYNTHESIS OF UNSYMMETRICAL PHOSPHODIESTERS

An efficient reagent for the phosphorylative coupling of two different alcohols should need no additional activation to carry out the double phosphorylation, should not generate symmetrical phosphodiesters, and should have an easily removable phosphate-blocking group, Z:




When intended for oligonucleotide syntheses, the reagent should also be able to phosphorylate selectively a primary alcohol in the presence of an unprotected secondary alcohol. Phosphorylating reagents having these properties have been prepared using as starting materials the CEP–$OCH_3$ shown in Fig. 1,[50,51,55,56] and the CAP–$OCH_3$ shown in Fig. 2.[57-61]

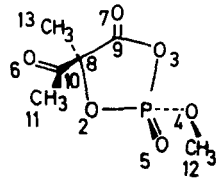
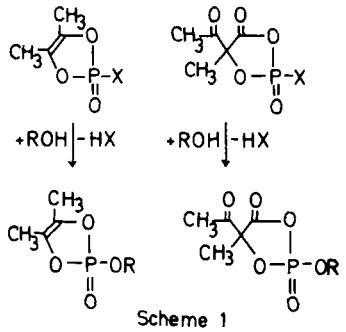


FIGURE 2 Methyl ester of cyclic anhydride of 2-phosphato-2-methyl-3-oxo-butanoic acid. A five-membered cyclic acyl phosphoryl derivative, or CAP–$OCH_3$. The numbering system is that of the x-ray crystallographic analysis (Ref. 59).

CEP–$OCH_3$ and CAP–$OCH_3$ can be transformed into reagents of the type CEP–X and CAP–X (Scheme 1), where X is a strongly electron-withdrawing group. Nucleophilic displacements by alcohols, ROH, occur exclusively with ring-retention in some of these reagents, to give CEP–OR and CAP–OR, respectively.

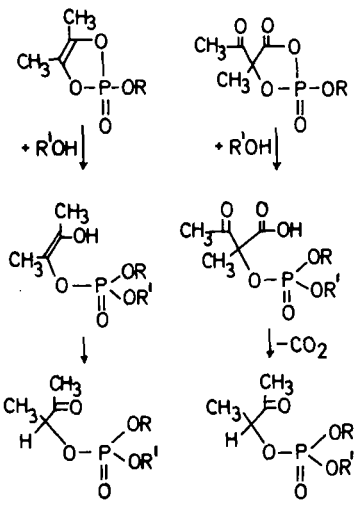


Scheme 1

The CEP–OR and CAP–OR are still phosphorylating reagents capable of reacting with another alcohol, R'OH, and depending on the structure of the two alkyl groups R and R' one can observe the exclusive formation of the unsymmetrical acyclic dialkylacetoinyl phosphate (Scheme 2). The latter are formed by somewhat different pathways: (a) by tautomerization of an intermediate acyclic enol phosphotriester in the case of CEP-esters; (b) by decarboxylation of an intermediate β-ketoacid in the case of CAP-esters. Apparently, the exclusive formation of the products of ring-opening in the alcoholyses of CEP–OR is related to the steric demands of both alkyl groups involved in the reaction R and R' as illustrated below.[53] The exclusive formation of the products of ring-opening in the alcoholyses of CAP–OR is closely dependent on the lifetime of the intermediate β-ketoacid. The reactions of several alcohols with CAP–$OCH_3$ in aprotic solvents give small (ca. 10-15%) of dimethylacetoinyl phosphate[57,58] $(CH_3O)_2P(O)(OAcn)$ which must have resulted from the reaction of CAP–$OCH_3$ with methanol formed by transesterification, i.e. by displacement with ring-retention:

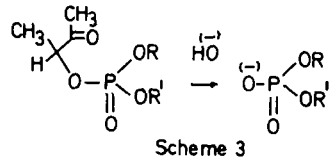
| | | | |
|---|---|---|---|
| Major product: | R'OH + CAP–$OCH_3$ | → | $(R'O)(CH_3O)P(O)(OAcn) + CO_2$ |
| Minor products: | R'OH + CAP–$OCH_3$ | → | $CH_3OH$ + CAP–OR' |
| | $CH_3OH$ + CAP–$OCH_3$ | → | $(CH_3O)_2P(O)(OAcn) + CO_2$ |

