Pseudo-Rotation in the Hydrolysis of Phosphate Esters

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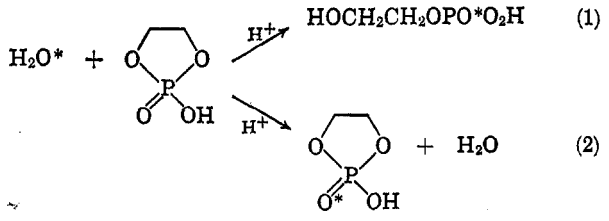
Five-membered esters of phosphoric acid are strained. They hydrolyze millions of times faster than their acyclic analogs, with ring opening and with retention of the ring. However, the phostonate **14** hydrolyzes rapidly but almost exclusively with ring opening, and cyclic phosphinates hydrolyze slowly. These facts have been correlated with the hypothesis that hydrolysis external to the ring proceeds through intermediates that undergo "pseudo-rotation," as shown, for example, in eq 5. Pseudo-rotation occurs subject to the constraints that (a) alkyl groups preferentially occupy equatorial positions and (b) five-membered rings span one equatorial and one apical position in trigonal bipyramids. Thus, the intermediate from a cyclic phosphinate should not form readily, and the phostonate **14** should hydrolyze only with ring opening, as observed. Further, the constraints lead to the prediction as to which oxyphosphoranes can, and which cannot, undergo pseudo-rotation; these predictions have been verified by nmr studies of the appropriate alkyloxyphosphoranes.

I. Introduction

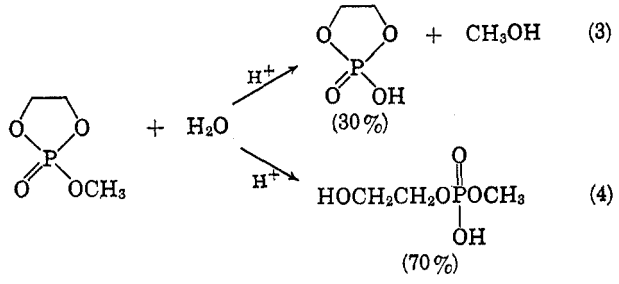
The hydrolyses in acid or base of five-membered cyclic esters of phosphoric acid proceed millions of times faster than those of their acyclic analogs.[1-4] A key finding[5] concerning these processes is that the hydrolysis of hydrogen ethylene phosphate is accompanied by rapid oxygen exchange into unreacted hydrogen ethylene phosphate (eq 1 and 2; the label is of course distributed among the oxygen atoms of the phosphoryl and hydroxyl groups).

Similarly, the hydrolysis of methyl ethylene phos-

(1) J. Kumamoto, J. R. Cox, Jr., and F. H. Westheimer, *J. Am. Chem. Soc.*, **78**, 4858 (1956).
(2) F. Covitz and F. H. Westheimer, *ibid.*, **85**, 1773 (1963).
(3) J. R. Cox, Jr., and B. Ramsay, *Chem. Rev.*, **64**, 317 (1964).
(4) T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms," Vol. 2, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 1–109.
(5) P. C. Haake and F. H. Westheimer, *J. Am. Chem Soc.*, **83**, 1102 (1961).

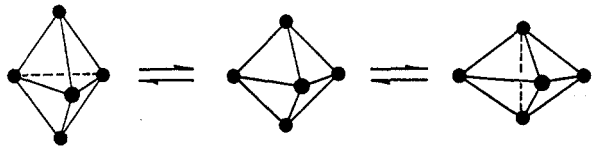


phate (which is analogous to oxygen exchange in hydrogen ethylene phosphate) is accompanied by the rapid hydrolytic cleavage of the methoxyl group;[2] the reaction in acid is one million times faster[6,7] than that for trimethyl phosphate. Although ring strain[8-11]



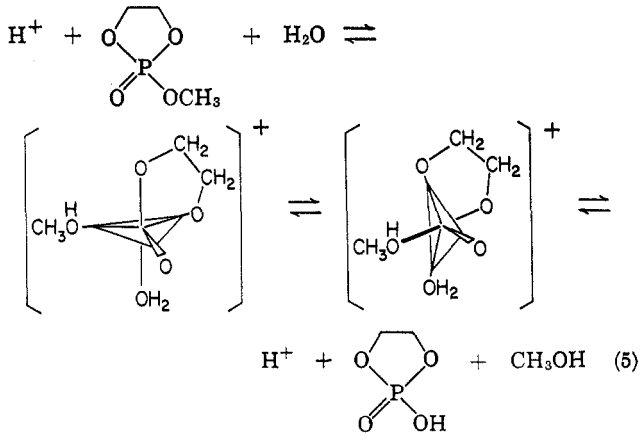
may account for the rapid opening of the ring in cyclic phosphates, the crucial question is how strain (or any feature of the ring structure) can enormously accelerate hydrolysis without ring opening. The answer to this question is predicated on the assumption[7,12-15] that hydrolysis external to the ring proceeds with "pseudo-rotation" between trigonal-bipyramidal intermediates.

Pseudo-rotation for compounds of pentacovalent elements is defined as the intramolecular process where a trigonal-bipyramidal molecule is transformed by deforming bond angles in such a way that it appears to have been rotated by 90° about one of the interatomic bonds. Thus, in the diagram below, the substituent that is toward the viewer remains fixed, while the vertical (apical) substituents are pushed backward and the horizontal (equatorial) substituents pulled forward so as to produce a tetragonal pyramid where the fixed substituent is at the apex. A continuation of the process leads to the second trigonal bipyramid, which appears to have been produced by rotating the first about the bond from the fixed substituent (the "pivot") to the central atom.



In this article, trigonal-bipyramidal molecules are represented by schematic diagrams where the phosphorus atom, which occupies the center of the trigonal bipyramid, is understood but not specifically lettered, and the five bonds to phosphorus are indicated by the usual conventions. The additional triangle is included to mark the equatorial plane and so aid visualization.

