

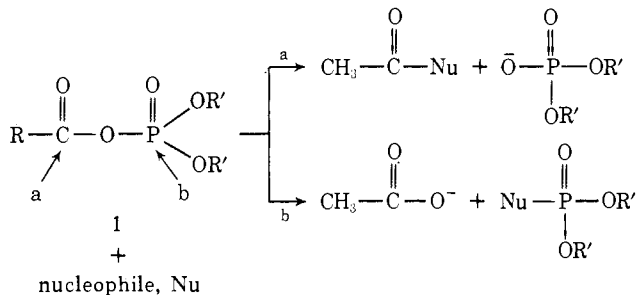
The Crystal and Molecular Structure of a Five-Membered Cyclic Acyl Phosphate ($\text{PO}_4\text{C}_6\text{H}_9\text{O}_2$)

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Abstract: The crystal and molecular structure of the first reported example of a five-membered cyclic acyl phosphate, $\text{PO}_4\text{C}_6\text{H}_9\text{O}_2$, was solved by X-ray crystallographic techniques. This compound crystallizes in space group $P\bar{1}$ with cell dimensions $a = 6.351$ (4) Å, $b = 8.520$ (5) Å, $c = 8.835$ (5) Å, $\alpha = 97.29$ (5)°, $\beta = 105.72$ (6)°, $\gamma = 95.24$ (5)° with $Z = 2$. Counter data were refined by full-matrix least squares to a residual of 4.0%. The five-membered ring is essentially planar, and the slight deviations from planarity approach the half-chair conformation. The phosphoryl oxygen is cis to an acetyl group attached to the ring, and a methoxy ligand to the phosphorus is cis to a methyl group on the ring. The bond distance of the anhydride C=O is relatively short; this, and other features of the molecule, are consistent with the operation of "competing resonance" which would endow the cyclic acyl phosphate with the properties of an energy-rich molecule. The PO_4 group is a distorted tetrahedron with angles ranging from 97.2 to 116.8°. The formation of a trigonal bipyramidal oxyphosphorane intermediate by the addition of nucleophiles to the phosphorus involves relatively small additional bond angle deformations. This factor, together with the relatively strong tendency of the acyloxy ligand to occupy the apical position in the trigonal bipyramid, are suggested as explanations for the extraordinary reactivity of the cyclic acyl phosphate as a phosphorylating agent toward water, alcohols, and phenols.

The importance of acyl phosphates, **1** ($\text{R}' = \text{H}$), in biochemistry has been recognized for some time.²⁻⁵ Acetyl phosphate, **1** ($\text{R} = \text{CH}_3$ and $\text{R}' = \text{H}$), is a high-energy compound^{3a,4b} with a standard free energy of hydrolysis, $-\Delta G^\circ$ (pH 7) = 10.3 kcal/mol, as compared with $-\Delta G^\circ$ (pH 7) = 3.3 kcal/mol for glucose 6-phosphate.



The thermodynamic characterization of a high-energy compound as one for which the negative free energy of hydrolysis under physiological conditions has a relatively large value³ is unequivocal. However, the factors that are responsible for this phenomenon are not clear at present. A widely accepted interpretation⁴ assumes that acyl phosphates are energy-rich compounds in the sense defined above³ due to the destabiliz-

ing influence of the electron-withdrawing phosphate group on the carbonyl function and to the decreased resonance energy of the starting material relative to the hydrolysis products ($\text{Nu} = \text{H}_2\text{O}$). These concepts are reasonable, but their validity cannot be assessed in view of the present lack of information on the molecular structure of acyl phosphates.

The mechanism of reactions of acyl phosphates presents a number of puzzling features. The acyclic acyl dialkyl and acyl aryl phosphates, e.g., $\text{CH}_3\text{COOP}(\text{O})(\text{OCH}_3)_2$ and $\text{CH}_3\text{COOP}(\text{O})(\text{OC}_6\text{H}_5)(\text{OH})$, are capable of acylating (path a) or phosphorylating (path b) various nucleophiles for reasons, and by mechanisms, which are not well understood.⁶⁻⁹

Five-membered cyclic acyl phosphates,¹⁰ which had been postulated as intermediates in the reactions of phosphoenolpyruvate esters,^{11,12} have recently become available.⁵ The crystalline methyl-CAP ester **4** is readily synthesized from the reaction of the oxyphosphorane¹³⁻¹⁵ **2** with phosgene. Two diastereomers, **4a** and **4b**, are formed in this reaction, but their respective configurations are not known with certainty.

The methyl-CAP, **4**, is attacked exclusively at the phosphorus atom by oxygen-containing nucleophiles

(1) (a) Montana State University. We (G. D. S. and C. N. C.) acknowledge support from the National Science Foundation, Grant GP-33538X. We are grateful to Montana State University for a grant of computing time. (b) State University of New York at Stony Brook. We (F. R., S. L. G., P. S.) acknowledge the support of this work by Grant CA-04769 from the Cancer Institute of the NIH and Grant GP-23018 from the National Science Foundation.

(2) The literature has been reviewed in ref 3, 4, and 5.

