The pH–Rate Profile for the Hydrolysis of Some Esters of a Bicyclic Phosphinic Acid. Evidence for Rate-Limiting Pseudorotation

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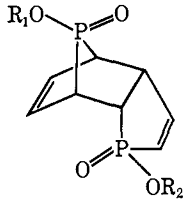
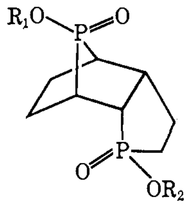
Abstract: The ethyl esters **1** and **4** of substituted bicyclic phosphinic acids undergo rapid hydrolysis of one of the two ester groups in both base and acid. We had previously suggested that this rapid reaction is necessarily accompanied by pseudorotation about the phosphorus atom. We have now established by nmr spectroscopy that the rapid reaction occurs as predicted at the phosphorus atom in the bridge position, where the maximum strain is localized. The pH–rate profiles for the hydrolysis of the esters **1** and **4** show that the rate is proportional to the hydroxide ion concentration at pH >8, is independent of acidity near pH 5, and is proportional to the hydrogen ion concentration around pH 2. However, the rate does not continue to rise in proportion to the acid concentration above 0.01 M, but reaches a maximum in about 0.2 M acid. The acidity and ionic strength at the maximum rate are too low to account for the deviation from a linear relationship between rate and acidity on the basis of a decrease in the activity of water or a salt effect. We therefore suggest that, at high acidity, the pseudorotation process itself becomes rate limiting.

In preliminary communications, the syntheses of the substituted esters, **1** and **4**, of bicyclic phosphinic acids have been outlined, and the rapid rate of hydrolysis of one of the two ester groups in each was observed.[1,2] In those communications, it was suggested that the rapid hydrolysis of these esters was caused by the intense strain at the bridge position (the 8 position[3]) of the molecule and that this strain is relieved by the formation of trigonal-bipyramidal intermediates where the ring occupies one apical and one equatorial position. We assumed that the subsequent steps require pseudorotation[5] about the phosphorus atom[6,7] so that in the over-all hydrolysis process a water molecule may enter from an apical position and an alcohol molecule may leave from an apical position, despite the fact that the ring system always occupies one of the apical positions of the trigonal-bipyramidal intermediate (see Discussion for details). This paticular case is complicated by the restraints[7] that must be placed upon trigonal-bipyramidal intermediates in phosphorus chemistry: a five-membered ring preferentially occupies one apical and one equatorial position[8-10] and alkyl substituents, as contrasted with fluorine atoms or alkoxy groups, preferentially occupy equatorial rather than apical positions (Muetterties' rule).[11-14] We previously postulated that the rapid hydrolysis of esters **1** and **4** occurs by way of intermediates with an alkyl substituent in the apical position, despite the penalty in energy to the formation of such a structure, because of the overriding relief of strain in the transition state that is involved. These arguments (and, indeed, the general arguments[6,7]) for pseudorotation as part of the hydrolysis process for phosphate, phosphonate, and phosphinate esters rest on the assumption that the transition states for hydrolysis closely resemble the corresponding trigonal-bipyramidal intermediates that undergo pseudorotation.



1, $R_1 = R_2 = C_2H_5$
2, $R_1 = H; R_2 = C_2H_5$
3, $R_1 = R_2 = H$



4, $R_1 = R_2 = C_2H_5$
5, $R_1 = H_1; R_2 = C_2H_5$
6, $R_1 = R_2 = H$

In the present investigation, the monoester monoacid **2** from the partial hydrolysis of **1** has been isolated, and it has been shown that partial hydrolysis of **1** occurs exclusively at the ester group on the methano bridge (*i.e.*, position 8), as previously postulated. Further-

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[1] R. Kluger, F. Kerst, D. G. Lee, and F. H. Westheimer, *J. Am. Chem. Soc.*, **89**, 3919 (1967).

[2] R. Kluger, F. Kerst, D. G. Lee, E. A. Dennis, and F. H. Westheimer, *ibid.*, **89**, 3918 (1967).

[3] Nomenclature and abbreviations. Dr. Kurt Leoning of the Chemical Abstracts Service has informed us that **1** may be named as 1,8-diethoxy-3a,4,7,7a-tetrahydro-4,7-phosphinidenephosphindole 1,8-dioxide; **4** may similarly be named as 1,8-diethoxyoctahydro-4,7-phosphinidenephosphindole 1,8-dioxide. In accordance with this scheme we have designated the phosphorus in the simple five-membered ring of the structure as occupying the 1 position, and the phosphorus atom in the bridge as occupying the 8 position. Since, however, the full names are awkward, we have here called **1** the "dimer" (it is the Diels–Alder dimer of 1-ethoxyphosphole 1-oxide[4]) and **4** the "reduced dimer."

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

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

[6] E. Dennis and F. H. Westheimer, *J. Am. Chem. Soc.*, **88**, 3431 (1966); E. Dennis and F. H. Westheimer, *ibid.*, **88**, 3432 (1966).

[7] F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).

[8] P. Haake and F. H. Westheimer, *J. Am. Chem. Soc.*, **83**, 1102 (1961).

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

[10] W. C. Hamilton, S. J. LaPlaca, and F. Ramirez, *ibid.*, **87**, 127 (1965); W. C. Hamilton, S. J. LaPlaca, F. Ramirez, and C. P. Smith, *ibid.*, **89**, 2268 (1967).

[11] E. L. Muetterties, W. Mahler, and R. Schmutzler, *Inorg. Chem.*, **2**, 613 (1963); E. L. Muetterties, W. Mahler, K. J. Packer, and R. Schmutzler, *ibid.*, **3**, 1298 (1964); E. L. Muetterties and R. A. Schunn, *Quart. Rev.* (London), 20, 245 (1966).

[12] R. Schmutzler and G. S. Reddy, *Inorg. Chem.*, **4**, 191 (1965); R. Schmutzler, *J. Am. Chem. Soc.*, **86**, 4500 (1964); R. Schmutzler, *Angew. Chem. Intern. Ed. Engl.*, **4**, 496 (1965); R. Schmutzler, *Advan. Fluorine Chem.*, **5**, 31 (1965).

[13] D. G. Gorenstein, and F. H. Westheimer, *J. Am. Chem. Soc.*, **89**, 2762 (1967); D. G. Gorenstein and F. H. Westheimer, *Proc. Natl. Acad. Sci. U. S.*, **58**, 1747 (1967).