The transesterification reaction is eliminated by the presence of catalytic amounts of triethylamine during the alcoholyses of CAP–$OCH_3$,[61] presumably because the amine catalyzes the decarboxylation step, and this interferes with the mechanism of transesterification.[58] This is in accord with the hypothesis of carboxyl-participation *via* a transient 5-membered cyclic acyl phosphate which had been proposed in connection with the mechanism of hydrolyses of esters of phosphoenolpyruvic acid.[62-64] The oxyphosphorane concept provides an adequate interpretation for all of these phenomena.[20,58]



Scheme 2

The acetoinyl group can be removed from the unsymmetrical dialkylacetoinyl phosphates by mild alkaline hydrolysis[54,56] (Scheme 3). There is little, if any, loss of the alkyl groups R or R′ in these hydrolyses.



Scheme 3



CEP–OR and CAP–OR have a preference for the primary alcohol function vs. the secondary alcohol function in diols. The degree of selectivity varies with the structure of the alkyl group, R, and of the alcohol, R′OH, involved in the reaction. Sometimes the selectivity is quite high, ca. 90:10 primary-OH vs. secondary-OH; however in the examples so far studied involving *esters* of the CEP- and CAP-families no exclusive primary-OH vs. secondary-OH phosphorylation of a diol has been achieved.

## MOLECULAR STRUCTURE AND REACTIVITY OF CEP–$OCH_3$ AND CAP–$OCH_3$

X-ray crystallographic analysis shows that the ring in CEP–$OCH_3$[51] (Fig. 1) and in CAP–$OCH_3$[59] (Fig. 2) is essentially planar. In both cases the plane of the ring is perpendicular to a second plane which contains the four-atom system: O(4), P, O(2), C(5) in CEP–$OCH_3$, and O(5), P, O(4), C(12) in CAP–$OCH_3$. In CEP–$OCH_3$ the methoxy group is directed back over the ring but in CAP–$OCH_3$ this orientation is not possible due to steric repulsion between the methoxy group and the methyl group C(13).

Table I shows that in both compounds the 5-membered ring is a highly irregular pentagon and the PO4-group has the geometry of a distorted tetrahedron. Table II suggests that the transformation of CEP–$OCH_3$ and of CAP–$OCH_3$ into oxyphosphoranes (Fig. 3) by addition of the nucleophile ROH to the apical position should be relatively easy. In CEP–$OCH_3$, the deformations in PO4 by contraction of three of the six O–P–O bond angles amount to $(-8°) + (-19°) + (-25°) = -52°$, which represents a net economy of 5° in the overall angle contraction in the actual PO4-geometry, as compared with contractions in the hypothetical regular tetrahedral PO4-group ($-52°$ vs. $-57°$); the deformations by expansion of the remaining three O–P–O bond angles amount to $+11° + 3° + 13° = +27°$, or a net economy of 6° in the overall angle expansion in the

actual vs. the hypothetical PO4-group (27° vs. 33°). In CAP–$OCH_3$ this effect is more significant: (−7°) + (−14°) + (−25°) = −46°, or a net economy of 11° in the overall angle contraction; +5° + 4° + 14° = +23°, or a net economy of 10° in the overall angle expansion.

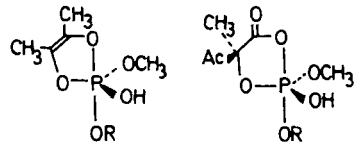


FIGURE 3 Oxyphosphorane intermediates derived from CEP–$OCH_3$ and CAP–$OCH_3$.

While CEP–$OCH_3$ and CAP–$OCH_3$ lose stability, relative to the corresponding compounds in which the phosphorus is not part of the ring, the reverse is true for the oxyphosphoranes which are derived from these cyclic phosphates. There is a great deal of intramolecular crowding in oxyphosphoranes and their stability is markedly increased by the presence of planar rings,[33-36] since the decrease in intramolecular crowding achieved by the ring outweighs the ring-strain associated with bond-angle deformations within the ring. On the other hand ring strain rather than intramolecular crowding is the main factor in determining stability in the phosphates.[24,42-47] Consequently there is both thermodynamic and kinetic advantage in adding oxygen-nucleophiles to CEP–$OCH_3$ and CAP–$OCH_3$ to form oxyphosphoranes.