(3) (a) W. P. Jencks, *Enzymes*, **6**, 339 (1962); (b) W. P. Jencks, "Handbook of Biochemistry," H. Sober, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1968, p J144.

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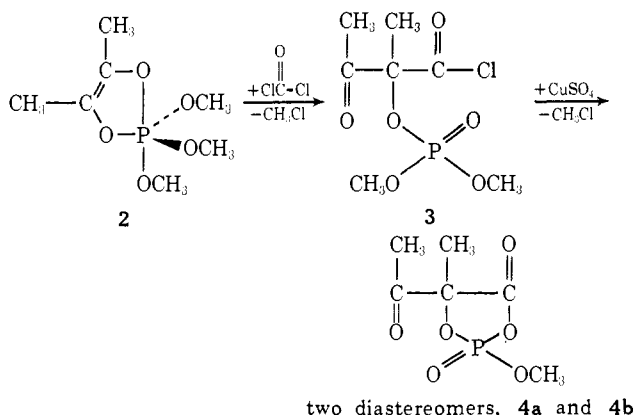
(14) F. Ramirez and I. Ugi, *Advan. Phys. Org. Chem.*, **9**, 25 (1971).

(15) P. Gillespie, F. Ramirez, I. Ugi, and D. Marquarding, *Angew. Chem., Int. Ed. Engl.*, **12**, 91 (1973).

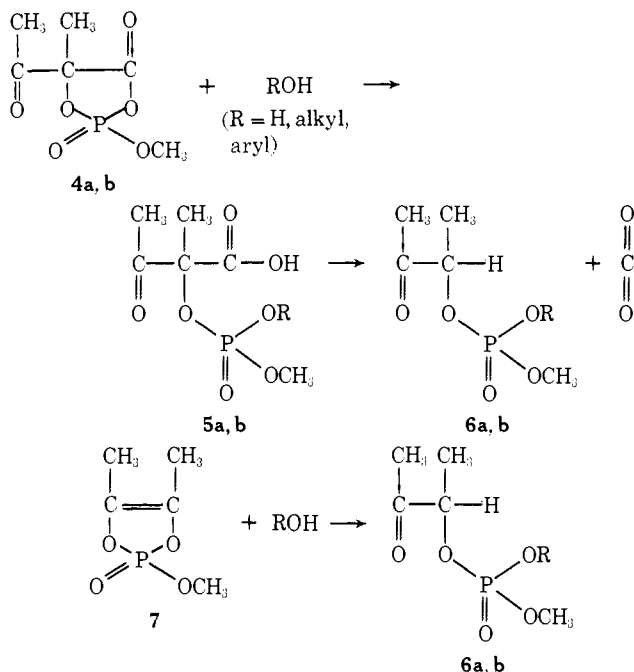
Table I. Spectral Data^a for the Five-Membered Cyclic Acyl Phosphates (**4**) and for an Enediol Cyclophosphate (**7**)

Compd no.	$\delta^{31}\text{P}$	¹ H Nmr signals				Main ir bands, cm ⁻¹
		—Ring substituents— τA	τB	Phosphorus substituent τC	$J_{\text{H-C-O-P}}^c$	
4a^b	-2.4	8.23	7.62	6.02	12.0	1838, 1748, 1445, 1316, 1190, 1136, 1087, 1064, 1010
4b	-2.7	8.13	7.66	6.02	12.0	
7^c	-11.5	8.10	None	6.24	11.5	1316, 1300, 1205, 1190, 1130, 1055

^a ³¹P shifts in ppm vs. H₃PO₄ = 0, in CH₂Cl₂ at 40.5 MHz. ¹H shifts in ppm vs. TMS = 10(τ), J in Hz, in CDCl₃ at 60 MHz. Ir spectrum in CH₂Cl₂. ^b Mp 82–84° (from CH₂Cl₂). ^c Reference 16.



and is, in fact, the most powerful phosphorylating agent known,⁵ even more reactive than the very powerful phosphorylating agent acetoinenediol cyclophosphate (**7**).¹⁶



The exclusive phosphorylation⁵ of oxygen-containing nucleophiles by methyl-CAP, **4** (path b), contrasts with the acylation of the same nucleophiles by six-membered cyclic acyl phosphates¹⁷ (path a). There are in fact striking differences between these two types of compounds.

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(17) J. F. Maracek and D. L. Griffith, *J. Amer. Chem. Soc.*, **92**, 917 (1970).

This paper describes the crystal and molecular structure of one of the diastereomeric methyl-CAP esters, **4a**. We were particularly interested in the configuration of the molecule. The reactions of alcohols with methyl-CAP, **4a**, are stereospecific,⁵ *i.e.*, they produce only one of the two possible diastereomeric β -keto- α -hydroxyacid phosphates, **5a**; consequently, knowledge of the configuration of the phosphorylating agent is highly desirable. Moreover, we hoped to correlate the extraordinary reactivity and selectivity of methyl-CAP, **4**, to some features of its molecular structure.

