THE JOURNAL OF Organic Chemistry®

VOLUME 43, NUMBER 19

SEPTEMBER 15, 1978

Crystal and Molecular Structure of Phosphates. 8.[1] The Cyclic Enediol Phosphoimidazole $(C_3H_3N_2)(PO_3)(CH_3C{=}CCH_3)$

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Received January 30, 1978

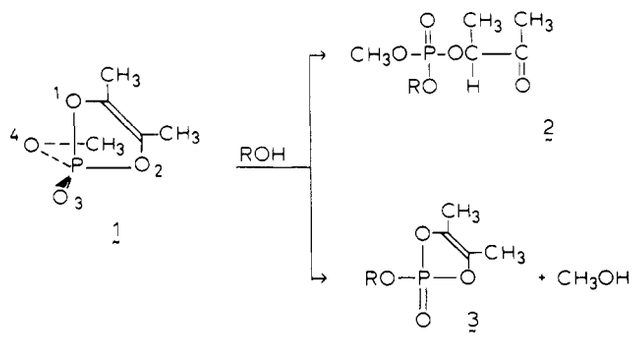
The crystal and molecular structure of *N*-(1,2-dimethylethenylenedioxyphosphoryl)imidazole, a powerful phosphorylating reagent, was solved by X-ray crystallographic methods. The compound crystallizes from benzene in space group $P\bar{1}$ of the triclinic system, with two molecules of the cyclic enediol phosphoimidazole, $C_7H_9O_3N_2P$, and one molecule of benzene in a unit cell of dimensions a = 6.766 (2), b = 7.637 (2), c = 12.125 (5) Å, α = 102.24 (3), β = 100.94 (3), γ = 98.78 (2)°; D_{calcd} = 1.34 g cm^{-3}, D_{meas} = 1.34 (1) g cm^{-3}. Data were obtained on a computer-controlled CAD-4 diffractometer. A multiple-solution direct methods technique was employed, and the structure was refined by full-matrix least-squares methods to a final R value of 4.8% on F based on 1216 independent structure amplitudes. The dioxaphospholene and imidazole rings are planar and orthogonal, with the isolated CH group of imidazole adjacent to the phosphoryl oxygen (P=O). The phospholene ring is an irregular pentagon (endocyclic O–P–O angle = 97.5°). The PO_3N group is a highly distorted tetrahedron with angles ranging from 97.5 to 118.3°. The P–N bond distance is 1.66 Å, and the phosphoryl and ester P–O distances are 1.44 and 1.59 Å, respectively. It is suggested that these departures from the respective pure single bond values reflect the existence of some p–d π bonding in the molecule. The structure and the reactivity of the phosphoimidazole are compared with those of the symmetrical pyrophosphate and the methyl phosphotriester analogues.

The molecular structure of the cyclic enediol phosphotriester 1 (Scheme I; abbreviated as CEP-OCH$_3$[3]) has been determined by X-ray crystallographic methods.[4] The dioxaphospholene ring is planar and orthogonal to another plane which includes the atoms C–O(4)–P–O(3). The methoxy group lies directly above the ring, with the carbon atom approximately centered between the two ring oxygens. CEP-OCH$_3$ reacts with alcohols to give a mixture of products resulting from a displacement at phosphorus with ring opening (acyclic triester **2**) and ring retention (cyclic triester **3**).

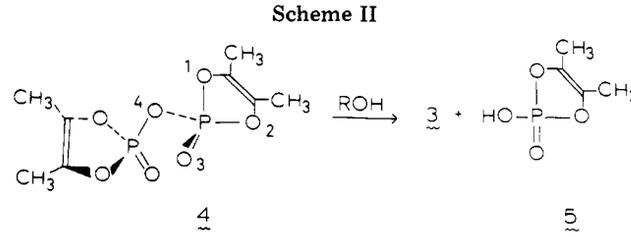
The structure of the cyclic enediol pyrophosphate **4** (Scheme II; CEP-OCEP[3]) has also been solved.[5] There are two independent molecules of the pyrophosphate in the asymmetric unit of the crystal. The two dioxaphospholene rings in both molecules are planar, but the dihedral angles formed by the two planes which contain the respective three-atom systems, O=P–O(4), of the anhydride function differ slightly (69 and 75°, respectively) in the two molecules. CEP-OCEP (**4**) is a powerful phosphorylating reagent,[6] and undergoes displacements at phosphorus with exclusive ring retention, as shown in Scheme II.

Another useful phosphorylating reagent is the cyclic enediol phosphoimidazole[7] **6** (Scheme III; CEP-IM[3]). This compound undergoes very rapid reactions with alcohols, giving exclu-

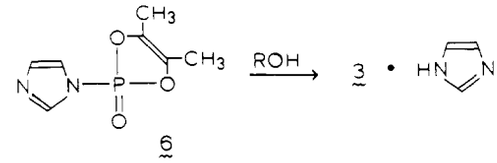
Scheme I



Scheme II



Scheme III



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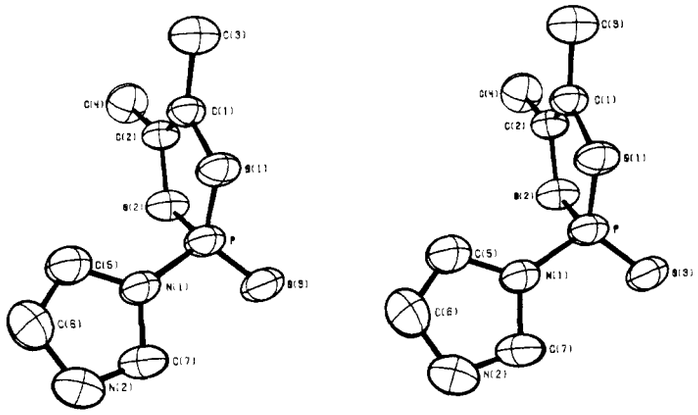


Figure 1. Stereoscopic drawing of one molecule of $C_7H_9O_3N_2P$. The 50% probability ellipsoids are shown. (Hydrogen atoms are omitted for clarity.)

sively the products of displacement with ring retention. This paper describes the crystal and molecular structure of CEP-IM (**6**), and compares the structural features of the three CEP derivatives, **1**, **4**, and **6**. In addition, possible correlations between the structures of the three compounds and their respective modes of reaction are discussed.

