Mechanism of Nucleophilic Displacement at Phosphorus in the Alkaline Hydrolysis of Phosphinate Esters[1,2]

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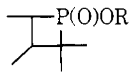
Abstract: The alkaline hydrolysis of several different phosphinate esters, R_2PO_2R', was studied in 60% dimethoxyethane–water or 33% dioxane–water. Rates are second order: $v = k[\text{ester}][\text{HO}^-]$. Oxygen-18 experiments demonstrate that hydroxide attack occurs only at phosphorus and that the phosphinyl oxygen does not exchange ^{18}O with solvent during hydrolysis. Activation enthalpies ranged from 12 to 16 kcal/mol, and activation entropies were near −30 gibbs. A comparison of rates for the strained, cyclic 2,2,3,4,4-pentamethyltrimethylenephosphinates with acyclic analogs shows acceleration of rate due to angle strain which indicates that the reaction involves a pentacoordinate intermediate. In methyl diisopropylphosphinate, an induction period preceded second-order kinetics; the observed data for the rate of hydrolysis fit a reaction mechanism with reversible formation of intermediate and rate-determining breakdown of intermediate to products. Rates were unusually sensitive to *O*-alkyl substituents: ρ^* is 11 for $(C_6H_5)_2PO_2R$ and δ is approximately 1. These unusual substituent effects appear to be due to the large change in the charge on the alkyl oxygen between ground state and transition state and to steric hindrance to solvation of the transition state which is an oxyanion. For acyl substituents in $R_2PO_2CH_3$, $\rho^* = 2.5$ per substituent as is true in $RCO_2C_2H_5$, but $\delta = 2.5$ which is considerably larger than for carboxylates. These results fit an addition–elimination mechanism for displacement at phosphorus in which the rate-determining step depends on the relative nucleophilicities of entering and leaving groups. In the alkaline hydrolysis of alkyl esters, the rate-determining step appears to be loss of alkoxide ion from the pentacoordinate intermediate.

Nucleophilic displacement reactions at tetrahedral carbon and trigonal carbon have been studied extensively and reaction mechanisms are quite well understood.[4] Displacement reactions at phosphorus have also received considerable attention, particularly the biochemically important phosphates and phosphonates.[5] However, phosphorus being multivalent is subject to different energy constraints than carbon and many mechanistic details remain unclear. In order to have a better understanding of phosphorus chemistry, we have undertaken a broad study of the chemistry of functional groups, X, in phosphinates, $R_2P(O)X$.[6] In this paper, we report our research on the alkaline hydrolysis of phosphinate esters,[7] including hydrolyses in oxygen-18 enriched media which enable us to determine whether hydroxide attacks at alkyl carbon or acyl phosphorus and if the chemical dynamics along the reaction coordinate allow exchange of the phosphinyl (R_2PO–) oxygen with solvent. A number of reaction parameters were varied so that certain kinetic effects could be isolated. The importance of the leaving group was weighed in an homologous series of three esters, diethylphosphinate (**1**), 2,2,3,4,4-pentamethyltrimethylenephosphinate (**2**), and diphenylphosphinate (**3**). The steric and electronic effects of phosphorus substituents were studied in derivatives of methyl phosphinates (**4** and **5**). Ring effects which require a consideration of pseudorotation,[8] and thus the existence of an intermediate, were studied in the

$(CH_3CH_2)_2P(O)OR$

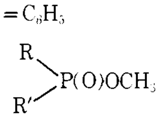
1a, $R = CH_3$
b, $R = CH_2CH_3$
c, $R = CH(CH_3)_2$



2a, $R = CH_3$
b, $R = CH_2CH_3$
c, $R = CH(CH_3)_2$
d, $R = C_6H_5$

$(C_6H_5)_2P(O)OR$

3a, $R = CH_3$
b, $R = CH_2CH_3$
c, $R = CH(CH_3)_2$
d, $R = C(CH_3)_3$
e, $R = n\text{-}C_3H_7$
f, $R = i\text{-}C_4H_9$
g, $R = CH_2C(CH_3)_3$



$RR'P(O)OCH_3$

4a, $R = C_6H_5$; $R' = H$
b, $R = C_6H_5$; $R' = CH_3$

$R_2P(O)OCH_3$

5a, $R = CH_3$
b, $R = C_2H_5$
c, $R = n\text{-}C_4H_9$
d, $R = C_6H_5CH_2$
e, $R = CH(CH_3)_2$

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(1) C. E. Diebert, *Diss. Abstr. B*, 27, 3849 (1967); (b) R. D. Cook, *ibid.*, **28**, 2763 (1968).

(2) Research supported by grants from the National Institute of Arthritis and Metabolic Diseases and the National Science Foundation, and by an Alfred P. Sloan Research Fellowship to P. H.

(3) Address correspondence to this author at Wesleyan University.

(4) (a) E. M. Kosower, "An Introduction to Physical Organic Chemistry," Wiley, New York, N. Y., 1968; (b) A. J. Parker, *Advan. Phys. Org. Chem.*, **5**, 173 (1967); (c) S. L. Johnson, *ibid.*, **5**, 237 (1967); (d) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, New York, N. Y., 1966.

(5) (a) J. R. Cox and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964); (b) C. A. Bunton, *Accounts Chem. Res.*, **3**, 257 (1970); (c) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 2, W. A. Benjamin, New York, N. Y., 1966; (d) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, Amsterdam, 1967, Chapter 10; (e) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, New York, N. Y., 1965.

(6) References may be found in D. A. Tyssee, L. P. Bausher, and P. Haake, *J. Amer. Chem. Soc.*, **95**, 8066 (1973).

(7) Some results have been reported in communications: (a) P. Haake, R. D. Cook, W. Schwarz, and D. R. McCoy, *Tetrahedron Lett.*, 5251 (1968); (b) P. Haake, D. R. McCoy, W. Okamura, S. R. Alpha, S. Y. Wong, D. A. Tyssee, J. P. McNeal, and R. D. Cook, *ibid.*, 5243 (1968); (c) P. Haake, C. E. Diebert, and R. S. Marmor, *ibid.*, 5247 (1968).

(8) (a) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968); (b) K. Mislow, *ibid.*, **3**, 321 (1970); (c) I. Ugi, D. Marquarding, H. Klusacek, P. Gillespie, and F. Ramirez, *ibid.*, **4**, 288 (1971).