Experimental Section

cis-2,4-Dioxo-2-methoxy-*r*-5-acetyl-5-methyl-2,2-dihydro-1,3,2-dioxaphospholane or Cyclic Anhydride of 2-Methylphosphate-2-methyl-3-oxobutanoic Acid (**4a**). The synthesis of methyl-CAP, **4**, and the isolation of the pure crystalline diastereomer, **4a**, were carried out as described;⁵ the spectral data are given in Table I.

X-Ray Crystallographic Data. Methyl-CAP, **4a**, was very sensitive to water vapor, and a crystal of it was sealed inside a Lindemann glass capillary. Since preliminary precession photographs indicated no systematic absences or symmetry elements, the space group was either $P1$ or $P\bar{1}$; the orientation of the Delaunay reduced cell was also determined.

Precise unit cell dimensions were determined by a least-squares fit of 20 independent 2θ values taken on a G.E. XRD-5 manual diffractometer using Mo $K\alpha$ radiation. The results are summarized in Table II. The density of this material was not measured because of its instability.

Table II. Crystal Data PO₄C₆H₉O₂

$a = 6.351$ (4)	$\alpha = 97.29$ (5)
$b = 8.520$ (5)	$\beta = 105.72$ (6)
$c = 8.835$ (5)	$\gamma = 95.24$ (5)
$P\bar{1}$	$Z = 2$
$\rho_c = 1.528$ g cm ⁻³	
$\mu(\text{Mo } K\alpha) = 3.074$ cm ⁻¹	

The crystal used for both the determination of the lattice parameters and the collection of the intensity data was mounted along a^* and bounded by {1·0·0}, {0·1·0}, and {0·0·1}. The dimensions of the crystal, measured as the perpendicular between the above parallel faces, were 1.54 × 0.51 × 0.26 mm, respectively. The intensity data were collected out to a 2θ of 40° using 60-sec θ - 2θ scans at a scan rate of 2° min⁻¹, counting backgrounds for 10 sec on either side of the peak. Three standard reflections were measured every 2 hr and showed no appreciable change throughout the data collection. Attempts were made to extend the data beyond a 2θ of 40°, but the standard reflections began to fall off rather rapidly and in several days the crystal had completely decomposed. A total of 828 reflections was scanned of which 740 were considered observed based on the criteria $I \geq 3\sigma(I)$. The unobserved data were given zero weight and were not used in the refinement. Backgrounds were corrected for counting time and the data were corrected in the normal manner for Lorentz and polarization factors.¹⁸

(18) The computer programs used were the following: NRC-2, data reduction program written by F. R. Ahmed and C. P. Sanderson;

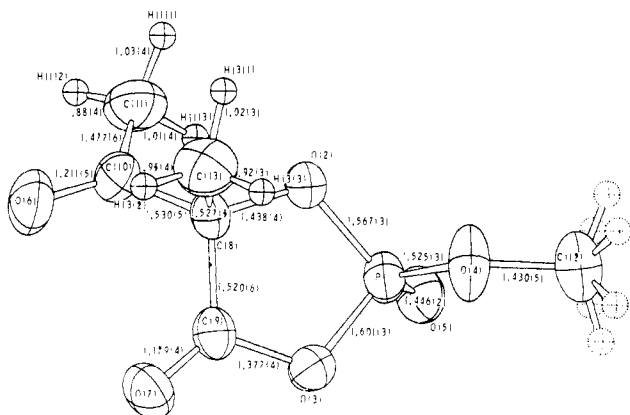


Figure 1. ORTEP drawing of the molecule illustrating bond distances with their standard deviations in parentheses. Thermal ellipsoids have been scaled to include 50% probability; hydrogen atoms have been assigned an isotropic temperature factor of 1.0 for clarity. The disordered hydrogens H12(1-6) are illustrated by dashed lines.

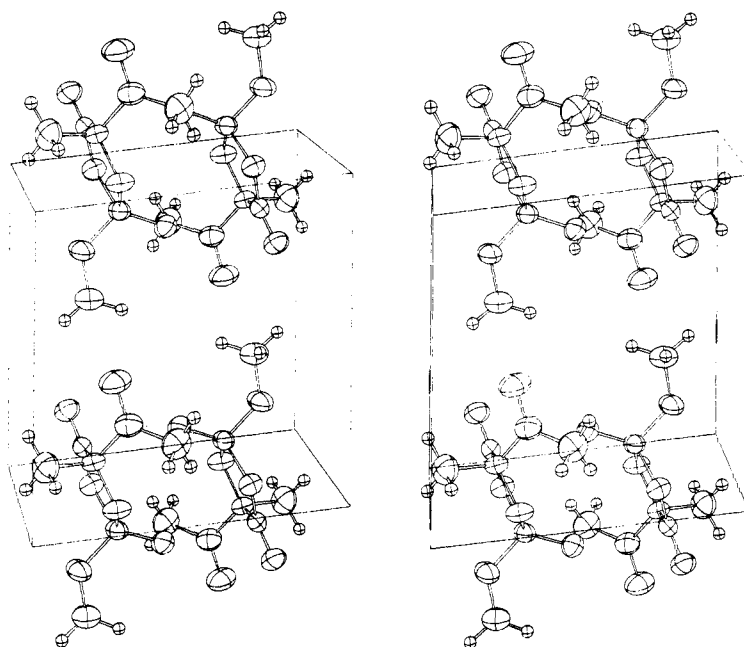


Figure 2. ORTEP drawing illustrating the packing of the molecules in the unit cell. The *c* axis is vertical, the *b* axis is nearly horizontal, while the *a* axis is directed into the plane of the paper. Thermal ellipsoids have been scaled to include 50% probability; hydrogen atoms have been assigned an isotropic temperature factor of 1.0 for the sake of clarity.