The significance of imidazole as a reversible carrier of phosphoryl groups in biochemistry has been recognized for a number of years.[8-10] Several structures pertinent to the present investigation have been elucidated by X-ray crystallographic methods: sodium phosphoramidate,[11] PO_3NH_3Na; phosphocreatine;[12] calcium 1,3-diphosphorylimidazole hexahydrate,[13] $Ca_{1.5}C_3H_3N_2(PO_3)_2{\cdot}6H_2O$; cyclophosphamide hydrate;[14] diphenylphosphinedimethylamide,[15] $(C_6H_5)_2P(O)N(CH_3)_2$; and trichlorobis(diethylphenylphosphine)-(diethylphenylphosphineiminato)ruthenium(IV).[16] The nature of the P–N bond in those compounds, and in other structures with higher P–N bond order, has received considerable attention.[17-21]

Experimental Section

***N*-(1,2-Dimethylethenylenedioxyphosphoryl)imidazole (6).** The compound was prepared as previously described.[7] A sample (0.5–1.0 g) was dissolved in warm benzene (~10 mL) and the solution was diluted with *n*-hexane (~10 mL). Crystals were obtained after 20 h at 5 °C.

Crystal Data. $C_7H_9O_3N_2P{\cdot}\frac{1}{2}C_6H_6$: triclinic; $P\bar{1}$; a = 6.766 (2), b = 7.637 (2), c = 12.125 (5) Å; α = 102.24 (3), β = 100.94 (3), γ = 98.79 (2)°; V = 588.9 (1) Å^3 ($\lambda_{Mo/Zr}$ 0.7107 at 21 °C); Z = 2 (one molecule plus one half of a solvent benzene molecule per asymmetric unit); D_{calcd} = 1.34 g cm^{-3}, D_{meas} (by flotation in cyclohexane–carbon tetrachloride) = 1.34 (1) g cm^{-3}; μ(Mo Kα) = 2.19 cm^{-1}.

Data Collection and Structure Refinement. Precession photographs and subsequent searching of reciprocal space showed the unit cell to be triclinic and of space group $P\bar{1}$. The cell dimensions were determined by a least-squares fit of the observed 2θ angles for 19 reflections centered automatically.

Three-dimensional intensity data were measured on a computer-controlled Enraf Nonius CAD-4 diffractometer using zirconium-filtered Mo Kα radiation with a colorless crystal of dimensions 0.34 × 0.49 × 0.54 mm. The data crystal was moisture sensitive, and was wedged inside a glass capillary tube along the diagonal axis [111], where it remained stable over the course of data collection. Data were collected by θ–2θ scans to 2θ (Mo Kα) = 55°. Absorption corrections were applied to 3758 observations using BNLABS, a local version of ORABS.[22]

The minimum and maximum corrections to F_o^2 were 0.914 and 0.935, respectively. The agreement between symmetry-equivalent intensities was R = 0.025. These intensities were averaged to give 1216 independent structure amplitudes with $F_o^2 > 3\sigma_{count}(F_o^2)$ with $\sigma(F_o^2)$ being based on Poisson counting statistics. The intensities of three standard reflections were measured periodically and were found to have fallen off to approximately 45% of their original values by the end of data collection. The decrease in intensity was uniform over the exposure time and the individual standards were scaled to the zero time standards. Background was measured on one-sixth of total scan width. Normal scans which did not result in sufficiently high precision on net intensity measurements were repeated at a slower speed. The takeoff angle was 5.60° and the diffracted beam was automatically corrected for coincidence losses.

Normalized structure factors (E's) were used in a multiple-solution direct methods technique as described by Germain, Main, and Woolfson[23] to determine phases from which an E map revealed the coordinates of all nonhydrogen atoms.

The structure was refined by full-matrix least squares, minimizing the function $\Sigma w\Delta^2$ with $\Delta = |F_o| - |F_c|$ with weights $w = 4F_o^2/\sigma^2(F_o^2)$ and $\sigma^2(F_o^2) = \sigma_{count}^2(I) + (0.03F^2)^2$. All 12 hydrogen atom positions were located by difference Fourier synthesis using low angle ($\sin\theta/\lambda < 0.35$) data. Atomic scattering factors for all nonhydrogen atoms were taken from a standard source,[24] while that for hydrogen was the best spherically averaged value of Stewart et al.[25]

The final least-squares cycles included anisotropic thermal parameters for the nonhydrogen atoms and individual isotropic thermal parameters on the hydrogen atoms. The final values of $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_2 = \{[\Sigma w||F_o| - |F_c||^2]/\Sigma w|F_o^2|\}^{1/2}$ were 0.048 and 0.047, respectively, and the error in an observation of unit weight was 1.67. The maximum density in a final difference electron density synthesis was 0.23 e Å^{-3}, approximately 45% of the height of a hydrogen atom peak. The final parameters are presented in Tables VA and VB (see paragraph concerning supplementary material at the end of this paper).