Specifically, the pseudo-rotation process that is postulated[7] to accompany the hydrolysis of methyl ethylene phosphate is illustrated in eq 5.



The five-membered ring occupies one apical and one equatorial position in the trigonal-bipyramidal intermediates. Pseudo-rotation takes place between the two bracketed intermediates, about the phosphoryl oxygen atom as pivot; this atom remains equatorial, while the substituents that were equatorial in the first intermediate move (relative to the viewer) somewhat forward to become apical, and the substituents that were apical move somewhat back to become equatorial. Of course the hydrolysis with ring opening does not require pseudo-rotation; it proceeds through an intermediate that resembles the transition state of an SN2 process.

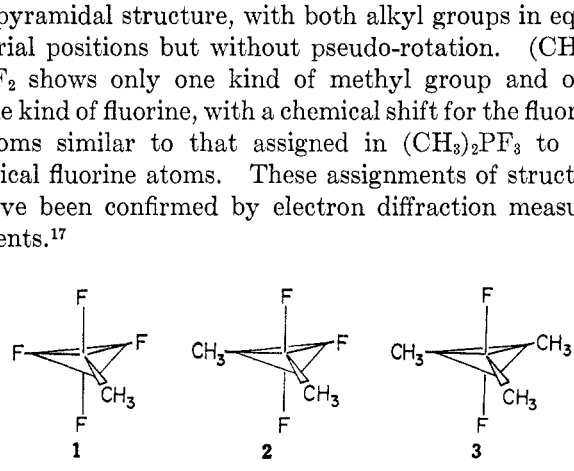
This review presents the evidence supporting the pseudo-rotation mechanism and shows how it will explain both the rapid hydrolysis of ester groups external to certain ring structures and a large body of additional and otherwise puzzling data. Although the hypothesis was originally applied to hydrolyses independently by Hamer[16] to explain his stereochemical results and by Dennis and ourselves[7] to explain kinetic data, this review will depart from historical sequence to present the experiments that support the pseudo-rotation hypothesis in stable pentacovalent phosphorus compounds before returning to a consideration of chemical reactions.

(6) F. Covitz, Ph.D. Thesis, Harvard University, 1965; *Dissertation Abstr.*, **27**, 22918 (1967).
(7) E. A. Dennis and F. H. Westheimer, *J. Am. Chem. Soc.*, **88**, 3432 (1966).
(8) J. R. Cox, Jr., R. E. Wall, and F. H. Westheimer, *Chem. Ind.* (London), 929 (1959).
(9) E. T. Kaiser, M. Panar, and F. H. Westheimer, *J. Am. Chem. Soc.*, **85**, 602 (1963).
(10) F. H. Westheimer, Special Publication No. 8, The Chemical Society, London, 1957, p 1.
(11) D. A. Usher, E. A. Dennis, and F. H. Westheimer, *J. Am. Chem. Soc.*, **87**, 2320 (1965).
(12) E. A. Dennis and F. H. Westheimer, *ibid.*, **88**, 3431 (1966).
(13) D. Gorenstein and F. H. Westheimer, *ibid.*, **89**, 2762 (1967).
(14) R. Kluger, F. Kerst, D. Lee, E. A. Dennis, and F. H. Westheimer, *ibid.*, **89**, 3918 (1967).
(15) R. Kluger, F. Kerst, D. Lee, and F. H. Westheimer, *ibid.*, **89**, 3919 (1967).
(16) N. K. Hamer, *J. Chem. Soc., Sect. B*, 404 (1966).

II. Pseudo-Rotation

a. Alkylfluorophosphoranes. Although electron diffraction[17-19] and other physical measurements[20-22] show that PF_5 is a trigonal bipyramid, only one kind of fluorine can be found in its nmr spectrum.[23] (The signal is a simple doublet, with $J_{P-F} = 1010$ cps.) In 1960 Berry[24] suggested that the nmr results might be explained by postulating that the positions of the fluorine atoms are rapidly equilibrated by pseudo-rotation.[25]

In a subsequent series of investigations, Muetterties and Schmutzler[26-32] examined and interpreted the nmr spectra of a large number of alkylfluorophosphoranes. For example, CH_3PF_4 shows only one kind of fluorine, and again pseudo-rotation can be invoked as the explanation for an interchange of fluorine atoms. However, whereas $(CH_3)_2PF_3$ shows only one kind of methyl group (proton nmr) it has two different kinds of fluorine atoms, in the ratio 2:1. These latter facts can best be rationalized on the basis of a trigonal-bipyramidal structure, with both alkyl groups in equatorial positions but without pseudo-rotation. $(CH_3)_3PF_2$ shows only one kind of methyl group and only one kind of fluorine, with a chemical shift for the fluorine atoms similar to that assigned in $(CH_3)_2PF_3$ to the apical fluorine atoms. These assignments of structure have been confirmed by electron diffraction measurements.[17]



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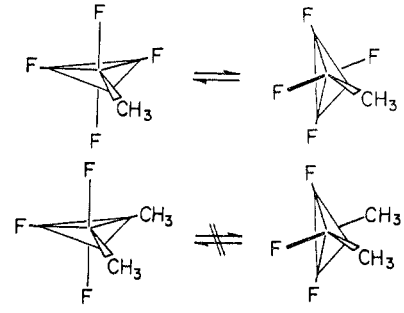
Muetterties and his coworkers have suggested[26] that the more electronegative fluorine atoms preferentially occupy the apical positions, whereas the less electronegative alkyl groups preferentially occupy equatorial positions. This hypothesis can explain the nmr data. In methyltetrafluorophosphorane, pseudo-rotation about the methyl group as pivot will permit this nonpolar group to occupy an equatorial position both before and after the internal transformation. On the other hand, in dialkyl- or trialkylfluorophosphoranes, pseudo-rotation should be inhibited. Only one alkyl group can occupy the pivot position; where the molecule contains two or more, pseudo-rotation necessarily forces a second alkyl group into an apical position; according to Muetterties' hypothesis, such a structure is of higher energy than one where the alkyl groups are all equatorial. Additional data



