pH–Rate Profiles for the Oxygen-18 Exchange and Epimerization of a Phosphetane Oxide. Rate-Limiting Pseudorotation

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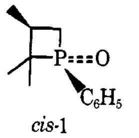
Abstract: pH–rate profiles for epimerization and ^{18}O exchange of 1-phenyl-2,2,3-trimethylphosphetane 1-oxide are presented. The profiles show that the rates of epimerization and exchange are proportional to hydroxide ion concentration at pH 9–12 and are independent of acidity between pH 4 and 8. Epimerization is slower than exchange by factors of 5–140 in this pH range. In the acid region, exchange is much faster (10^4-fold at 4 *M* HCl) than epimerization, and only the former reaction is proportional to the hydrogen ion concentration. A rate maximum observed in dilute acid for the slower epimerization reaction is interpreted as evidence that pseudorotation of the pentacovalent intermediates is rate limiting. A rate maximum observed for exchange in strong acid is ascribed to a decrease in the activity of water.

Recent attention has been focused upon the interpretation of the rate maxima observed in the acid hydrolyses of phosphate esters[1] and phosphinate esters.[2] Rate maxima in 1–5 *N* acid have been generally ascribed to a decrease in the activity of water[1,3] while the rate maximum in dilute acid for a strained bicyclic phosphinate ester has been interpreted as evidence for rate-limiting pseudorotation[4] of a pentacovalent intermediate.[2,5] We now wish to report the first example of a compound which shows *both a rate maximum in strong acid due to a decrease in the water activity and a rate maximum in dilute acid due to rate-limiting pseudorotation.* This study also presents the first pH–rate profiles for epimerization and ^{18}O exchange of a phosphine oxide, 1-phenyl-2,2-3-trimethylphosphetane 1-oxide (**1**). It is hoped that the study will further help to unravel the factors responsible for the disparate results previously observed in the reactions of phosphine oxides[6–12] and firmly establish the important role played by the pentacovalent intermediate in the reactions of these compounds.


cis-1

Experimental Section

Materials. Synthesis of 1-Phenyl-2,2,3-trimethylphosphetane 1-Oxide (1). A mixture of the two isomers of **1** was prepared according to the procedure of Cremer.[13] Repeated recrystallization of the 20:80 (cis:trans) mixture from cyclohexane resulted in enrichment of the cis isomer[14] into the supernatant (mp 53–56° for 75% cis) and fractional separation of 96% trans crystals (mp 87°).

Preparation of 1-Phenyl-2,2,3-trimethylphosphetane 1-[^{18}O]-Oxide (1-^{18}O). Labeled phosphine [^{18}O]oxide was prepared by heating for 2 days at 100° 0.5 g of **1** in 1.0 ml of 70% $H_2{}^{18}O$ (Dia-Prep) which had been made acidic (pH < 1) with anhydrous HCl gas. Simple high-vacuum distillation of the two-phase mixture into a liquid nitrogen trap allowed quantitative recovery of the labeled water and HCl. The recovered, labeled phosphine oxide was recrystallized.

Buffers. Reagent grade buffer salts were used throughout without any additional purification. Redistilled water and freshly distilled dioxane were employed. Since the reactions were run at 100.8°, the pH's of the buffers at 85, 90, and 95° were determined and the values extrapolated to 100.8°. The pH's were measured in a Radiometer TTA31 thermostated micro titration assembly on a Radiometer PHM 26 pH meter fitted with the special high-temperature glass electrode, Type G202CH, and external KCl salt bridge B530 connected to a Type K4018 calomel electrode. The meter was calibrated against NBS standard buffers.[15] Both temperature and pH were measured in the same Radiometer thermostated vessel under a flow of argon, and the pH's are believed accurate to ±0.1 pH unit. Unfortunately, the pH's of some of the weakly alkaline buffers tended to drift under the extended reaction times (several weeks or *months*) and the elevated temperature of the reaction. It is not believed that the buffer instability introduced any significant errors in the results obtained, however.

Kinetic Methods. Epimerization Rates. A mixture enriched to 75% in the cis isomer of **1** was dissolved in the appropriate nonalkaline buffer solution and sealed in an nmr tube under argon. Epimerization was followed by observing the nmr integrations for the 2-methyl groups of the isomers. In 0.01 *M* KOH or more concentrated base solutions reactions were followed either in specially constructed alkali-resistant Corning 7280 glass nmr tubes (Wilmad), in Nmr Specialties Teflon liners for normal nmr tubes, or in screw cap, all-Teflon 5-ml sample tubes. In the latter case, the phosphetane oxide was quantitatively extracted from the neutralized solution with $CHCl_3$, and the nmr spectra were taken of the $CHCl_3$ solution. In order to economize on the amount of sample used in the kinetic run, the original extracted phosphine oxide (after evaporation of the $CHCl_3$) was redissolved in fresh base solution and epimerization continued on that sample. In most cases the

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[1] C. A. Bunton, *Accounts Chem. Res.*, **3**, 257 (1970), and references therein.

[2] R. Kluger and F. H. Westheimer, *J. Amer. Chem. Soc.*, **91**, 4143 (1969).

[3] P. Haake and G. Hurst, *ibid.*, **88**, 2544 (1966).

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

[5] The dilute acid maximum in the pH–product profile for the hydrolysis of methyl ethylene phosphate represents the only other example of such dilute acid maxima: R. Kluger, F. Covitz, E. Dennis, L. D. Williams, and F. H. Westheimer, *J. Amer. Chem. Soc.*, **91**, 6066 (1969).

[6] K. L. Marsi, *ibid.*, 4724 (1969).

[7] W. Hawes and S. Trippett, *Chem. Commun.*, 295 (1968).

[8] K. E. DeBruin, G. Zon, K. Naumann, and K. Mislow, *J. Amer. Chem. Soc.*, **91**, 7027 (1969).

