Table XI

Ester	Reaction	E_a, kcal mole^{-1}	ΔS^*, eu
Glycero	Hydrolysis	23.4 ± 0.4	−21.5
Glycero	Rearrangement (1→2)	19.1 ± 0.9	−18.8
Glycero	Rearrangement (2→1)	18.4 ± 0.9	−17.4
Propanediol	Hydrolysis	30.1 ± 0.4	−2.3

The acid-catalyzed hydrolysis of glycero dihydrogen phosphate is seen to involve the most negative entropy of activation; this result seems to support the above conclusion based on the Zucker–Hammett hypothesis that a water molecule participates in the rate-determining step of hydrolysis. A fairly similar conclusion can be derived for the mechanism of the rearrangement reaction, which also has a rather negative entropy of activation. On the other hand, the hydrolysis of propanediol phosphate has an entropy of activation of only −2.3 and is thus intermediate in behavior between a uni- and a bimolecular reaction. For the hydrolysis of isopropyl[21] and of *t*-butyl[22] dihydrogen phosphates, which undergo acid-catalyzed hydrolysis by a completely unimolecular mechanism, entropies of activation of +8.2 and +7.2 eu were found.

The ^{18}O-tracer experiments showed that the acid-catalyzed rearrangements and hydrolysis of the glycero dihydrogen phosphates and of propanediol dihydrogen phosphate occur only with P–O bond breakage. This result is similar to that recently reported for the hydrolysis of some phostonates, cyclic esters of hydrogen propylphosphonic acid, which are also cleaved only with P–O bond fission.[23]

The predominance of P–O bond fission during ring formation, ring opening, and hydrolysis of 2-hydroxy-substituted phosphate esters explains the retention of configuration in reactions of such asymmetric phosphates.

Acknowledgment. This investigation was supported by Research Grant GM-05842 from the U. S. Public Health Service.

(23) A. Eberhard and F. H. Westheimer, *J. Am. Chem. Soc.*, 87, 253 (1965).

Reactions of Methyl Chloromethylphosphinate with Nucleophiles[1]

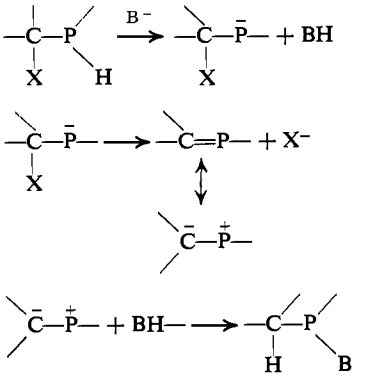
H. Goldwhite and D. G. Rowsell

Contribution from the Department of Chemistry, California State College at Los Angeles, Los Angeles, California 90032. *Received March 18, 1966*

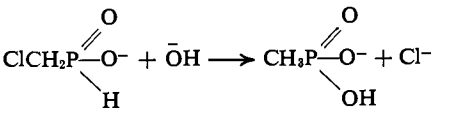
Abstract: A wide spectrum of reactivity is shown by methyl chloromethylphosphinate. Thus, it reacts with methoxide ion, methylamine, and dimethylamine to produce derivatives of methylphosphonic acid. An addition occurs with ketene diethyl acetal in the presence of tertiary amine. With thiophenoxide a displacement of chloride occurs. Reaction with Grignard reagents yields tertiary phosphine oxides; studies with deuterated compounds indicate that two mechanisms—an elimination–addition sequence and a hydride shift—may be important in this process.

A number of reactions in which a compound containing the group CXPH (where X is a halogen) is converted by reaction with an appropriate nucleophile into a compound of the type CHPB (where B is an alkoxy, amino, or hydroxyl group) have been described.[2,3]

It was suggested[2] that polyfluoroalkylphosphines react with nucleophiles by an elimination–addition process in which an intermediate, highly reactive, phosphaalkene is generated. The suggested mechanism is summarized in the following equations.