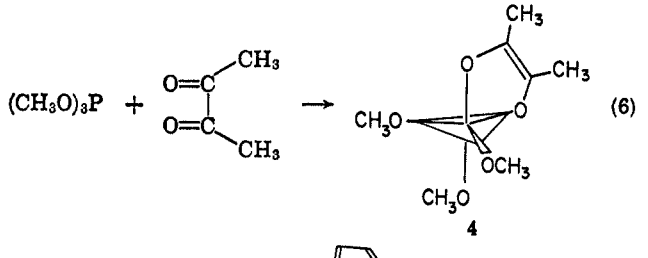
supporting Muetterties' hypothesis comes from the nmr spectrum[33] of H_2PF_3 which, at low temperatures, shows separate signals for apical and equatorial fluorine atoms.[33a] These data are consistent with the assumption that the position of substituents is not a function of their size, but presumably of their polarity.

The theoretical argument[34-37] for placing the more polar substituents in the apical positions is that the p_z and d orbitals are directed in space, and so can provide good overlap with polar atoms that pull electrons away from phosphorus. However, the equatorial sp^2 orbitals (to the extent that they have s character) will bond best with electrons close to phosphorus, *i.e.*, with substituents that are electron donating or at least not electron withdrawing. These arguments are quite general and apply to the trigonal-bipyramidal transition state for displacement reactions at carbon (utilizing only the p_z orbital) as well as to reactions of second row elements.

b. Alkyloxyphosphoranes. A large variety of phosphoranes, including many alkyloxyphosphoranes,[38-41] have been synthesized. In 1958, Birum and Dever[42]

(17) L. S. Bartell and K. W. Hansen, *Inorg. Chem.*, **4**, 1775, 1777 (1965).
(18) L. O. Brockway and J. Y. Beach, *J. Am. Chem. Soc.*, **60**, 1836 (1938).
(19) H. Braune and P. Pinnow, *Z. Physik. Chem.*, **B35**, 239 (1937).
(20) H. S. Gutowsky and A. D. Liehr, *J. Chem. Phys.*, **20**, 1652 (1953).
(21) J. E. Griffiths, R. P. Carter, Jr., and R. R. Holmes, *ibid.*, **41**, 863 (1964).
(22) R. R. Holmes, R. P. Carter, Jr., and G. E. Peterson, *Inorg. Chem.*, **3**, 1748 (1964).
(23) H. S. Gutowsky, D. W. McCall, and C. P. Slichter, *J. Chem. Phys.*, **21**, 279 (1953).
(24) R. S. Berry, *ibid.*, **32**, 933 (1960).
(25) For a differing view, see J. H. Letcher and J. R. Van Wazer, *ibid.*, **45**, 2926 (1966).
(26) E. L. Muetterties, W. Mahler, and R. Schmutzler, *Inorg. Chem.* **2**, 613 (1963).
(27) E. L. Muetterties, W. Mahler, K. J. Packer, and R. Schmutzler, *ibid.*, **3**, 1298 (1964).
(28) E. L. Muetterties and R. A. Schunn, *Quart. Rev.* (London), **20**, 245 (1966).
(29) R. Schmutzler and G. S. Reddy, *Inorg. Chem.*, **4**, 191 (1965).
(30) R. Schmutzler, *J. Am. Chem. Soc.*, **86**, 4500 (1964).
(31) R. Schmutzler, *Angew. Chem. Intern. Ed. Engl.*, **4**, 496 (1965).
(32) R. Schmutzler, *Advan. Fluorine Chem.*, **5**, 31 (1965).
(33) P. M. Treichel, R. A. Goodrich, and S. B. Pierce, *J. Am. Chem. Soc.*, **89**, 2017 (1967).
(33a) S. B. Pierce and C. D. Cornwell have shown by microwave spectroscopy that the hydrogen atom of HPF_4 is equatorial (*J. Chem. Phys.*, in press).
(34) P. C. Van Der Voorn and R. S. Drago, *J. Am. Chem. Soc.*, **88**, 3255 (1966).
(35) H. Bent, *Chem. Rev.*, **61**, 275 (1961).
(36) D. P. Craig, R. S. Nyholm, A. Maccoll, L. E. Orgel, and L. E. Sutton, *J. Chem. Soc.*, 332 (1954).
(37) R. J. Gillespie, *Can. J. Chem.*, **38**, 818 (1960); **39**, 318 (1961); *J. Chem. Soc.*, 4672, 4679 (1963).
(38) L. Anschütz, H. Boedeker, W. Broeker, and F. Wenger, *Ann.*, **454**, 71 (1927).
(39) L. Horner, H. Oediger, and H. Hoffmann, *ibid.*, **626**, 26 (1959).
(40) D. B. Denney and H. M Relles, *J. Am. Chem. Soc.*, **86**, 3897 (1964).
(41) L. D. Quin in "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press Inc., New York, N. Y., 1967, pp 47-96.

and Kukhtin[43] reported a novel method of preparation of an alkoxyphosphorane containing a five-membered ring (eq 6); the chemistry of related compounds has been developed largely by Ramirez and his coworkers.[44-50] (See Quin[41] and Ramirez[49,50] for reviews.)