[9] D. Samuel and B. L. Silver, *Advan. Phys. Org. Chem.*, **3**, 123 (1965).

[10] L. Horner and H. Winkler, *Tetrahedron Lett.*, 3271 (1964).

[11] D. B. Denney, A. Tsolis, and K. Mislow, *J. Amer. Chem. Soc.*, **86**, 4486 (1964).

[12] M. Halman and S. Pinchas, *J. Chem. Soc.*, 3264 (1958).

[13] S. E. Cremer and R. J. Chorvat, *J. Org. Chem.*, **32**, 4066 (1967).

[14] This assignment is based upon the analogous X-ray structure and properties of a related phosphetane oxide: C. N. Caughlan and M. Hague, *Chem. Commun.*, 1229 (1968); ref 9; S. E. Cremer and B. C. Trivedi, *J. Amer. Chem. Soc.*, **91**, 7220 (1969).

[15] V. Bower and R. Bates, *J. Res. Nat. Bur. Stand.*, **59**, 261 (1957).

Table I. Rate Constants for ^{18}O Exchange and Epimerization of **1** in 10% Dioxane–Buffer at 100.8°, I = 0.05 *M*

pH at 100.8°	Buffer[a]	$k \times 10^6$, sec^{-1}: Epimerization	$k \times 10^6$, sec^{-1}: Exchange
1.45	0.05 *M* HCl	1.01, 1.09, 1.06,[c] 1.04[d]	
1.6	0.025 *M* HCl, KCl	1.13	
1.9[b]	DCl, KCl in D_2O	0.74, 0.74	5.77
2.0	0.01 *M* HCl	1.16, 1.32	8.0, 10.5,[e] 11.5
2.64	0.05 *M* phosphate, HCl	1.13	
2.98	0.001 *M* HCl		3.3
3.14	0.05 *M* phthalate		3.04
3.32	0.05 *M* phosphate, HCl	0.92	
3.73	0.05 *M* phthalate, HCl	0.96	
4.34	0.005 *M* phthalate		1.13
4.26	0.05 *M* phthalate	0.77, 0.83	3.2
4.35[b]	0.05 *M* phthalate in D_2O	0.62, 0.64	0.48[f]
4.80	0.2 *M* phosphate	0.83	
5.30	0.05 *M* phosphate		1.05
5.36	0.005 *M* phthalate	0.82	1.9
6.24	0.05 *M* phthalate	0.80	0.96[h]
7.77	0.05 *M* phosphate	0.81, 0.83	
7.95	0.05 *M* phosphate		1.55
8.64	0.05 *M* phosphate	0.83	0.90
9.38	Fisher pH 9 buffer 0.05 *M* borate–carbonate	0.91, 1.06	4.8
9.35	Fisher pH 10 buffer 0.05 *M* carbonate		2.75
10.2[g]	0.01 *M* KOH		3.6
11.3[g]	0.1 *M* KOH	2.66, 2.74	77.4
12.3[g]	1.0 *M* KOH	26	

[a] Buffers made up to ionic strength with KCl. [b] pD = pH "meter reading" + 0.4 at ~25°: T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961). [c] 0.05 *M* KCl added. [d] 0.2 *M* KCl added. [e] 70% cis. [f] 0.005 *M* phthalate in D_2O, pD 4.48. [g] pK_a = 12.3 at 100°: R. Keller, "Basic Tables in Chemistry," McGraw-Hill, New Yoik, N. Y., 1967, p 226. [h] 0.01 *M* phosphate buffer.

concentration of **1** was 0.4–0.5 *M* when the reaction was followed directly in the nmr tube. Because of the limited solubility of the oxide in purely aqueous buffer solutions, 10% (w/w) dioxane was normally added. Because the temperature dependence of the pH's was determined for the purely aqueous solutions only, the pH's for the actual kinetic runs in 10% dioxane are reported for these aqueous solutions. However, the small amount of dioxane added shifts the measured pH's only slightly; correction for the dioxane may in fact introduce greater uncertainty than simple neglect of its effect.[16] Good first-order kinetics were obtained and, surprisingly, no decomposition of the phosphetane oxide was observed in any of the solutions even after several months at 100°!

^{18}O Exchange Rates. Rates for exchange of 95% *trans*-**1** (enriched to 70% ^{18}O) in the appropriate buffer solutions were determined by quantitative ir spectroscopy on a Beckman 521 grating spectrometer. Samples were sealed in Pyrex tubes or, for alkaline solutions, placed in a specially constructed Teflon/Kel-F screw top vessel fitted with a Teflon/Kel-F high-pressure valve. Aliquots were serially removed from a themostated temperature bath either by quenching one of the Pyrex tubes in ice-water or drawing off a sample by opening the value of the Teflon/Kel-F vessel. The phosphetane oxide was quantitatively extracted from the aqueous aliquots with $CHCl_3$, the organic layer evaporated, and the residue dissolved in 75 μl of CCl_4 (concentration of oxide generally 0.23 *M*). Absorbances at both 1207 cm^{-1} (s, *trans*-**1**-^{16}O), and 1188 cm^{-1} (s, *trans*-**1**-^{18}O) for the phosphoryl stretching frequencies were monitored in 0.1-mm NaCl sealed ir cells and shown to obey Beer's law and to yield the same good first-order kinetics. A tight isosbestic point at 1194 cm^{-1} indicated that ^{18}O exchange was the only process being observed except in the slow, neutral pH region where trans to cis isomerization was also occurring more slowly.[17] Interestingly, the intensity of the absorbances at 1225–1228 and 1166–1168 cm^{-1} changed at the same rate as the major phosphoryl stretching frequencies. An example of the type of spectra obtained is shown in Figure 1. As a further check on this convenient and simple kinetic procedure, several mass spectral runs on a Perkin-Elmer Model 270 mass spectrometer monitoring the M and M + 2 ions were shown to yield similar exchange rates.