TABLE I
Some bond angles (°) in CEP–$OCH_3$ and CAP–$OCH_3$

| CEP–$OCH_3$ (Fig. 1) | | CAP–$OCH_3$ (Fig. 2) | |
|---|---|---|---|
| O(3)–P–O(1) | 98.5 | O(3)–P–O(2) | 97.2 |
| P–O(1)–C(1) | 109.8 | P–O(2)–C(8) | 114.0 |
| O(1)–C(1)–C(2) | 110.2 | O(2)–C(8)–C(9) | 105.4 |
| C(1)–C(2)–O(3) | 115.3 | C(8)–C(9)–O(3) | 109.6 |
| C(2)–O(3)–P | 106.2 | C(9)–O(3)–P | 113.0 |
| O(3)–P–O(1) | 98.5 | O(3)–P–O(2) | 97.2 |
| O(1)–P–O(2) | 106.8 | O(2)–P–O(4) | 106.0 |
| O(3)–P–O(2) | 108.9 | O(3)–P–O(4) | 104.2 |
| O(1) P–O(4) | 116.8 | O(2)–P–O(5) | 116.8 |
| O(3)–P–O(4) | 115.6 | O(3)–P–O(5) | 115.2 |
| O(4)–P–O(2) | 109.5 | O(5)–P–O(4) | 115.3 |

An additional factor favoring the addition of nucleophiles to CEP–$OCH_3$ and CAP–$OCH_3$ is the relatively apicophilicity[20,30-32] of the enol-oxygen, and in particular of the acyloxy-ligand, which must appear in the

An additional factor favoring the addition of nucleophiles to CEP–$OCH_3$ and CAP–$OCH_3$ is the relatively strong apicophilicity[20,30-32] of the enol-oxygen, and in particular of the acyloxy-ligand, which must appear in the apical skeletal position of the oxyphosphorane intermediate.

CEP–$OCH_3$ and CAP–$OCH_3$ are indeed strong phosphorylating agents toward alcohols and phenols. The approximate half-life for the reaction of one mol equivalent of methanol with CEP–$OCH_3$ is one minute at 20° in a 0.3M carbon tetrachloride solution. The addition of one mol equivalent of methanol to a 0.1M deuterochloroform solution of CAP–$OCH_3$ results in the complete disappearance of the latter in less than 15 seconds at 24°. An order of magnitude for the relative rates of these phosphorylations can be obtained from the reactions with tert-butyl alcohol; the half-life for the reaction of this alcohol with CEP–$OCH_3$ is ca. 8 days, and with CAP–$OCH_3$ it is only about 3 minutes, both at 24° in 0.1M deuterochloroform.

Steric factors in oxyphosphoranes have another important bearing in the behavior of CEP–$OCH_3$ and CAP–$OCH_3$. The apical positions of the trigonal bipyramid are subject to more steric hindrance than the

equatorial positions. There should be steric advantage in the placement of the relatively less bulky primary alkoxy-group than of the more bulky secondary alkoxy-group at the apex of the oxyphosphorane. Hence the phosphorylation of primary alcohols by these reagents should be favored to a significant degree over that of secondary alcohols.

TABLE II

Deviations in the PO4-group from regular tetrahedron and bond-angle deformations[a] in the conversion of the PO4-group of CEP–$OCH_3$ and CAP–$OCH_3$ into a trigonal bipyramidal oxyphosphorane.

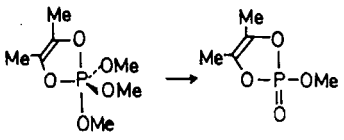
| Bond-angle | Deviation from 109.5° | Deformation (°) |
|---|---|---|
| | CEP–$OCH_3$ (Fig. 1) | |
| O(3)–P–O(1) | –11 | – 8 |
| O(3)–P–O(2) | – 1 | –19 |
| O(3)–P–O(4) | + 6 | –25 |
| O(4)–P–O(2) | 0 | + 11 |
| O(1)–P–O(4) | + 7 | + 3 |
| O(1)–P–O(2) | – 3 | + 13 |
| | CAP–$OCH_3$ (Fig. 2) | |
| O(3)–P–O(2) | –12 | – 7 |
| O(3)–P–O(4) | – 5 | –14 |
| O(3)–P–O(5) | + 6 | –25 |
| O(5)–P–O(4) | + 6 | + 5 |
| O(2)–P–O(5) | + 7 | + 4 |
| O(2)–P–O(4) | – 3 | + 14 |

[a] Three bonds in PO4 contract to 90° and three bonds expand to 120°. Contractions would be: 3 X (–19) = 57°; and expansions would be: 3 X (11) = 33°, from the regular tetrahedral PO4.

