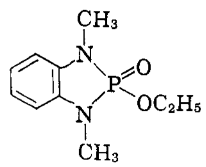
# Communications to the Editor

## The Rates of Hydrolysis of Esters of Cyclic Phosphinic Acids[1]

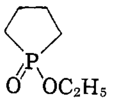
*Sir:*

Strained[2,3] five-membered cyclic esters of phosphoric[4] and phosphonic[5] acids undergo hydrolysis $10^5$ to $10^8$ times as fast as their open-chain analogs. The rapid hydrolysis applies equally to the opening of the ring and to the acid hydrolysis of the methyl group in methyl ethylene phosphate[6] or methyl pinacol phosphate[7] or to oxygen exchange in hydrogen ethylene phosphate;[8] these latter reactions occur without ring opening. We have now found that the same phenomenon also obtains for alkaline hydrolysis; phenyl ethylene phosphate,[9] methyl ethylene phosphate, and the phenyl ester, A, of a diamidate[10] hydrolyze rapidly compared to their acyclic analogs, and hydrolysis occurs with preservation of the ring. An obligatory trigonal bipyramidal intermediate or transition state, with the ring spanning one equatorial and one apical position, was postulated for such reactions[8] so as to effect a diminution in angle strain during the reaction process; this postulation was subsequently verified by an X-ray crystallographic study of a stable pentaoxyphosphorane.[11]

However, our recent investigations show that the ethyl esters, B, C, and D, of saturated and unsaturated five-membered cyclic phosphinic acids[12] do not exhibit greatly enhanced rates of reaction, but instead undergo acid and alkaline hydrolysis at rates comparable to those of their open chain analogs, E, F, and G, respectively. The values for $k_B/k_E$, $k_C/k_F$, and $k_D/k_G$, are, respectively: in acid, 1, 1, and 3; in alkali, 4, $^1/_7$, and $\sim$60. Since B, C, and D are probably strained,[3] the low rates of hydrolysis were unexpected. These low rates can, however, be interpreted in terms of a mechanism[13] that postulates a trigonal bipyramid as intermediate in the hydrolysis of the esters of acids of phosphorus and further assumes that placing an alkyl group in an apical position of such a bipyramid is energetically less favorable than placing it in an equatorial position (or, alternatively, that the apical positions are favored for oxygen atoms). This postulate for unstable intermediates in hydrolysis is analogous to that previously established by Schmutzler and others for the structures of the stable alkylfluorophosphoranes, $R_nPF_{5-n}$, where alkyl groups occupy equatorial positions.[14] The relief of strain in forming a trigonal bipyramidal intermediate is presumed to be insufficient in B, C, and D to overcome the barrier to placing an alkyl group in an apical position, while angle strain prevents placing the ring in a diequatorial position. Presumably, however, the barrier to placing an alkyl group in an apical position can be overcome in those cases where the relief of strain associated with the presence of a C–P–C angle of 90° in a trigonal bipyramid is sufficiently large. Preliminary results[15] have suggested that an appropriate example has been achieved with the Diels–Alder dimer of 1-ethoxyphosphole 1-oxide;[16] here the phosphabicycloheptene structure is highly strained and results in rapid hydrolysis in both acid and base of one (but only one) of the ester groups.



A



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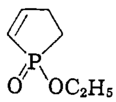

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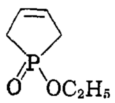

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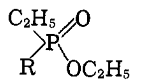

E, R = $C_2H_5$
F, R = $CH_2{=}CH$
G, R = $CH_2{=}CHCH_2$

The hydrolyses were studied with nuclear magnetic resonance techniques (Varian A-60) by taking advantage of the difference in the chemical shift and splitting of the methylene hydrogen atoms in the ethyl groups of the esters of the phosphinic acids and in the ethanol produced by hydrolysis. In addition, the peaks for the methylene group of the ethyl residue in the ester, but not in ethanol, respond to decoupling when the sample is irradiated with the appropriate frequency for phosphorus (*ca.* 24.29 Mc/sec), using an NMR Specialties heteronuclear spin decoupler.

E, F, and G were prepared by treating diethyl ethylphosphonite[17] with ethyl bromide for E,[18] dibromoethane followed by base for F,[19] or allyl bromide for G.[19] The compositions of these very hygroscopic new liquid compounds, or of those compounds prepared by

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[1] This work was supported by the National Science Foundation under Grant No. GP-2098. One of us (E. A. D.) holds an NIH Predoctoral Fellowship, 5-F1-GM-20,008.