Table I. Rate Constants for the Alkaline Hydrolysis of Phosphinate Esters. Variation of Leaving Group

System	R	Temp, °C	10^4k, M^{-1} sec^{-1} [a]	Rel k (75°)
(a) **1** in 60% $(CH_3OCH_2)_2$–H_2O	CH_3	30.1	6.44 ± 0.16	
		50.1	28.3 ± 0.4	
		58.7	38.4 ± 0.9	
		75.4	109 ± 2	157
	CH_2CH_3	30.1	0.546 ± 0.01	
		50.1	2.36 ± 0.17	
		58.7	4.11 ± 0.16	
		75.4	14.7 ± 0.3	21
		75.4	18.7 ± 0.7 (μ = 0.06 M)	
		75.4	19.4 ± 1.0 (μ = 0.03 M)	
		75.4	22.2 ± 0.5 (μ = 0.01 M)	
	$CH(CH_3)_2$	50.1	0.150 ± 0.005	
		62.5	0.341 ± 0.013	
		75.4	0.693 ± 0.010	1
(b) **2** in 60% $(CH_3OCH_2)_2$–H_2O	CH_3	75.4	173 ± 5	37
		75.0	305 (μ = 0.01 M)	
	CH_2CH_3	30.1	18.4 (μ = 0.01 M)	
		75.4	41.3 ± 0.5	9
		75.0	73.9 (μ = 0.01 M)	
	$CH(CH_3)_2$	75.4	4.70 ± 0.14	1
		75.0	7.59 (μ = 0.01 M)	
	C_6H_5	30.1	6050 (μ = 0.01 M)	3000
(c) **3** in dioxane–H_2O[b]	CH_3	35.0	59.7 ± 1.2	
		43.0	107 ± 1	
		50.0	147 ± 2 (138)[c]	320
		60.1	304 ± 5	
	CH_2CH_3	35.0	4.19 ± 0.03	
		50.0	12.1 ± 0.2 (11.4)[c]	26
		74.8	52.2 ± 1.7	
	$CH_2CH_2CH_3$	50.0	(4.94 ± 0.02)	12
	$CH(CH_3)_2$	35.0	0.134 ± 0.002	
		50.0	0.457 ± 0.005 (0.429)	1
		74.8	2.74 ± 0.01	
	$CH_2CH(CH_3)_2$	50.0	(2.26 ± 0.02)	5
	$C(CH_3)_3$	75.1	9.8[d] (μ = 0.05 M)	
	$CH_2C(CH_3)_3$	50.0	(0.397 ± 0.004)	0.9
3 in 60% $(CH_3OCH_2)_2$–H_2O	CH_3	75.4	430 ± 9	195
	CH_2CH_3	75.4	32.8 ± 0.9	15
	$CH(CH_3)_2$	74.5	2.22 ± 0.04	1

[a] Most rate constants are an average of two or more determinations with [ester] and [NaOH] in the range 0.1–0.01 M. The ionic strength (μ) = 0.10 M except where indicated; μ = [NaOH] + [$NaClO_4$]. The ± values are the largest standard deviations of the k's which were determined by least-squares analysis of the data. Complete data may be found in the theses.[1] Runs with [ester] ≠ [HO^-] demonstrated that the second-order kinetics are due to first-order dependence on each. [b] The solvent was 33% dioxane–67% water (v/v) except for those rates in parentheses for which the solvent was 50% dioxane–50% water (v/v). [c] These rates were not measured but are obtained from the rate constant in 33% dioxane by multiplying by 0.94, an empirical factor from the rates of the isopropyl ester. [d] First-order rate constant; units are sec^{-1}.

Table II. Second-Order Rate Constants for the Alkaline Hydrolysis of $R_2P(O)OCH_3$. Effect of Substituents at Phosphorus

R_2	Temp, °C	10^2k, M^{-1} sec^{-1} [a,b]	Rel k (75°)
$(CH_3)_2$	30.1	3.40 ± 0.08	50
	50.1	11.8 ± 0.5	
$(CH_3CH_2)_2$	30.1	0.064 ± 0.002	
	50.1	0.283 ± 0.004	1
	75.4	1.09 ± 0.02	
$(n\text{-}C_4H_9)_2$	75.4	0.308 ± 0.001	0.3
$(C_6H_5CH_2)_2$	75.4	1.15 ± 0.03	1
$(C_6H_5)_2$	75.4	4.3	4
$(i\text{-}C_3H_7)_2$	75.4	0.03[c]	0.03
C_6H_5, CH_3	50.1	10.5 ± 0.2	37
C_6H_5, H	30	~100[d]	$>10^3$

[a] Most rate constants are an average of two or more determinations; ester and base concentrations are in the range 0.005–0.02 M. The ionic strength was constant at 0.1 M. [b] The ± values are standard deviations of the individual k's determined by least-squares analysis of the data. [c] This rate followed an induction period; see text. [d] Too fast for an accurate determination.

four-membered cyclic phosphinates (**2**) and in the five-membered phospholenes (**6**).

Results

Kinetic Studies. The rates of saponification of several different phosphinate esters were studied by titrimetric methods in 60% dimethoxyethane–water (v/v) or 33% dioxane–water (v/v). Variations of concentrations of esters and base demonstrated that the rates of hydrolysis are first order in ester and first order in base, rate = k_2[ester][OH^-]. The single exception, *tert*-butyl diphenylphosphinate, was observed to hydrolyze with a first-order rate dependence. In this case, there is strong evidence for an elimination reaction since this ester undergoes pyrolysis very rapidly and since isobutylene is a hydrolysis product.[9]

The rates of hydrolysis were found to be highly dependent on the nature of the phosphorus and oxygen substituents (Tables I and II, respectively). As the *O*-alkyl group is changed from methyl to isopropyl, the rate constant decreases by a factor of 40–300 depending upon the phosphorus substituents. There is a large salt effect for **2** (Table I, system b) which probably is

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[9] Elimination reactions of these esters have been studied: P. Haake and C. E. Diebert, *J. Amer. Chem. Soc.*, **93**, 6931 (1971).

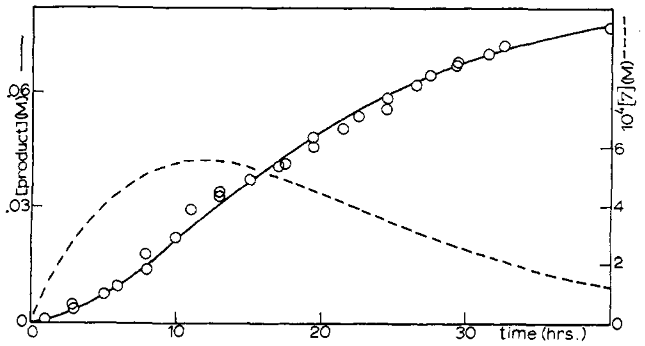


Figure 1. The rate of production of product (—) and intermediate (**7**) (- - - - ·) in the alkaline hydrolysis of methyl diisopropylphosphinate. The points come from two separate experiments and the lines are the output from the analog computer.

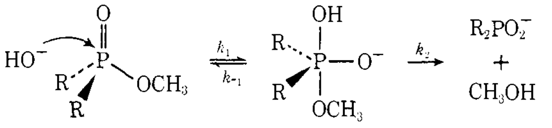
due to the very different properties of HO$^-$ and the transition state.

The log k values for (**3**) (Table I, system c) correlate fairly well with σ^* alone,[10] and the slope, $\rho^* = 13$, is unusually large. These log k values do not correlate well with E_s. The Taft equation, which combines both steric and polar effects (eq 1),[10] was applied to our data

$$\log (k/k_{\mathrm{CH_3}}) = \sigma^*\rho^* + \delta E_s \qquad (1)$$

in the form $[\log (k/k_{\mathrm{CH_3}})]/\sigma^* = \delta E_s/\sigma^* + \rho^*$ which enables graphical analysis and therefore has the advantage of displaying trends in the data and deviant points. We obtained a fair fit for **3**, but the polar reaction constant is still very high, $\rho^* = 11$. By contrast, the steric effect of the alcohol group is relatively small, $\delta = 0.6$. There is only the minimum number of points for determining ρ^* and δ in the diethylphosphinates and trimethylenephosphinates: for **1**, $\rho^* = 8$, $\delta = 1.5$; for **2**, $\rho^* = 6$, $\delta = 1$.