[14] F. Ramirez, J. F. Pilot, O. P. Madan, and C. P. Smith, *J. Am. Chem. Soc.*, **90**, 1275 (1968).

more, the pH–rate profiles for the hydrolyses of **1** and **4** have been determined. In dilute acid solution, the rates increase proportionally with hydrogen ion concentration but level off when the concentration reaches 0.2 *M;* these facts are here interpreted in the light of the theory of pseudorotation.

The structures of this series of compounds were suggested by their chemistry. The structures of the series have been anchored by Chiu and Lipscomb[15] by an X-ray determination of the structure and geometry of the dimer. In particular, their work shows that the ring system is *endo*, and designates the stereochemistry of the ethyl ester groups around the phosphorus atoms. In this connection we note sadly that stereochemistry about the phosphorous atom at position 1 was incorrectly transcribed[7] from a preliminary communication from Chiu and Lipscomb; the correct stereochemistry is shown here.

Experimental Section

Materials. The dimer and reduced dimer, **1** and **4**, were prepared by the method previously published.[1,2,4] The hydrolysis of **1** to **2** was conducted as follows.

Dimer (1.47 g, 0.049 mol) was allowed to stand at room temperature for 4 hr in 50 ml of water. Evaporation of the water yielded an oil from which crystals could be obtained by addition of acetone–water; yield: 1.30 g (92%) of the monohydrate, mp 111–113°. The principal ir bands occur at 3.3, 5.8 (broad, water), 6.35, 7.50, 8.40, 9.75, 10.00, 10.40, 11.80, 12.05, 12.40, 12.60, and 13.70 μ. *Anal.* Calcd for $C_{10}H_{14}O_4P_2 \cdot H_2O$: C, 43.18; H, 5.80; P, 22.27; neut equiv, 278. Found: C, 43.49; H, 5.90; P, 22.27; neut equiv, 290. Exact mass was determined on an AEI MS 9 high resolution mass spectrometer by Dr. John Wright: calculated (for the anhydrous acid) 260.0366; found, 260.0368.

The hydrolysis of **1** to **3** occurred in 90% yield when 2.0 g (6.9 mmol) of **1** was refluxed in 50 ml of 4 *N* hydrochloric acid for 7 days. The solution was freed of excess hydrochloric acid by repeated evaporation and resolution in water, and the residue crystallized from acetone–water; mp 102–104°; principal ir bands at 6.35, 7.50, 11.90, and 13.70 μ (and a broad water band above 7). *Anal.* Calcd for $C_8H_{10}O_4P \cdot 2H_2O$: C, 35.83; H, 5.26; P, 23.10; neut equiv, 134. Found: C, 36.18; H, 5.29; P, 23.35; neut equiv, 140.

Resynthesis of the Dimer 1 from the Monoester Monoacid 2. Monoacid hydrate (1.25 g, 0.044 mol) was dissolved in 30 ml of absolute ethanol. The solution was dried over Linde Molecular Sieves, Type 3A, and decanted. The dry solution was titrated with diazoethane in ether to a persistent yellow end point and then concentrated under vacuum; the residue was taken up in carbon tetrachloride. The nmr spectrum of the solution (there was a small residue that was discarded) was similar to that of known dimer, but extra peaks which appeared in the region of absorption of methyl protons suggested that the product was a mixture of *syn* and *anti* stereoisomers about the phosphorus atom in position 8. Chromatography of the residue in 1:1 ethyl acetate–carbon tetrachloride on a 3 × 0.5 in. Florisil column yielded crystalline dimer, mp 124–126°, that did not depress the melting point of authentic material, and which showed the same nmr, ir, and mass spectra as those of the dimer. The yield, however, was only 11% from diacid.

The reduced diacid 6 was obtained when the reduced diester **4** was refluxed for 1 week in 10 *N* hydrochloric acid. After the hydrochloric acid was removed by repeated evaporation and resolution of the product, the residue was crystallized from moist acetone. Recrystallization from acetone–water gave **6**, mp 254–255°. *Anal.* Calcd for $C_8H_{14}O_2P_2$: C, 40.69; H, 5.97; P, 26.23. Found: C, 40.74; H, 5.81; P, 25.94. The nmr spectrum showed no peaks for ethoxyl groups. Compound **6**, when treated with diazoethane in ethanol, gave a residue (presumably a mixture of stereoisomers) that yielded a mass spectrum (obtained for us by Mr. L. David Williams) that was indistinguishable with respect to parent peak and pattern of decomposition products with that of **4**.

Methyl Ethyl Ester. Monoester monoacid monohydrate **2** (0.80 g) was dissolved in 5 ml of dry methanol and titrated with a freshly distilled ethereal solution of diazomethane. The solvent was evaporated and the high-resolution mass spectrum of the residue determined: calcd for $C_{11}H_{16}O_4P_2$, 274.0523; found, 274.0521. The nmr spectrum shows two sets of peaks in the region of absorption for the $-OCH_3$ protons, and so suggests that the product is a mixture of stereoisomers about the phosphorus atom in position 8.

All elemental analyses were conducted by Galbraith Laboratories, Knoxville, Tenn.

Methods. Proton nmr spectra were determined with a Varian A-60 nmr spectrometer equipped with a NMR Specialties heteronuclear spin decoupler and Hewlett-Packard sidebander at a nominal frequency of 24.3 MHz. Phosphorus nmr spectra were determined with a Varian V 4311 nmr spectrometer, at 24.28 MHz, with sidebander and frequency counter; shifts were measured as Δ values in parts per million (ppm) downfield from 85% phosphoric acid.

Rates. a. Nmr Method. For the dimer, the ester was dissolved in 0.5 ml of perchloric acid in water, or of deuterated perchloric acid in D_2O, and the hydrolysis followed by measuring the heights of the peaks at 1.40 and 1.02 ppm downfield from the signal for TMS. (The standard was a solution of TMS in chloroform, and its position was determined immediately before taking each spectrum.) The spectrum of the dimer before any reaction had occurred is shown in Figure 1. The method of identifying positions 1 and 8 is described in the section on Products. Using these results, we note that the peak at δ 1.4 is the lowest field peak of the triplet from the methyl protons of the ethoxy group on the phosphorus atom at position 1 (*i.e.*, the nonbridge position) whereas the peak at δ 1.02 is the highest field peak of the triplet of the methyl protons of the ethoxy group on the phosphorus atom at the 8 (bridge position). In water, the signal from the solvent is of course intense, and the side-bands prominent, but these absorptions are sufficiently far downfield that they do not interfere with the necessary measurements.