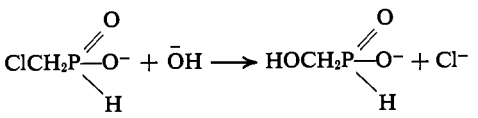
One reaction of this type has been described for compounds containing pentavalent phosphorus.[3] This reaction is the slow conversion of chloromethylphosphinic acid into methylphosphonic acid by aqueous sodium hydroxide solution. Some hydroxymethylphosphinic acid is also produced. It has recently been



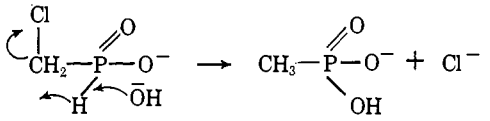
(1) This investigation was supported by Research Grant No. CA-07182 from the National Cancer Institute, Public Health Service; it was presented, in part, at the Western Regional Meeting of the American Chemical Society, Los Angeles, Calif., Nov 1965.

(2) H. Goldwhite, R. N. Haszeldine, and D. G. Rowsell, *J. Chem. Soc.*, 6875 (1965).

(3) E. Uhing, K. Rattenbury, and A. D. F. Toy, *J. Am. Chem. Soc.*, 83, 2299 (1961).

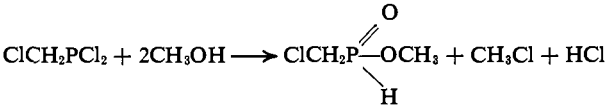


shown by experiments with deuterated compounds that the mechanism of the reaction giving methylphosphonic acid involves the nucleophilic attack of a hydroxide ion at phosphorus together with a 1,2-hydride ion shift.[4]



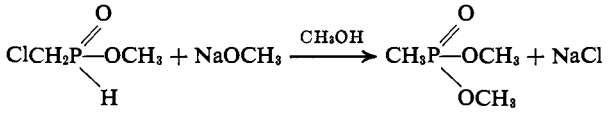
It was considered to be of interest to study a compound of this type containing pentavalent phosphorus in a nonaqueous system. In this work it was found that methyl chloromethylphosphinate reacted with a variety of nucleophilic reagents giving products containing a methyl group directly attached to phosphorus.

A number of alkyl alkylphosphinates have been prepared.[5] The esters of the lower alkylphosphinates were obtained in low or moderate yield by the addition of alcohols to alkylphosphonous dichlorides under reduced pressure.[6] However, the most satisfactory method for the preparation of methyl chloromethylphosphinate was to add chloromethylphosphonous dichloride slowly to a large excess of methanol at 0–10° and at reduced pressure to remove the methyl chloride and hydrogen chloride produced in the reaction.

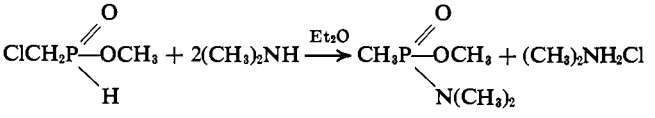


The yield of phosphinate was approximately 80% by this procedure.

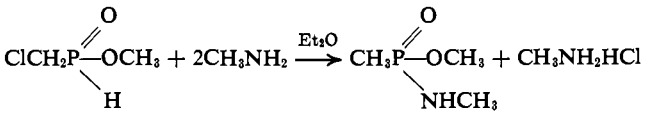
A rapid reaction was observed when methyl chloromethylphosphinate was added to a methanolic solution of sodium methoxide at 0°. Sodium chloride was precipitated and dimethyl methylphosphonate was identified as the other product.



A similar reaction took place between methyl chloromethylphosphinate and primary or secondary amines in ether solution. Dimethylamine gave methyl N,N,P-trimethylphosphonamidate

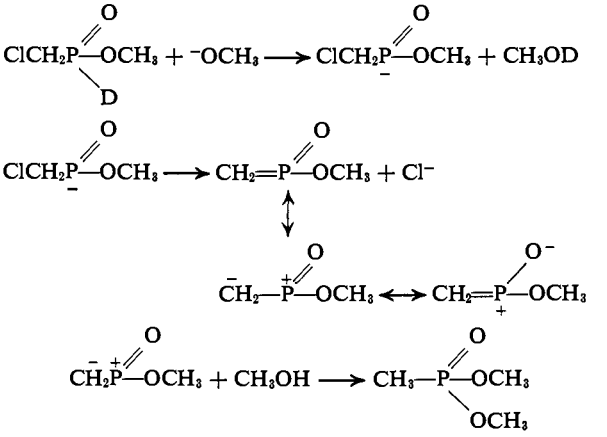


and methylamine gave methyl N,P-dimethylphosphonamidate.