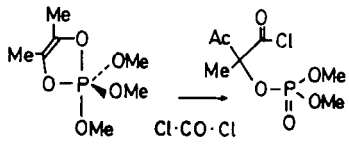


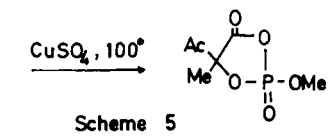
## SYNTHESES OF CEP–$OCH_3$ AND CAP–$OCH_3$

CEP–$OCH_3$ was first prepared in 30% of the theory by hydrolysis of the biacetyl-trimethyl phosphite oxyphosphorane[50] (Scheme 4). A convenient large-scale preparation involves the reaction of the oxyphosphorane with acetyl bromide in acetonitrile solution, which gives crystalline CEP–$OCH_3$ in 90% of the theory.[55]




Scheme 4




Scheme 5

CAP–$OCH_3$ is obtained from the same oxyphosphorane, as shown in Scheme 5.[57-59] First, the oxyphosphorane is allowed to react with phosgene at 0° in hexane or in methylene chloride solution. The resulting α-phosphato-β-ketoacid chloride is then pyrolyzed in the presence of copper sulfate to give the two possible diastereomers of CAPOCH$_3$. The isomer with *cis*-$CH_3$CO/O (Fig. 2) is obtained by crystallization from ether,

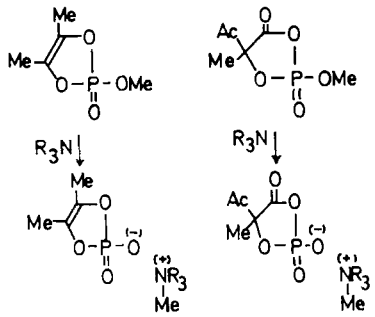
and the mixture of isomers in the mother liquid is re-equilibrated by catalytic amounts of pyridine to produce more *cis*-isomer (ca. 70% of the theory).

The exocyclic O-acylation shown in Scheme 4 and the C-acylation depicted in Scheme 5 illustrate the versatility of the cyclic pentaoxyphosphoranes in organic synthesis.[37]

## CEPO-SALTS AND CAPO-SALTS

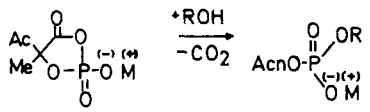
Tertiary amines convert CEP–$OCH_3$ and CAP–$OCH_3$ into the corresponding quaternary ammonium salts of the $CEPO^{(-)}$ and $CAPO^{(-)}$ anions (Scheme 6). These attacks by nitrogen-nucleophiles on carbon contrast with the attacks by oxygen-nucleophiles on phosphorus. However, the stereomutation of the *cis*- and *trans*-$CH_3CO/O$ isomers of CAP–$OCH_3$ brought about by catalytic amounts of pyridine shows that there is a transient and reversible involvement of the nitrogen with the phosphorus in these systems.

The crystalline N-methylpyridinium CEPO-salt is obtained in 87% of the theory when pyridine and CEP–$OCH_3$ are allowed to react in benzene solution at 80°. The non-crystalline and the low-melting CAPO-salts[58,60] made respectively from the reactions of pyridine and of γ-picoline with CAP–$OCH_3$ in benzene or in methylene chloride solution at 25° are obtained in ca. 90% of the theory. These salts are insoluble in benzene, but soluble in methylene chloride. The CAPO-salt from nicotinamide melts at 112-113° and has limited solubility in methylene chloride; it can be made in benzene or in methylene chloride solutions at reflux temperatures. Other CAPO-salts are prepared by similar procedures, and all of them are soluble in pyridine.