For the reduced dimer, the rate of hydrolysis in D_2O was followed by comparing the area of the multiplet at δ 4.2 (from the methylene protons of the two ethoxy groups) with the quartet at δ 3.5 that corresponds to the signal from the methylene group of the ethanol produced in hydrolysis. (Of course, in the first step of the hydrolysis, only half of the signal at δ 4.2 disappears.) Nmr tubes containing a specified amount of substrate in deuterated perchloric acid–D_2O solution were placed in a thermostat at 100°. The tubes were withdrawn for analysis periodically, with rapid cooling (and, when rate measurements were resumed, subsequent rapid rewarming) of the nmr tubes.

Nmr methods were also used to follow the saponification of the second ester group of the reduced dimer. An NMR Specialties Teflon tube liner in ordinary glass nmr tubes was used. To prepare starting material, reduced dimer was treated with 1 equiv of sodium hydroxide in water at room temperature. The solution was then evaporated to remove alcohol, and the resulting monosodium salt of the monester was dissolved in a solution of known concentration of NaOD in D_2O. The rate of further hydrolysis of this ester was measured; nmr was used to follow the appearance of ethanol and the disappearance of the multiplet for the methylene group of the ethoxy group of the ester.

b. pH-Stat Method. The rates of hydrolysis of the dimer between pH 2 and 10 were followed with a Radiometer TTT1b automatic titrator connected to an Aminco automatic buret with recording attachment and a Radiometer "C" electrode. The rates of alkaline hydrolysis of the reduced dimer were similarly followed, using a Radiometer "B" electrode. A weighed amount of substrate was dissolved in a small amount of ethanol and injected into the reaction vessel with a syringe.

The rates from pH 3 to 6 are slow, so that a determination of the complete rate curve by the pH-Stat method is difficult. The rates for the hydrolysis of the dimer were found by measuring the uptake of alkali during the first 5 to 10% of the reaction, and calculating the constants from this initial rate. Although the results are therefore subject to somewhat greater error than those at other acidities, the reproducibility of the experiments and the consistent values of the second-order rate constant over the pH range in question provide assurance that the results are approximately correct.

c. Vpc Method. The hydrolysis of the reduced dimer was followed in 0.001 *M* and 0.01 *M* $DClO_4$ solution by a vpc method. (The nmr method could not be applied, since the phosphinic acid, produced in the hydrolysis of moderately concentrated solutions of the ester, would raise the acidity above 0.01 *M*.) The vpc method, developed in these laboratories by Mr. Franklin Mirer, is a modification of the standard procedure of McNair and Bonelli.[16] A 0.25-

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(15) Y.-Y. Chiu and W. N. Lipscomb, *J. Am. Chem. Soc.*, **91**, 4150 (1969).

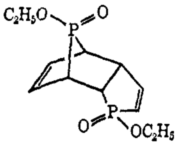
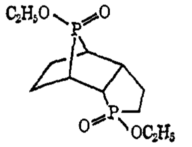
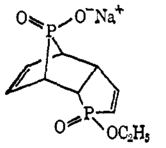
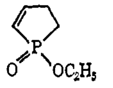
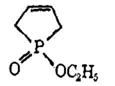
(16) H. M. McNair and E. J. Bonelli, "Basic Gas Chromatography," Varian Aerograph, Walnut Creek, Calif., 1968, pp 111–139.

ml aliquot of the reaction mixture, containing 0.5% butanol as a standard, was transferred on a vacuum line in an apparatus with Teflon stopcocks and West Glass Co. Vyton O-ring joints, in order to avoid absorption of ethanol by stopcock grease. The distillate was then analyzed on a Hewlett-Packard 5754A research chromatograph, using a flame ionization detector and an 8 ft × 0.25 in. column of 10% sorbitol-silicone oil on 60–80 mesh Chromosorb W. The flow rate for helium was 45 cc/min, the column temperature 80°, and the injection temperature 160°.

Results

^{31}P Nmr Spectra. The results for ^{31}P nmr spectra are given in Table I.

Table I. ^{31}P Chemical Shifts

Compound	Concn, *M*, solvent	Chemical shift,[b] Δ
	1, $CHCl_3$ 1, pH 4 buffer	70, 83 75, 81
	1, $CHCl_3$	70, 77
	1, H_2O or 0.1, HCl	78
	Neat liquid	69[a]
	Neat liquid	68[a]

[a] E. A. Dennis, Ph.D. Thesis, Harvard University, 1967. [b] In parts per million downfield from 85% H_3PO_4.

Products. The nmr spectra of dimer **1** of the monoester monoacid **2** and of the diacid **3** are shown in Figure 1.

The original diester **1** has been regenerated by treating the monoacid monoester **2** with diazoethane. The formation of the original dimer by such a mild process, even though in low yield, from a single compound (pure, crystalline monoester monoacid) demonstrates that the hydrolysis took place without structural reorganization. In addition, the nmr spectrum of the diacid **3** shows that it contains four vinyl and four methine protons; the positions and splittings of these protons are very similar to those in the diester. These facts also suggest that no rearrangement accompanies hydrolysis. The most characteristic peaks are the two doublets at δ 7.0 and 7.1. These correspond to one-half of one proton, and are similar in position and coupling constants to the peaks that have been identified by Weitkamp and Korte[17] as belonging to the β proton in 1-ethoxy-2-phospholene 1-oxide (**7**). The identification of the position of the free acid group in the monoacid monoester **3** depends critically on the modification of this signal that occurs when the phosphorus atoms are decoupled.