Effect of Imidazole on Reactions of Alkyl 1,2-Dimethylethenylene Phosphates with Alcohols. Methyl, 2-methyl-1-propyl, 2-propyl, and cyclopentyl 1,2-dimethylethenylene phosphates (**1**, **3**) were prepared as described.[6a,7] A weighed sample of the CEP-OCH_3 (**1**) or CEP-OR (**3**) was dissolved in $CDCl_3$, and the solution was allowed to reach a constant temperature of 25 °C. An equimolar amount of the alcohol R'OH (and 1 molar equiv of imidazole when indicated) dissolved in $CDCl_3$ was added. The solutions were 0.20 M in cyclic phosphate. The ^{1}H NMR spectrum of the solution was determined immediately and then repeatedly until it became apparent that the thermodynamic mixture of products had been obtained. Analyses of these mixtures of products were performed on a Hewlett Packard 5830A gas chromatograph using $\frac{1}{8}$ in. × 2 ft, 10% Carbowax 20M column (injection temperature, 200 °C; TCD temperature, 200 °C; column temperature, 140–170 °C depending on the compound). The carrier gas was helium at 40 mL/min. The dialkyl 3-oxo-2-butyl phosphates, which are known compounds,[6a,7,26] are stable under the specified conditions. The results of the experiments are summarized in Table V. Further confirmation of the course of the reactions was obtained by ^{31}P NMR measurements (at 40.5 MHz), with the aid of the following data: ^{31}P +11.7 ± 0.7 ppm for CEP-OR, and −2.0 ± 1.0 ppm for (RO)(R'O)P(O)OAcn, in $CDCl_3$ (positive values are downfield from H_3PO_4 = 0).

Discussion of Results

Molecular Structure of the Phosphoimidazole 6. The asymmetric unit of the crystal consists of one molecule of the phosphoimidazole (depicted in Figure 1) and one-half of a molecule of benzene. The contents of the unit cell are displayed in Figure 2. Table I gives the bond distances and angles,

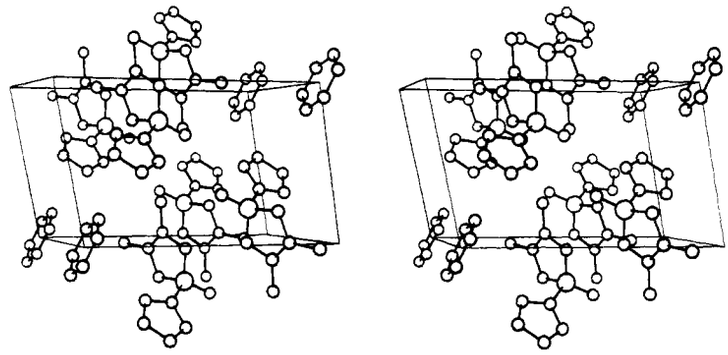


Figure 2. Stereoscopic drawing showing the unit cell contents ($Z = 2$) with all molecules completed. The view is approximately along a, and b is vertical.

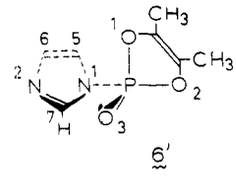
Table I. Bond Distances (Å) and Angles (deg) Involving Nonhydrogen Atoms[a,b]

Distances			
P–N(1)	1.659 (3)	C(1)–C(2)	1.285 (5)
P–O(1)	1.577 (2)	C(1)–C(3)	1.468 (5)
P–O(2)	1.586 (3)	C(2)–C(4)	1.490 (5)
P–O(3)	1.441 (3)	C(5)–C(6)	1.331 (6)
C(1)–O(1)	1.437 (4)	C(B1)–C(B2)	1.351 (7)
C(2)–O(2)	1.424 (4)	C(B2)–C(B3)	1.378 (7)
C(5)–N(1)	1.376 (5)	C(B3)–C(B1′)	1.347 (7)
C(7)–N(1)	1.390 (5)		
C(6)–N(2)	1.383 (6)		
C(7)–N(2)	1.287 (6)		
Angles			
In Cyclic Phosphate			
O(1)–P–O(2)	97.5 (1)	O(1)–C(1)–C(3)	113.7 (4)
O(1)–P–O(3)	117.8 (2)	O(2)–C(2)–C(4)	113.8 (4)
O(2)–P–O(3)	118.3 (2)	C(1)–C(2)–C(4)	133.0 (4)
O(1)–P–N(1)	106.4 (1)	C(2)–C(1)–C(3)	134.6 (4)
O(2)–P–N(1)	104.3 (2)		
O(3)–P–N(1)	110.8 (2)		
P–O(1)–C(1)	109.0 (2)		
P–O(2)–C(2)	108.5 (2)		
O(1)–C(1)–C(2)	111.7 (3)		
O(2)–C(2)–C(1)	113.2 (3)		
In Imidazole			
N(1)–C(7)–N(2)	112.3 (4)	N(2)–C(6)–C(5)	110.8 (4)
C(5)–N(1)–C(7)	104.8 (4)	P–N(1)–C(5)	128.4 (3)
C(6)–N(2)–C(7)	105.1 (4)	P–N(1)–C(7)	126.8 (3)
N(1)–C(5)–C(6)	107.0 (4)		
In Benzene			
C(B1)–C(B2)–C(B3)	119.6 (6)	C(B2)–C(B1)–C(B3′)	121.0 (6)
C(B2)–C(B3)–C(B1′)	119.4 (5)		

[a] Numbers in parentheses here and in succeeding tables are estimated standard deviations in the least significant digits. [b] Bond distances and angles involving hydrogen atoms are included in the supplementary material (Table IB).

and Table II describes several dihedral angles between planes and the best least-squares planes.