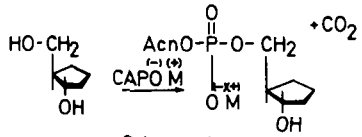
Scheme 6

The CAPO-salts phosphorylate monofunctional alcohols in pyridine or in methylene chloride solutions to give salts of alkylacetoinyl phosphates *via* the β-oxo-butanoic acid intermediates (Scheme 7[60]). Equimolar amounts of the reagents are mixed at 0° in a given solvent and the solution is kept overnight at 25°. The products are isolated in satisfactory yields by evaporation of the solvent and treatment of the residue with benzene, in which the salts are insoluble. Sometimes the salts derived from nicotinamide crystallize from the pyridine solution upon addition of ether.



M=$R_3NMe$; Acn = $(CH_3CO)(CH_3)CH$

Scheme 7

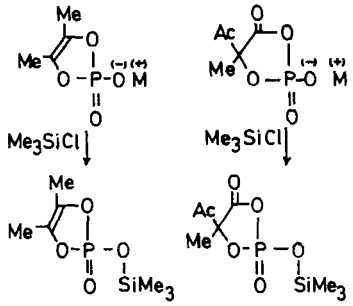


Scheme 8

The CAPO-salts phosphorylate selectively the primary-OH of a diol in the presence of its unprotected secondary-OH (Scheme 8[60]). The reaction is carried in pyridine solution, at −40° with the pyridine-derivative

or at 0° with the nicotinamide-derivative. *Trans*-2-hydroxymethylcyclopentanol is used here as a model for a nucleoside.

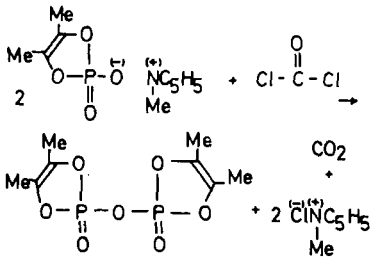
The CAPO-salts cannot, as yet, be used as reagents for the synthesis of phosphomonoesters $(RO)P(O)(OH)_2$ because the acetoinyl group has not so far been removed from alkylacetoinyl phosphodiesters, although this group is easily removed from dialkylacetoinyl phosphotriesters.[54] No work has been reported on phosphorylations with CEPO-salts. The $CEPO^{(-)}$ anion is a more powerful nucleophile than the $CAPO^{(-)}$ anion. Both salts react with trimethylchlorosilane to give the corresponding silyl esters, $CEP{-}OSi(CH_3)_3$[56] and $CAP{-}OSi(CH_3)_3$,[65] in 70% of the theory, the former in benzene suspension at 0°, the latter in methylene chloride solution at 25° (Scheme 9).



Scheme 9

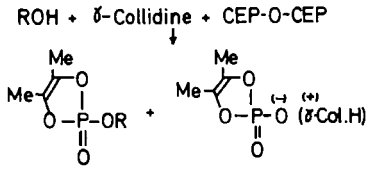
## ACETOINENEDIOLCYCLOPYROPHOSPHATE (CEP–O–CEP)[56]

Scheme 10 illustrates the preparation of the CEP–X reagent in which X is the electron-withdrawing CEPO-group. The crystalline pyrophosphate is obtained in 85% of the theory from the reaction of phosgene with N-methylpyridinium CEPO-salt in benzene at 0°.



Scheme 10

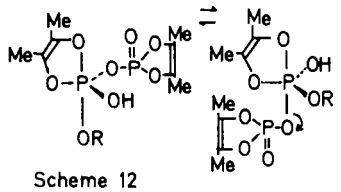
The CEP-pyrophosphate is formed regardless of the mole ratio of the starting materials. Apparently, CEP–O–CO.Cl is formed as an intermediate and reacts with more CEPO-salt in a relatively faster second step. The CEP-pyrophosphate is a convenient reagent for the introduction of the CEP-group into alcohols and phenols ("CEP-ylation"), as shown in Scheme 11. A methylene chloride solution containing equimolar amounts of the alcohol ROH and the base γ-collidine is added to one mol equivalent of the CEP-pyrophosphate in the same solvent at 0°. The reaction is allowed to proceed at 0° for 30-60 minutes, at 20° for 2-3 hours for the more reactive alcohols, and at 0° for 2 hours and 20° for 2-3 hours for the less reactive alcohols and the phenols. The purification of the product is very simple, since ethers dissolve the CEP–OR and CEP–OAr, but not the γ-collidinium CEPO-salt. The latter is not wasted, since it can be reconverted into CEP–O–CEP by techniques analogous to those which convert the N-methylpyridinium CEPO-salt into CEP–O–CEP.