A correction for absorption was made using Tompa's method;¹⁹ transmission factors varied from 0.96 to 0.98. The variance of each *F* was calculated by a slight modification of the method of Abrahams.²⁰

$$\sigma^2(F) = (F^2\sigma^2(I)/4I^2) + (F^2\sum k_i^2/4 \times 10^4)$$

$$w(F) = 1/\sigma^2(F)$$

The summation term in this expression was estimated to be 47.3 and included the estimated errors from the following sources: long range instability of the instrument, λ contamination, and errors

NRC-8, Fourier program, written by F. R. Ahmed, National Research Council, Ottawa, Ontario, Canada; ORFLS, the full-matrix least-squares program written by W. R. Busing, K. O. Martin, and H. S. Levy, Oak Ridge National Laboratory, Oak Ridge, Tenn.; and ORTEP, written by C. K. Johnson, Oak Ridge National Laboratories, Oak Ridge, Tenn. These have been adapted for the XDS Sigma-7 computer. The rest of the programs were written by G. D. Smith, E. L. Enwall, and C. N. Caughlan, Montana State University, Bozeman, Mont.

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(20) S. C. Abrahams, *Acta Crystallogr., Sect. A*, **25**, 165 (1969).

in the absorption correction. Atomic scattering factors for non-hydrogen atoms were taken from the International Tables for X-Ray Crystallography;²¹ both real and imaginary terms were applied to phosphorus. The hydrogen scattering factors used were those of Stewart, Davidson, and Simpson.²²

Structure Determination and Refinement. The position of the phosphorus and the four oxygen atoms which are bound to it was located from a three-dimensional Patterson map. It was clear from this map that two phosphate groups were present and were related to each other by a center of symmetry. The space group was thus assumed to be $P\bar{1}$. The positions of these atoms were then refined by full-matrix least squares, minimizing the function $\sum w\Delta F^2$. The subsequent Fourier synthesis revealed the positions of all the rest of the nonhydrogen atoms. Positional parameters and isotropic thermal parameters were then refined to an *R* factor ($R = \sum |F_o - F_c| / \sum |F_o|$) of 10.8%. Further refinement, using anisotropic thermal parameters, reduced the *R* to 7.2%. At this point, a difference Fourier was calculated and showed the positions of the hydrogen atoms on two of the three methyl groups; however, the hydrogen atoms of the third methyl group appeared to be uniformly distributed in a circle around C(12). The positions of six hydrogen atoms were calculated using a carbon-hydrogen bond distance of 1.00 Å and an oxygen-carbon-hydrogen angle of 109.46° such that the hydrogens were related to each other by a

sixfold axis. These disordered hydrogen atoms were assigned an occupation factor of 0.5 and arbitrarily given isotropic temperature factors of 4.0; neither positional nor thermal parameters were refined for these six atoms. The refinement of positional parameters, anisotropic thermal parameters for nonhydrogen atoms, and isotropic temperature factors for the six hydrogen atoms whose positions were located from the difference Fourier reduced the *R* to 4.0%; the largest shift divided by the standard deviation was 0.2 at the end of the refinement. The *R* factor for both the observed data was 5.1% while the weighted *R_w* ($R_w = [\sum w\Delta F^2]^{1/2} / [\sum wF_o^2]^{1/2}$) was 6.3%. *S*, the standard deviation of an observation of unit weight ($S = [\sum w\Delta F^2 / (m - n)]^{1/2}$ where *m* is the number of observations and *n* is the number of parameters), was calculated to be 1.81. A final difference Fourier was calculated and showed no significant peaks in the vicinity of the disordered methyl group; the largest peaks on this map were ± 0.3 e Å⁻³ and were found near the phosphorus atom.

(21) "International Tables for X-Ray Crystallography," Vol. III, Knoch Press, Birmingham, England, 1962, Tables 3.3.1A and 3.3.2C.