Nmr Spectra. Proton nmr spectra were carried out on a Varian A-60A nmr spectrometer. A Bruker HFX-90 spectrometer operated at 36 MHz was used for the determination of the phosphorus nmr spectra.

Results

Rate Constants. The first-order rate constants for epimerization and exchange are presented in Tables I and II and the pH–rate profiles in Figure 2. While the

Table II. Rate Constants for Epimerization and ^{18}O Exchange of **1** in Strong Acid–10% Dioxane (w/w), 100.8°

H_0[a]	Acid, concn	$k \times 10^6$, sec^{-1}: Epimerizn	$k \times 10^6$, sec^{-1}: Exchange
−4.3	18 *N* H_2SO_4		13.4[d]
−4.0	11.6 *M* HCl		41.3[d]
−4.0	11.6 *M* DCl–D_2O[b]		55.0[d]
−3.3	9.3 *M* HCl		70.0[d]
−1.4	4.0 *M* HCl[c]	0.14	462[d]
−0.63	1.9 *M* HCl	0.52	394[d]
−0.08	0.8 *M* HCl	0.77	265
	0.8 *M* HCl + 3 *M* KCl	0.27	
0.20	0.5 *M* HCl	0.87	
0.55	0.25 *M* HCl	0.98	
0.98	0.1 *M* HCl	1.01, 1.07,[e] 1.16[e]	70
1.12	0.075 *M* HCl	0.91	

[a] H_0 values at 25°: F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 1 (1957). Unfortunately the acidity function for HCl has not been determined at 100°. However, as pointed out by C. H. Rochester, "Acidity Functions," Academic Press, New York, N. Y., 1970, pp 38–40, 223–224, the variation of H_0 with temperature, dH_0/dT, is small and approximately independent of acid strength up to 80°. The effect of 10% dioxane on the acidity function is also expected to be small and therefore the well-defined function at 25° has been chosen. [b] Acidity function given for H_0 since D_0 has not been defined for concentrated DCl–D_2O solutions. The two scales are expected to be quite similar, though: C. H. Rochester, footnote *a*, p 36. [c] Dioxane partially reacts at this acid concentration. [d] No dioxane. [e] 0.05 *M* KCl added.

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[16] L. G. Van Uitert and C. G. Haas, *J. Amer. Chem. Soc.*, 75, 451 (1953).

[17] The slight increases in the absorbances of shoulders at 1199 cm^{-1} (cis ^{16}O) and 1185 cm^{-1} (cis ^{18}O) did not interfere with our calculations.

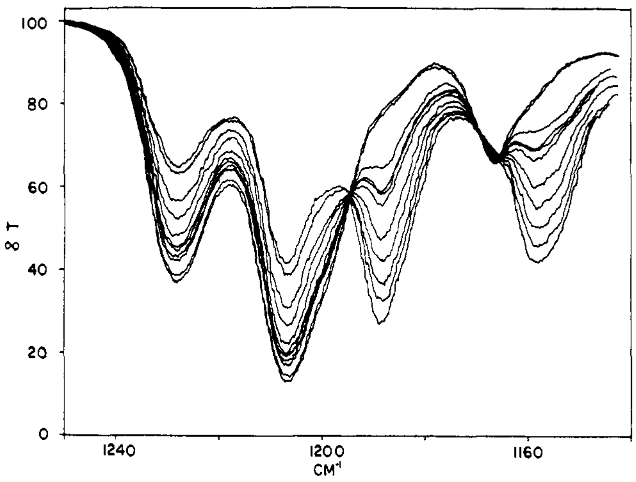

Figure 1. Ir spectra following the rate of ^{18}O exchange (see text).

rate constants are independent of phosphetane oxide concentration, they are dependent upon the buffer concentration (see Table III). Therefore, the points in the profiles were obtained by extrapolating the rate constants to zero buffer concentration. Actually this was only necessary for the exchange reaction and, then, only around neutral pH where buffer catalysis was most noticeable. While there may be some buffer catalysis in the epimerization reaction, the observed differences are within the experimental errors (*ca.* ±10% in the rate constants).

Table III. Buffer Catalysis in the ^{18}O Exchange and Epimerization of **1** at 100.8°, 10% Dioxane

Buffer composition	pH	$k \times 10^6$, sec^{-1} Epimerizn	$k \times 10^6$, sec^{-1} Exchange
0.001 M NaH_2PO_4[a]	4.13	0.75	
0.05 M NaH_2PO_4	4.80	0.83	
0.05 M NaH_2PO_4-0.15 M KCl	4.80	1.03	
0.2 M NaH_2PO_4	4.59	1.13	
0.005 M phthalate[a]	4.34		1.10
0.05 M phthalate	4.26	0.77, 0.83	3.2
0.005 M phthalate[a]	5.30		1.05
0.05 M phthalate	5.36		1.9

[a] Made to ionic strength 0.05 M with KCl.

Determination of the pK_a for 1. The pK_a for the phosphoryl group of **1** was determined by an nmr titration procedure similar to that described by Haake.[18] It was possible to follow both the variation in the ^{31}P chemical shift and the *gem*-dimethylphosphorus coupling constants as a function of the degree of protonation of the phosphoryl group. The ^{31}P chemical shift for *trans*-**1** in 10% dioxane-acid varies from −48.2 ppm (*vs.* 85% H_3PO_4) in 1.0 M HCl to −55.4 ppm in 6.6 M HCl. The *gem*-dimethylphosphorus coupling constant for the downfield doublet changes from 18.00 Hz in 1.0 M HCl to 20.60 Hz in 36.0 M H_2SO_4. Plots of log $(BH^+)/(B)$ *vs.* H_0 gave a pK_a of *ca.* −3. However, as observed by Haake[18] for acyclic phosphine oxides, the plots are curved and show slopes less than unity (0.38).