Scheme 11

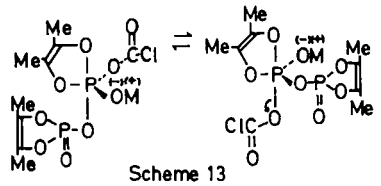
The following CEP–OR have been isolated in 90% of the theory by the reaction of Scheme 11: R=$CH_3$, $C_2H_5$,[66,67] $(CH_3)_2CHCH_2$, $C_6H_5CH_2$, $CH_2BrCH_2$, $CCl_3CH_2$, cyclo-$C_5H_9$, $(CH_3)_2CH$, $(CCl_3)(CH_3)CH$, $(CCl_3)_2CH$, and $(CF_3)_2CH$. Examples of CEP–OAr are those with Ar=$C_6H_5$ and *p*-$NO_2.C_6H_4$.

Evidently the success of this CEP-ylation procedure rests on the much higher phosphorylating power of CEP–O–CEP relative to CEP–OR and the CEPO-anion, as would be expected on the basis of the oxyphosphorane concept. The formation of an oxyphosphorane intermediate by addition of the alcohol to CEP–O–CEP is favored by the electron-withdrawing power of the CEPO-ligand (Scheme 12). Regular PI by the TR-mechanism, with the ring providing the ligand-pair, places the apicophilic CEPO-ligand in an apical skeletal position. The driving force for the displacement with ring-retention is the apical departure of the $CEPO^{(-)}$ anion, which is a better leaving group than the $RO^{(-)}$ anion. The CEPO-departure leads to a more stable product, CEP–OR, than the original CEP–O–CEP.




Scheme 12

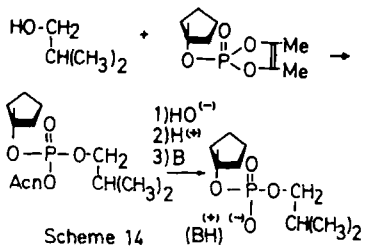
The synthesis of CEP–O–CEP itself is understandable from the oxyphosphorane concept (Scheme 13). The oxyphosphorane intermediate is favored by the two electron-withdrawing ligands; regular PI by the TR-mechanism moves the apicophilic $ClCO_2^-$-ligand to the apex. The driving force for the formation of the high-energy CEP–O–CEP is the loss of $CO_2$ and chloride ion from the intermediate.




Scheme 13

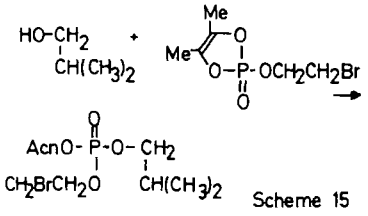
## PHOSPHORYLATIVE COUPLING OF TWO ALCOHOLS BY CEP–O–CEP

The synthesis of an unsymmetrical phosphodiester by means of the CEP-pyrophosphate is illustrated in Scheme 14. Cyclopentanol is first CEP-ylated by the technique described in the previous section. Isobutanol is then added to the CEPO-cyclopentyl in methylene chloride solution at 0°. The reaction is allowed to proceed at 20° for 5 hours, the solvent is evaporated, and the cyclopentylisobutylacetoinyl phosphate is purified by molecular distillation. The CEP-ylation step proceeds in 90%, and the coupling step in 95% of the theory.

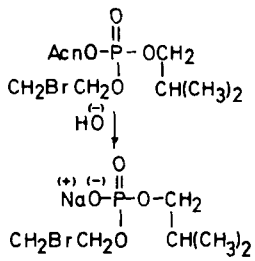


Scheme 14

To remove the acetoinyl group, one mol equivalent of sodium carbonate is added to a solution of the phosphotriester in water: acetonitrile (2:1). The mixture is kept overnight at 20°, and is extracted with methylene chloride. The aqueous solution is acidified, the phosphodiester is extracted into methylene chloride and then converted into the crystalline dicyclohexylammonium salt in ether; the salt is isolated in 88% of the theory. Cyclopentylbenzylacetoinyl phosphate is obtained in 95% of the theory by the same procedure (Scheme 14). The reaction of isobutanol with CEPO-(2-bromoethyl) gives 2-bromoethylisobutylacetoinyl phosphate in 95% of the theory (Scheme 15). The acetoinyl group can be removed from the 2-bromoethylisobutylacetoinyl phosphate without any further effect on the molecule (Scheme 16).