(6)

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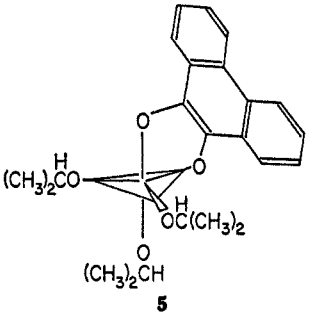
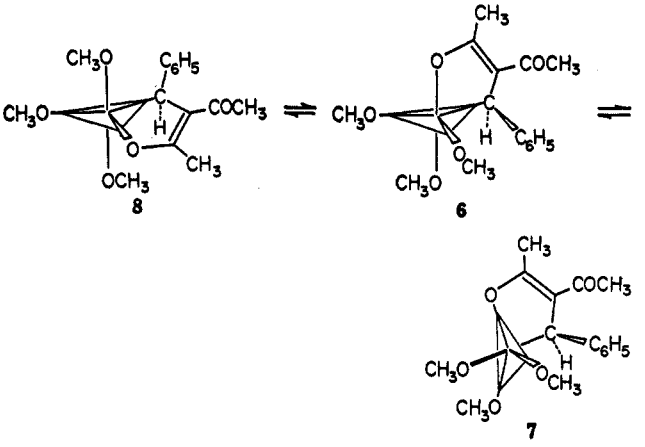


5

The structures of two crystalline modifications of **5** have been determined[51-53] by X-ray crystallography; the five-membered ring spans one apical and one equatorial position in a trigonal bipyramid, and the ring angle at phosphorus is close to 90°. This structure is analogous to that previously suggested[5] for the intermediate in the hydrolysis of phosphate esters on the assumption that the intermediate is a trigonal bipyramid.

The nmr spectrum of **4** shows only one kind of methoxyl group,[48,54] even at −100°. A single methoxyl nmr signal is to be expected if the compound can undergo ready pseudo-rotation, in analogy with PF_5. A better test of the pseudo-rotation hypothesis, however, can be obtained by examining the nmr spectra of alkyl- (or aryl-) oxyphosphoranes. Presumably in these compounds, the more electronegative oxygen atoms preferentially are apical, relegating the alkyl substituents to equatorial positions. Compounds with five-membered rings, however, are more restricted than simple alkylfluorophosphoranes. Consider, for example, compound **6**, where the alkyl group presumably occupies an equatorial position. Pseudo-rotation about either of the equatorial methoxyl groups as pivot would force an alkyl group into an axial position as in **7**, whereas pseudo-rotation about the alkyl group as pivot would place the ring in a diequatorial position as in **8**, with a bond angle at phosphorus of 120°. Such an expansion of the bond angle at phosphorus is accompanied by considerable ring strain[5,11] and is therefore expected to be inhibited. (In the diagram shown, the formula for



8 6

7

8 has been rotated in space in order to clarify the position of the ring.)

When the nmr spectrum of **6** is determined at room temperature[48] it shows only one kind of methoxyl group. However, its spectrum was reexamined[13] (Figure 1) in the light of the theoretical argument reviewed here and found to be temperature dependent. The additional data are consistent with the assumption that, at low temperatures, the molecule is locked into a single trigonal-bipyramidal configuration. All the signals for the methoxyl groups are of course split by phosphorus, with J_{P-H} = 12.4 (average), 10.5 (apical), and 13.5 (equatorial) cps. At low temperatures in deuterioacetone the areas of the peaks for the methoxyl group are 1:2, corresponding to one apical and two equatorial methoxy groups. In deuteriochloroform the peaks for the three methoxyl groups are all separate, as (barring coincidence) they should be because of the asymmetric environment (phenyl *vs.* hydrogen) of the equatorial methoxy groups.

The contrast between the effect of change in temperature on the nmr spectrum of **4** and the effect on that of **6** illustrates the "preference rules" for the structures of phosphoranes.[7,13] These are (a) that the more polar atoms preferentially occupy apical positions and the less polar atoms equatorial positions and (b) that five-membered rings are best placed so as to span one equatorial and one apical position. Rule (a) holds less strictly for phosphoranes substituted with oxygen than for those substituted by fluorine, as might be expected since oxygen is less electronegative than fluorine.

Whereas $(CH_3)_2PF_3$ maintains a single conformation,

(42) G. H. Birum and J. L. Dever, 134th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1958, Abstracts, 101P.
(43) V. A. Kukhtin, *Dokl. Akad. Nauk SSSR*, **121**, 466 (1958); *Chem. Abstr.*, **53**, 11056 (1959).
(44) F. Ramirez and N. Desai, *J. Am. Chem. Soc.*, **82**, 2652 (1960).
(45) F. Ramirez and N. Desai, *ibid.*, **85**, 3252 (1963).
(46) F. Ramirez, A. V. Patwardhan, H. J. Kugler, and C. P. Smith, *Tetrahedron Letters*, 3053 (1966).
(47) F. Ramirez, O. P. Madan, N. B. Desai, S. Meyerson, and E. M. Banas, *J. Am. Chem. Soc.*, **85**, 2681 (1963).
(48) F. Ramirez, O. P. Madan, and S. R. Heller, *ibid.*, **87**, 731 (1965).
(49) F. Ramirez, *Pure Appl. Chem.*, **9**, 337 (1964).
(50) F. Ramirez, *Bull. Soc. Chim. France*, 2443 (1966).
(51) W. C. Hamilton, S. J. LaPlaca, and F. Ramirez, *J. Am. Chem. Soc.*, **87**, 127 (1965).
(52) W. C. Hamilton, S. J. LaPlaca, F. Ramirez, and C. P. Smith, *ibid.*, **89**, 2268 (1967).
(53) R. D. Spratley, W. C. Hamilton, and J. Ladell, *ibid.*, **89**, 2272 (1967).
(54) V. A. Kukhtin, K. M. Kirillova, R. R. Shagidullin, Yu. Yu. Samitov, N. A. Lyazina, and N. F. Rakova, *Zh. Obshch. Khim.*, **32**, 2039 (1962).