The dioxaphospholene ring is a planar and irregular pentagon. The imidazole ring is also planar, and is orthogonal to the dioxaphospholene ring, with the isolated C(7)–H group of imidazole adjacent to the phosphoryl oxygen, P=O (cf. formula 6′). The angles ∠CH_3–C–C (av 134°) and ∠CH_3–C–O



6′

Table II

A. Some Dihedral Angles between Planes Defined by Three Atoms

plane 1	plane 2	angle, deg
N(1), C(5), C(7)	P, O(1), O(2)	86.2 (3)
O(3), P, N(1)	P, N(1), C(7)	8.8 (4)
C(4), C(2), C(1)	C(2), C(1), C(3)	1.7 (9)

B. Equations of Best Least-Squares Planes and Deviations of Individual Atoms from Planarity (Å)

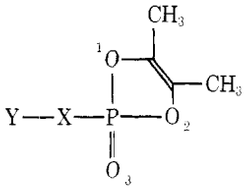
1. P, N(1), C(7), N(2), C(6), C(5)
   $4.883x - 5.592y - 3.125z = 4.672$
   P, 0.000; N(1), 0.006; C(7), 0.000; N(2), −0.002; C(6), −0.004; C(5), 0.000
2. P, O(1), C(1), C(2), O(2), C(3), C(4)
   $3.007x - 0.644y + 9.355z = -3.744$
   P, −0.005; O(1), 0.020; C(1), −0.007; C(2), −0.004; O(2), 0.026; C(3), −0.017; C(4), −0.040
3. O(3), P, N(1), C(7), N(2), C(6), C(5)
   $4.996x - 5.282y - 3.823z = 4.677$
   O(3), 0.084; P, −0.016; N(1), 0.010; C(7), −0.059; N(2), −0.026; C(6), 0.062; C(5), 0.082
4. plane through benzene molecule (three independent atoms)
   $-0.527x - 4.850y + 10.786z = -5.409$
   C(B1), 0.001; C(B2), 0.001; C(B3), 0.001

(av 114°) suggest repulsion between the two methyl groups attached to the sp^2 carbons of the dioxaphospholene ring.

The phosphate group, PO_3N, is a highly distorted tetrahedron as can be seen in Table III, which lists also the corresponding data for the pyrophosphate and phosphotriester analogues, 4 and 1. The most interesting features are the consistently small endocyclic ∠O(1)–P–O(2) angles and the relatively large ∠O(1)–P–O(3) and ∠O(2)–P–O(3) angles. The remaining endo- and exocyclic ∠O(1)–P–X and ∠O(2)–P–X angles and the exocyclic ∠O(3)–P–X angle are relatively closer to the tetrahedral 109.5° value. The net effect of these angle deformations is to displace the dioxaphospholene ring away from the phosphoryl oxygen, O(3), and toward atom X in the three CEP derivatives.

Another noteworthy feature pertains to the P–X bond distances. The P–N bond in the phosphoimidazole is significantly shorter than the P–N bond in phosphocreatine,[12] sodium phosphoramidate[11] (1.77 Å), and calcium 1,3-diphosphorylimidazole[13] (av 1.78 Å), but of about the same length as that in diphenylphosphinedimethylamide[15] (1.68 Å). The shorter bonds possibly reflect some p–d π bonding[21] involving the lone electron pairs on the nitrogen atom and the phosphorus d orbitals. However, the extent of the p–d π bonding appears to be less significant in the phosphoimidazole than in the pyrophosphate[5] and the phosphotriester[4] analogues, since the respective deviations from the P–N and P–O pure single bond distances[19,20] are 6.7, 9.0, and 13%. The anhydride

Table III. Bond Distances and Angles in the PO_3X Group of Cyclic Enediol Phosphoryl Derivatives



atoms[a]	phospho-imidazole[b]	pyrophos-phate[c]	phospho-triester[d]
P-O(1)	1.58	1.58	1.59
P-O(2)	1.59	1.58	1.57
P-O(3)	1.44	1.44	1.38
P-X	1.66[e]	1.60[f]	1.53[f]
O(1)-P-O(2)	97.5	98.4	98.5
O(1)-P-O(3)	117.8	118.7	116.8
O(2)-P-O(3)	118.3	117.4	115.6
O(1)-P-X	106.4	102.4	106.8
O(2)-P-X	104.3	105.4	108.9
O(3)-P-X	110.8	112.4	109.5
P-X-Y	127.6[g]	127.5[h]	122.0[g]

[a] Pure single bond distances: P-O = 1.76 Å, P-N = 1.78 Å, ref 19 and 20. [b] Present work. [c] Reference 5. [d] Reference 4. [e] X = N. [f] X = O. [g] Y = C. [h] Y = P.

P-O(4) bond is somewhat longer than the corresponding ester P-O(4) bond, suggesting relatively less p-d π bonding in the former, since the lone electron pairs on O(4) are sheared by two dioxaphospholene rings in the pyrophosphate.

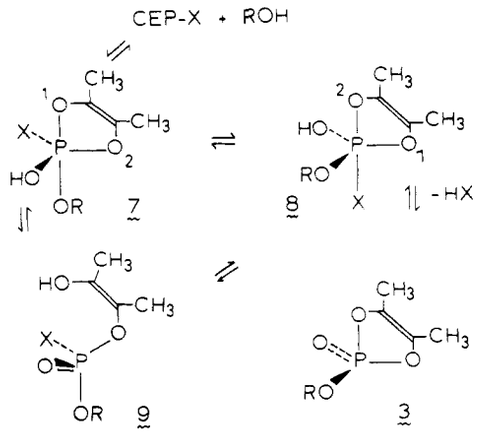
As expected, the P-O(3) bonds are the shortest of their kind in the three CEP derivatives, presumably reflecting the highest extent of p-d π bonding. The endocyclic P-O(1) and P-O(2) bonds are also relatively short, i.e., about 10% less than the pure single bond distance, and this is also consistent with the relatively large $\angle$O(1)-P-O(3) and $\angle$O(2)-P-O(3) angles.