The rate effects produced by varying the R substituents in $R_2PO_2CH_3$ are shown in Table II. Rate constants decrease in the order: methyl > benzyl ~ ethyl > n-propyl ≫ isopropyl. For the diisopropyl ester (**5e**) an induction period of 90 min was observed to precede good second-order kinetics (Figure 1). Rate curves were analyzed by analog computer with a circuit corresponding to eq 2; an excellent fit was observed with $k_1 = 0.24 \times 10^{-2}\ M^{-1}\ \mathrm{sec}^{-1}$, $k_{-1} = 1.6 \times 10^{-2}\ \mathrm{sec}^{-1}$, and $k_2 = 0.20 \times 10^{-2}\ \mathrm{sec}^{-1}$. This solution to eq 2 enables one to plot the concentration of intermediate (**7**) during the reaction (the dashed line in Figure 1). Consistent with this interpretation of the data, good second-order kinetics begin after the intermediate begins its exponential decay in concentration. This kinetic behavior was reproducible in several different experiments.



(2)

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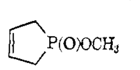
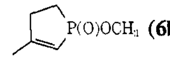
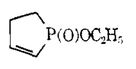
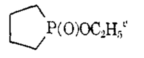
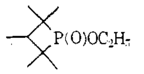
The data in Table II do not correlate well with σ^* or E_s alone; there is a poor correlation with eq 1 giving $\rho^* = 2.5$ and $\delta = 2.5$ per substituent.

The kinetic effect of incorporating phosphorus into four- and five-membered ring systems is given in Table III. The 2-phospholenes hydrolyze somewhat slower than the pentamethyltrimethylenephosphinates but the rates are remarkably similar. In fact, only one large effect was observed in this series: the 3-phospholene ester hydrolyzes at least 40 times faster than the corresponding 2-phospholene ester.[11]

Table III. Second-Order Rate Constants for the Alkaline Hydrolysis of Cyclic Phosphinate Esters

Ester	Temp, °C	10^3k, M^{-1} sec^{-1} [a]	Rel k[b]
$(C_2H_5)_2P(O)OCH_3$	50.1	2.83 ± 0.4	.1
 P(O)OCH$_3$ (**6a**)	50.1	119 ± 4	42
 P(O)OCH$_3$ (**6b**)	50.1	3.51 ± 0.10	1.2
$(C_2H_5)_2P(O)OC_2H_5$	75.4	14.7 ± 0.03	1
 P(O)OC$_2$H$_5$ (**6c**)	75.4	2.08 ± 0.08	1.5
 P(O)OC$_2$H$_5$[c]			4.0
 P(O)OC$_2$H$_5$	75.4	4.13 ± 0.05	2.9

[a] Most rate constants are an average of two or more determinations; ester and base concentrations range from 0.01 to 0.1 M; ionic strength is 0.1 M; solvent is 60% dimethoxyethane-water. The ± values are the largest standard deviations of the individual k's which were determined by least-squares analysis of the data. [b] Relative to diethylphosphinates for which the rates of the methyl ester at 50° and the ethyl ester at 75° are set equal to 1.0. [c] Relative rate from E. A. Dennis and F. H. Westheimer, *J. Amer. Chem. Soc.*, **88**, 3431 (1966).

The alkaline hydrolyses of several phosphinate esters were studied over a temperature range, and the activation parameters were determined (Table IV). Although there is some uncertainty in ΔS^*, it should be reliable to ±5 eu.[12] With the exception of isopropyl diethylphosphinate and the trimethylenephosphinate

Table IV. Activation Parameters for the Alkaline Hydrolysis of Phosphinate Esters

Ester	ΔG^*, kcal/mol	ΔH^*, kcal/mol	ΔS, gibbs
1a[a]	23.6	12.3	−32
1b[a]	25.0	14.3	−31
1c[a]	27.2	12.5	−42
2b[c]	23.9	16.5	−21
3a[b]	21.7	12.1	−30
3b[b]	23.3	12.9	−32
3c[b]	25.4	15.5	−31

[a] Solvent is 60% dimethoxyethane–40% water, $T = 75.4°$, and $\mu = 0.1\ M$. [b] Solvent is 33% dioxane–67% water, $T = 50.0°$ and $\mu = 0.1\ M$. [c] Solvent is 60% dimethoxyethane–40% water, $T = 75.0°$, and $\mu = 0.01\ M$.

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(10) R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **74**, 3120 (1952); in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.

(11) The rates of saponification of other phospholenes and phosphole 1-oxides have been reported: F. B. Clarke III and F. H. Westheimer, *J. Amer. Chem. Soc.*, **93**, 4541 (1971).

(12) S. W. Benson, "Foundations of Chemical Kinetics," McGraw-Hill, New York, N. Y., 1960.

ester, the activation entropies are consistently −31 ± 1 eu.[13]

Oxygen-18 Studies. Four phosphinate esters and two phosphinic acids were subjected to hydrolysis conditions in ^{18}O-enriched water. Results of ^{18}O analyses of materials isolated from partial and complete hydrolyses are given in Table V. The Q values in the last column represent the atoms of solvent oxygen introduced into acid during hydrolysis and therefore the fraction of P–O bond fission. Although there is a slight deviation of Q from 1.00, the data clearly demonstrate complete attack by hydroxide ion at phosphorus in these four esters. Furthermore, no solvent oxygen was incorporated into unhydrolyzed esters or phosphinate anions; the result for diethylphosphinate anions is ambiguous because the acid and sodium salt are hygroscopic and the results are less accurate than for other phosphinate compounds. Although we observe no exchange into the esters, these results only enable a lower limit on the ratio of rate of hydrolysis to rate of exchange of phosphinyl oxygen, $k_H/k_E > 200$.

Table V. Oxygen-18 Content of Compounds Isolated from Hydrolysis

		Atom % oxygen-18[a]			
Substrate[b]	H_2O	Initial substrate	Phosphinic acid	Recovered ester	Q[c]
3a	1.795	0.204	0.977		0.97
3c	1.77	0.202	0.986		1.00
3c	1.796	0.202	0.984	0.205	0.98
3, R = H	1.763	0.202	0.202		
1a[d]	1.84	0.202	0.948	0.202	0.88
1, R = Na[d]	1.84	0.195	0.212		
2a	1.84	0.197	1.016		0.99
2, R = H	0.191		0.192		

[a] Most values are an average of several determinations. [b] Both [substrate] and [NaOH] are 0.10 M. [c] Q = (atom % excess ^{18}O in R_2PO_2H)(2)/(atom % excess ^{18}O in H_2O). [d] Both the acid and sodium salt of diethylphosphinate are hygroscopic which may account for the low Q value for ester hydrolysis and the high atom % oxygen for the salt; after ester hydrolysis, the acid was finally isolated from a solution made with unlabeled water.