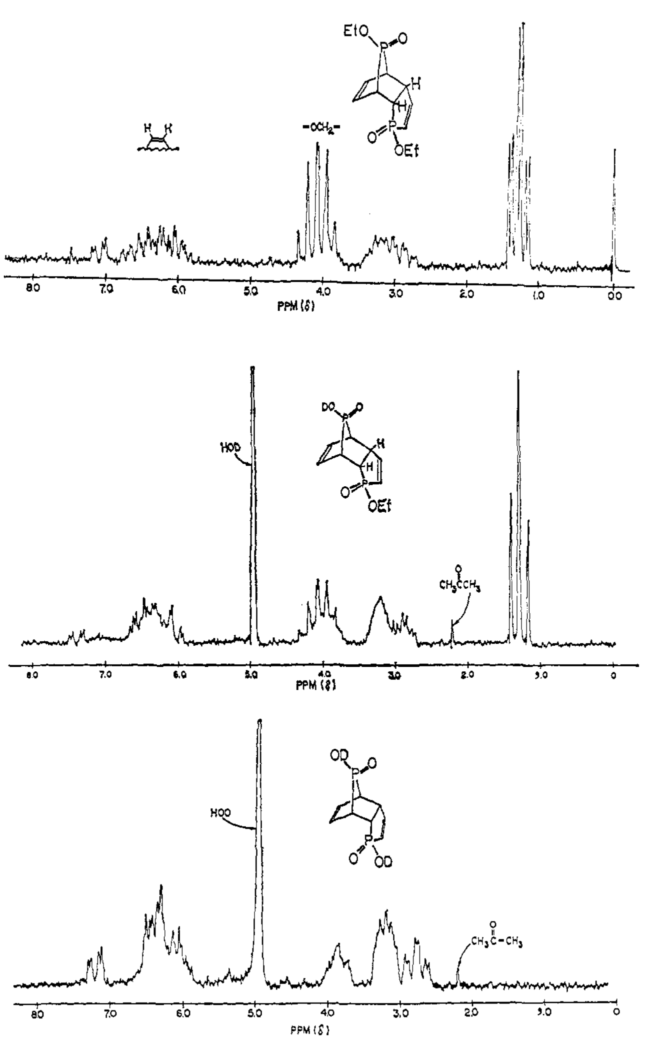
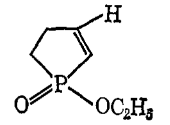


Figure 1. Nmr spectra for the dimer (top), for the corresponding monoacid monoester (center), and for the corresponding diacid (bottom). The signal at 0.0 in the top spectrum is that from tetramethylsilane. The two doublets beyond δ 7.0 in all the spectra represent half of the proton at position 3.



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Decoupling of one of the phosphorus atoms (Δ 70) causes the collapse of one of the two overlapping quintets to a quartet in the region of the signals from the methylene groups of the ethoxy groups of the dimer. At the same time the signals from the proton identified above collapse (see Figure 2). On the other hand, decoupling at the other phosphorus atom (Δ 83) causes collapse of the second quintet to a quartet in the region of the signals from the ethoxy groups of the dimer, but although the decoupling causes changes in the signals in the olefinic region of the spectrum, it does not affect the signals from the specific proton that gives the two doublets at δ 7.0 and 7.1. Analogy with the work of Weitkamp and Korte[17] suggests that the phosphorus atom (Δ 70) that causes the splitting of the specific β proton must be at the 1 position.

(17) H. Weitkamp and F. Korte, *Z. Anal. Chem.*, 204, 245 (1964).

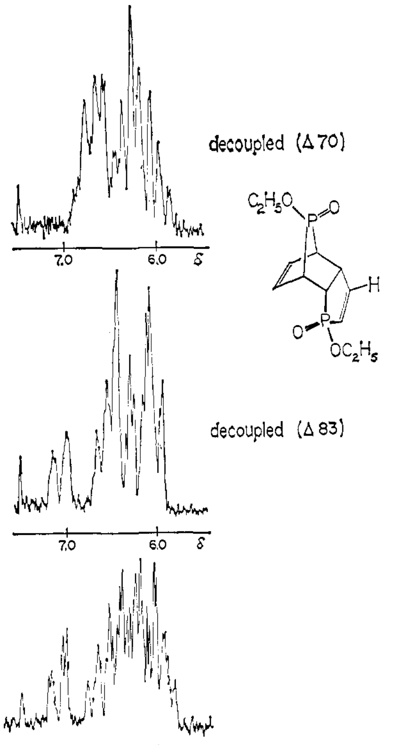


Figure 2. The signals from the olefinic protons of the dimer. The upper spectrum shows the results of heteronuclear decoupling for phosphorus at Δ 70, the center spectrum shows decoupling at Δ 83, while the lowest spectrum was obtained without decoupling. The signals at δ 7.0 and 7.1 collapse only with decoupling at Δ 70 (top spectrum).

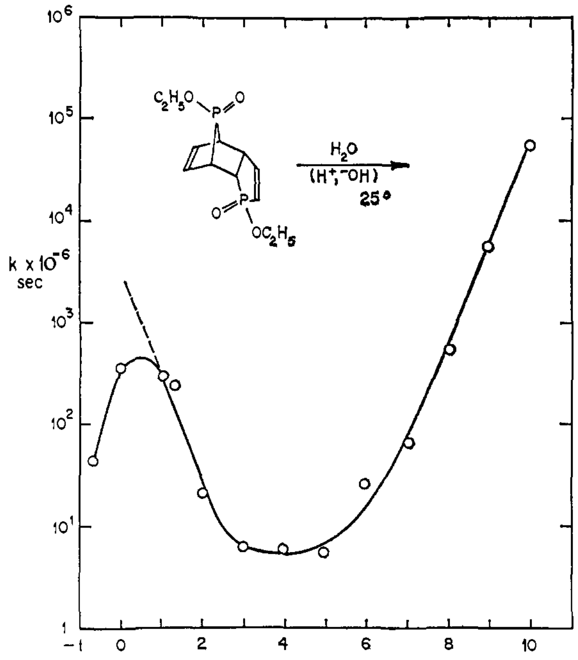


Figure 3. pH–rate profile for the hydrolysis of the dimer in water. The points are experimental, and the solid line interpolates these data and, within experimental error, follows eq 1, except that, in strong acid, the abscissa represents the negative of the logarithm of the hydrogen ion concentration, rather than pH.

In the statements above, the positions of the ^{31}P signals from the two phosphorus atoms have been given for purposes of identifying them. However, our heteronuclear decoupler is not calibrated to show parts per million downfield from 85% phosphoric acid. Decoupling is obtained at two frequencies separated by 13 ppm at 24.3 MHz; we have therefore identified the higher of these frequencies with that of the phosphorus atom with Δ 70 and the lower of these frequencies with the phosphorus atom with Δ 83.

Unfortunately, the signals from the two phosphorus atoms of the monoester monoacid as well as the corresponding signals of the monoester monoanion fall too close together to be resolved, and therefore cannot be decoupled individually (see Table I). An elaborate nmr test was therefore designed to determine where hydrolysis occurs.