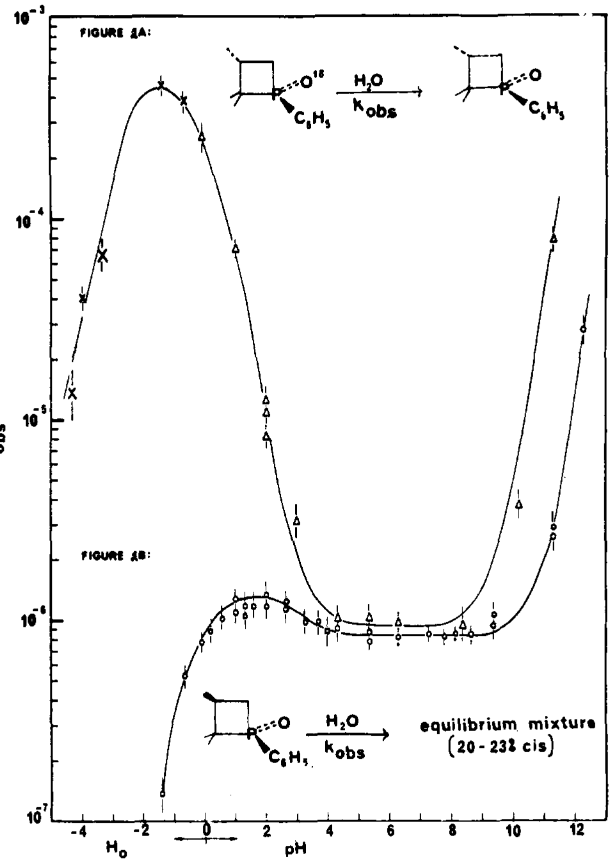

Figure 2. (A) pH–rate profile for the ^{18}O exchange of the phosphetane oxide **1** in 10% (w/w) dioxane–buffer (Δ) or buffer (×) extrapolated to zero buffer concentration at 100.8°. Ionic strength was maintained at 0.05 M for most points. The solid line was generated from eq 2. (B) pH–rate profile for the epimerization of the phosphetane oxide **1** in 10% (w/w) dioxane–buffer (○) at 100.8°. Ionic strength was maintained at 0.05 M for most points. The smooth curve was generated from eq 1.

Discussion

Kinetics and Mechanisms. While numerous mechanistic schemes may be shown to be consistent with either pH–rate profile, we believe that the mechanism offered in Scheme I is the most attractive alternative for several reasons. First, this mechanism satisfactorily predicts the pH–rate profiles for both exchange *and* epimerization. Thus, steady-state treatment of this mechanism gives the rate laws shown in eq 1 and 2 (the

$$k_{\text{obsd}}{}^{\text{epimerization}} = \frac{k_a + k_b{}^*C_{H^+}}{1 + h_0/K_{\text{app}}} + k_c(^-OH) \quad (1)$$

$$k_{\text{obsd}}{}^{\text{exchange}} = k_d{}^*f(C_{H^+}) + k_e + k_f(^-OH) \quad (2)$$

asterisk designates correction for protonation of the substrates, p$K_a \simeq -3$).

The solid lines in Figure 2 are drawn according to eq 1 and 2, where $k_a = 8.5 \times 10^{-7}$ sec^{-1}, $K_{app}k_b = 12.0 \times 10^{-7}$ sec^{-1}, $k_c = 2.7 \times 10^{-5}$ sec^{-1} M^{-1}, $K_{app} = 7.0 \times 10^{-4}$ M, $k_d = 7.0 \times 10^{-4}$ sec^{-1} M^{-1}, $k_e = 9.5 \times 10^{-7}$ sec^{-1}, $k_f = 7.7 \times 10^{-4}$ sec^{-1} M^{-1}, and $f(C_{H^+})$ is either equal to C_{H^+} in dilute acid or is a complex function of acidity and water activity in the strong acid region.[19] Although the individual kinetic

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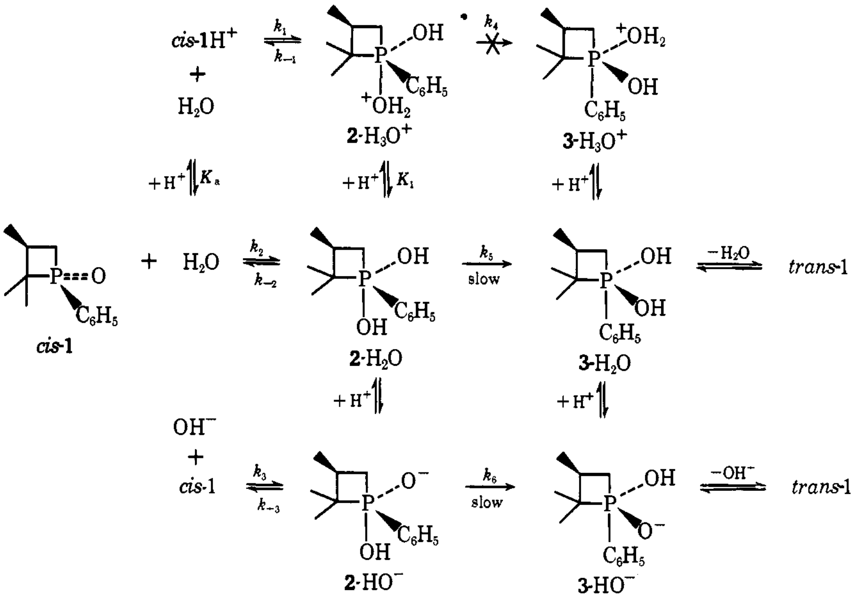
[18] P. Haake, R. D. Cook, and G. H. Hurst, *J. Amer. Chem. Soc.*, **89**, 2650 (1967).