Discussion

Evidence for an Intermediate. Generally, in displacement reactions where stable, associative intermediates could exist, the hypothesis[14] of an intermediate provides a useful starting point for both experiment and theory, because it is reasonable that an intermediate along the reaction pathway should lower the activation energy relative to pathways that do not involve intermediates. The large number of stable pentacoordinate[15] phosphorus compounds and the need to apply the principle of pseudorotation in order to explain certain experimental data suggest that this hypothesis is correct for many displacement reactions at phosphorus.[8] However, this hypothesis is not invariably correct.[16] We have found unimolecular cleavages of P–X bonds in the solvolysis of di-*tert*-butylphosphinyl chloride[14] and in the acid-catalyzed solvolysis of *p*-nitroanilides;[6] the dissociative nature of these reactions precludes an associative intermediate. In closely related bimolecular reactions, the P–X bonds appear to be so labile that stable, associative intermediates do not intervene.[16,17]

We have suggested[16] a criterion for stable intermediates *vs.* direct displacements in associative reactions. The rate of **2**, with its strained ring, is compared to other analogous, acyclic systems such as **5e**:[17] in reactions proceeding through an intermediate, ring strain can be relieved in the intermediate, and this causes an increased rate of reaction; in reactions in which the *normal* mechanism is direct displacement, ring strain causes a decreased rate of reaction.[16,17]

In the reaction on which this paper is focused, the alkaline hydrolysis of phosphinates, the kinetics and oxygen-18 studies indicate bimolecular attack of HO^- at phosphorus. The ring strain in **2** causes a 100-fold increase in rate: $k(\mathbf{2a})/k(\mathbf{5e}) = 10^2$ (Tables II and III). This supports the hypothesis of a pentacoordinate intermediate and reaction *via* eq 2. Additional, more direct evidence for an associative intermediate comes from the kinetics of hydrolysis of **5e** as described in the Results. Therefore, the rest of this discussion is based upon eq 2 and reaction through the pentacoordinate intermediate, **7**.

One can postulate kinetic and thermodynamic reasons that methyl diisopropylphosphinate (**5e**), unlike the other esters studied, requires an induction period for accumulation of **7** before second-order kinetics can be observed. The steric effect of the two isopropyl substituents in **5e** should decrease k_1 significantly because of the HO^-–isopropyl interactions in the transition state; therefore, the *rate* of generation of **7** will be much slower for **5e** than for the other esters which were studied. However, in the fully formed intermediate, **7**, the 120° C–P–C angle enables relief of steric interactions between the two isopropyl groups which are tetrahedrally disposed in the ground state; therefore, *the amounts of* **7** *present at equilibrium* should be greater for **5e** than for the other esters. Consequently, the induction period may be due to the combination of kinetically slower formation of the intermediate and the need to accumulate more intermediate before second-order kinetics can be observed. Examination of the rate constants we have observed for **5e** indicates that these hypotheses may be subject to experimental test by direct spectroscopic detection of an intermediate.

Substituent Effects. Alkaline hydrolysis of phosphinate esters is a similar reaction to alkaline hydrolysis of carboxylate esters in which tetrahedral intermediates have been demonstrated.[4,18] Our knowledge of mechanisms is considerably more sophisticated for displacement at carbon than displacement at phosphorus.

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(13) ΔS^*'s of −25 and −31 eu have previously been reported for *cis*- and *trans*-2,2,3,4,4-pentamethyltrimethylenephosphinate, respectively: G. Aksnes and K. Bergesen, *Acta Chem. Scand.*, **21**, 1587 (1967).

(14) P. Haake and P. S. Ossip, *J. Amer. Chem. Soc.*, **93**, 6924 (1971).

(15) In this paper, we distinguish between coordination number and valency: R_2PO_2R' is pentavalent but tetracoordinate. In discussing pentacoordinate, trigonal-bipyramidal intermediates, we use "apical" to denote the two substituents at the two apices of the bipyramid and "basal" to denote the three substituents at the common base of the bipyramid.

(16) P. Haake, R. D. Cook, T. Koizumi, P. S. Ossip, W. Schwarz, and D. A. Tyssee, *J. Amer. Chem. Soc.*, **92**, 3828 (1970).

(17) For a detailed analysis of this problem, see T. Koizumi and P. Haake, *ibid.*, **95**, 8073 (1973).

(18) S. A. Shain and J. F. Kirsch, *J. Amer. Chem. Soc.*, **90**, 5848 (1968).

Table VI. Relative Rates of Reaction at Phosphorus and Carbon

Reaction	Solvent	Temp, °C	Relative rates for R			Ref
			CH_3	CH_3CH_3	$CH(CH_3)_2$	
$HO^- + (C_6H_5)_2PO_2R$	33% dioxane	50	320	27	1	This work
$HO^- + (C_2H_5)_2PO_2R$	60% $(CH_3OCH_2)_2$	75	157	21	1	This work
$HO^- + R_2PO_2CH_3$	60% $(CH_3OCH_2)_2$	75	1700	35	1	This work
HO^- + **2**	60% $(CH_3OCH_2)_2$	75	40	10	1	This work
Average for X + RY(SN2)			1200	40	1	*a*
Average for X + RCH_2Y(SN2)			33	13	1	*a*
$HO^- + CH_3CO_2R$	40% dioxane	35	11	5	1	*b*
$HO^- + CH_3CO_2R$	70% acetone	25	15	7	1	*c*
$HO^- + CH_3CH_2CO_2R$	70% acetone	25	22	8	1	*c*
$HO^- + C_6H_5CO_2R$	60% dioxane	35	19	6	1	*b*
$HO^- + (CH_3)_3CCO_2R$	Water	15	89	17	1	*d*
$HO^- + CH_3PO_3R_2$	Water	80	570	43	1	*e*
HO^- + RP(O)(O-*i*-Pr)$_2$	Water	119		6	1	*e*

[a] A. Streitwieser, *Chem. Rev.*, **56**, 585 (1956). [b] C. K. Hancock, B. J. Yager, C. P. Falls, and J. O. Schreck, *J. Amer. Chem. Soc.*, **85**, 1297 (1963). [c] R. W. A. Jones and J. D. R. Thomas, *J. Chem. Soc. B*, 661 (1966). [d] E. J. Salmi and R. Leimu, *Suom. Kemistilehti B*, **20**, 43 (1947). [e] R. F. Hudson and L. Keay, *J. Chem. Soc.*, 2463 (1956).

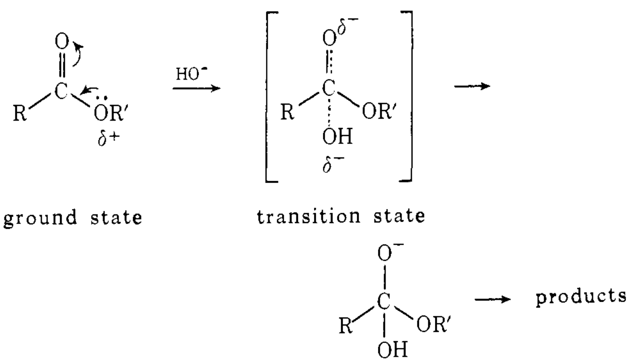
Therefore, we compare in Table VI relative rates of nucleophilic attack at tetrahedral and trigonal carbon with those at tetrahedral phosphorus.

Analysis of the data in Table II and in a previous paper[7b] demonstrates that the attack of hydroxide at phosphorus in phosphinate esters is about as dependent on the electronic effects of acyl substituents as the analogous reaction in carboxylates: for $ArCO_2C_2H_5$, $\rho = 1.9$;[19] for $RCO_2C_2H_5$, $\rho^* = 2.48$;[10] for $Ar_2PO_2CH_3$, $\rho = 2.1$;[7] and for $R_2PO_2CH_3$, $\rho^* = 2.5$. For each of the latter two series, we used the sum of σ values for the two acyl substituents.