This test is supplied by nmr spectra of the mixture of isomers of the methyl ethyl ester. The chemical positions of the two ester groups in this molecule have been established as follows. The proton nmr spectrum shows that the methyl ethyl ester consists of a mixture of two (presumably stereoisomeric) compounds. Decoupling can be achieved at three separate frequencies. One of these corresponds to the frequency of absorption of the phosphorus atom at position 1 in both isomers (Δ 70). When the mixed methyl ethyl esters are irradiated with this frequency (a) the specific vinyl signals at δ 7.0 and 7.1 are collapsed, (b) the quintet for the signal from the methylene group of the ethoxyl group is collapsed to a quartet, but (c) the complex signal from the two stereochemically different methoxyl groups is untouched. From a, it is clear that this decoupling involves the phosphorus atom at position 1; from b and c it is apparent that the ethoxyl group is attached to this phosphorus atom, and the methoxyl group must therefore be attached at the other phosphorus atom. These conclusions are confirmed by irradiation at the two other phosphorus frequencies (one for each of the two diastereomeric esters) where (d) the signal from the special proton of the vinyl region is unaffected, (e) the signal from the methylene group of the ethoxyl group is unaffected, but (f) each irradiation simplifies the signal from the methoxyl region in the manner expected if it saturated the signal from the phosphorus at position 8 in only one of two isomers. These data establish that the methoxyl group is attached to the phosphorus atom of position 8. Since the methoxyl group was introduced by reaction of diazomethane with the monoester monoacid, the free acid group in the latter must have been at position 8.

The products obtained in both acidic and basic hydrolysis of the dimer are the same; the nmr spectra have been compared in alkaline solutions of D_2O and are identical. Therefore both acidic and basic hydrolysis occurs preferentially at the bridge position.

Kinetics. The pH–rate profile for the hydrolysis of the dimer is shown in Figure 3. The corresponding data are collected in Table II.

The data for the rates of hydrolysis of the reduced dimer are collected in Tables III and IV and the pH–rate profile in Figure 4.

Discussion

Rates of Hydrolysis. The data here presented show that the hydrolysis of the dimer **1** takes place first at the ester group attached at the phosphorus atom at

Table II. Rates of Hydrolysis of the Dimer at 25°

pH	$HClO_4$, *M*	Added salt, *M*	Method	$k \times 10^4$, sec^{-1}
	5.0		Nmr	0.45
	1.0		Nmr	3.5
	0.10	$NaClO_4$, 0.9	Nmr	3.0
	0.10	$NaClO_4$, 5.0	Nmr	0.40
	0.05	$NaClO_4$, 1.0	Nmr	2.5
2.0		$NaClO_4$, 0.1	pH-Stat	0.2
3.0		$NaClO_4$, 0.1	pH-Stat	0.060
4.0		$NaClO_4$, 0.1	pH-Stat	0.060
5.0		$NaClO_4$, 0.1	pH-Stat	0.055
6.0		$NaClO_4$, 0.1	pH-Stat	0.15
7.0		$NaClO_4$, 0.1	pH-Stat	0.65
8.0		$NaClO_4$, 0.1	pH-Stat	5.5
9.0		$NaClO_4$, 0.1	pH-Stat	55
10.0		$NaClO_4$, 0.1	pH-Stat	550

Table III. Rates of Hydrolysis of the Reduced Dimer in D_2O at 100°

$DClO_4$ concn, *M*	Method	$NaClO_4$ concn, *M*	$k \times 10^5$, sec^{-1}
0.0010	Vpc		0.1
0.010	Vpc		0.5
0.05	Nmr	0.90	2.0
0.10	Nmr	0.75	7.0
0.25	Nmr	0.75	6.0
0.50	Nmr		7.0
0.50	Nmr	0.50	6.0
1.0	Nmr		6.0
2.0	Nmr		6.0
6.3	Nmr		20

Table IV. Rates of Hydrolysis of Reduced Dimer in H_2O at 30° (pH-Stat Method)

pH	$k \times 10^4$, sec^{-1}
10.0	2.0
10.4	5.1
10.5	5.7
11.0	25
11.1	27
($k_{OH^-} = 1.4\ M^{-1}\ sec^{-1}$)	

the bridge position; the rate data previously published[2] show that the reaction is very much faster at the first than at the second ester. The data are summarized in Table V.

The rates of hydrolysis for the dimer and reduced dimer at the ester groups on the bridge are obviously much greater than those for their acyclic analogs. However, since the rates were not determined (and could not conveniently have been determined) at a common temperature, the figures here given must be compared after approximate extrapolations to a common temperature. Fortunately, since the ratios of rates are large, exact numbers are not needed in order to draw qualitative conclusions from them. Making allowance for temperature, the rate constant for the alkaline hydrolysis of the dimer **1** is about 4 × 10^4 as large as that for its monocyclic analog **8**. In acid solution, the rate for the hydrolysis of the ester group bridge of **1** at 25° is 200 times as large as that for **8** at 100°; the ratio, extrapolated to a common temperature, is probably of the order of 10^5. The rate ratios are smaller for the reduced dimer, where the rate of hydrolysis of **2** at the ester group on the bridge in acid is only about 50 times as great as that for its monocyclic analog **9**; the rate ratio in alkali is however 10^4. The solvent deuterium isotope effect is small.

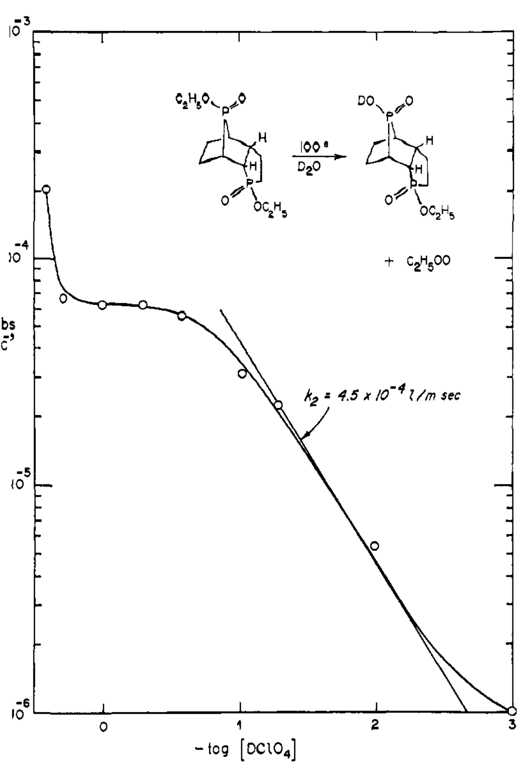


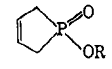
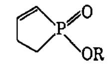
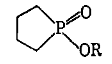
Figure 4. pH-rate profile, in the acid region, for the reduced dimer. The points are experimental; the straight line, with a rate constant of 4.5 × 10^{-4} M^{-1} sec^{-1}, lies close to the experimental points in the region where the rate is approximately proportional to acidity.