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Table III

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
P	0.4313 (1)	0.3159 (1)	0.1017 (1)	0.0235 (5) ^a	0.0116 (2)	0.0085 (2)	-0.0004 (2)	0.0038 (2)	0.0016 (1)
O(2)	0.1981 (4)	0.2897 (3)	-0.0235 (2)	0.0201 (8)	0.0186 (5)	0.0080 (4)	0.0022 (5)	0.0035 (5)	0.0010 (4)
O(3)	0.5643 (4)	0.2442 (3)	-0.0154 (3)	0.0197 (8)	0.0146 (5)	0.0105 (5)	0.0039 (4)	0.0032 (5)	0.0011 (3)
O(4)	0.4247 (5)	0.1913 (3)	0.2105 (3)	0.0501 (12)	0.0141 (5)	0.0084 (5)	-0.0051 (6)	0.0026 (6)	0.0018 (4)
O(5)	0.5145 (4)	0.4773 (2)	0.1822 (3)	0.0297 (10)	0.0113 (4)	0.0118 (5)	-0.0015 (5)	0.0054 (5)	-0.0004 (3)
O(6)	0.0840 (5)	0.2668 (3)	-0.4412 (3)	0.0391 (12)	0.0246 (6)	0.0097 (5)	0.0080 (6)	0.0020 (6)	0.0006 (4)
O(7)	0.5087 (4)	0.1544 (3)	-0.2743 (3)	0.0320 (11)	0.0163 (5)	0.0126 (5)	0.0054 (5)	0.0096 (6)	0.0012 (4)
C(8)	0.1949 (6)	0.2128 (4)	-0.1789 (4)	0.0218 (14)	0.0129 (6)	0.0073 (6)	0.0017 (7)	0.0042 (7)	0.0003 (5)
C(9)	0.4349 (6)	0.2005 (4)	-0.1705 (4)	0.0259 (14)	0.0091 (6)	0.0094 (7)	0.0011 (7)	0.0046 (8)	0.0020 (5)
C(10)	0.0859 (6)	0.3108 (4)	-0.3050 (5)	0.0211 (13)	0.0164 (7)	0.0100 (8)	-0.0011 (8)	0.0016 (8)	0.0005 (6)
C(11)	-0.0258 (7)	0.4460 (5)	-0.2589 (5)	0.0263 (14)	0.0195 (7)	0.0195 (8)	0.0079 (8)	0.0067 (8)	0.0022 (6)
C(12)	0.4964 (7)	0.2248 (5)	0.3806 (5)	0.0465 (18)	0.0203 (8)	0.0112 (8)	0.0040 (10)	0.0071 (9)	0.0026 (6)
C(13)	0.0641 (7)	0.0463 (4)	-0.2135 (5)	0.0305 (15)	0.0149 (7)	0.0195 (9)	-0.0027 (8)	0.0065 (9)	0.0006 (6)
H13(1)	-0.079 (5)	0.064 (4)	-0.187 (4)	5.9 (8) ^b					
H13(2)	0.061 (6)	-0.009 (4)	-0.315 (5)	9.7 (12)					
H13(3)	0.134 (4)	-0.010 (3)	-0.137 (3)	3.7 (6)					
H11(1)	-0.163 (6)	0.405 (4)	-0.227 (5)	8.3 (10)					
H11(2)	-0.076 (7)	0.493 (4)	-0.342 (4)	7.7 (10)					
H11(3)	0.082 (6)	0.507 (4)	-0.158 (4)	7.7 (10)					
H12(1)	0.366	0.233	0.422	4.0					
H12(2)	0.450	0.328	0.417	4.0					
H12(3)	0.597	0.328	0.415	4.0					
H12(4)	0.661	0.232	0.418	4.0					
H12(5)	0.577	0.137	0.423	4.0					
H12(6)	0.429	0.137	0.425	4.0					

^a The form of the anisotropic temperature factor expression is $\exp(-\sum_{i=1}^3 \sum_{j=1}^3 h_i h_j \beta_{ij})$. ^b Isotropic temperature factors are given for hydrogen atoms.

A $\delta(R)$ probability plot²³ was found to be essentially linear. The equation of the least-squares line through the plot had a slope of 1.61 and an intercept of 0.09. The fact that the slope is greater than one indicates that the standard deviations are underestimated. This is probably due to the fact that a variance was not included in $\sigma^2(F)$ for the anisotropic error.²⁰ In order to obtain this quantity it is necessary to measure intensities of symmetry related reflections which is not possible on a quarter-circle instrument such as the G.E. XRD-5.

Results

The final positional and thermal parameters are listed in Table III.²⁴ Figure 1 is an ORTEP drawing of the molecule and includes the bond distances.

Figure 2 is a stereopair illustrating the packing of the molecules in the unit cell. The closest intermolecular contact is 2.4 Å and occurs between the ketone oxygen, O(6), and the disordered hydrogens of C(12).

The bond angles are listed in Table IV. No angles, or distances, are listed for the disordered hydrogens; the H-C(12)-O(4) angles are 109.5°, while all H-C(12) distances are 1.00 Å.

An examination of Table V indicates that the five-membered ring is essentially planar. The atoms which are farthest from this plane are the sp³ C(8) and the sp² C(9) with distances of -0.043 and 0.048 Å, respectively. The deviations from planarity of the various atoms in the ring may best be described as approaching the half-chair conformation.²⁵ The equation of the least-squares plane for the anhydride O(7) and the five-membered ring is included in Table V; the atom farthest from this plane is C(8) with a distance of 0.060 Å.

The dihedral angle between the plane of the five-membered ring and the plane made up of atoms P, O(4), O(5), and C(12) is 90.9°. The perpendicularity

(23) S. C. Abrahams and E. T. Keve, *Acta Crystallogr., Sect. A*, **27**, 157 (1971).

(24) See paragraph at end of paper regarding supplementary materials.

(25) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 250.