These observations on OR groups are important. (1) Variation of *O*-alkyl groups has a much larger effect on the rates of hydrolysis of phosphinic esters than of carboxylic esters. (2) The data on acetate and pivalate esters indicate that the effect of *O*-alkyl groups depends on the size of the acyl group. (3) Although more data are needed, it appears that alkyl groups attached to phosphorus have far less effect on the rate of $^-$OH attack on phosphorus than alkyl groups attached to oxygen even in the very bulky diisopropyl esters. (4) The effects observed by us for phosphinates with one *O*-alkyl group are quite close to those for phosphonates where there are two *O*-alkyl groups. In cholinesterase inhibition by dialkyl phosphorofluoridates, the reactivation of inhibited enzyme follows a similar rate dependence on alkyl groups to that observed here: the dimethylphosphoryl poisoned enzyme is reactivated 20 times more quickly than the diethylphosphoryl enzyme and over 1000 times more quickly than the diisopropylphosphoryl enzyme.

More research will be required to fully understand these observations. However, we believe that the source of these large *O*-alkyl substituent effects is related to the mechanism of hydrolysis of phosphinate esters and the contrast with carboxylates is due to the difference in mechanism. Substituent effects must be considered in the context of total structural changes between ground states and transition states. It is also important to consider that substituent effects will vary in different structural environments and in different reactions. For example, detailed studies on carboxylates demonstrate that the substituent effects are different for *O*-alkyl and acyl substituents. The dramatic contrast between solution and gas-phase acidity of alcohols[20] may have its source in the polarizability of alkyl substituents. Therefore, different reactions will produce different changes in molecular environment between ground state and transition state leading to different substituent effects.

In benzoates, oxygen-18 studies have demonstrated that the rate-determining step is formation of the tetrahedral intermediates.[18]



Therefore, *O*-alkyl substituents may have their primary effect in the ground state; because of the π interaction of the oxygen atom with the carbonyl group, the alkyl oxygen will be partially positive and withdraw electrons from the alkyl groups. This interaction resembles that for acyl substituents (on which the σ^* scale[10] is based) enough to give a correlation of rates for acetate esters: $\rho^* = 1.34$, $\delta = 0.7$.[21]

In phosphinates, the substituent effects are quite different. For example, the correlation of data for $R_2PO_2CH_3$ with σ^* and E_s is poor. The correlation of alkyl substituents is fair and leads to very large ρ^* values of 8 and 11 for **1** and **3**, respectively. We suggest that there are two important factors which explain these unusually large values and they require rate-determining breakdown of the pentacoordinate intermediate in eq 2. First, the total structural change

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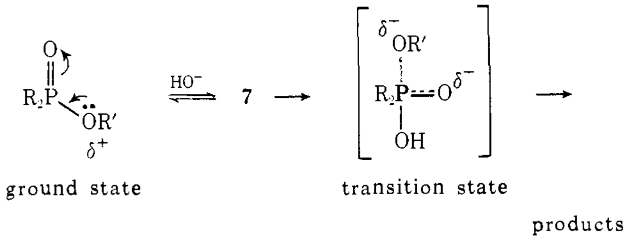
(19) M. L. Bender and R. J. Thomas, *J. Amer. Chem. Soc.*, **83**, 4189 (1961).

(20) (a) Alcohols in solution: J. Hine and M. Hine, *ibid.*, **74**, 5266 (1952); P. Ballinger and F. A. Long, *ibid.*, **82**, 795 (1960); (b) thiols: M. M. Kreevoy, B. E. Eichinger, F. E. Stary, E. A. Katz, and J. H. Sellstedt, *J. Org. Chem.*, **29**, 1641 (1964); M. M. Kreevoy, E. T. Harper, R. E. Duvall, H. S. Wigus III, and L. T. Ditsch, *J. Amer. Chem. Soc.*, **82**, 4899 (1960); (c) alcohols in the gas phase: J. I. Brauman and L. K. Blair, *ibid.*, **92**, 5986 (1970); (d) theoretical: N. C. Baird, *Can. J. Chem.*, **47**, 2306 (1969).

(21) C. K. Hancock, B. J. Yager, C. P. Falls, and J. O. Schreck, *J. Amer. Chem. Soc.*, **85**, 1297 (1963).

at the alkyl oxygen is much larger than in carboxylates.



That is, the alkyl oxygen changes from partial positive in the ground state to partial negative in the transition state, and the polarizable alkyl groups will respond to this large change. The ρ^* for pK_a's of ROH in solution is about 4,[20a] and the ρ^* for pK_a's of RSH is 3.4.[20b] This gives some indication of the effect of interaction of substituents with negative oxygen in solution. The data in Table VI for benzoates and acetates give some indication of the effect of interaction of substituents with partial positive oxygen.

Second, the transition state (and the pentacoordinate intermediate) are oxyanions which will have high solvation requirements. The two phenyl groups on **3** (which has the highest ρ^* of 11) would be expected to force the *O*-alkyl into a conformation such that a large alkyl group (such as isopropyl) will hinder solvation of the negative oxygen atom. Space-filling molecular models support this concept very well. Although there is a fair correlation of log k for $(C_6H_5)_2PO_2R$ with σ^*, the neopentyl rate is highly deviant because it is so slow. The neopentyl group would be particularly effective in hindering solvation.

Steric hindrance to solvation should be considerably greater in pentacoordinate intermediates from phosphinate esters than in tetracoordinate intermediates from carboxylate esters because of the greater crowding inherent in placing five rather than four groups around a central atom. However, since σ^* values are based on the alkaline hydrolysis of acyl-substituted carboxylates, steric hindrance to solvation appears to be incorporated into σ^* values. Although all the carboxylates show a similar trend in rates in Table VI, those with larger acyl substituents show larger effects, and pivalate esters in particular demonstrate the probable effect of steric hindrance to solvation in the transition state in the alkaline hydrolysis of carboxylates.

In summary, although substituent effects are complex and this discussion could be amplified considerably, it appears that the large ρ^* values for alkaline hydrolysis of phosphinates require rate-determining decomposition of the pentacoordinate intermediate (eq 2) so that three factors can all contribute to σ^*: (1) interaction of substituents with a partial positive alkyl oxygen in the ground state, (2) interaction of substituents with a partial negative alkyl oxygen in the transition state, and (3) steric hindrance to solvation of the transition state which is an oxyanion.

The suggestion has been made[22] that alkaline hydrolysis of phosphonates proceeds by attack of ^-OH on phosphorus largely on the basis of values of activation energies. This approach can be misleading and the large rate effects cause concern that HO^- reacts by SN2 attack at carbon since the relative rates observed here are similar to those for SN2 displacement on carbon. However, the observed second-order kinetics, the results of our studies with oxygen-18 enriched water, and this analysis of substituent effects all demonstrate that the alkaline hydrolysis of these phosphinates proceeds by a process involving attack of hydroxide on phosphorus resulting in cleavage of the P–O bond. It seems likely therefore that the reasoning for phosphonate hydrolyses[22] is correct.

Salt Effect. There is a large salt effect which was most extensively explored in the alkaline hydrolysis of ethyl diethylphosphinate (Table I); the reaction is slowed on increasing the concentration of salt. The above discussion of substituent effects involved the hypothesis that the transition state is a large organic oxyanion with considerable steric hindrance to solvation. This hypothesis would also lead to less interaction of salt with the transition state than with hydroxide ion the anion in the ground state. Therefore, addition of salt will lower the activity of hydroxide ion considerably more than the activity of the transition state, and this will cause net retardation of the rate.