The imidazole ring is a somewhat distorted pentagon. The C(7)-N(2) bond, which is formally double bonded in the heterocycle formula, is significantly shorter than the other three C-N bonds, as would be expected if it had a higher π-bond character. In other features, the ring is unexceptional with respect to unsubstituted[27] and *N,N*-diphosphorylated[13] imidazole.

Ring Retention and Ring Opening in Displacements at Phosphorus in Cyclic Enediol Phosphoryl Derivatives. In reactions with alcohols, the pyrophosphate **4** and the phosphoimidazole **6** give exclusively the product of ring retention at a relatively rapid rate, while the phosphotriester **1** generates mixtures of the products of ring opening and ring retention at a much slower rate. It is apparent from the data in Table III that these differences cannot be attributed to major differences in bond angles and bond distances in the three compounds. A possible mechanism for these phosphorylation reactions is shown in Scheme IV, in terms of the oxyphosphorane intermediate hypothesis[28-31] for displacements at a P(4) center.

The first step of the reaction is the addition of alcohol to P(4) to give the oxyphosphorane **7**; this step may be rate limiting in most, but not necessarily in all, cases.[30b] The formation of **7** involves relatively small additional bond angle deformations beyond those already present in the cyclic phosphate. Cyclic *phosphates*, in general, lose stability relative to the corresponding acyclic compounds mainly as a result of ring strain.[4,31] On the other hand, cyclic *oxyphosphoranes* with small and nearly planar rings gain stability relative to the corresponding acyclic oxyphosphoranes, since there is a great

Scheme IV



deal of intramolecular crowding in P(5) and the decrease in crowding resulting from the introduction of the rings outweighs any ring strain associated with bond angle deformation in P(5).[32] The extraordinary reactivity of the CEP derivatives relative to their acyclic analogues can be reasonably ascribed to these two combined effects, which increase ground state and decrease intermediate state (and presumably the corresponding transition state) energies. These effects are considerably greater in five-membered cyclic unsaturated phosphates[4] than in the corresponding saturated analogues.[31,33-35]

The P(5) intermediate **7** can undergo ring opening before or after undergoing permutational isomerization,[36-38] **7** $\rightleftharpoons$ **8**; the resulting acyclic product **9** is involved in a subsequent enol $\rightleftharpoons$ keto equilibrium, which favors the latter. The isomerization step, **7** $\rightleftharpoons$ **8**, opens a new reaction possibility, namely, the apical departure of ligand X to give the product of ring retention, **3**. These steps are influenced by certain properties of ligands X and OR. The position of equilibrium **7** $\rightleftharpoons$ **8** depends on the relative apicophilicities[37] of X vs. RO. Apicophilicity[37,39] is a function of ligand electronegativity[40] and size. The equatorial and apical positions of P(5) differ in the extent to which the lone electron pairs on the atoms of the ligands which occupy those positions engage in p-d π bonding with the phosphorus d orbitals.[37] There appears to be more back-donation of electrons to the phosphorus d orbitals from an atom in the equatorial position than from the same atom in the apical position. Other things being equal, the higher the electronegativity of a ligand, the higher its apicophilicity, since a relatively electronegative group is better able to support electronic charge, and this is one of the factors required for apical occupancy. The equatorial and apical positions in P(5) differ also in the extent to which the ligands are subject to steric interactions with other ligands. An equatorial ligand encounters only two close 90° interactions, while an apical ligand encounters three such interactions. The 120° interactions among equatorial groups are of less significance. Therefore, other factors being equal, the lower the steric demand of X, the higher its apicophilicity.

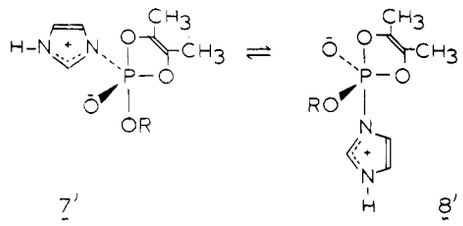
From these considerations, it is reasonable to assume that ligand X = CEPO- in the pyrophosphate **4** is more apicophilic than ligand X = RO- of the triester **1**. This is in line with the stronger acidity of the conjugate acid of the ligands themselves, XH = CEP-OH vs. ROH. Within a series of CEP-OR compounds, this trend in apicophilicity is also noted[7,26] when the alkyl group R contains electron-withdrawing substituents, e.g., $(Cl_3C)_2CH$. With respect to the imidazolyl ligand, it is conceivable that its apicophilicity is influenced by the basic properties of the group. Imidazole itself is relatively basic: $C_3H_3N_2H_2^+ \rightleftharpoons C_3H_3N_2H + H^+$, p$K$ 6.9, and the formation of the zwitterion **7'** depicted in Scheme V is possible in view of

Table IV. Effect of Imidazole on Reactions of Alkyl 1,2-Dimethylethenylene Phosphates with Alcohols, CEP-OR + R'OH → (RO)(R'O)P(O)OAcn[a] + $(RO)_2P(O)OAcn$[b] + $(R'O)_2P(O)OAcn$,[b] in 0.2 M $CDCl_3$ at 25 °C