[19] Bunton has derived several rate-acidity expressions to explain the rate maxima observed in some phosphate ester hydrolyses in this

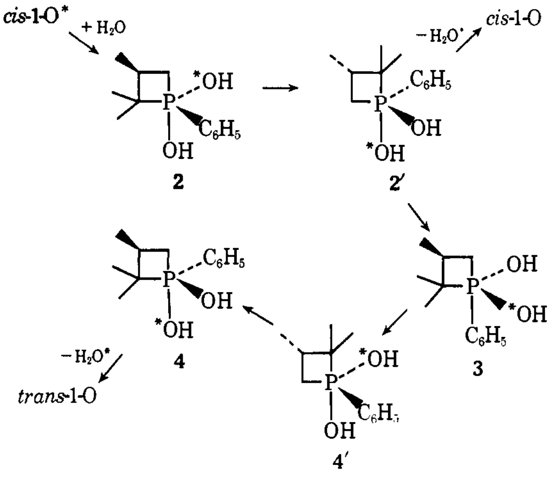
Scheme I. Mechanistic Scheme for ^{18}O Exchange and Epimerization of **1**.



parameters are complex functions of the rate and equilibrium constants of Scheme I, the parameters for exchange and epimerization must be and, in fact, are closely interrelated. As discussed in the Appendix, these parameters are mutually consistent with each other and the microscopic rate constants of Scheme I. Furthermore, deletion of any of the rate constants or equilibrium constants from this mechanism makes it impossible to reproduce the profiles. (These facts alone, of course, do not prove that our mechanism is the correct one.)

Pseudorotation Theory. Second, and more important, however, the essential features of these profiles and mechanism are consistent with our evolving understanding of the nature of pentacovalent phosphoranes and pseudorotation theory.[4,20] The mechanism of Scheme I assumes that an initial hydration step is acid, water, or base catalyzed (k_1, k_2, or k_3). The three pentacovalent intermediates, **2**, may then either pseudorotate to epimerize the phosphorus center (*via* k_4, k_5, or k_6), or alternatively may dehydrate (k_{-1}, k_{-2}, or k_{-3}) to effect exchange of the phosphoryl oxygen with the solvent. Scheme II shows in more detail the actual pseudorotation steps required for these reactions (for the neutral phosphoranes only). Note that Schemes I and II imply a common mechanism for both epimerization and exchange. It is encouraging then that the pH–rate profiles for exchange and epimerization in the region from pH 3 to 12 are quite similar, except that epimerization for the trans isomer is slower than exchange by a factor of 5 at neutral pH and by a factor of 140 in base. The most dramatic difference occurs in the acid region where the two processes follow different dependency upon acid concentration. Around 4 *M* HCl, exchange, which is acid catalyzed, is nearly 10^4 times faster than epimerization, which after having reached a modest rate maximum at pH 2, has shown a falloff in rate with increasing acidity. If we reasonably assume that both the exchange and epimerization processes require formation of the same pentacovalent intermediates, **2**, then some step after the initial hydration of the phosphetane oxide must be rate limiting for the slower epimerization reaction. We propose that *this slower process represents rate-limiting pseudorotation of the pentacovalent intermediates.*

Scheme II. Detailed Reaction Pathway for Epimerization and ^{18}O Exchange of **1**[a]



[a] The equatorial substituents sticking out of the plane of the paper have been used as the "pivots"[4] for the pseudorotation steps.

The following arguments may be advanced in support of this statement. As shown in Scheme II hydration (and thereafter exchange) requires placing one of the electropositive ring carbons in an axial position of the trigonal-bipyramid intermediate, **2**-H_2O. This represents only a *single* violation of the Muetterties polarity rule[21,22] which requires placing the most electronegative groups axial. However, pseudorotation to effect epimerization requires formation of a phosphorane intermediate, **3**-H_2O, which simultaneously forces both a ring carbon and phenyl group diaxial (a *double* violation of the Muetterties rule). This probably is the basis for the additional energy barrier for epimerization.

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strong acid region.[1] Unfortunately, we have not been able to fit the exchange data in strong acid with similar kinetic treatments; $f(C_{H^+})$ is therefore only an empirical relationship.

(20) R. S. Berry, *J. Chem. Phys.*, **32**, 933 (1960).

(21) E. L. Muetterties and R. A. Schunn, *Quart. Rev., Chem. Soc.*, **20**, 245 (1966).

(22) D. Gorenstein and F. H. Westheimer, *J. Amer. Chem. Soc.*, **92**, 634 (1970).

Finally, we observe rate maxima in acid solution for both exchange and epimerization. Most significantly, the positions of the two maxima occur in very different regions of acid strength. By analogy to previous explanations for this behavior in the hydrolyses of phosphate esters[1] and phosphinate esters,[3] we may assign the strong acid (*ca.* 4 *M* HCl) rate maximum for the exchange reaction to a decrease in the activity of water.[23] However, this cannot also be the explanation for the rate maximum for epimerization, which occurs around pH 2 where the activity of water is near unity. As initially proposed by Kluger and Westheimer[2,5] this type of maximum must be related to rate-limiting pseudorotation of the *neutral* phosphorane. Thus, the increase in rate in dilute acid for both exchange and epimerization is probably due to acid-catalyzed hydration and formation of the phosphorane conjugate acid, **2**-H_3O^+. Now assuming that epimerization can only occur through pseudorotation of the neutral intermediate (*i.e.*, $k_4 \ll k_5$), then the epimerization rate will increase with increasing acidity due to the pathway

$$\mathbf{1} + H^+ + H_2O \rightleftharpoons \mathbf{2}\text{-}H_3O^+ \xrightarrow{-H^+} \mathbf{2}\text{-}H_2O \longrightarrow \mathbf{3}\text{-}H_2O$$

since more of the neutral intermediate, **2**-H_2O, will be formed *via* this additional route. However, since the overall pathway (**1** + H_2O → **3**-H_2O) is *not* acid catalyzed, we would expect a leveling off of the rate at higher acidity. The presence of a rate maximum rather than a plateau in this moderate acid region must again be due to a decrease in the activity of water as represented by the decrease in the ratio of C_{H^+}/h_0. Note that eq 1 does not include an empirical function such as the $f(C_{H^+})$ of eq 2; yet it quite closely describes the observed falloff in rate for epimerization.