Steric Effects. Although the steric reaction constants for *O*-alkyl substituents are only 0.5–1, we have discussed above the large steric effect on solvation of the transition state. Why does not this steric effect appear in the steric reaction constant? In any utilization of substituent constants, one must keep in mind the reactions for which they have been measured. The definitions[10] of σ^* and E_s would lead to incorporation into σ^* of steric hindrance to solvation of the oxyanion transition state in the alkaline hydrolysis of esters.

Acyl substituents in phosphinates cause large steric effects which appear in the steric reaction constant. Using Taft's E_s values, $\delta = 1$ for $RCO_2C_2H_5$,[10] but $\delta = 2.6$ per acyl substituent for $R_2PO_2CH_3$ (Table II). The steric compression on addition of HO^- to *tetrahedral* phosphorus must be larger than an addition of HO^- to *trigonal* carbon, and resemble the effects of carbon substituents in SN2 reactions (Table VI). Even larger steric effects were found in the solvolysis of phosphinyl chlorides[14] where nucleophilic attack is definitely rate determining. This adds evidence to the hypothesis discussed above that there is steric inhibition of nucleophilic attack but steric stabilization of a pentacoordinate intermediate in reactions of phosphinates, $R_2P(O)X$.

The Rate-Determining Step. The induction period for methyl diisopropylphosphinate (**5e**) and the kinetic analysis of the data demonstrate that $k_{-1} > k_2$ indicating that k_2 is rate determining (eq 2 and Figure 1). The above analysis of alkoxide substituent effects supports this as a general conclusion for the alkaline hydrolysis of phosphinate esters. The large ρ^* values for **1** and **3** indicate that there is partial negative charge on alkoxide oxygen in the transition state. This is only compatible with rate-determining breakdown of **7** to products—that is, k_2 is rate determining.

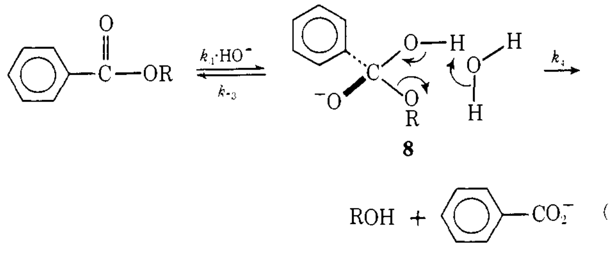
The question of rate-determining step can also be fruitfully approached by examination of the relative barriers expected for loss of HO^- and RO^- from the intermediate (**7**, eq 2). It has been shown that basicity of the nucleophile is the most important factor in determining relative rates of attack at tetracoordinate,

[22] R. F. Hudson and L. Keay, *J. Chem. Soc.*, 2463 (1956).

pentavalent phosphorus;[23] this is the microscopic reverse of k_{-1} and k_2. Therefore, the relative heights of the barriers for decomposition of 7 to ester (k_{-1}) or products (k_2) should depend on the relative basicity of the two leaving groups. Since alkoxide ions are more basic than hydroxide ions, we should expect $k_2 < k_{-1}$; that is, a rate-determining conversion of intermediate to products.

When the leaving group is less nucleophilic than the entering group, the relative barriers on reactant and product sides of the intermediate should be reversed. In such cases, the reaction constant will be a measure of the electronic effects for intermediate formation only, and should therefore be reduced. In fact, we have observed this in a study on the alkaline hydrolysis of $(C_6H_5)_2PO_2Ar$ where phenoxide is a better leaving group than hydroxide ion and ρ is reduced to 2.2.[7b] Although this value is quite large, it is consistent with ρ values for reactions of aryl acetates[24a] and with concepts of bonding to phosphorus.[24b,c]

Comments on the Alkaline Hydrolysis of Carboxylic Esters. In carboxylic esters, the relative energy barriers on the reactant and product sides of the intermediate are related to the ratio of rate of hydrolysis to rate of carbonyl–oxygen exchange. Assuming fast exchange of protons in **8** (eq 3), k(hydrolysis)/k(exchange) is



8

(3)

k_4/k_{-3} which would be unity if the energies of the transition states for intermediate and product formation were identical. In methyl and ethyl benzoates, hydrolysis is faster than exchange and ethyl esters show a lower k_h/k_{ex} ratio than methyl esters.[18] Therefore, the relative barriers are defined for **8** (eq 3): $k_4 > k_{-3}$. If $k_2 < k_{-1}$ in eq 2, why is $k_4 > k_{-3}$ in eq 3? A possible explanation involves proton transfer concurrent with loss of RO$^-$ as shown in **8** so that k_4 involves a considerably better leaving group than is possible for k_{-3}. On the other hand, in **7** the pentacoordinate geometry which is greatly preferred should be the one shown where the HO and RO groups are apical,[8] and with this geometry, proton transfer to the RO group would be impossible. An alternative explanation involves base catalysis in k_4. Further research is needed to resolve these and other problems.[25]

Ring Effects. There have been several studies of the effects on displacement reactions of incorporating phosphorus into four- and five-membered ring systems. Five-membered cyclic esters of phosphonic and phosphoric acids are hydrolyzed 10^5–10^9 times as rapidly as corresponding six-membered cyclic esters and open-chain analogs.[8a,26] In phosphonium salts, the four- and five-membered ring systems undergo reaction much more rapidly than the six-membered ring systems.[27] On the other hand, the four-membered highly substituted trimethylene–phosphorus ring does not appear to accelerate the saponification rate in **2** when compared to diethylphosphinate esters.[7] However, although **2b** undergoes alkaline hydrolysis at about the same rate as **1**, it is 10^2 times faster than $(i\text{-}C_3H_7)_2PO_2CH_3$ (Table II) and 10^5 times faster than $(t\text{-}C_4H_9)_2PO_2C_2H_5$.[16,28] Therefore, two compensating effects occur in **2**: steric retardation by four α-methyl groups which is balanced by strain acceleration due to relief of strain in the trigonal bipyramidal intermediate.[8,29] The strain acceleration and the previously observed stereochemistry[8,29] support the presence of a pentacoordinate intermediate in these reactions.

Geometry and the Charge of the Pentacoordinate Intermediate. It is significant, in view of rate-determining breakdown of intermediate to product, that we have not been able to observe any ^{18}O exchange during the alkaline hydrolysis of either $(C_6H_5)PO_2R$ or $(C_2H_5)_2PO_2R$ in $^{18}OH_2$ enriched solvents. Polarity arguments[30] support **7** as the most likely geometry for the initially formed intermediate. Since displacement at phosphorus appears to require that groups enter and leave at apical positions of a trigonal bipyramid,[8a] the lack of ^{18}O exchange in **1a** and **3a** is evidence for a high barrier to any process that would make the O$^-$ and OH substitutents equivalent in **7**. At least one pseudorotation and one proton transfer are required for identity of O$^-$ and OH in **7**. Using Berry pseudorotations (BPR),[8,30] it is necessary to generate high energy geometries of trigonal-bipyramidal intermediates during the course of these operations. Therefore, on this basis, it is reasonable that ^{18}O exchange does not occur.

On the other hand, if turnstile pseudorotations[8c] are possible, it appears that it should be possible to have concurrent proton exchange and turnstile pseudorotation which would take **7** in one step into an equivalent configuration differing only in that the two oxygens have exchanged identities. Either turnstile pseudorotation is not an allowed pathway or it has too high energy here—possibly because of the need for concurrent proton exchange.