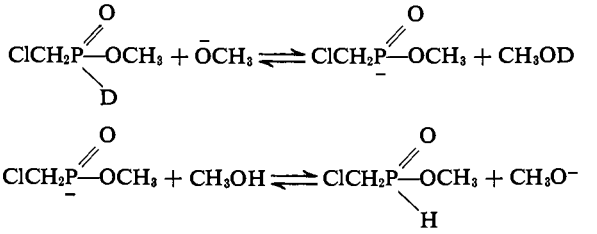


In the expectation that a study of these reactions with deuterated compounds might illuminate the mechanism of reaction, methyl chloromethylphosphinate-P-*d* was synthesized by adding chloromethylphosphonous dichloride to methanol-*d*.

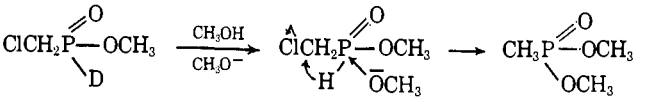
The reaction between methyl chloromethylphosphinate-P-*d* and sodium methoxide in methanol solution gave dimethyl methylphosphonate which was shown by ^1H nuclear magnetic resonance (nmr) spectroscopy to contain a negligible amount of deuterium. This result is consistent with an elimination–addition mechanism of the following type.



However, in a separate ^1H nmr experiment it was found that methyl chloromethylphosphinate-P-*d* in CH_3OH rapidly exchanged the deuterium attached to phosphorus with the hydroxylic ^1H of the solvent giving methyl chloromethylphosphinate. This suggests that an exchange process of the type

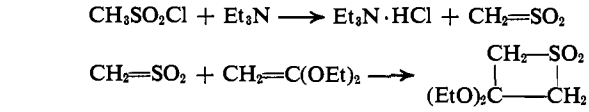


might be sufficiently rapid in methanolic methoxide that the previous result might not necessarily exclude a 1,2-hydride shift mechanism of the following type.

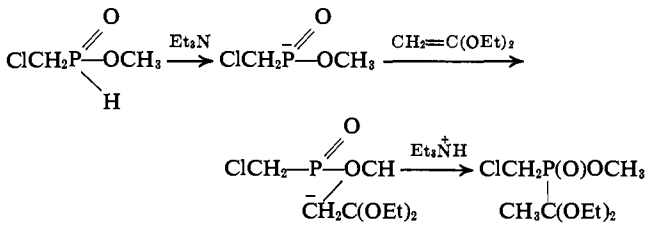


Since the result was inconclusive, other reaction conditions were sought for evidence supporting one or another of the proposed mechanisms. It was hoped that the phosphaalkene intermediate, suggested in the elimination–addition sequence, might undergo cycloaddition to a suitably activated olefin. Work with reactions considered to involve sulfene intermediates has shown that these reactive intermediates can be trapped by ketene diethyl acetal to produce cyclic compounds.[7]

(4) C. E. Griffin, E. H. Uhing, and A. D. F. Toy, *J. Am. Chem. Soc.*, 87, 4757 (1965).
(5) A. W. Frank, *Chem. Rev.*, **61**, 389 (1961).
(6) B. A. Arbuzov and N. I. Rizpolozhensky, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 843 (1952); A. N. Pudovik and D. K. Yarmukhametova, *ibid.*, 543 (1952).
(7) W. E. Truce and J. R. Norrell, *J. Am. Chem. Soc.*, **85**, 3231 (1963).