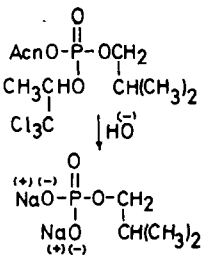
Scheme 15



Scheme 16



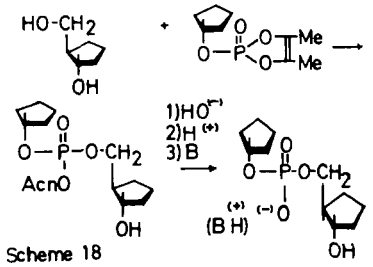
The reaction of isobutanol with CEP–O–(1,1,1-trichloro-2-propyl) yields the corresponding phosphotriester in 95% of the theory (Scheme 17). In this case hydrolysis removes both the acetoinyl and the trichloroisopropyl groups simultaneously with the formation of isobutyl phosphate. A small amount of isobutylacetoinyl phosphate (ca. 10%) is observed as by-product in this hydrolysis; apparently the differences in the rates of hydrolysis of the acetoinyl and the trichloroisopropyl groups from the phospho*triester* is not large enough to prevent the formation of some isobutylacetoinyl phosphate, which as a phospho*diester* is resistant to further hydrolysis.



*Scheme 17*

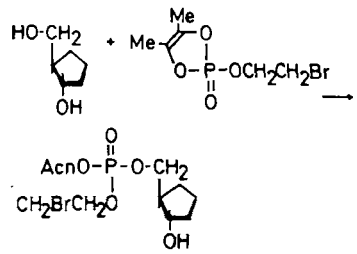
The reaction in Scheme 14 is of the type needed to establish the oligonucleotide bond between the C3′- and C5′-positions of a nucleoside pair. The reactions in Schemes 15, 16 and 17 are of the type needed to achieve the protection-*cum*-phosphorylation of the C5′–OH of a nucleoside in preparation for the synthesis of an oligonucleotide. The model in Scheme 16 permits the removal of one phosphate-blocking group (Acn) in one step, and the removal of another blocking group ($CH_2BrCH_2$) in another step. Work is now in progress to develop reagents to remove the $CH_2BrCH_2$-group from phosphodiesters. The model in Scheme 17 permits the removal of both blocking groups in one operation.

A dinucleotide model is readily synthesized as shown in Scheme 18: CEP–O.cyclo-$C_5H_9$ phosphorylates selectively the primary-OH of *trans*-2-hydroxymethylcyclopentanol in the presence of its unprotected secondary-OH. The proportion of primary-OH vs. secondary-OH phosphorylation is about 90:10 when the reaction is carried out using equimolar amounts of the two reagents in 0.3M methylene chloride solution at 20° for 6 hours. The reaction is not as straightforward as it appears in Scheme 18, since after the disappearance of all the CEP–O.cyclo-$C_5H_9$, in the 1:1 reaction with the diol, there is still some diol present (ca. 5-10%). This could mean that some CEP–O.cyclo-$C_5H_9$ is being diverted into the formation of a *bis*-phosphotriester, probably by reaction with the primary-OH of the product of secondary-OH phosphorylation. It seems less likely that the *bis*-phosphotriester results from further phosphorylation of the secondary-OH of the product of primary-OH phosphorylation. This phenomenon is being studied in detail because it may reflect a hyper-activation of one alcohol function by a phosphate group in the monophosphotriester of a diol, possibly by a hydrogen-bonding type of interaction. The dinucleotide model is obtained after hydrolysis as described above.