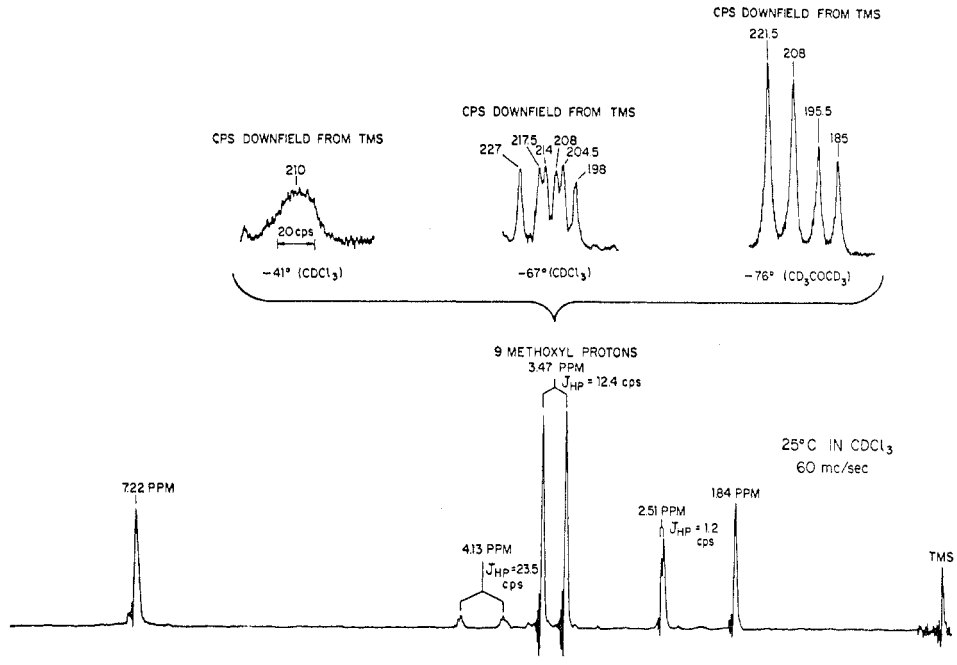
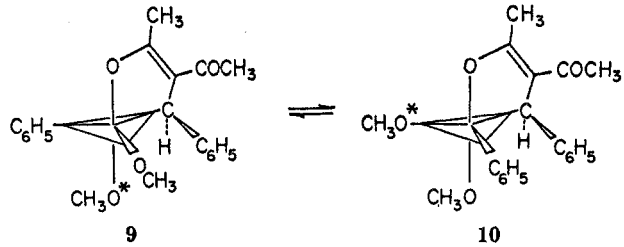


Figure 1. The nmr spectrum of compound **6**. Only the signals from the methoxyl groups are shown at temperatures other than 25°.

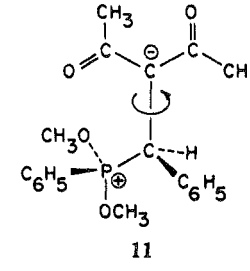
compound **6** presumably can pseudo-rotate at room temperature; its structure is frozen only around −70°. Probably pseudo-rotation to equilibrate the methoxyl groups takes place through **7** as a high-energy intermediate, very much as the interconversion of the two chair conformers of cyclohexane takes place through the boat form as a high-energy intermediate.

The example here cited is one of several that have been examined in our laboratory. Structures **9** and **10** are perhaps of interest.[55,56] If one assumes that the ring angle at phosphorus may not be expanded to 120° and that one may not place the alkyl and aryl groups simultaneously in the two apical positions, then there is only one pathway (with four steps) for pseudo-rotation from **9** to **10**. At low temperatures (−11°) the *cis* and *trans* isomers **9** and **10** are stable and distinguishable, but at +86° they are in rapid equilibrium. Interestingly, the pseudo-rotation mechanism predicts that, even though **9** and **10** are in equilibrium, the starred and unstarred methoxyl groups do not become equivalent. The pertinent ^1H nmr spectra are shown in Figure 2; they are explained in detail elsewhere.[55,56]



9 **10**

Perhaps the most interesting feature of these spectra is that, at high temperatures (156°), the aliphatic



11

methyl groups become equivalent, although the two methoxyl groups do not. This almost certainly results from the thermal opening and closing of the five-membered ring, through the zwitterion **11**. Evidence[46] for this type of ionization[45,54] had previously been advanced; the discovery[55,56] of two separate equilibration processes with the same compound reinforces the interpretation that has been offered for the nmr data and strengthens the case for pseudo-rotation.

c. Other Examples. Other examples of pseudo-rotation in phosphorus compounds are of interest. Wittig and his collaborators[57] introduced the idea of pseudo-rotation to explain the chemistry of pentaarylphosphoranes, and, in a definitive stereochemical study, Hellwinkel[58] substantiated the hypothesis. Katz[59] suggested pseudo-rotation to explain the inversion of 9-phenyl-9-phosphabicyclo[4.2.1]nonatriene.

III. Hydrolysis of Cyclic Phosphates

a. Reaction Rates. Cyclic phosphates were first investigated in derivatives of glycerol[60,61] and in cyclic

(55) D. Gorenstein and F. H. Westheimer, *Proc. Natl. Acad. Sci. U. S.*, **58**, 1747 (1967).
(56) F. Ramirez, J. F. Pilot, O. P. Madan, and C. P. Smith, *J. Am. Chem. Soc.*, **90**, 1275 (1968).
(57) G. Wittig, *Bull. Soc. Chim. France*, 1162 (1966).
(58) D. Hellwinkel, *Ber.*, **99**, 3628, 3660 (1966).
(59) T. J. Katz, C. R. Nicholson, and C. A. Reilly, *J. Am. Chem. Soc.*, **88**, 3832 (1966).
(60) O. Bailly and J. Gaumé, *Bull. Soc. Chim. France*, **2**, 354 (1935).
(61) M. C. Bailly, *Compt. Rend.*, **206**, 1902 (1938); **208**, 443 (1939).

phosphates derived from nucleosides.[62,63] Later the rate differences were put on a semiquantitative basis.[1,3,4,64] Although accurate data at a common temperature are still not available, it appears that the hydrolysis of ethylene phosphate, in acid or base, occurs at phosphorus about 10^8 times faster than does that of dimethyl phosphate.[1,3,5] The rate of hydrolysis of methyl ethylene phosphate[2] exceeds that of trimethyl phosphate by "only" a factor of 10^6. By contrast, the rates of hydrolysis of six-[65] and seven-membered[66,67] cyclic phosphates are more or less normal, *i.e.*, more or less like those of acyclic phosphates.