R	registry no.	R'	registry no.	no catalyst $t_{1/2}$[c]	unsym,[a] %	sym,[b] %	imidazole (1 molar equiv) $t_{1/2}$	unsym, %	sym, %
CH_3	933-43-7	CH_3	67-56-1	25 min		100	fast[d]		100
$(CH_3)_2CHCH_2$	16764-09-3	$(CH_3)_2CHCH_2$	78-83-1	4 h		100	2 min		100
c-C_5H_9	55894-98-9	c-C_6H_9	96-41-3	28 h		100	15 min		100
CH_3		$(CH_3)_2CHCH_2$			54[e]	46		70	30
$(CH_3)_2CHCH_2$		CH_3			83	17		92	8
CH_3		$(CH_3)_2CH$	67-63-0		47	53		69	31
$(CH_3)_2CH$	55894-99-0	CH_3			92	8		98	2
CH_3		c-C_5H_9			46	54		66	34
c-C_5H_9		CH_3			91	9		98	2

[a] Unsymmetrical dialkyl 3-oxo-2-butyl phosphates. [b] Symmetrical dialkyl 3-oxo-2-butyl phosphates. [c] Time at which [CEP-OR] = [$(RO)_2P(O)OAcn$], from ^1H NMR spectra when the reagents are mixed in equimolar amounts; ref 26b. [d] Too fast to measure by the present technique. [e] Data from ref 26a; other data from present investigation.

Scheme V



the expected acidity of the equatorial P(5)–OH group.[30c] In this hypothesis, the protonated imidazolyl ligand becomes a relatively strong apicophile, and the isomerization to 8′ is a favorable process.

The rate of elimination of ligand X from the apical position of the oxyphosphorane 8 depends on the nucleofugicity of X. It would be expected that the CEPO ligand is more nucleofugic than the CH_3O ligand on the basis of the usual arguments derived from considerations of the corresponding acid ionization constants: CEP-OH ⇌ $CEPO^-$ + H^+ ($pK \sim 1.5$) vs. CH_3OH ⇌ CH_3O^- + H^+ ($pK \sim 15$). These eliminations of ligand X from oxyphosphorane 8 compete with the elimination of the enolate ligand, whose nucleofugicity is intermediate between the CEPO and CH_3O ligands. Since imidazole is a very weak acid,[41] $C_3H_3N_2H$ ⇌ $C_3H_3N_2^-$ + H^+ (pK 14.2), it might be construed that the imidazolyl ligand is weakly apicofugic; however, the group that is eliminated from the oxyphosphorane 8′ (Scheme V) is the neutral imidazole and not its conjugate base, which brings the behavior of the phosphoimidazole **6** in line with that of the pyrophosphate **4**.

From the reversibility of the steps in Scheme IV it follows that the observed product distribution in the reactions under thermodynamic control depends on the stabilities of the CEP-X compounds, **1**, **4**, and **6**, and the stabilities of the corresponding cyclic and acyclic products, **3** and **9** (and the keto tautomer), respectively. Our data[7,42,43] are consistent with the following sequences of decreasing energy contents in these compounds: CEP-OCEP > CEP-IM > CEP-OCH_3 ~ CEP-OR; and (CEPO)(OR)P(O)OAcn > (IM)(OR)P(O)OAcn > (CH_3O)(OR)P(O)OAcn. Consequently, one observes exclusively the products of ring retention from the phosphorylation of alcohols by **4** and **6**, while one observes the products of ring opening from the phosphorylation of alcohols by **1**, although in the latter case the appearance of symmetrical acyclic triesters reflects the intermediate formation of some of the product of ring retention as discussed in the following section.

Effect of Imidazole on the Reaction of Cyclic Enediol Phosphotriesters with Alcohols. Imidazole significantly increases the rate of the reaction of alcohols with cyclic phosphotriesters, CEP-OR. This effect is shown in the first three entries of Table IV, which refer to reactions in which the alcohol and the triester contain the same alkyl group.

Table IV includes a series of reactions in which the alkyl groups in the alcohol and the triesters are different. In those cases symmetrical as well as unsymmetrical dialkyl 3-oxo-2-butyl phosphates are produced according to the following equations:

$$\text{CEP-OR} + \text{R'OH} \rightarrow (\text{RO})(\text{R'O})\text{P(O)OAcn} \quad (1)$$

$$\text{CEP-OR} + \text{R'OH} \rightarrow \text{CEP-OR'} + \text{ROH} \quad (2)$$

$$\text{CEP-OR} + \text{ROH} \rightarrow (\text{RO})_2\text{P(O)OAcn} \quad (3)$$

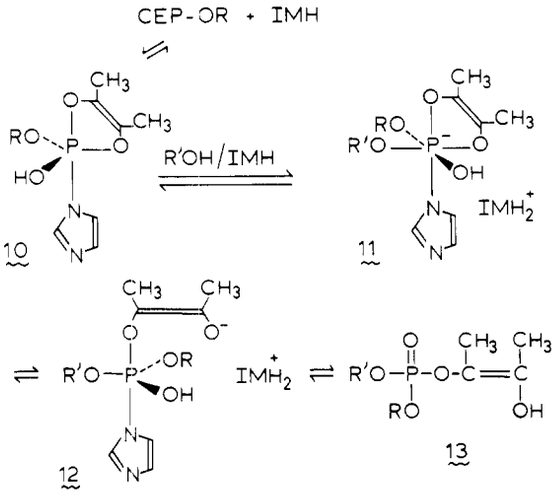
$$\text{CEP-OR'} + \text{R'OH} \rightarrow (\text{R'O})_2\text{P(O)OAcn} \quad (4)$$

Equation 2 corresponds to substitution at phosphorus with ring retention, and the proportion of unsymmetrical to symmetrical triesters reflects the ratio of ring opening to ring retention in these reactions. Several conclusions can be drawn from Table IV.