Table IV

O(2)-P-O(3)	97.2 (1)	C(10)-C(11)-H11(1)	110 (2)
O(2)-P-O(4)	106.0 (2)	C(10)-C(11)-H11(2)	109 (3)
O(2)-P-O(5)	116.8 (1)	C(10)-C(11)-H11(3)	105 (2)
O(3)-P-O(4)	104.2 (2)	H11(1)-C(11)-H11(2)	106 (4)
O(3)-P-O(5)	115.2 (1)	H11(1)-C(11)-H11(3)	106 (3)
O(4)-P-O(5)	115.3 (2)	H11(2)-C(11)-H11(3)	121 (4)
P-O(2)-C(8)	114.0 (2)	C(8)-C(13)-H13(1)	104 (2)
P-O(3)-C(9)	113.0 (2)	C(8)-C(13)-H13(2)	112 (2)
P-O(4)-C(12)	124.5 (3)	C(8)-C(13)-H13(3)	107 (2)
O(2)-C(8)-C(9)	105.4 (3)	H13(1)-C(13)-H13(2)	120 (3)
O(2)-C(8)-C(10)	109.8 (3)	H13(1)-C(13)-H13(3)	104 (3)
O(2)-C(8)-C(13)	109.4 (3)	H13(2)-C(13)-H13(3)	108 (3)
C(9)-C(8)-C(10)	112.7 (3)		
C(9)-C(8)-C(13)	110.1 (3)		
C(10)-C(8)-C(13)	109.3 (3)		
O(3)-C(9)-O(7)	122.1 (3)		
O(3)-C(9)-C(8)	109.6 (3)		
O(7)-C(9)-C(8)	128.2 (3)		
O(6)-C(10)-C(8)	117.6 (3)		
O(6)-C(10)-C(11)	122.9 (4)		
C(8)-C(10)-C(11)	119.4 (3)		

of these two planes is not unusual and is also found in acetoinenediol cyclophosphate,^{16b} another five-membered cyclic phosphate with a planar ring. In the latter case, however, the methoxy group is directed back over the ring. This orientation is not possible in methyl-CAP, **4a**, because of steric repulsion between the methoxy group and the methyl group C(13). Nevertheless, it is interesting that the two planes are perpendicular since there is no mandatory steric requirement for it. In fact, molecular models would seem to indicate that there are several orientations which are at least as favorable, sterically, as the one observed.

The dihedral angle between the five-membered ring and the plane consisting of atoms O(6), C(8), C(10), and C(11) was calculated to be 50.4°.

Discussion

X-Ray crystallography proves that the crystalline

Table V. Least-Squares Equations of Planes^a

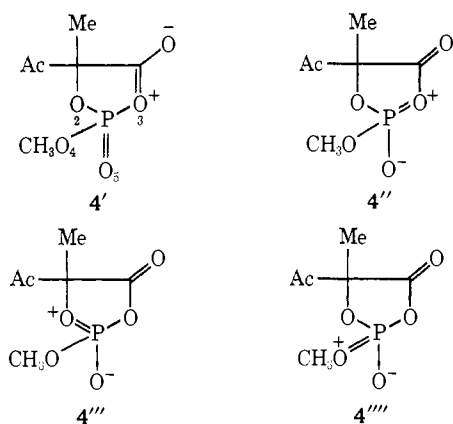
	A	B	C	D	Σ
P, O(2), O(3), C(8), C(9)	0.1448	0.9626	-0.2292	2.574	0.006
P, O(2), O(3), O(7), C(8), C(9)	0.1284	0.9692	-0.2102	2.552	0.011
P, O(4), O(5), C(12)	0.9861	-0.1659	-0.0048	1.789	3 × 10 ⁻⁵
C(8), C(11), C(10), O(6)	0.7927	0.5844	0.1735	2.132	8 × 10 ⁻⁴
O(3), O(7), C(8), C(9)	0.0976	0.9805	-0.1705	2.414	4 × 10 ⁻⁴

^a The equation of the plane is $Ax + By + Cz - D = 0$, where A , B , and C are direction cosines, D is the perpendicular distance from the plane to the origin, and Σ is the sum of the squares of the deviations of the atoms from the least-squares plane. The orthogonal coordinate system from which these values are calculated is defined by x along the a axis, y in the ab plane, and z along the c^* axis.

diastereomer of methyl-CAP, **4a**, which has mp 82–84° and $\delta^{31}\text{P} = -2.4$ ppm, has the phosphoryl oxygen cis to the acetyl group. The trans isomer, **4b**, with $\delta^{31}\text{P} = -2.7$ ppm has, so far, not been obtained in crystalline state. These results confirm the tentative configurational assignments that were made⁵ on the basis of the relative positions of the ¹H nmr signals in the two isomers (Table I).

Several points are worth noting concerning the bond distances shown in Figure 1. The anhydride carbonyl distance C(9)–O(7) is shorter, 1.179(4) Å, than that reported for several γ -lactones: 1.202(3) Å and 1.200(3) Å in 5-hydroxy-2,3-norbornanedicarboxylic acid γ -lactone²⁶ and 1.205(5) Å in 2,3,6-trimethylgalactano- γ -lactone.²⁷ Possibly this is due to the distortion of the angles around the sp^2 -hybridized C(9) which forms part of the ring. Another way of looking at this problem is in terms of "competing resonance"^{4a} as discussed below.