The reason for the large rate difference has been the subject of much debate, and the rate factors have been compared and contrasted with those for lactones,[68] lactams,[69] cyclic sulfates,[9,70] cyclic sulfites,[71–74] cyclic phosphites,[6] phostones,[75] and sultones.[76] The chief driving force for the rapid reaction is presumably ring strain. The heat of hydrolysis of methyl ethylene phosphate[8,9] exceeds that of dimethyl hydroxyethyl phosphate or of trimethyl phosphate by 5–6 kcal/mole. Similarly, ethylene sulfate liberates 5–6 kcal more heat on hydrolysis than does dimethyl sulfate.[9] The heats of hydrolysis of the cyclic sulfites[71,74] and phosphites[6] are more or less normal and these compounds, in contrast to the sulfates and phosphates, show only modest rate enhancement for cyclic compounds.[71–74] However, no special heat effect has been observed in the opening of the cyclic phosphate of cytosine.[77]

The strain energy of the cyclic phosphates has been estimated[11] by minimizing the energy in the ring with respect to all possible variations in bond angles. The absolute values obtained depend on the values chosen for the bending force constants and are therefore uncertain. However, the bond angles within the ring, calculated for minimum strain, are not sensitive to the choice of force constants and permitted the computation prior to its determination by X-ray crystallography[78] of the ring angle (99°) at phosphorus in methyl ethylene phosphate. The small value of this angle provides independent experimental evidence for ring strain.

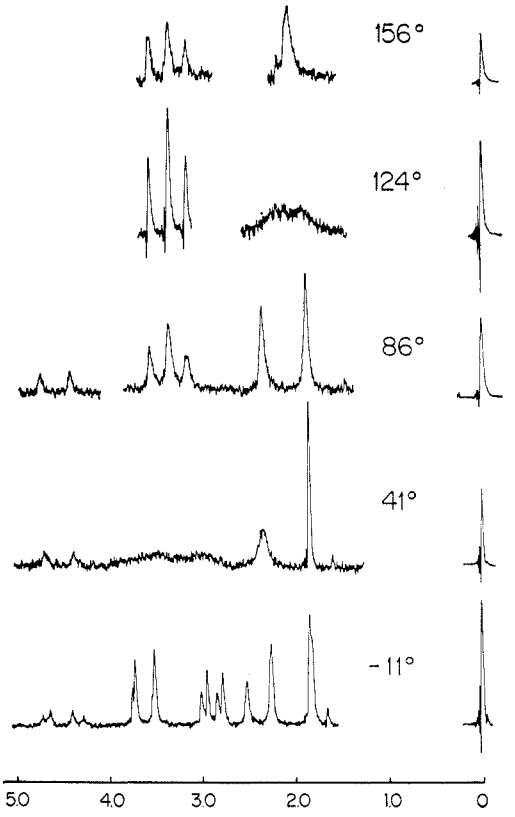


Figure 2. Nmr spectrum at various temperatures of compounds **9** and **10** in bromobenzene as solvent. Tetramethylsilane was used as an internal standard. The aromatic region of the spectrum is obscured by the solvent.

Furthermore, minimization of the strain energy for a possible trigonal-bipyramidal intermediate shows a large decrease in energy on forming the intermediate with a 90° angle at phosphorus (ring in the equatorial–apical conformation) and a large increase in strain energy on forming an intermediate with a 120° angle at phosphorus (ring in diequatorial conformation), regardless of the choice of force constants.

The rate of hydrolysis of methyl ethylene phosphate in base exceeds that of trimethyl phosphate by a factor of about 10^6, corresponding to a difference in free energy of activation of about 8.5 kcal/mole. The difference in energy of activation for these hydrolyses[2] is comparable (about 7.5 kcal/mole), but both figures exceed the thermochemical difference in energy of 5–6 kcal/mole. The latter then provides most, but not all, of the explanation for the rapid reaction of this cyclic phosphate.

b. Hydrolysis *External* to the Ring. As explained in the Introduction, a key finding for the hydrolysis of cyclic phosphates was the rapid oxygen exchange that accompanies the hydrolysis of hydrogen ethylene phosphate[5] (eq 1 and 2). Oxygen exchange proceeds about 20% as fast as does hydrolysis. Since the hydrolysis occurs about 10^8 times faster than that for hydrogen dimethyl phosphate, it follows that the oxygen exchange is about 2×10^7 times faster than the hydrolysis of dimethyl phosphate.

Other examples of rapid hydrolysis where the ring is

(62) R. Markham and J. D. Smith, *Biochem. J.*, **52**, 552 (1952).
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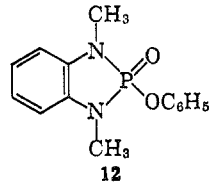
preserved include the hydrolysis of methyl ethylene phosphate[2] (eq 3 and 4), of phenyl ethylene phosphate,[7,12] of the diamidate[79] **12** in base (10^6 times faster than **13**), of methyl pinacol phosphate,[80] and of the methyl ester of the cyclic phosphate of $2\alpha,3\beta,4\beta,5\alpha$-tetramethyl-2,5-dimethoxytetrahydrofuran-3,4-diol.[47]

The rate of hydrolysis of a five-membered phostonate is almost as fast relative to that of its acyclic analog as for the corresponding phosphates. On the other hand, in the one example so far studied[7] (the hydrolysis of the methyl ester of propylphostonic acid (**14**)) the hydrolysis occurs almost exclusively with ring opening, and the rates of hydrolysis[12,81] of simple cyclic phosphinates, such as **15–17**, are not much greater than those of their acyclic analogs, **18–20**.