(a) In the absence of imidazole, the reactions must be under kinetic control, since the proportion of unsymmetrical to symmetrical triesters varies significantly in the pair of reactions CEP-OCH_3 + $(CH_3)_2CHCH_2OH$ and CEP-$OCH_2CH(CH_3)_2$ + CH_3OH. According to Scheme IV, the product composition in both reactions should approach the same value after several cycles of permutational isomerization. Other examples listed in Table IV confirm the generality of this phenomenon. The size of the alkyl group, R, present in the triester, CEP-OR, seems to have the greatest effect on the product composition. When R is relatively small (i.e., CH_3), the amount of symmetrical triester is higher; in fact, the product composition does not vary much in the three reactions of CEP-OCH_3 listed, although the size of the alcohols, R'OH, varies significantly.

(b) Imidazole significantly alters the ratio of the product of ring opening and ring retention in these reactions.[7,26] Further investigation of this phenomenon in the present work confirms its generality. Moreover, in spite of the effects of imidazole on rate and product composition, the heterocycle is not incorporated into the products. A $CDCl_3$ solution containing equimolar amounts of CEP-OR and imidazole is stable for several days[42] (except for a relatively slow demethylation in the case of CEP-OCH_3). Scheme VI provides a reasonable explanation for these observations. In this hypothesis, imidazole adds to the cyclic triester to form the oxyphosphorane **10**; this intermediate is an isomer of 8′ (Scheme V) with a proton in the equatorial oxygen rather than on the apical imidazolyl ligand. For thermodynamic reasons,[42] **10** does not

Scheme VI



undergo further reaction in the absence of alcohols. However, in the presence of alcohols, a P(6) intermediate **11** is generated. This step, P(5) + R'OH ⇌ P(6), could be rate limiting, since the structure of the alcohol has a marked effect on the rate of disappearance of CEP-OR in the reaction CEP-OR + R'OH + [IMH] ⇌ (R'O)(RO)P(O)OAcn. A collapse of the P(6) intermediate (**11**) with ring opening yields a new P(5)' intermediate (**12**) and then the observed acyclic triester (upon enol–keto tautomerization of **13**). The ring-opening step **11** ⇌ **12** accounts for the effect of imidazole on the unsymmetrical/symmetrical triesters shown in Table IV. Other experimental observations in support of the P(6) intermediate hypothesis have been previously offered.[7,26,44,46]

The demonstrated imidazole catalysis of the reaction CEP-OR + R^1OH suggests the possibility that imidazole may also catalyze the reaction CEP-IM (**6**) + ROH ⇌ CEP-OR + IMH; i.e., the latter reaction could be autocatalytic. This deduction is, in fact, supported by observations made on the reaction CEP-IM + $(CH_3)_3COH$ ⇌ CEP-$OC(CH_3)_3$ + IMH.

Conclusions

The X-ray analysis of three CEP-X derivatives discloses similar molecular structures in the crystals, in spite of different behavior in reactions with alcohols. These differences can be rationalized in terms of the oxyphosphorane intermediate hypothesis for displacement at P(4) centers. The new structure of the cyclic enediol phosphoimidazole reveals a relatively small shortening of the P–N bond due, possibly, to a modest participation of p–d π bonding. The orientation of the imidazolyl ring in the conformation of the molecule can be accounted for simply on steric grounds, although more subtle stereoelectronic interactions of the type recently discussed in acyl phosphonates[45] are not ruled out.

Registry No.—**6**, 57648-76-7; imidazole, 288-32-4; $C_7H_9O_3N_2P \cdot \frac{1}{2}C_6H_6$, 67145-87-3.

Supplementary Material Available: Table IB, carbon–hydrogen bond distances (Å) and angles (deg); Table VA, positional and thermal parameters for nonhydrogen atoms; Table VB, calculated hydrogen atom positions (3 pages). Ordering information is given on any current masthead page.

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(3) CEP = cyclic enediol phosphoryl or 1,2-dimethylethenylenedioxyphosphoryl. Acn = 3-oxo-2-butyl. IMH = imidazole. P(4), P(5), P(6) = four-, five-, six-coordinate phosphorus.

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moiety, >P(O)(OAcn), already represents a relatively energy-rich phosphate bond, i.e., an α-ketol or sugarlike phosphate, as shown by the following hydrolysis (see ref 30a): $(CH_3O)_2P(O)(OAcn) + HO^- \rightarrow (CH_3O)_2P(O)O^- + HO{\cdot}Acn$; $k_2 = 360$ L mol^{-1} s^{-1} (25 °C, pH 7.7–8.3). Only 5% of the alternate hydrolysis products are observed: $(CH_3O)P(O)(OAcn)O^- + CH_3OH$ (see ref 43).

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(46) **Note Added in Proof:** It should be emphasized that the P(5) ⇌ P(6) intermediate hypothesis is advanced in connection with reactions of *phosphotriesters* exclusively, and may not be operative in reactions of phosphomonoesters and diesters where other mechanistic alternatives may be favored.