[2] J. R. Cox, Jr., and F. H. Westheimer, *J. Am. Chem. Soc.*, **80**, 5441 (1958); E. T. Kaiser, M. Panar, and F. H. Westheimer, *ibid.*, **85**, 602 (1963).

[3] D. A. Usher, E. A. Dennis, and F. H. Westheimer, *ibid.*, **87**, 2320 (1965).

[4] J. Kumamoto, J. R. Cox, Jr., and F. H. Westheimer, *ibid.*, **78**, 4858 (1956); H. G. Khorana, G. M. Tener, R. S. Wright, and J. G. Moffatt, *ibid.*, **79**, 430 (1957).

[5] A. Eberhard and F. H. Westheimer, *ibid.*, **87**, 253 (1965).

[6] F. Covitz and F. H. Westheimer, *ibid.*, **85**, 1773 (1963).

[7] M. G. Newton, J. R. Cox, Jr., and J. A. Bertrand, *ibid.*, **88**, 1503 (1966).

[8] P. C. Haake and F. H. Westheimer, *ibid.*, **83**, 1102 (1961).

[9] K. A. Petrov, E. E. Nifant'ev, and L. V. Fedorchuk, *Vysokomolekul. Soedin.*, **2**, 417 (1960); *Chem. Abstr.*, **54**, 24373*a* (1960).

[10] F. Kerst, unpublished.

[11] W. C. Hamilton, S. J. La Placa, and F. Ramirez, *J. Am. Chem. Soc.*, **87**, 127 (1965).

[12] U. Hasserodt, K. Hunger, and F. Korte, *Tetrahedron*, **19**, 1563 (1963).

[13] E. A. Dennis and F. H. Westheimer, *J. Am. Chem. Soc.*, **88**, 3432 (1966)

[14] R. Schmutzler, *Angew. Chem. Intern. Ed. Engl.*, **4**, 496 (1965).

[15] D. Lee, unpublished.

[16] D. A. Usher and F. H. Westheimer, *J. Am. Chem. Soc.*, **86**, 4732 (1964).

[17] M. Sander, *Ber.*, **93**, 1220 (1960).

[18] A. I. Razumov, O. A. Mukhacheva, and S. Do-Khen, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 894 (1952); *Chem. Abstr.*, **47**, 10466 (1953).

[19] G. Kamai and V. S. Tsivunin, *Dokl. Akad. Nauk SSSR*, **128**, 543 (1959); *Chem. Abstr.*, **54**, 7538*i* (1960).

new methods, were established by high-resolution mass spectrometry; agreement with theory was within 3 ppm.

Further investigations are under way to test the hypotheses here advanced.

**Edward A. Dennis, F. H. Westheimer**
*James Bryant Conant Laboratory of the Department of Chemistry*
*Harvard Univeristy, Cambridge, Massachusetts*
*Received June 3, 1966*

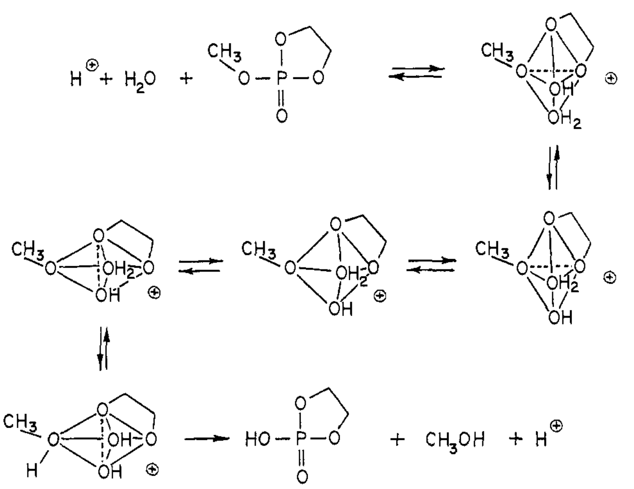
## The Geometry of the Transition State in the Hydrolysis of Phosphate Esters[1]

*Sir:*

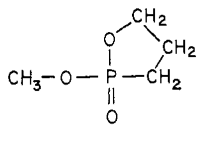
Five-membered cyclic esters of phosphoric and phosphonic acids undergo acid and alkaline hydrolysis at rates $10^5$–$10^8$ times as fast as their acyclic analogs;[2,3] some of these reactions, in both acid and base, occur at these enhanced rates without ring cleavage.[4-8] An analysis of these facts led to the hypothesis[4] (a) that these hydrolyses proceed by way of a trigonal bipyramidal intermediate where the ring is constrained to span one apical and one equatorial position. Now, in the accompanying communication,[7] consideration of the rates of hydrolysis of cyclic phosphinates has led us to the further hypothesis (b) that, with phosphorus compounds, a strong preference obtains for placing oxygen atoms in the apical positions and alkyl groups in the equatorial positions of trigonal bipyramids; the restrictions parallel those discovered by Schmutzler and his collaborators[9] for the structures of the alkylfluorophosphoranes, $R_nPF_{5-n}$.