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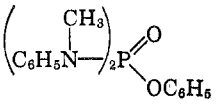

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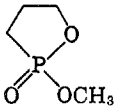

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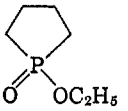

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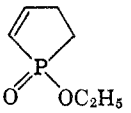

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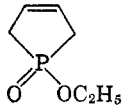

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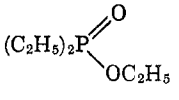

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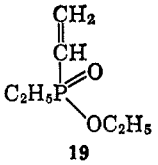

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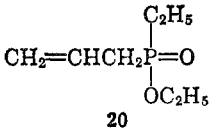

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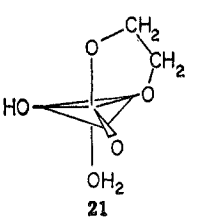
What is the driving force for the hydrolysis *external* to the ring? If ring strain is responsible, how does it cause hydrolysis of a group external to the ring, without ring opening, and why is there no accelerated hydrolysis of ester groups external to the ring in cyclic phosphinates? These are the questions with which this review is primarily concerned.

c. Microscopic Reversibility. When ethylene hydrogen phosphate is subjected to acid hydrolysis or oxygen exchange a water molecule presumably adds to the compound to form a trigonal bipyramid with the ring in one apical and one equatorial position,[5,7,16] to form **21**. Protonation of **21** to yield **22** would provide a good intermediate for ring opening. Protonation of the hydroxyl group, as in **23**, however, does not provide an adequate intermediate for oxygen exchange, since reaction *via* **23** would demand that a water molecule enter a trigonal bipyramid at an apical position and leave from an equatorial one. This sequence would violate the principle of microscopic reversibility.



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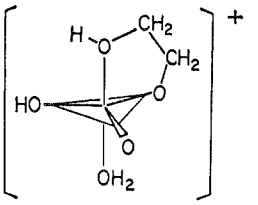

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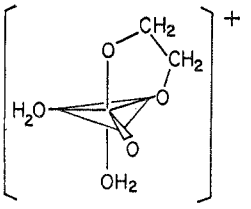

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Several alternative possibilities (other than pseudo-rotation) have been examined to see whether they are microscopically reversible, subject to the following further restraints: (i) a single mechanism should account for the hydrolysis of all the compounds here shown, and (ii) methanol and ethanol are sufficiently similar to water that we are entitled to insist that an alcohol molecule leave an intermediate from a position geometrically analogous to that which water occupies on entering it. At one time the hypothesis was advanced[5] that water molecules might both enter and leave, during ^{18}O exchange into hydrogen ethylene phosphate, from equatorial positions. This sequence will satisfy the requirements of microscopic reversibility but it is inconsistent with the chemistry of **14**. Under the "preference rules," the intermediate from **14** is presumably "frozen" in a trigonal bipyramid where the methylene group of the ring is equatorial and the oxygen atom of the ring is apical. If both entering and leaving groups were necessarily equatorial, then the ring of **14** would not open on hydrolysis. This is contrary to experiment. An additional possibility would allow a water molecule to enter from an apical position and an alcohol molecule to leave by an equatorial position provided that the exact reverse were also allowed, *i.e.*, that a water molecule enter from an equatorial position and an alcohol molecule leave from an apical one. However, this again is inconsistent with the chemistry of **14** (*vide infra*) where hydrolysis occurs only with ring cleavage.

d. Pseudo-Rotation. By contrast, the hypothesis that pseudo-rotation may, and sometimes must, accompany the hydrolysis of phosphate esters is consistent with the data so far known. Furthermore, the hypothesis has predictive value; it led to the discovery of some of the kinetic data and low-temperature nmr results.

e. The Mechanistic Argument for Pseudo-Rotation. The mechanism for the hydrolysis of methyl ethylene phosphate, involving pseudo-rotation (eq 5), provides (i) a pathway where the ring occupies one apical and

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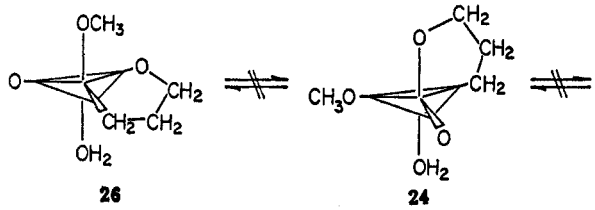
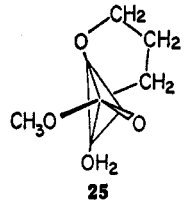
(80) M. G. Newton, J. R. Cox., Jr., and J. A. Bertrand, *J. Am. Chem. Soc.*, **88**, 1503 (1966).
(81) G. Aksnes and K. Bergesen, *Acta Chem. Scand.*, **20**, 2508 (1966).

one equatorial position, (ii) a 90° ring angle, with reduction in strain, for intermediates leading either to ring opening or to hydrolysis external to the ring; the mechanism therefore explains how ring strain can induce rapid reaction external to the ring; and (iii) a mechanism that is consistent with the (expanded) principle of microscopic reversibility. In the symmetrical intermediate or transition state the pivot group presumably occupies the apex of a tetragonal pyramid, and the entering and leaving groups occupy equivalent positions. The mechanism allows the ring to occupy one of the apical positions at all times, while nevertheless one group enters and another leaves from the second apical position.