The anhydride P–O(3) bond is longer than the endocyclic ester P–O(2) bond, which is in turn longer than the exocyclic ester P–O(4) bond. This may be attributed to the "competing resonance"^{4a} effect mentioned above in connection with the energy-rich character of the acyl phosphates. Note that four resonance structures, **4'**, **4''**, **4'''**, and **4''''**, can be written for the CAP



molecule **4**; a significant contribution of **4''**, **4'''**, and **4''''** to the hybrid implies a relatively large double-bond character for the anhydride carbonyl C(9)–O(7), which is consistent with the relatively short bond distance and the abnormally high stretching frequency in the infrared found for this group; cf. Table I, $\nu_{\text{C=O}} = 1838 \text{ cm}^{-1}$. Furthermore, the sequence of bond distances, P–O(4) < P–O(2) < P–O(3), could reflect a decreasing double-bond character in those P–O single

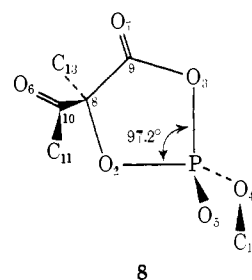
(26) G. Chapuis, A. Zalkin, and D. H. Templeton, *Acta Crystallogr., Sect. B*, **29**, 2642 (1973).

(27) B. Sheldrick, *Acta Crystallogr., Sect. B*, **29**, 2631 (1973).

bonds due to decreasing contributions from resonance forms **4''''** > **4'''** > **4''**. In this interpretation, "competing resonance" results mainly from the relatively small contribution to the resonance hybrid of structures representing the usual carboxylate resonance, **4'**, and, perhaps to a lesser extent, of one of the structures representing phosphate resonance, **4''**. This sort of "competing resonance" is absent in the hydrolysis products of the acyl phosphates, namely, the carboxylic and phosphoric acids, accounting qualitatively for the unusually large free energy of hydrolysis of acyl phosphates.

The sp^3 C–O bonds in methyl-CAP, **4a**, are all of about the same length, and they are slightly longer than the sp^2 C–O bonds, as expected. The C(sp^3)–C(sp^2) single-bond distances show some differences; two of these distances, C(8)–C(10), 1.530(5) Å, and C(8)–C(9), 1.520(6) Å, pertain to a tetrasubstituted tetrahedral carbon and are, as expected, longer than the third distance, C(11)–C(10), 1.477(6) Å.

An examination of the bond angles reveals some interesting features of the methyl-CAP, **4a**, which are best discussed with the aid of formula **8**.



The PO_4 group has the geometry of a distorted tetrahedron, with three angles smaller and three angles larger than that of the regular tetrahedron.

Bond angle	Deviation from 109.5°	Bond angle	Deviation from 109.5°
O(3)–P–O(2)	-12	O(5)–P–O(4)	+6
O(3)–P–O(4)	-5	O(5)–P–O(2)	+7
O(3)–P–O(5)	+6	O(4)–P–O(2)	-3

There is now ample evidence for the hypothesis that nucleophilic displacements at four-coordinate phosphorus occur *via* trigonal bipyramidal five-coordinate phosphorus intermediates.^{14, 15, 28–34} The transforma-

(28) The literature has been reviewed in ref. 14, 15, and 28–33.

(29) W. E. McEwen, *Top. Phosphorus Chem.*, **2**, 1 (1965).

(30) G. Kamai and G. M. Ushcheva, *Russ. Chem. Rev.*, **35**, 601 (1966).

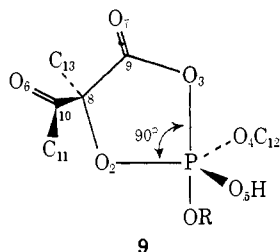
(31) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).

(32) K. Mislow, *Accounts Chem. Res.*, **3**, 321 (1970).

(33) R. F. Hudson and C. Brown, *Accounts Chem. Res.*, **5**, 204 (1972).

(34) W. S. Wadsworth, S. Larsen, and H. Lee Horton, *J. Org. Chem.*, **38**, 256 (1973).

tion of methyl-CAP, **8** (\equiv **4a**), into an oxyphosphorane, **9**, by addition of the nucleophile ROH to the apical position is relatively easy. Three of the bonds must contract to a value of 90° (apical-equatorial angle). If the tetrahedron were regular, this would correspond to an over-all bond-angle contraction of about $3(-19) = -57^\circ$, but from the actual distorted tetrahedron this contraction amounts to only $(-7^\circ) + (-14^\circ) + (-25^\circ) = -46^\circ$, a net economy of 11° in the over-all angle contraction. Moreover, three of the bonds must expand to a value of 120° (diequatorial angle). If the tetrahedron were regular, this would amount to an over-all angle expansion of about $3(11^\circ) = 33^\circ$, but from the actual distorted tetrahedron, it is $+5^\circ + 4^\circ + 14^\circ = +23^\circ$, or a net economy of 10° in the over-all angle expansion.