Other charge states are possible for the pentacoordinate intermediate besides the monoanion shown in **7**. Since hydrolysis is first order in [HO$^-$], formation of the intermediate would have to be rate determining if a neutral intermediate or a dianion were the reactive precursor to product. We have discussed above the inconsistency of the ρ^* for *O*-alkyl groups with rate-determining formation of intermediate. Also, the lack of ^{18}O exchange may be inconsistent with significant concentrations of a neutral or dianionic intermediate because, in these charge states, proton transfer would not be required in order to exchange the entering

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[23] J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).

[24] (a) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1938); (b) D. W. J. Cruickshank, *ibid.*, 5486 (1961); (c) D. P. Craig, A. Maccoll, R. S. Nyholm, L. E. Orgel, and L. E. Sutton, *ibid.*, 332 (1954).

[25] W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, Chapter 10.

[26] J. Kumamoto, J. R. Cox, Jr., and F. H. Westheimer, *J. Amer. Chem. Soc.*, **78**, 4858 (1956); A. Eberhard and F. H. Westheimer, *ibid.*, **87**, 253 (1965); P. Haake and F. H. Westheimer, *ibid.*, **83**, 1102 (1961).

[27] G. Aksnes and K. Bergesen, *Acta Chem. Scand.*, **19**, 931 (1965); **20**, 2508 (1966); S. E. Cremer, B. C. Trivedi, and F. L. Weitl, *J. Org. Chem.*, **36**, 3226 (1971).

[28] W. Hawes and S. Trippett, *Chem. Commun.*, 577 (1968).

[29] K. L. Marsi, *J. Amer. Chem. Soc.*, **93**, 6351 (1971), and references therein.

[30] R. J. Gillespie, *J. Chem. Soc.*, 4672 (1963); E. L. Muetterties and R. A. Schunn, *Quart Rev., Chem. Soc.*, **20**, 245 (1966).

Table VII. Physical Constants and Carbon–Hydrogen Analyses

Ester	Bp (°C (mm)) or mp (°C) (lit.)	Anal: Carbon Calcd	Anal: Carbon Found	Anal: Hydrogen Calcd	Anal: Hydrogen Found
$(CH_3)_2PO_2CH_3$	78.5–79.5 (12) (78.5–79.5 (12))[a]				
$(C_2H_5)_2PO_2CH_3$	78 (10) (86 (12))[b]				
$(C_2H_5)_2PO_2C_2H_5$	87–89 (12) (91–92 (14))[c]				
$(C_2H_5)_2PO_2CH(CH_3)_2$	85 (12) (94 (14 mm))[b]				
$[(CH_3)_2CH]_2PO_2CH_3$	89.5–90.5 (12)	51.19	51.04	10.44	10.31
$(n\text{-}C_4H_9)_2PO_2CH_3$	110 (5) (95 (3 mm))[d]				
$(C_6H_5CH_2)_2PO_2CH_3$	71–72 (75)[e]				
$C_6H_5(H)PO_2CH_3$	Molecular distillation (102 (2 mm))[f]				
$C_6H_5(CH_3)PO_2CH_3$	95–96 (0.2) (83–85 (0.1))[g]				
$[p\text{-}(CH_3)_2NC_6H_4]_2PO_2CH_3$	157–158	64.13	64.14	7.28	7.55
$(p\text{-}ClC_6H_4)_2PO_2CH_3$	87.5–88.5	51.85	52.01	3.68	3.85
$(m\text{-}NO_2C_6H_4)_2PO_2CH_3$	135–136	48.46	48.67	3.44	3.58
6b	76–77 (0.35)	49.31	49.53	7.58	7.62
6c	Molecular distillation (75–78 (0.1))[h]				
6a	Molecular distillation (102–103 (9))[i]				
2a	58–59 (0.4) (66–69 (0.2))[j]	56.82	57.06	10.06	9.95
2b	53–55 (0.2)	58.80	58.85	10.31	10.23
2c	53–55 (0.1)	60.52	60.73	10.62	10.66
2d	102–104 (0.1)	66.65	66.54	8.39	8.43

[a] H. Reinhardt, D. Bianchi, and O. Mölle, *Chem. Ber.*, **90**, 1656 (1957). [b] A. I. Razumov and O. A. Mukhacheva, *Tr. Kazan. Khim.-Tekhnol. Inst.*, **18**, 42 (1953). [c] A. I. Razumov and O. A. Mukhacheva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 854 (1952). [d] L. L. Burger and R. M. Wagner, *J. Chem. Eng. Data*, **3**, 310 (1958). [e] S. Litthauer, *Chem. Be* **22**, 2144 (1889). [f] H. Goncalves, F. Mathis, and R. Wolf, *Bull. Soc. Chim. Fr.*, 1595 (1961). [g] M. Green and R. F. Hudson, *J. Chem.* c., 3129 (1958). [h] V. Hasseradt, K. Hunger, and F. Korte, *Tetrahedron*, **19**, 1563 (1963). [i] N. A. Razumova and I. M. Treskunova, *Zh. C hch. Khim.*, **34**, 2949 (1964). [j] Reference 35.

oxygen atom with the phosphinyl oxygen atom and the barriers to pseudorotation would be expected[8,30] to be much less because these two oxygen atoms would then have identical polarity. That is, the data in this paper indicate that the reactive pentacoordinate intermediate is a monoanion and significant concentrations of dianionic or neutral intermediates are not formed. At this point, these conclusions must be regarded as hypotheses until they are subjected to further experimental test in a wider variety of systems.

The above discussion does not take into account possible deformation of regular trigonal-bipyramidal geometry in pentacoordinate intermediates. Both the O^- substituent in **7** and the four-membered ring in **2** may lead to deformation of pentacoordinate geometry which would have important consequences to the chemical dynamics of reactions through pentacoordinate intermediates.[31]

Experimental Section

Materials. Technical diphenylchlorophosphine $(C_6H_5)_2PCl$, was obtained from Victor Chemical Co., and was used without further purification. Methyl, ethyl, and isopropyl alcohols were purified by standard methods.[32] Sodium hydroxide, sodium perchlorate, and sodium metal were supplied by J. T. Baker and Co. Sodium methoxide and carbon dioxide (99.99%) were obtained from Matheson Coleman and Bell. Reagent grade mercuric chloride was sublimed before use and reagent grade mercuric cyanide was vacuum dried. Oxygen-18-enriched water was obtained from Yeda Research and Development Ltd. Freshly distilled[32] 1,2-dimethoxyethane or purified[32] dioxane and CO_2-free distilled water were used in all rate studies.

Equipment. All titrations were performed in a Radiometer TTTI automatic titrator. The 46/44 mass ratios of carbon dioxide were measured with a consolidated Electrodynamics Corporation 21-620 mass spectrometer equipped with an isotope ratio accessory. A Associated Electrical Industries MS-9 mass spectrometer was u d to obtain mass spectra of the phosphorus compounds. All n spectra were recorded on a Varian A-60A spectrometer, and in ed spectra were determined with a Perkin-Elmer 421 spectro otometer. Melting points were determined with a Mel-Temp heating block and are corrected.