Absolute Configuration of Glycerol Derivatives. 5.[1] Oxprenolol Enantiomers

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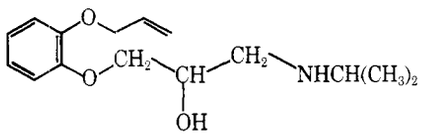
Received April 7, 1978

Synthesis of the optical isomers of oxprenolol [(2*R*)- and (2*S*)-1-(isopropylamino)-3-(*o*-allyloxyphenoxy)-2-propanol ((2*R*)- and (2*S*)-**1**)] was accomplished starting from (2*R*)- and (2*S*)-1-tosyloxypropane-2,3-diol acetonide. Cupra A CD spectra are reported for the intermediate diols [(2*R*)- and (2*S*)-1-(*o*-allyloxyphenoxy)-2,3-propanediol ((2*R*)- and (2*S*)-**3**)] and the oxprenolol isomers. These spectra were consistent with the previous results, allowing assignment of the absolute configuration based on transitions in the 285 nm region. The NMR spectra of the oxprenolol enantiomers (2*R*)- and (2*S*)-**1** in the presence of a chiral shift reagent, Eu(hfbc)$_3$, and of the amides formed from optically active α-methoxy-α-trifluoromethylphenacetyl chloride (Mosher reagent) were examined. The spectra of the diastereoisomeric amides showed upfield shifts of partial resonances for the isopropyl methyl groups, which result from shielding effects of the aromatic ring of the acyl fragment. The assignments were confirmed by use of specifically deuterated oxprenolol amides.

Oxprenolol [3-(*o*-allyloxyphenoxy)-1-(isopropylamino)-2-propanol (**1**)] is an important β-adrenergic blocking agent of the 3-aryloxy-1-(alkylamino)-2-propanol type. Many of the drugs in this class have significant therapeutic utility in a wide variety of cardiovascular disorders.[2] Oxprenolol and others are used extensively in Europe in the treatment of cardiac arrhythmias, angina pectoris, and hypertension.[3] Some of the related compounds have useful effects in other unrelated disease states.[4]



The absolute configuration of β-adrenergic blocking agents of the 3-aryloxy-1-(alkylamino)propanol type is extremely important in the determination of pharmacological properties and metabolic disposition of these agents. Differences in pharmacological activity of the optical isomers in in vitro assays show differences of up to 50–500-fold between individual enantiomers.[5a–c] Differences in rates of uptake into tissues[5d] and in rates of metabolism[5e] of the individual enantiomers are also observed. Previous work has noted a significant difference in the in vitro pharmacological activity (blockade of isoproterenol induced contraction of bronchial muscle) of the resolved enantiomers of oxprenolol of 10–35-fold,[5c] with the (−)-enantiomer being more active. Although the (−)-enantiomer was likely to have the 2*S* absolute configuration, based on the analogy of the sign of optical rotation, compared to other aryloxypropanolamines, the assignment was not unequivocal. Absolute configuration of enantiomers of many of these agents have been assigned on the basis of experience with the Horeau method.[6] Few instances of establishment of absolute configuration by unequivocal means are reported.[7]

We had previously noted that individual enantiomers of the 3-aryloxy-1-amino-2-propanol nucleus of known chirality can readily be prepared from optically active glycerol derivatives of known absolute configuration, which are obtained from naturally occurring mannitol.[7d] This paper reports extension of the use of this method to the oxprenolol isomers. The results of NMR experiments on these enantiomers in the presence of a chiral shift reagent, Eu(hfbc)$_3$, and on the diastereomeric amides prepared using Mosher reagent and the Cupra A CD spectra of the individual enantiomers of oxprenolol and the intermediate diols are reported.

Synthesis

Preparation of (2*R*)- and (2*S*)-oxprenolol [(2*R*)- and (2*S*)-**1**] was accomplished utilizing (2*R*)-3-tosyloxy-1,2-propanediol acetonide [(2*R*)-**2**] and the corresponding (2*S*)-acetonide [(2*S*)-**2**], respectively. Both are derived from (2*S*)-glyceraldehyde 2,3-acetonide,[7d,8] which is readily available from (2*R*,3*S*,4*S*,5*R*)-mannitol 1,2,5,6-diacetonide.[9] The synthesis (Figure 1) of the (2*R*)-oxprenolol [(2*R*)-**1**] was accomplished by allowing catechol monoallyl ether to react with an equimolar quantity of (2*R*)-3-tosyloxy-1,2-propanediol acetonide [(2*R*)-**2**] and a 1 molar excess of NaOMe (EtOH–H_2O). The resulting intermediate (2*R*)-3-(*o*-allyloxyphenoxy)-1,2-propanediol acetonide was hydrolyzed to afford the corresponding (2*R*)-diol [(2*R*)-**3**]. Diol (2*R*)-**3** was converted to its monotosylate [(2*S*)-**4**][10] using an equimolar quantity of tosyl chloride in pyridine–benzene. Epoxide formation from tosylate (2*S*)-**4** was effected using an equimolar quantity of NaOMe in aqueous MeOH, affording (2*R*)-3-(*o*-allyloxyphenoxy)-1,2-epoxypropane [(2*R*)-**5**].[10] Ring opening with isopropylamine at 110 °C gave the desired (2*R*)-oxprenolol [(2*R*)-**1**]. The synthesis of the (2*S*)-oxprenolol [(2*S*)-**1**] was achieved in an analogous fashion starting with (2*S*)-1-tosyloxy-2,3-propandediol acetonide [(2*S*)-**2**].

The magnitude of the optical rotations of the synthesized enantiomers were very similar to that reported for one of the enantiomers prepared by resolution,[5c] $[\alpha]_D$ +5.4 and −5.7° compared to $[\alpha]_D$ +5.5 ± 0.5°, suggesting that the synthetic processes occur without major racemization. Since none of the reaction steps involve a chiral center, major epimerization would not be expected.

0022-3263/78/1943-3641$01.00/0