A major achievement of the pseudorotation theory is its accurate prediction that the conjugate acid **2**-H_3O^+ should not be able to pseudorotate to **3**-H_3O^+. Since this would require a *triple* violation of the polarity rule (the electronegative OH_2^+ group is placed in an unfavorable equatorial position and the carbon groups are placed in the unfavorable diaxial position), this must be an energetically forbidden process!

Additional Evidence. In addition to the preceding kinetic and pseudorotation arguments, several other lines of evidence may be offered in justification of the mechanism in Schemes I and II. The observation of buffer catalysis[24] only in the exchange reaction argues strongly for a rate-limiting proton-transfer step. The absence of buffer catalysis in the epimerization process[25] is consistent with our belief that some subsequent step (pseudorotation) is largely rate limiting for the slower epimerization reaction. The large solvent isotope effect for the exchange reaction (2.4 at pH 4.4 and 1.75 at pH 2, Table IV) further supports the suggestion that exchange involves a rate-limiting proton transfer in the hydration step.[26] As expected, epimerization, which is not hydration rate limiting, shows only small isotope effects. The inverse solvent isotope effect of 0.75 for exchange in concentrated hydrochloric acid is quite similar to the values found for the A2 reaction of simple phosphate monoesters in strong acid. Both reactions would presumably involve rate-limiting hydration of the conjugate acid.[1]

Table IV. Solvent Isotope Effects

pH or pD (or acid concentration)	$(k_H/k_D)_{\text{epimerizn}}$	$(k_H/k_D)_{\text{exchange}}$
11.6 *M* HCl or DCl		0.75 ± 0.1
2.0 ± 0.1	1.6 ± 0.2	1.75 ± 0.2
4.4 ± 0.1	1.3 ± 0.1	2.4 ± 0.2

Finally a large (*ca.* 300%) negative salt effect in strong acid supports our explanation for the epimerization rate maximum.[27]

Alternative Schemes and Comments. Throughout this discussion it has been assumed that axial water attack and axial water leaving are required features of our mechanism in Schemes I and II. Westheimer[4] has justified this belief on microscopic reversibility grounds; that is, if axial attack is the lowest energy pathway in the forward direction, the microscopic reverse (axial leaving of water) must also be the lowest energy path in the reverse direction. Mislow,[28] however, has argued that a broader interpretation of microscopic reversibility[29] could readily take into account a mechanism involving axial attack, and equatorial leaving as long as the reverse process, equatorial attack and axial leaving, was simultaneously possible.

While our results do not require this alternative interpretation of microscopic reversibility, they do require some form of expanded theory. Thus, if microscopic reversibility arguments were rigorously followed, exchange would have to pass through **4**-H_2O (Scheme II) or its epimer where both methylene and labeled oxygen are in the axial positions. Since loss of labeled water from **4**-H_2O would result in epimerization, the exchange and epimerization rates would have to be identical. The fact that the rates are *not* identical resigns us to the position that **2′**-H_2O is the intermediate which loses labeled water in the exchange reaction. Unfortunately **2**-H_2O and **2′**-H_2O are not identical, differing in that the former has an axial methylene group while the latter has an axial isopropylidene group. Model phosphorane studies[30] have shown that structures such as **2**-H_2O should probably be at least 7 kcal more stable than **2′**-H_2O structures. (The pseudorotation barrier for placing an isopropylidene group axial is 7 kcal greater than the barrier for placing a methylene group axial.) If H_2O enters axial opposite to the ring methylene group (**2**-H_2O) and yet H_2O^* leaves axial opposite to the ring isopropylidene group (*via* **2′**-H_2O), then we must concede that H_2O must be able to enter or leave

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[23] Protonation of the phosphetane oxide may be an important factor as well.

[24] From the limited data of Table III, it may be shown that both the monoanion and the neutral phthalic acid species are catalytically active components of the buffer. There is no question that exchange is subject to general acid catalysis then, and it is possible that the monoanion may function as a general base catalyst. Unfortunately other less ambiguous monofunctional buffers were not studied.

[25] Actually, Table III shows that there may be a small amount of buffer catalysis in the exchange reaction. As derived in the Appendix, hydration must be partially rate determining around neutral pH for epimerization since $k_{-2}/k_5 \simeq 5$–10, implying that k_5 is not solely rate limiting.

[26] Solvent isotope effects greater than 30–40% imply some proton transfer in the transition state: W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 267.

[27] A similar observation has been made by Kluger and Westheimer[5] for explaining the dilute acid maximum in their study.

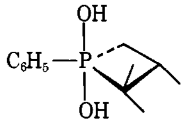
[28] K. Mislow, *Accounts Chem. Res.*, **3**, 321 (1970).

[29] R. L. Burwell, Jr., and R. G. Pearson, *J. Phys. Chem.*, **70**, 300 (1966).

[30] D. Gorenstein, *J. Amer. Chem. Soc.*, **92**, 644 (1970).

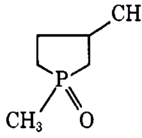
axial, opposite to either the isopropylidene or methylene groups.[31]

One mechanism which can more confidently be eliminated from consideration is the pseudorotation pathway *via* the ring diequatorial intermediate **5**. If the reaction were to pass through this intermediate, the rate of epimerization should be the same as the rate of exchange, since every labeled oxygen displacement would invert the phosphorus center. The 10^4-fold faster rate of exchange in acid thus argues against this pathway. Furthermore, as originally hypothesized by Westheimer[4,32] and shown by Ramirez,[33] Denney,[34] and ourselves[22,30] placing a small ring in the diequatorial position of a trigonal bipyramid is a violation of the strain rule[35] and should effectively prevent such a structure from being formed in these reactions.