In contrast to the rates of hydrolysis for the ester group on the bridge of the dimer or reduced dimer, the ester group in the simple five-membered ring is hydrolyzed more slowly than that in monocyclic phosphinate esters. Thus the second ester group of the dimer hydrolyzes in acid only $^2/_7$ as fast as does its analog **7** and hydrolyzes in base only $^1/_{30}$ as fast. Similarly, the second ester group in the reduced dimer hydrolyzes in acid only $^1/_9$ as fast as does its analog **9** and hydrolyzes in base at a rate (extrapolated to a common temperature) that is probably only $^1/_{1000}$ as great.

Strain Energies. The enormous acceleration in the rates of acid and base hydrolysis of the phosphinate ester group at the bridge position, especially for the dimer, relative to those in acyclic phosphinate esters can be correlated with the strain in the dimer and reduced dimer. In our earlier publications,[1,2] this strain was assumed on the basis of the analogy of the structure to that of the corresponding bicycloheptane derivatives. However, since then, Chiu and Lipscomb[15] have found by X-ray crystallography that the C–P–C bond angle at position 8 in **1** has the extraordinarily low value of 87°, and other angles in the bridged system are also compressed.[15] If the force constant for bending the C–P–C angle is similar to that for the C–C–C angle, then a crude estimate[18] suggests that the strain energy in the bridged ring system approximates 30 kcal/mol. Probably the actual strain is

(18) Estimated by the method of F. H. Westheimer, in "Steric Effects in Organic Chemistry," M. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 523 ff.

Table V. Summary of Rates of Hydrolysis of Dimer and Reduced Dimer[a]

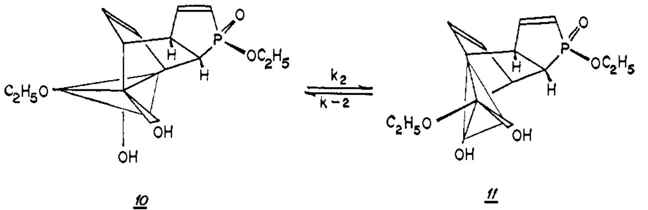
Compound	Temp, °C	k,[b] M^{-1} sec^{-1} (acid) first ester group	Temp, °C	k,[b] M^{-1} sec^{-1} (acid) second ester group	Temp, °C	k, M^{-1} sec^{-1} (base) first ester group	Temp, °C	k, M^{-1} sec^{-1} (base) second ester group
Dimer **1**	25	3×10^{-3}	100	2×10^{-6}	30	6×10^{2c}	25	1×10^{-5}
 **8**	100	1×10^{-5}			25	1×10^{-2}		
 **7**	100	7×10^{-6d}			25	3×10^{-4}		
Reduced dimer **4**	100	4×10^{-4e}	100	1×10^{-6d}	30	2^{f}	91	3×10^{-5d}
 **9**	100	9×10^{-6}			25	1×10^{-4}		

[a] Determined by nmr methods unless otherwise noted. [b] These are second-order rate constants, and apply only to that region of the pH–rate profile where the first-order rate constant is proportional to the concentration of hydrogen ions. [c] As a result of a type-setting error, this number was erroneously reported as 6 × 10 (*i.e.*, too low by a factor of 10) in our preliminary communication.[2] [d] In D_2O. [e] Determined by vpc. [f] Determined by pH-Stat.

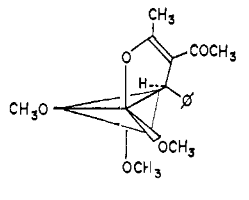
even greater. The strain in a bicycloheptane has been estimated[19] as 25.7 kcal/mol, where the bond angle[20] at the bridge position is about 95°. The much greater deflection from the tetrahedral bond angle for the phosphorus compound represents either higher strain energy, or a lower force constant, or both.

The question then arises as to how much of the strain energy is released in the formation of a bipyramidal intermediate during hydrolysis and how much of it is available for kinetic acceleration. A crude estimate of the loss of strain energy at the C–P–C angle and relief of strain elsewhere suggests that around 15 kcal/mol might be so available if it were not for an unfavorable structural feature of the trigonal-bipyramidal intermediate **10** and of its diastereomeric pseudorotamers, of which **11** is an example. The intermediate for hydrolysis requires that an alkyl group be placed in the apical position of a trigonal bipyramid; as stated in the introductory section, such bonding is energetically unfavorable.[7,11] The amount of the energy barrier is not known, but the study of the nmr spectrum of **12** suggests that the activation energy for the pseudorotation of this compound, through an intermediate with an apical P–C bond, is around 10–12 kcal/mol. Similar values for the activation energy have also been estimated for several other alkyloxyphosphoranes where one carbon atom in a five-membered ring is placed in an apical position.[21]

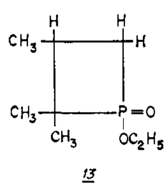
Nevertheless the strain energy released in forming a trigonal-bipyramidal intermediate[22] from **1** is probably far greater than that required to form **10**; these considerations provide at least a qualitative explanation for the rapid rates reported in Tables II–IV. In compounds such as **7**, **8** and **9**, formation of a trigonal-bipyramidal intermediate should lead to a relief of strain, but this relief of strain is more or less compensated by the increase in energy needed to place an alkyl group in an apical position in a trigonal bipyramid. As the net results of these opposing factors, the rates of hydrolysis for these compounds are not expected to be extraordinarily large.[2] A similar example where strain is sufficient to overcome the barrier to placing an alkyl substituent in the apical position has recently been presented by Hawes and Trippett,[23] who found that the rate of hydrolysis of **13** enormously exceeds that expected for an ester of an equally hindered acyclic phosphinic acid. Hawes and Trippett have also interpreted



10 **11**



12



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their results in terms of pseudorotation, although they have assumed that the favored intermediate in their acyclic analog will involve an apical *t*-butyl group. This assignment requires the assumption that steric or other forces in the compound are sufficient to override the barrier[11] to placing alkyl groups in the apical position.