Synthesis of Esters. Known methods[32–35] were used for synthesis and purification of the esters which were investigated.[1] Table VII reports physical constants for all the esters and elemental analyses (Miss H. King, UCLA Microanalytical Lab.) for previously unreported esters. For all compounds, mass,[36] nmr, and infrared spectra were consistent with structural assignments.[1] The syntheses and properties of the diphenylphosphinate esters have been described.[9]

Alkyl Dialkylphosphinate Esters (1). These esters were prepared by dropwise addition of dialkylphosphinyl chloride (0.1 mol) in benzene (50 ml) to the sodium alkoxide (0.1 mol) in the corresponding alcohol (25 ml). Sodium chloride was filtered off and the solvent removed by distillation. The ester was purified by distilling through a spinning band column using a thermocouple for determination of boiling point. The dibenzyl ester was purified by recrystallization.[9,33,34]

Dimethylphosphinyl and diethylphosphinyl chlorides were made from the reaction of sulfuryl chloride (3 mol) and the appropriate tetraalkylbiphosphine disulfide (1 mol) in benzene.[33,34] Diisopropylphosphinyl chloride and di-*n*-butylphosphinyl chloride were prepared from isopropylmagnesium bromide (4 mol) and trichlorophosphine sulfide (1 mol).[37]

2,2,3,4,4-Pentamethyltrimethylenephosphinate Esters (2). The methyl, ethyl, and isopropyl esters were prepared by the dropwise addition of 2,2,3,4,4-pentamethyltrimethylenephosphinyl chloride[35] (0.03 mol) in the appropriate alcohol (10 ml) to sodium alkoxide (0.03 mol) in alcohol. The mixtures were stirred for 3 days at room temperature (R = CH_3, C_2H_5) or at reflux temperature (R = *i*-C_3H_7). The solvent was removed and the residue taken up in water and extracted with methylene chloride. The esters were purified by distillation.

The phenyl ester was prepared by adding the acid chloride (0.03 mol) in absolute benzene (25 ml) to a suspension of sodium pheno-

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(31) P. Haake, unpublished results. These questions have also been addressed recently by K. E. DeBruin and J. R. Petersen, *J. Org. Chem.*, **37**, 2272 (1972).

(32) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., New York, N. Y., 1956; K. B. Wiberg, "Laboratory Techniques in Organic Chemistry," McGraw-Hill, New York, N. Y., 1960, p 246.

(33) K. Sasse, "Methoden der Organischen Chemie," Vol. 12, Part 2, Georg Thieme Verlag, Stuttgart, 1963.

(34) L. Maier, *Chem. Ber.*, **94**, 3056 (1961).

(35) J. J. McBride, Jr., E. Jungermann, J. V. Killheffer, and R. J. Clutter, *J. Org. Chem.*, **27**, 1833 (1962).

(36) P. Haake and P. S. Ossip, *Tetrahedron*, **24**, 565 (1968).

(37) P. J. Christen and L. M. van der Linde, *Recl. Trav. Chim. Pays-Bas*, **78**, 549 (1959).

late (0.03 mol) in absolute benzene (50 ml). The mixture was refluxed overnight and the work-up was as described above.

Other Esters. Methyl phenylphosphinate (**4a**) was prepared from phenylphosphinyl chloride and sodium methoxide. Methyl methylphenylphosphinate (**4b**) was prepared from methylphenylphosphinyl chloride and $NaOCH_3$. Methyl diarylphosphinate esters (**6**) were prepared by the addition of diazomethane to the appropriate diarylphosphinic acid.

Rate Measurements. The solvents used were 33% dioxane–67% water (v/v) or 60% dimethoxyethane–40% water (v/v).[38] For slower reactions, a solution containing known amounts of ester and base was prepared at room temperature, thoroughly mixed, and placed in a constant-temperature bath. Sodium perchlorate was added where necessary to constant ionic strength. For faster rates, separate solutions of ester and base were prepared, brought to reaction temperature, and mixed. At appropriate time intervals, aliquots were removed and hydroxide ion titrated with standard perchloric acid; alternatively, the aliquot was quenched with perchloric acid and back-titrated with standard base to a pH of 8.45.

The titration volumes were related to concentrations of ester and base, and rate constants were obtained from both graphical analyses and computer programs utilizing a least-squares approach.[39,40] More detailed data are available.[1]

Analog Computation. In order to fit the data for hydrolysis of **5e** (Figure 1), a circuit corresponding to eq 2 was designed.[40] We fit the data for concentration of product as a function of time. The resistors were measured accurately when the fit was satisfactory, and it was shown that 5% errors in any of the resistors led to changes in the calculated curve exceeding error in the experimental curve.

Oxygen-18 Experiments. The reaction solutions were prepared using 1.8% ^{18}O-enriched water. The phosphinates isolated from enriched solvent were reisolated from solvent containing unenriched water to ensure freedom from ^{18}O contamination.

Phosphinates were analyzed for ^{18}O by conversion to CO_2 with a 1:1 mixture of $HgCl_2$–$Hg(CN)_2$ at 450°.[18,41] Water was equilibrated with CO_2 by the method of Cohn[42] and was also treated with $HgCl_2$–$Hg(CN)_2$ to give CO_2.[43,44] The CO_2 could be obtained in a nearly pure state by a trapping procedure previously described.[26,45] Complete mass spectra were taken to ensure the purity of the CO_2 sample. The reliability of the method was checked by control experiments using unlabeled materials. The accuracy of the mass spectrometer was checked regularly by determination of the oxygen-18 content of CO_2 from a cylinder kept for this purpose. On this particular spectrometer, it was found that 75 μ was the minimum CO_2 pressure required for consistent results.

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(38) Both solvents were found suitable for these kinetic studies. However, in both media, acidic substances are formed by prolonged heating. Of the two solvents, dimethoxyethane was less prone to decomposition.

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(45) When the dialkylphosphinic acids were treated with HgCl alone,[46] many of the CO_2 samples were contaminated with ethylene. The purest samples of CO_2 were obtained when iodine was used to trap the ethylene. When diphenylphosphinic acid was heated with $HgCl_2$ alone[46] or with guanidine hydrochloride,[47] little or no CO_2 was obtained and, in the latter case, the CO_2 that was collected was badly contaminated with impurities.

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Rates and Mechanisms in the Rearrangements of Vinylmethylenecyclopropane and Vinylethylidenecyclopropane[1]

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Abstract: Vinylmethylenecyclopropane rearranges in the gas phase or in solution to give 3-methylenecyclopentene. The first-order rate constant in the gas phase is given by the expression $k = 10^{11.5}\exp(-26{,}000/RT)$. This activation energy is about the same as the lowest estimate of the energy of the 2,3 bond of the reagent, therefore not allowing an unequivocal choice between a diradical mechanism and a concerted process. In solution the activation energy is about the same, although the A factor is larger by a factor of 2. Vinylethylidenecyclopropane also rearranges. The two geometric isomers rearrange at different rates, each yielding a different mixture of 3-ethylidenecyclopentene and 3-methylene-4-methylcyclopentene. Two compounds appear transiently in the reaction of the faster isomer. They are identified as *cis*- and *trans*-3-methyl-2-vinyl-1-methylenecyclopropane. Rates of all interconversions have been studied, and [1,3]-sigmatropic shifts can alone account for all the products, although some [3,3] shifts are not excluded. Arguments favoring but not requiring concerted mechanisms are presented.

The facile rearrangement of vinylmethylenecyclopropane has been reported,[3] as have those of several of its derivatives.[4] The question of mechanism is

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