We now wish to report that the methyl ester of propylphostonic acid, A, undergoes hydrolysis at an enhanced rate but almost exclusively with ring cleavage; using nmr and vpc techniques, less than one part in 500 of methanol could be detected in the reaction product, and preliminary rate measurements indicate that part of this methanol arises from the subsequent hydrolysis of the major product, methyl hydroxypropylphosphonate. This result contrasts sharply with that for the acid-catalyzed hydrolysis of methyl ethylene phosphate, where 30% of the product arises from hydrolysis of the methyl ester group without ring opening. The rates of these reactions—both ring openings and hydrolysis without ring opening (where it occurs)—are nearly a million times those of their acyclic analogs.

These data may tentatively be explained by assuming (c) that the hydrolysis of phosphates may, and in some instances must, involve a "pseudo-rotation" of trigonal bipyramidal intermediates, analogous to the "pseudo-rotation" that has been postulated[10] to explain the rapid interchange of fluorine atoms in $PF_5$ and[9] in $RPF_4$. The mechanism[11] is illustrated for the acid-catalyzed hydrolysis of methyl ethylene phosphate to produce methanol and ethylene hydrogen phosphate. The scheme can be formulated as a symmetrical one. Water adds to occupy an apical position in a trigonal bipyramid; the shift of a proton produces an equatorial water molecule that can serve as "pivot" for pseudo-rotation. The pseudo-rotation places a methoxy group in the apical position of a new trigonal bipyramid; after a proton shift, a methanol molecule can leave from this apical position. In both trigonal bipyramids, the five-membered ring spans one apical and one equatorial position, with reduced ring strain. The corresponding hydrolysis with ring opening can occur from the original trigonal bipyramid with a proton shift but without pseudo-rotation.



On the other hand, such a pseudo-rotation must be energetically unfavorable for the trigonal bipyramid formed from methyl propylphostonate by addition of water and a proton. Pseudo-rotation of the trigonal bipyramid, B, about the methylene group as pivot would force the five-membered ring into a diequatorial configuration with the C–P–C ring angle expanded toward 120°; this would introduce considerable strain into the intermediate. Pseudo-rotation about the equatorial hydroxyl group of B as pivot would force the methylene group into an apical position; the unfavorable energy of alkyl groups in the apical positions was postulated as (b) above and was the subject of the previous communication.[7] In neither case, then, can pseudo-rotation occur readily in the trigonal bipyramid derived from methyl propylphostonate. Since the methoxy group cannot assume an apical position, it is retained in the product; hydrolysis occurs with ring opening.



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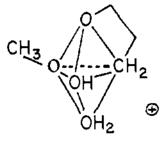

B

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[1] This work was supported by the National Science Foundation under Grant No. GP-2098. One of us (E. A. D.) holds an NIH Predoctoral Fellowship, 5-F1-GM-20,008.

[2] J. Kumamoto, J. R. Cox, Jr., and F. H. Westheimer, *J. Am. Chem. Soc.*, **78**, 4858 (1956); H. G. Khorana, G. M. Tener, R. S. Wright, and J. G. Moffatt, *ibid.*, **79**, 430 (1957).

[3] A. Eberhard and F. H. Westheimer, *ibid.*, **87**, 253 (1965).

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[5] F. Covitz and F. H. Westheimer, *ibid.*, **85**, 1773 (1963).

[6] M. G. Newton, J. R. Cox, Jr., and J. A. Bertrand, *ibid.*, **88**, 1503 (1966).

[7] E. A. Dennis and F. H. Westheimer, *ibid.*, **88**, 3431 (1966).

[8] F. Kerst, unpublished.

[9] R. Schmutzler, *Angew. Chem. Intern. Ed. Engl.*, **4**, 496 (1965), and references therein.

[10] R. S. Berry, *J. Chem. Phys.*, **32**, 933 (1960).

[11] The mechanism has certain features in common with that postulated for displacement reactions of some octahedral platinum complexes; see R. G. Pearson and F. Basolo, "Mechanisms of Inorganic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1958, p 189.