The slow hydrolysis of the second ester group in **2** (and similarly in **5**) must also be explained. As explained above, one does not expect that relief of strain

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(19) G. J. Gleicher and P. von R. Schleyer, *J. Am. Chem. Soc.*, **89**, 582 (1967), estimated the strain in norbornane. *Cf.* also citations in ref 14.

(20) A. C. MacDonald and J. Trotter, *Acta Cryst.*, **19**, 456, (1965), determined the bond angle for 7-norbornenyl brosylate.

(21) D. Gorenstein, submitted for publication.

(22) It is not yet clear whether **10** represents one of two transition states for the reaction or a high-energy intermediate. Perhaps in special cases, such as that here discussed, the tetragonal pyramid, such as that formed during the pseudorotation between **10** and **11**, is actually an intermediate.

(23) B. W. Hawes and S. Trippett, *Chem. Commun.*, 578 (1968).

in forming a trigonal-bipyramidal intermediate at the phosphorus atom of position 1 will do more than compensate, more or less, for the energy barrier to placing an alkyl group in the apical position. However, the rates are even slower than would be anticipated by comparison with those of analogous acyclic phosphinates. In our earlier communication,[2] we suggested tentatively that the slow rate might be caused by electrostatic effects, provided that the dimer **1** had the *exo* configuration. Now that it has been shown[15] by X-ray crystallography that the geometry is *endo*, that explanation is clearly invalid. Probably the correct explanation is steric; Rothberg and Russo[24] have offered a steric explanation for similar data for the attack of I^- on tosyl derivatives of methanoperhydroindenes.

pH–Rate Profiles. The pH–rate profile for the hydrolysis of the dimer is shown in Figure 3. The observed first-order rate constant, between pH 1 and 10, can be represented by

$$k_{\text{obsd}} = k_{\text{H}^+}(\text{H}^+) + k_{\text{w}} + k_{\text{OH}^-}(\text{OH}^-) \qquad (1)$$

where $k_{\text{H}^+} = 3.0 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$, k_{w} (the "water rate") $= 5.0 \times 10^{-6}\ \text{sec}^{-1}$, and $k_{\text{OH}^-} = 5.5 \times 10^{3}\ M^{-1}\ \text{sec}^{-1}$. This much of the pH–rate profile is conventional; the interesting part of the profile concerns the maximum in the rate that it attained in 0.05–0.2 *M* acid.

The reduced dimer shows a plateau (rather than a maximum) in its pH–rate profile around 0.1 *M* acid (Figure 4). The region where the rate is proportional to the hydrogen ion concentration is short, and the second-order rate constant correspondingly uncertain. In strong acid the rate of hydrolysis rises, whereas that for the dimer falls. Although we have not examined this hydrolysis in detail, we suggest that the increase in rate corresponds to the onset of carbon–oxygen fission.

The pH–rate profiles for many phosphate esters show a maximum in acidic solution. In particular, the hydrolysis of *p*-nitrophenyl phosphate[25] shows a maximum at about 4 *M* in perchloric acid and about 5 *M* in hydrochloric acid; the hydrolysis of *p*-nitrophenyl diphenyl phosphate shows a maximum at about 2.5 *M* acid and that of triphenyl phosphate at about 1.5 *M* acid in 60:40 v/v dioxane–water,[26] and *p*-nitrophenyl diphenyl phosphinate shows a maximum at about 1.5 *M* perchloric acid in 40:60 v/v dioxane–water.[27] These maxima are highly sensitive to ionic strength, so that the rates of hydrolysis of *p*-nitrophenyl diphenyl phosphate in solutions of HCl and LiCl in dioxane–water as solvent do not show maxima; the rates continue to rise as the acid concentration is increased even up to 8 and 10 *M*. These data led Barnard, *et al.*, Bunton, *et al.*, and Haake and Hurst to conclude that the maxima were caused by the selective hydration of the intermediate relative to the starting materials. The maximum, and even the decrease in rate with increasing acidity, was postulated to be caused by the decrease in the activity of water in the strongly acid solutions.[24]

This explanation may or may not[28] account for the rate maxima previously observed, but it will certainly not account for those here reported. In the previous cases studied, the rate maximum occurs at 1.5–4 *M* acid, where the activity of water is somewhat reduced over that in dilute solutions. Furthermore, the salt effects upon the reaction are large and negative. However, in the present instances, the rate maximum occurs at 0.05–0.2 *M* acid, where the activity of water is nearly unity.[29] Therefore, some entirely different explanation is required to account for the observed fact.[30]

Rate-Limiting Pseudorotation. One possibility that should be considered is that the rate-limiting step for the over-all reaction changes from the formation of a pentacovalent intermediate in dilute acid to pseudorotation in strong acid solutions, as illustrated by eq 3.

$$\begin{gathered}
\text{E} + \text{H}^+ + \text{H}_2\text{O} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{EH}_3\text{O}^+ \\
\text{EH}_3\text{O}^+ \overset{K}{\rightleftharpoons} \text{EH}_2\text{O} + \text{H}^+ \\
\text{EH}_2\text{O} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \text{E}'\text{H}_2\text{O} \qquad (3) \\
\text{E}'\text{H}_3\text{O}^+ \overset{K'}{\rightleftharpoons} \text{E}'\text{H}_2\text{O} + \text{H}^+ \\
\text{E}'\text{H}_3\text{O}^+ \xrightarrow{k_3} \text{products}
\end{gathered}$$

Here E represents the ester **1**, EH_2O represents the hydrated ester **10**, and EH_3O^+ represents the protonated form of **10**. The step (eq 1) controlled by the rate constants k_2 and k_{-2} is pseudorotation, and converts EH_2O (**10**) into $E'H_2O$ (**11**). $E'H_2O$ then decomposes through its conjugate acid to complete a symmetrical mechanism.[6,7] Water enters an apical position in a cationic trigonal-bipyramidal intermediate, and an alcohol molecule leaves from an apical position in a similar intermediate.

It is here assumed that pseudorotation takes place through the unprotonated hydrate, EH_2O and that the conjugate acid, EH_3O^+, does not serve as an intermediate in pseudorotation. This assumption is a reasonable one. An extension of Muetterties' rule[11] (that electron-withdrawing substituents are placed preferentially in apical positions) suggests that the proton in EH_3O^+ should be attached to an apical substituent, since a protonated oxygen atom is more electron withdrawing than an electrically neutral one. If this pref-

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(24) I. R. Rothberg and R. V. Russo, *Chem. Commun.*, 998 (1967).