However, the most rigid test of the hypothesis comes from examining the rates of reaction of the phostonate and phosphinate esters. First, the hypothesis predicts (and explains) the experimental fact that **14** undergoes hydrolysis rapidly with ring opening, but not with loss of the external methoxyl group. Inspection of **24** shows that the trigonal-bipyramidal intermediate cannot readily undergo pseudo-rotation, for pseudo-rotation about the equatorial carbon atom as pivot would expand the ring angle to 120°, whereas pseudo-rotation about either of the other two equatorial substituents as pivot would push the alkyl substituent into an apical position. If the compound cannot readily pseudo-rotate, it cannot place the methoxyl group in an appropriate (*i.e.*, apical) position for a leaving group. In fact, the hydrolysis occurs with >99.8% ring opening and <0.2% exocyclic cleavage.



26 **24**



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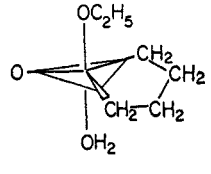
Furthermore, the rate of reaction of the cyclic phosphinates should be low since there is no way to form a trigonal-bipyramidal intermediate of low energy from **15–17**; either the ring angle must be expanded to 120°, as in **27**, or else an alkyl group must replace an oxygen atom in an apical position, as in **28**. Although neither



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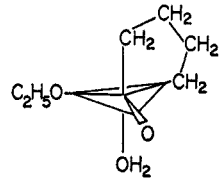

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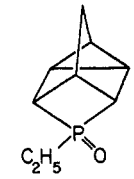
of these intermediates is forbidden, the formation of either will necessarily be accompanied by an increase in energy.

f. Highly Strained Phosphinates. If, however, phosphinates are synthesized with very high strain energy, then the relief of strain in forming a trigonal-bipyramidal intermediate might exceed the barrier to placing an alkyl group in an axial position. A few such highly strained compounds have been prepared and studied. Samuel and Silver[82] have found that oxygen atoms exchange in the phosphoryl group of compound[83] **29**; by contrast, most phosphine oxides undergo exchange sluggishly if at all. Quantitative kinetic data have been obtained for bicyclic compounds with phosphorus at a bridge position. 1-Ethoxyphosphole 1-oxide[84] (**30**) dimerizes[15,85] to **31**, and this can be reduced to **32**; by analogy with bicycloheptene derivatives,[86] the bond angle at the 7 position of the bicyclic system (*i.e.*, at phosphorus) must be constricted. In sharp contrast to the simple cyclic phosphinates, which do not hydrolyze rapidly, the first ester groups of both **31** and **32** are hydrolyzed very rapidly when compared either to the second ester group in the same molecule or to their simple cyclic analogs or to acyclic analogs.



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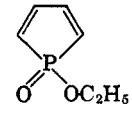

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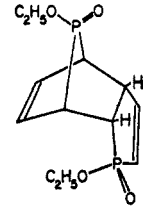

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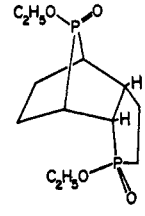

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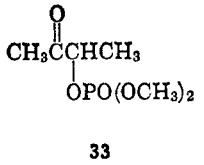
g. Other Systems. Early in 1966, Hamer[16] concluded, from considerations of stereochemistry, that the transition state in the hydrolysis of phosphoramidates resembled that for an SN2 process and tentatively offered the idea of pseudo-rotation to reconcile his results with those for oxygen exchange in hydrogen ethylene phosphate.[5]

Recently Frank and Usher[87] have found that the hydrolysis of **33** proceeds with production of methanol,

(82) D. Samuel and B. L. Silver, *Advan. Phys. Org. Chem.*, **3**, 123 (1965).
(83) M. Green, *Proc. Chem. Soc.*, 177 (1963).
(84) D. A. Usher and F. H. Westheimer, *J. Am. Chem. Soc.*, **86**, 4732 (1964).
(85) The stereochemistry of **31** has been determined by X-ray crystallography (private communication from Y.-Y. Chieu and W. N. Lipscomb).
(86) G. D. Sargent, Ph.D. Thesis, Harvard University, 1963.
(87) D. S. Frank and D A. Usher, *J. Am. Chem. Soc.*, **89**, 6360 (1967).



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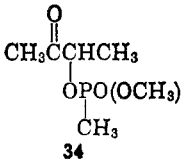

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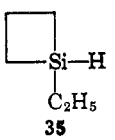
whereas that of **34** proceeds with formation of acetoin and methyl methylphosphonate; they have explained these results by the pseudo-rotation hypothesis and the "preference rules"[7] here reviewed.

Although the pseudo-rotation theory will probably have little application in carbon chemistry (where metastable trigonal-bipyramidal intermediates probably cannot be found), it should prove useful in describing the mechanism, and in predicting the rates, of reactions of second-row and other elements. In particular, the theory probably provides the correct explanation for the rapid hydrolysis of highly strained silicon derivatives[88-90] such as **35** and **36** and may prove relevant to sulfur chemistry.



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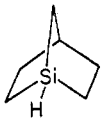

36

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(88) L. H. Sommer, "Stereochemistry, Mechanism and Silicon," McGraw-Hill Book Co., Inc., New York, N. Y., 1965.
(89) L. H. Sommer, O. F. Bennett, P. G. Campbell, and D. R. Weyenberg, *J. Am. Chem. Soc.*, **79**, 3295 (1957).
(90) L. H. Sommer and O. F. Bennett, *ibid.*, **79**, 1008 (1957); L. H. Sommer, W. P. Barie, Jr., and D. R. Weyenberg, *ibid.*, **81**, 251 (1959).

Additions and Corrections

Volume 1, 1968

F. H. Westheimer: Pseudo-Rotation in the Hydrolysis of Phosphate Esters.

Page 77. The sentence beginning on the next to last line should read as follows: Recently Frank and Usher[87] have found that the hydrolysis of **34** proceeds with production of methanol, whereas that of **33** proceeds with formation of acetoin and dimethyl phosphate; they have explained these results by the pseudo-rotation hypothesis and the "preference rules"[7] here reviewed.