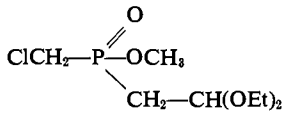


However a similar reaction using methyl chloromethylphosphinate in place of methanesulfonyl chloride gave methyl (1,1-diethoxyethyl)chloromethylphosphinate. This product was presumably formed by the ionic addition of the phosphinate across the double bond of the acetal. It appears that this addition reac-



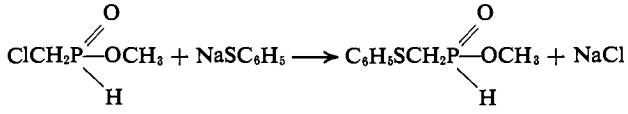
tion is faster than alternative reaction processes involving phosphaalkene intermediates.

The structure of the product was confirmed by hydrolysis to chloromethylphosphinic acid, and by nmr spectroscopy. The ^1H nmr spectrum of the product had a doublet at $\delta = 1.45$ ppm with $J_{HCP} = 11.9$ cps, with an area equivalent to three protons. This eliminates the alternative structure



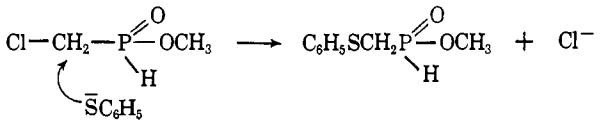
The addition of other phosphinates to ketene diethyl acetal has been observed.[8]

The reaction between methyl chloromethylphosphinate and sodium thiophenoxide in thiophenol solution gave methyl phenylthiomethylphosphinate. The



structure of the product was confirmed by infrared and nmr spectroscopy. The presence of a hydrogen atom directly attached to phosphorus was established, and the spectra were not compatible with any alternative structures containing a methyl group attached to phosphorus.

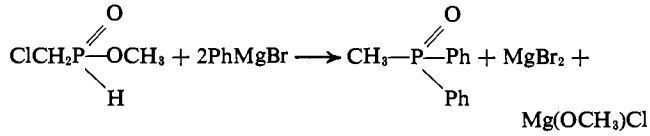
In contrast to alkoxide, thiophenoxide reacts at the saturated carbon center and not at the phosphorus atom in methyl chloromethylphosphinate.



This result is consistent with the known reactivity of thiophenoxide ion. Thiophenoxide is a weak base and hence does not favor the elimination–addition process. Furthermore, thiophenoxide is a better nucleophile than alkoxide at saturated carbon, whereas the reverse is true at phosphorus.[9] Methyl chloromethylphosphinate contains both saturated carbon and phosphorus centers. Alkoxides react exclusively at phosphorus, whereas the nucleophilicity of thiophenoxide for phosphorus appears to be significantly lower than that of alkoxide, so that reaction occurs exclusively at carbon.

Chloromethylphosphinic acid undergoes a similar reaction with alkyl and aryl mercaptans in the presence of alkali hydroxide to give (alkyl or aryl)thiomethyl phosphinic acids.[10] The difference in reactivity of a nucleophile at a carbon and at a phosphorus center is again observed in the alkaline hydrolysis of chloromethylphosphinic acid.[3] Only 12% of the reaction follows a path due to attack of hydroxide ion at carbon, whereas 80–88% follows the path due to attack at phosphorus.

The reaction between methyl chloromethylphosphinate and an excess of phenylmagnesium bromide gave a tertiary phosphine oxide, methyldiphenylphosphine oxide, as the final product. The reaction appeared to take place in two stages; the first product was an ether-insoluble solid, probably a magnesium complex. This solid was then hydrolyzed by water or hydrochloric acid to give the phosphine oxide. This



reaction is analogous to those reported above with alkoxides and amines in that the $ClCH_2PH$ system is converted into a CH_3PB system by reaction with a base—the Grignard reagent. In addition, the alkoxy group attached to phosphorus has been replaced by a phenyl group. This latter reaction has been well established.[11]