5

Previous Studies. The role of the pentacovalent intermediate in the reactions of cyclic phosphate esters,[32,36] cyclic phosphinate esters,[2] and cyclic phosphonium salts[37,38] is now well established. This is not true, however, for the reactions of phosphine oxides.[6–12] Although it has recently been suggested that the phospholane oxide **6** epimerizes readily (2 hr, refluxing concentrated HCl) *via* addition of H_2O and formation of a pentacovalent intermediate,[6] the pentamethylphosphetane oxide **7** was recovered unisomerized under similar conditions.[7,8,39] In contrast, the quadracyclic phosphetane oxide **8** undergoes facile ^{18}O exchange in strong acid.[9] Understanding of the role of the pentacovalent intermediate in the reactions of acyclic phosphine oxides is similarly confused.[10,12] At the onset of this work it was hoped that a study such as this would help us understand the various factors responsible for these conflicting results. However, while at the present time we are in the position to offer some helpful conclusions (as well as a bit of conjecture and a note of caution), some disturbing problems still exist. Certainly one possible explanation for these disparate results may be found in the unexpected pH dependence for the rate of epimerization and exchange found in the phosphetane oxide **1**. Recall that the rate of epimerization of **1** *falls off* in acid solution and, hence, it may not be unusual that in the very strong acid solutions commonly employed in previous studies, some phosphine oxides undergo no observable epimerization. The facile ^{18}O exchange of **8** is now understandable in terms of the observed *acid catalysis found only for exchange* in **1**. The absence of epimerization in the pentamethylphosphetane oxide **7** is also understandable in the context of the additional *gem*-dimethyl group barrier. However, it is still difficult to explain why the five-membered ring phospholane oxide **6** epimerizes so much more readily than the four-membered ring oxide **1**.



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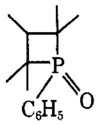

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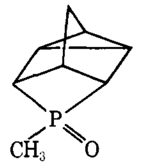

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To understand the basis for this difficulty, it is necessary to expand upon our previous discussion of the strain rule. For some time now[4] it has been recognized that the ring strain associated with incorporating a tetrahedral phosphorus atom in a small ring system can be relieved through formation of a pentacovalent intermediate.[40] While ring strain energy will be released through this mechanism in compounds **1** and **6**, a less polar ring carbon will be forced into an axial position, in violation of the polarity rule. This must partially or even wholly[28,41] cancel some of the strain energy that is to be gained. A simple extension of these principles would indicate that a more highly strained ring system would release a greater amount of strain energy in forming a trigonal-bipyramid intermediate and thereby further overcome the barrier to placing a ring carbon in an axial position.[42] Thus, based upon these considerations, the smaller four-membered ring phosphine oxide **1** should be more highly strained and, hence, *more reactive* than Marci's five-membered ring oxide **6**. Why, then, the more rapid rate of epimerization for **6**? This is the root of the difficulty, and unfortunately, while pseudorotation theory allows us to understand much about these reactions, much apparently is still to be learned.[43]

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(31) Actually an additional opposing factor may make this dual mode of attack and leaving more acceptable by decreasing the *ca.* 7-kcal energy requirement favoring an axial methylene group. Thus a steric factor favoring water approach from the less hindered, methylene side of the phosphetane oxide (resulting in an axial isopropylidene group) may be operating as well.

(32) (a) P. C. Haake and F. H. Westheimer, *J. Amer. Chem. Soc.*, **83**, 1102 (1961); (b) E. A. Dennis and F. H. Westheimer, *ibid.*, **88**, 3432 (1966).

(33) F. Ramirez, C. P. Smith, and S. F. Pilot, *ibid.*, **90**, 6726 (1968).

(34) D. Z. Denney, D. W. White, and D. B. Denney, *ibid.*, **93**, 2066 (1971).

(35) The basis for this rule is the recognition that in order to minimize ring strain a four- or five-membered ring prefers to occupy one axial and one equatorial site in a trigonal bipyramid. A corollary to this rule requires that a diequatorial ring be disallowed, for ring expansion to 120° in the two equatorial positions should increase ring strain.

(36) R. Kluger, F. Covitz, E. Dennis, L. D. Williams, and F. H. Westheimer, *ibid.*, **91**, 6066 (1969).

(37) K. E. DeBruin and K. Mislow, *ibid.*, **91**, 7393 (1969).

(38) S. E. Cremer, R. J. Chorvat, and B. C. Trivedi, *Chem. Commun.*, 769 (1969).

(39) We have also found that 7 is unreactive at pH 2 in 40% dioxane at 100° for *several* months.

(40) Assuming that the strain rule is obeyed, the ring spans one axial and one equatorial position of the trigonal-bipyramid structure (C–P–C angle of 90°).

(41) This argument has been shown to nicely explain why five-membered phosphinate esters do *not* hydrolyze much faster than their acyclic analogs: ref 4, 35b, and G. Aksnes and K. Bergesen, *Acta Chem. Scand.*, **20**, 2508 (1966).

(42) Kluger and Westheimer have concluded that this must be the explanation for the enhanced rate of hydrolysis of a highly strained bicyclic phosphinate ester.[2]

(43) One possible explanation is that the epimerization mechanism for the two oxides proceeds through two entirely different mechanisms. As suggested by Mislow,[26] the ring diequatorial, direct displacement process that we have shown is not important in our reaction may, in fact, be the preferred mechanism for inversion in larger ring phosphorus compounds. This mechanism may easily be tested by a comparison of the rates of ^{18}O exchange and epimerization for a phospholane oxide. We hope that additional studies in progress exploring these possibilities will be able to provide final solution to these questions.