Scheme 18

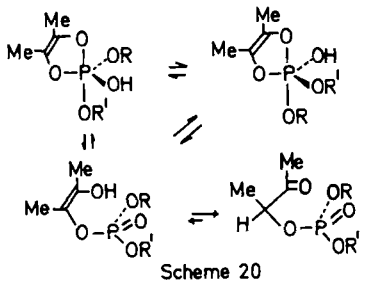
Another example of selective phosphorylation of *trans*-2-hydroxymethyl-cyclopentanol is shown in Scheme 19. The reaction was carried in 0.3M methylene chloride solution with equimolar amounts of the two reagents for 2 hours at 0°, followed by 5 hours at 20°. The results were analogous to those described for the reaction of the diol with CEP–O.cyclo-$C_5H_9$.




Scheme 19

The oxyphosphorane concept accounts for the ring-opening in the reaction of an alcohol R′OH with a CEP–OR, as shown in Scheme 20. Apical entrance of R′OH produces an oxyphosphorane intermediate which collapses to the enol tautomer, and ends as the keto tautomer, before the regular or the irregular PI has produced the second oxyphosphorane with apical-OR. Or if some of the latter is formed it collapses with ring opening before it loses the RO-group. The loss of the RO-group would probably result in the formation

of a symmetrical dialkylacetoinyl phosphate. Apparently the combined bulk of both alkyl groups R and R′ affects the stability of the oxyphosphorane and insures the formation of the unsymmetrical phosphotriester.

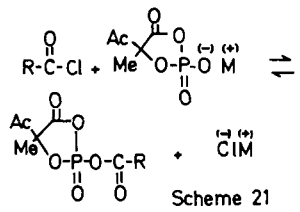


Scheme 20

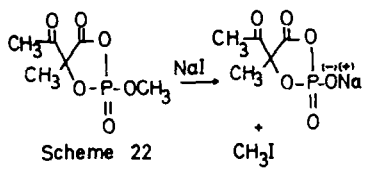
## CAP–X COMPOUNDS

No satisfactory CAP–X reagent, analogous to the CEP–X reagent, has as yet been developed.[68] The reaction of the quaternary ammonium CAPO-salts (Scheme 6) with phosgene, or with oxalyl chloride, is quite complex[61] and does not result in a CAP–O–CAP analogous to the CEP–O–CEP (Scheme 10).

In homogeneous solution, an equilibrium seems to be established between an acyl halide and a CAPO-salt on the one hand and the corresponding acyloxy-CAP and the quaternary ammonium halide on the other hand, with the equilibrium lying far to the left in most cases (Scheme 21). For example, there is no evidence of reaction in a homogenous methylene chloride solution containing equimolar amounts of 3,5-dinitrobenzoyl chloride and the N-methylpyridinium CAPO-salt.[61,68,69] However, the same acyl halide reacts with a suspension of the N-methylnicotinamide CAPO-salt to give some 3,5-dinitrobenzoyloxy-CAP. Apparently, N-methylnicotinamide chloride (MCl in Scheme 21) is less soluble in methylene chloride than N-methylnicotinamide CAPO-salt, and the equilibrium is shifted to the right. An analogous situation appears to be encountered in the reaction of arylsulfonyl halides with the quaternary ammonium CAPO-salts.[61,68,69]



Scheme 21



Scheme 22

A more promising approach to CAP–X reagents utilizes the crystalline sodium CAPO-salts,[69] which are obtained in excellent yield when CAP–$OCH_3$ is treated with sodium iodide in acetone solution[70,71] (Scheme 22).

Research on practical methods of making CAP-reagents is continuing, since the extraordinary reactivity of such compounds is needed in order to phosphorylate certain types of alcohols. The much higher rate of phosphorylation of alcohols with CAP–$OCH_3$ vs. CEP–$OCH_3$, and the extraordinary rate of phosphorylation of alcohols with a CEP–X reagent, which were discussed above, emphasize the potential for phosphorylation of the CAP–X reagents.

## ACKNOWLEDGEMENT

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19. The following abbreviations are used in this paper: P(4), P(5) = four-, five-coordinate phosphorus; PI = permutational isomerization; TR = turnstile rotation; Acn = acetoinyl or $(CH_3CO)(CH_3)CH-$ ; CEP–$OCH_3$ = cycluc enediol phosphoryl–$OCH_3$; CAP–$OCH_3$ = cyclic acyl phosphoryl-$OCH_3$.
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