The following experiments were carried out to investigate the mechanism of this reaction. In experiment 1, the methyl chloromethylphosphinate-P-*d* was allowed to react with phenylmagnesium bromide and the resulting complex was decomposed with an excess of H_2O. In experiment 2, methyl chloromethylphosphinate was allowed to react with phenylmagnesium bromide and the complex was decomposed with D_2O. In each experiment the methyldiphenylphosphine oxide produced was isolated by an identical procedure and the amount of deuterium present in the methyl group attached to phosphorus was determined by ^1H nmr spectroscopy. The nmr spectrum of methyldiphenylphosphine oxide shows a doublet at $\delta = 1.2$ ppm with $J_{HCP} = 13.8$ cps, and a complex region at $\delta = 6.8$ ppm due to the C_6H_5 groups. The amount of deuterium incorporated in the product was estimated by comparing the area of the CH_3P doublet with that of the C_6H_5P multiplet.

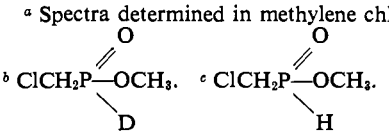
In a control experiment (experiment 3) methyldiphenylphosphine oxide, prepared by the action of aqueous sodium hydroxide solution upon methyltriphenylphosphonium iodide,[12] was treated with phenylmagnesium bromide, the product was decomposed with D_2O, and the work-up procedure described for experiments 1 and 2 was followed. It was found that no

(8) H. Goldwhite and D. G. Rowsell, unpublished observations.
(9) J. R. Cox, Jr., and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964).
(10) E. H. Uhing and A. D. F. Toy, French Patent 1,356,435 (April 7, 1964); *cf. Chem. Abstr.*, **61**, 688 (1964).
(11) K. D. Berlin, T. H. Austin, M. Peterson, and N. Nagabhushanam, "Topics in Phosphorus Chemistry," Vol. I, M. Grayson and E. J. Griffith, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 34.
(12) L. Horner, H. Hoffmann, and H. G. Wippel, *Chem. Ber.*, **91**, 64 (1958).

Table I. Grignard Reactions with Deuterated Compounds

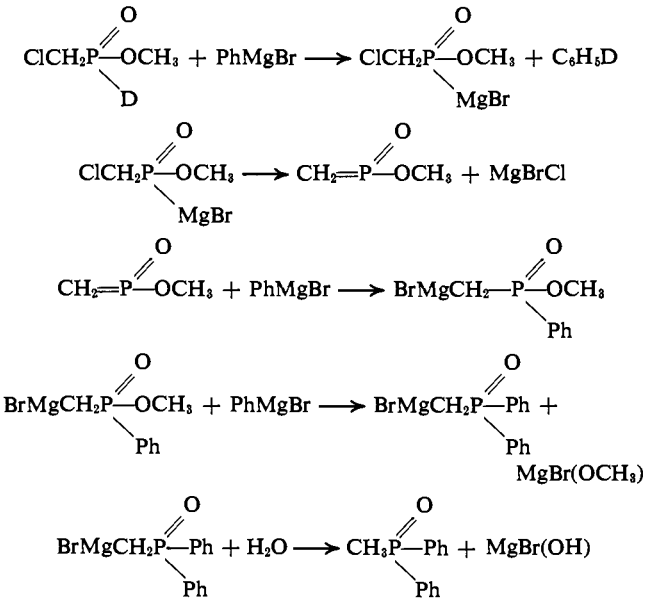
Experiment No.	Starting material, mmoles	Method of hydrolysis	Peak area[a] C_6H_5/CH_3	Benzene produced, mmoles	% CH_2D-Ph_2PO estd in product
1	10.0[b]	H_2O	4.3	3.6	62
2	10.0[c]	D_2O	3.8	3.8	33
3	...	D_2O	3.2	...	0

[a] Spectra determined in methylene chloride solution (20% w/v).