The angles formed by the phosphoryl oxygen, O(5), the phosphorus, either one of the two endocyclic oxygens, O(3) (anhydride) and O(2) (ester), and the exocyclic oxygen, O(4) (ester), are all larger than the regular tetrahedral angle. On the other hand, the O(4)-P-O(2) angle formed by the two ester-oxygens and the phosphorus is smaller than the regular tetrahedral angle. Most organic phosphates, cyclic or acyclic, exhibit one relatively small O-P-O bond angle.^{35,36}

The five-membered ring in **4a** (\equiv **8**) is a highly irregular pentagon, with the following sequence of bond angles, moving counterclockwise from the endocyclic ester O(2) in formula **8**: 97 , 113 , 109 , 105 , and 114° .

The endocyclic sp^3 carbon, C(8), is a nearly perfect tetrahedron, the only exception being the endocyclic bond O(2)-C(8)-C(9) = 105° .

The bond angles around the anhydride carbonyl agree fairly well with those found in γ -lactones. The angles observed in the cyclic acyl phosphate are C(8)-C(9)-O(3) = $109.6(3)^\circ$; C(8)-C(9)-O(7) = $128.2(3)^\circ$; and O(3)-C(9)-O(7) = $122.1(3)^\circ$. The corresponding angles observed in 5-hydroxy-2,3-norbornanedicarboxylic acid γ -lactone²⁶ (two molecules in the asymmetric unit) are $109.4(2)^\circ$, $109.3(2)^\circ$, $129.2(2)^\circ$, $128.6(2)^\circ$, $121.4(2)^\circ$, and $122.1(2)^\circ$, while those for 2,3,6-trimethylgalactono- γ -lactone²⁷ are $109.8(4)^\circ$, $128.5(5)^\circ$, and $121.6(4)^\circ$.

The bond angles around the anhydride carbonyl vary somewhat from those of the usual sp^2 carbon (120°): C(8)-C(9)-O(3) = 109° ; C(8)-C(9)-O(7) = 128° ;

(35) J. Kraut, *Acta Crystallogr.*, **14**, 1146 (1961).

(36) M. A. Viswamitra, B. S. Reddy, M. N. G. James and G. J. B. Williams, *Acta Crystallogr., Sect. B*, **28**, 1108 (1972).

O(3)-C(9)-O(7) = 122° . On the other hand, the angles around the ketone carbonyl are unexceptional.

The P-O-C bond angles are rather flexible and they vary from 124.5° for P-O(4)-C(12) to 113.0° for P-O(3)-C(9).

In summary, it is suggested that the extraordinary reactivity of methyl-CAP,⁵ **4**, toward oxygen nucleophiles is due to three factors: (1) the strong apicophilicity^{37,38} of the acyloxy ligand; (2) the stability inherent in oxyphosphoranes with a five-membered ring in the apical-equatorial position;^{13,14,38,39} (3) the inherent instability of the methyl-CAP itself. There is a great deal of intramolecular crowding in oxyphosphoranes,^{39,40} and their stability is markedly increased by the presence of four- and five-membered rings, since the decrease in intramolecular crowding in the oxyphosphorane achieved by the ring outweighs the ring strain associated from bond angle deformations within the ring. On the other hand, ring strain rather than intramolecular crowding is the main factor in determining the stability in the tetrahedral or nearly tetrahedral four-coordinate phosphorus compound. A five-membered cyclic phosphate, in particular the cyclic acyl phosphate, **8** (\equiv **4a**), loses stability, relative to the corresponding compounds in which the phosphorus is not part of the ring. There is both thermodynamic and kinetic advantage in adding water, alcohols, or phenols to the acyl phosphate, **8** (\equiv **4a**), in particular since by doing this the strongly apicophilic^{37,38} acyloxy ligand goes apical and the moderately apicophilic oxygen-containing groups also appear apical.

Six-membered rings are less planar than five-membered rings and contribute less to the stabilization of oxyphosphoranes, relative to the acyclic systems. Consequently, the phosphorylating tendency of the six-member cyclic acyl phosphates is less pronounced than that of the five-membered analogs. As the tendency to phosphorylate decreases, the acylation reaction becomes relatively dominant, and this accounts for the behavior of the cyclic^{5,17} and the acyclic^{6,7} families of acyl phosphates.

Supplementary Material Available. A listing of calculated and observed structure factors in electrons will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105×148 nm, $24\times$ reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for \$3.00 for photocopy or \$2.00 for microfiche, referring to code number JACS-74-2698.

(37) Quantum mechanical considerations (ref 38) that take into account d-orbital effects classify the ligands of a given set attached to five-coordinate phosphorus into *apicophilic* and *apicophobic*. In many cases the apicophilic ligands correspond to the most electronegative atoms of the set.

(38) P. Gillespie, P. Hoffmann, H. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E. A. Tsois, and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, **10**, 687 (1971).

(39) I. Ugi and F. Ramirez, *Chem. Brit.*, **8**, 198 (1972).

(40) W. C. Hamilton, S. J. LaPlaca, F. Ramirez, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 2268 (1967).