(25) P. W. C. Barnard, C. A. Bunton, D. Kellerman, M. M. Mhala, B. Silver, C. A. Vernon, and V. A. Welch, *J. Chem. Soc., B*, 227 (1966).

(26) C. A. Bunton, S. J. Farber, and E. J. Fendler, *J. Org. Chem.*, **33**, 29 (1968).

(27) P. Haake and G. Hurst, *J. Am. Chem. Soc.*, **88**, 2544 (1966).

(28) An alternative explanation postulates these steps

$$\begin{gathered}
(\text{RO})_2(\text{ArO})\text{PO} + \text{H}_2\text{O} + \text{H}^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (\text{RO})_2(\text{ArO})\text{P(OH)}_2 + \text{H}^+ \\
(\text{RO})_2(\text{ArO})\text{P(OH)}_2 \xrightarrow{k_2} (\text{RO})_2\text{PO(OH)} + \text{H}^+ + \text{ArO}^-
\end{gathered} \qquad (2)$$

This scheme does not violate microscopic reversibility, or an expanded version of microscopic reversibility, since phenoxide or nitrophenoxide ion is a much better leaving group than hydroxide or alkoxide ion. If the hydrolyses follow this scheme, the rates would become independent of acidity at high acid concentrations. The decrease in rate in 1.5–5 *M* acid would still be caused by the decrease in water activity as postulated by Barnard,[25] Bunton,[26] Haake,[27] and their collaborators, but the decrease in water activity would not have to overcome an expected increase in rate with increasing acidity, but would operate against a rate that, at constant water activity, would be independent of acidity.

(29) P. A. H. Wyatt, *Discussions Faraday Soc.*, **24**, 162 (1958).

(30) Measurements in 95% acetic acid (such as those carried out with other compounds by K. B. Wiberg and F. J. Evans, *J. Am. Chem. Soc.*, **80**, 3019 (1958)) show that the reduced dimer is not appreciably protonated at $H_0 = -0.4$. Therefore the maximum is not caused by extensive protonation of the phosphinate esters.

erence is substantial, then the protonated intermediate cannot readily pseudorotate, since a pseudorotation would place the protonated oxygen atom in an equatorial position. Even if these considerations are not binding, the concentrations of the protonated species may be too low to permit it to serve as an intermediate for pseudorotation.

The kinetic equation that corresponds to (3) is

$$\frac{-\mathrm{d(ester)}}{\mathrm{d}t} = \frac{k_1k_2k_3K\mathrm{(ester)(H^+)}}{k_{-1}k_2\mathrm{(H^+)} + k_{-1}k_{-2}K' + k_2k_3K} = k_{\mathrm{obsd}}\mathrm{(ester)} \quad (4)$$

The only differences between the acidity of **10** and **11**, or their rates of decomposition, are probably statistical, so as a good first approximation, $k_{-1} = k_3$, $k_{-2} = 2k_2$, and $K' = 2K$, so that

$$k_{\mathrm{obsd}} = \frac{\frac{1}{5}k_1\mathrm{(H^+)}}{\frac{k_3\mathrm{(H^+)}}{5k_2K} + 1} \quad (5)$$

The kinetic equations (4 -5) show that, at low hydrogen ion concentration, the rate is proportional to acidity, but at high hydrogen ion concentration, the rate becomes independent of acidity. Experimentally, the rate for the dimer becomes more or less independent of acidity in the region from pH 1 to 0. In stronger acid, the rate is lower. This decrease in rate at high acidity is a salt effect of the type previously[25–27] discussed; the data of Table II show that the rate is decreased by large concentrations of sodium perchlorate as much as by large concentrations of acid. However, the rate maximum at 0.05–0.2 *M* acid is unlikely to be caused by a salt effect and has therefore to be ascribed to rate-limiting pseudorotation.

Rate Constant for Pseudorotation. The data in hand are insufficient to estimate the rate constant for pseudorotation. Although we might estimate that k_{-1} or k_3 has the maximum value permitted[31] in solution of about 10^{10} sec^{-1}, we cannot at present estimate K, the ionization constant for a protonated oxyphosphorane. The ionization constants are known[27] for the protonation of some esters of tetracovalent phosphorus acids, but the alkoxy derivatives of pentacovalent phosphorus are insufficiently stable to permit a determination or estimation of the ionization constants of the conjugate acids. Without such constants, the rate for pseudorotation cannot be estimated directly.

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(31) M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, 3, 1 (1964).

The Molecular and Crystal Structure of $P_2O_4C_{12}H_{18}$, 1,8-Diethoxy-3a,4,7,7a-tetrahydro-4,7-phosphinidenephosphindiole 1,8-Dioxide. A Diels–Alder Dimer of 1-Ethoxyphosphole 1-Oxide

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Abstract: The molecular structure of a compound $P_2O_4C_{12}H_{18}$ shows a tricyclic system, in agreement with the chemical evidence. In addition, the ring juncture is shown to be *endo*, and the stereochemistry of O atoms and O–C_2H_5 units at the P atoms is established. The P atom at the bridge has a C–P–C angle of 87°, strained considerably more than that of 96° in the *endo*-fused ring. The higher hydrolytic reactivity of this bridge P atom has been associated with this additional strain by Westheimer and his associates, who have proposed a transition state in detail for the reaction at the P atoms of this and related molecules. The unit cell is orthorhombic, and there are four molecules in the unit cell of dimensions a = 12.61, b = 15.30, and c = 7.24 Å. The space group is Pba2, and the data taken at $-40°$ yield a value of $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.10$ for the 846 independent X-ray maxima.

Westheimer[1] and his associates have shown that the rate of hydrolysis of five-membered cyclic phosphate esters, *e.g.*, methyl ethylene phosphate, is greater by over a millionfold than the rate of hydrolysis of trimethyl phosphate. This enhancement of rate applies both to ring opening and to hydrolysis of the ester group external to the ring.[2–4] This latter hydrolysis is elegantly conceived[4] to lead to a trigonal-bipyramidal transition state, which diminishes strain in the five-membered ring by accommodating a near 90° O (apical)–P–O (equatorial) angle in the ring, and which is followed

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

(2) P. C. Haake and F. H. Westheimer, *J. Am. Chem. Soc.*, 83, 1102 (1961).

(3) F. Covitz and F. H. Westheimer, *ibid.*, 85, 1773 (1963).

(4) E. A. Dennis and F. H. Westheimer, *ibid.*, 88, 3431, 3432 (1966).