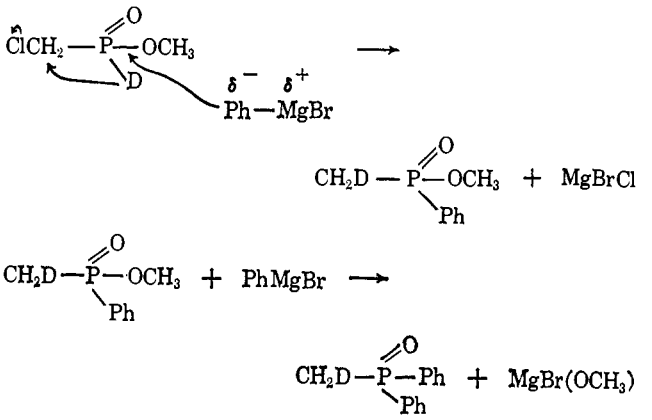
deuterium had been incorporated in the phosphine oxide by this process. The results are summarized in Table I.

If the sole reaction path is an elimination–addition process then the product from experiment 1 should contain no deuterium, whereas the product from experiment 2 should be CH_2DPh_2PO. This is illustrated in the following equations.



The replacement of the methoxy group by a phenyl group could occur at any stage in the reaction sequence.

A "pure" hydride-shift mechanism would result in the retention of deuterium in the product from experiment 1, whereas, no deuterium should be observed in the product from experiment 2.



The results given in Table I suggest that both types of mechanisms are operating in this reaction, and that the major reaction path is the hydride-shift mechanism.

Strong confirmation for this suggestion arises from the observation that a 35% yield of benzene is obtained in the reaction of methyl chloromethylphosphinate with phenylmagnesium bromide. This presumably represents the elimination–addition mechanism's contribution to the total reaction and is in good agreement with the extent of deuteration of the product observed in experiment 2, which was 33%.

In summary then, at least five possibilities appear to exist for the reactions of systems CXPH (X = halogen) with nucleophiles: (i) a displacement reaction on carbon, such as was observed in the reaction of thiophenoxide ion with methyl chloromethylphosphinate; (ii) a hydride-shift reaction, induced by the attack of a nucleophile on phosphorus; (iii) a combination of i and ii, observed in the reaction of hydroxide ion with chloromethylphosphinate ion;[3] (iv) an elimination–addition sequence, which appears to be necessary to explain the attack of nucleophiles on certain polyfluoroalkylphosphines;[2] (v) a combination of ii and iv, observed in the reaction of Grignard reagents with methyl chloromethylphosphinate.

Since combinations of reaction paths have been observed in some systems it seems clear that the energy differences between possibilities i, ii, and iv may be quite small in certain systems. At this early stage in the study of these reactions it is not possible to predict which reaction path(s) will be followed by any specific system.

Experimental Section

Nuclear magnetic resonance spectra (^1H) were determined on a Varian A-60 spectrometer. Table II summarizes the spectra of all new compounds. Chemical shifts are reported in parts per million downfield from internal $(CH_3)_4Si$. Volatile materials were handled in a conventional vacuum system.

Preparation of Methyl Chloromethylphosphinate. Chloromethylphosphonous dichloride was prepared by the method of Uhing, Rattenbury, and Toy.[3]

Methanol (50 ml) was added to a two-necked flask fitted with a dropping funnel and connected to a condenser and receiver which was in turn connected to a large trap cooled to −196°. The flask was cooled to 5–10° and chloromethylphosphonous dichloride (15.1 g, 100 mmole) was slowly added *via* the dropping funnel. The volatile material produced was collected in the trap cooled to −196°. When the addition of chloromethylphosphonous dichloride had been completed, the pressure in the apparatus was slowly reduced and then maintained at 0.2 mm until no more material collected in the cold trap. The reaction flask was then heated and methyl chloromethylphosphinate (10.1 g, 79 mmoles, 79%), bp 55–57° (0.2 mm), was obtained.

Anal. Calcd for $C_2H_6ClO_2P$: C, 18.7; H, 4.7. Found: C, 18.9; H, 4.7.

Hydrolysis of Methyl Chloromethylphosphinate. Methyl chloromethylphosphinate (0.2 g) was added to a solution of sodium hydroxide (1.0 g) in water (15 ml). After 1 hr at room temperature the nmr spectrum was obtained and comparison with a spectrum of an authentic sample[3] showed that chloromethylphosphinic acid was the only product.