Appendix. Relationship between Rate Equations and Mechanism

A steady-state solution of the chemical equations of Scheme I yields, after deletion of minor terms, rate eq 1 and 2, where[44]

$$k_a^* = k_2k_5/(k_{-2} + k_5) \qquad k_b^*K_{app} = \frac{K_1k_1k_5}{k_{-1}K_a}$$

$$k_c^* = k_3k_6/(k_{-3} + k_6) \qquad K_{app} = \frac{K_1(k_{-2} + k_5)}{k_{-1}}$$

$$k_d = k_1/K_a$$

$$k_e = k_{-2}k_2/(k_{-2} + k_5) \qquad k_f = k_3k_{-3}/(k_{-3} + k_6)$$

Now either the epimerization data taken separately (k_a and k_b) or the exchange data taken separately (k_e and k_d) may be used to calculate the rate ratio of the water-catalyzed hydration step (k_2) to the acid-catalyzed hydration step (k_1)

$$k_a/k_bK_a = k_2/k_1 \approx 10^{-6} \qquad \text{(assuming } K_a \approx 10^3\ M\text{)}$$

and

$$k_e/k_dK_a = k_2/k_1 \approx 10^{-6}$$
$$\text{(assuming } k_e \approx k_2\text{; see } k_e/k_a \text{ ratio)}$$

Either *independent* calculation shows that acid-catalyzed hydration is 10^6 times faster than the water rate. This is encouraging evidence that exchange and epimerization follow a common mechanism, hopefully that of Scheme I. Similarly, $k_e/k_a = k_{-2}/k_5 \approx 5.5$, $k_1 \approx 7 \times 10^{-1}$ sec^{-1}, and $k_2 = 1.1 \times 10^{-6}$ sec^{-1}, and since $k_f/k_c = k_{-3}/k_6 \approx 140$, $k_3 \approx k_f = 7.7 \times 10^{-4}$ sec^{-1} M^{-1}, $k_2/k_3 \approx 10^{-3}$ M. These results indicate that hydration is partially rate limiting for epimerization in neutral solution; on the other hand, pseudorotation is entirely rate limiting for epimerization in strong base and acid. This is reasonable since the water-catalyzed hydration step is so inefficient compared to the acid- or base-catalyzed[45] hydration step.

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[44] In order to allow a direct comparison of the above rate terms, the observed epimerization rate constants (designated by an asterisk) were corrected for reaction of the trans isomer only

$$k_{obsd} = k_{cis} + k_{trans}$$

$$K_{eq} = (\text{trans})/\text{cis} = k_{cis}/k_{trans} \simeq 4$$

[45] Unfortunately, we find it difficult to say anything more about the base-catalyzed reaction.

Vinyl Ether Hydrolysis. IV. Catalysis in Dilute Hydrofluoric Acid Solutions[1]

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Contribution from the Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois 60616. *Received August 12, 1971*

Abstract: The hydrolysis of four vinyl ethers (ethyl vinyl, phenyl isopropenyl, and methyl and ethyl cyclohexenyl) was found to be catalyzed strongly by molecular hydrofluoric acid (HF), but not at all by the hydrogen bifluoride ion (HF_2^-) present in dilute aqueous hydrofluoric acid buffers. This result agrees with the outcome of a previous investigation of the catalytic activity of aqueous hydrofluoric acid solutions, provided that an error in the earlier work is corrected, and is consistent also with the molecular structures of HF and HF_2^-. The catalytic strength of HF is in all cases nearly an order of magnitude greater than expected on the basis of Brønsted relations using carboxylic acid data; these deviations can be understood on electrostatic grounds.

In dilute aqueous solution, hydrogen fluoride ionizes as an acid (eq 1) and also associates with fluoride ion

$$HF \rightleftharpoons H^+ + F^- \qquad (1)$$

(eq 2); these solutions therefore contain three acidic

$$HF + F^- \rightleftharpoons HF_2^- \qquad (2)$$

species, HF, H^+, and HF_2^-. This complexity, however, might still leave the catalytic activity of these solutions fairly simple if HF_2^- were to be as poor a proton donor as expected on the basis of its molecular structure: it is a linear, negatively charged species with hydrogen at the center,[2] from which it should be fairly difficult to remove a proton, much harder than from HF. Nevertheless, in an earlier investigation of this matter,[3] the conclusion was reached that HF and HF_2^- have comparable acid catalytic strengths.

In a preliminary account of the present work,[4] we pointed out that this previous conclusion was based upon a faulty kinetic analysis; we also reported that HF catalyzes the hydrolysis of ethyl vinyl ether but HF_2^- does not. That work is described here in detail, and additional data for the hydrolysis of several other vinyl ethers by HF are presented. The latter are of special interest in view of the fact that HF gives up a proton without undergoing structural reorganization, which might make it a better catalyst than other acids of similar pK_a whose ionization is accompanied by extensive changes.[5]

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[1] (a) This research was supported by grants (GP 6580 and GP 9253) from the National Science Foundation; (b) part III: A. J. Kresge, H. L. Chen, Y. Chiang, E. Murrill, M. A. Payne, and D. S. Sagatys, *J. Amer. Chem. Soc.*, **93**, 413 (1971).

[2] K. Nakamoto, "Infrared Spectra of Inorganic and Coordination Compounds," 2nd ed, Wiley, New York, N. Y., 1970, pp 82–84; W. C. Hamilton and J. A. Ibers, "Hydrogen Bonding in Solids," W. A. Benjamin, New York, N. Y., 1968, pp 108–113.

[3] R. P. Bell and J. C. McCoubrey, *Proc. Roy. Soc., Ser. A*, **234**, 192 (1956).

[4] A. J. Kresge and Y. Chiang, *J. Amer. Chem. Soc.*, **90**, 5309 (1968).