Reaction between Methyl Chloromethylphosphinate and Sodium Methoxide. A solution of sodium methoxide (0.60 g, 11.0 mmoles) in methanol (25 ml) was cooled to 0° and methyl chloromethylphosphinate (1.35 g, 10.5 mmoles) was slowly added with stirring. The precipitate of sodium chloride was removed by filtration, and the filtrate was concentrated under reduced pressure. Distillation of the residue gave dimethyl methylphosphonate (0.90 g, 7.3 mmoles, 67%), bp 35–40° (0.2 mm), identified by infrared and nmr spectroscopy.

Table II. ^1H Nmr Spectra

	CH_3OP		CH_3NP		PH			CH_2P		
	δ, ppm	J_{HCOR}, cps	δ, ppm	J_{HCNP}, cps	δ, ppm	J_{PH}, cps	J_{HCPH}, cps	δ, ppm	J_{HCP}, cps	Other
$ClCH_2P(O)(H)OCH_3$	3.57	11.1			6.55	545	2.0	3.60 ($ClCH_2$)	8.2	
$CH_3P(O)(N(CH_3)_2)OCH_3$	3.38	11.5	2.53	9.8				1.21 (CH_3)	16.8	
$CH_3P(O)(NHCH_3)OCH_3$	3.57	11.5	2.51	12.2				1.39 (CH_3)	16.9	J_{HNCH} = 4 cps
$ClCH_2P(O)(CH_3C(OC_2H_5)_2)OCH_3$	3.82	10.3						3.75 ($ClCH_2$)	6.4	J_{HCP} = 11.9 cps; δ_{CH_3} = 1.45 ppm (CH_3CP); J_{CH_3-H} = 7.3 cps (CH_3CH_2O)
$C_6H_5SCH_2P(O)(H)OCH_3$	3.38	10.9			6.53	528	2.0	3.18 (SCH_2)	11.0	

Reactions between Methyl Chloromethylphosphinate and Amines. Methyl chloromethylphosphinate (6.0 g, 46.7 mmoles) was dissolved in ether (100 ml). Dimethylamine (5.4 g, 137 mmoles) was condensed in from the vacuum system. After 1 hr at room temperature, the dimethylamine hydrochloride was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was distilled under reduced pressure to give methyl N,N,P-trimethylphosphonamidate (4.0 g, 29 mmoles, 62%), bp 50–51° (0.5 mm).

Anal. Calcd for $C_4H_{12}NO_2P$: C, 35.0; H, 8.8. Found: C, 34.3; H, 8.9.

In a similar reaction, methyl chloromethylphosphinate (1.3 g, 10.1 mmoles) and methylamine (2.0 g, 64.5 mmoles) gave methyl N,P-dimethylphosphonamidate (0.9 g, 7.3 mmoles, 73%).

Reaction between Methyl Chloromethylphosphinate and Ketene Diethyl Acetal in the Presence of Triethylamine. A mixture of methyl chloromethylphosphinate (2.6 g, 20.2 mmoles), ketene diethyl acetal (2.5 g, 21.6 mmoles), and triethylamine (2.0 g, 20.0 mmoles) was heated at 100° for 3 hr. Distillation gave methyl (1,1-diethoxyethyl)chloromethylphosphinate (0.9 g, 3.4 mmoles 17%), bp 90–95° (0.01 mm).

Anal. Calcd for $C_8H_{18}ClO_4P$: C, 39.3; H, 7.4. Found: C, 38.6; H, 7.3.

A sample of the product was hydrolyzed with dilute hydrochloric acid. The aqueous solution was shown by nmr to contain chloromethylphosphinic acid.

Reactions between Methyl Chloromethylphosphinate and Grignard Reagents. Methyl chloromethylphosphinate (4.0 g, 31.1 mmoles) in ether (25 ml) was slowly added to a solution of methylmagnesium bromide in ether (25 ml of 3 *N* solution), at −10°. The ether was evaporated and the residue was dissolved in 2 *N* hydrochloric acid (50 ml). The nmr spectrum of this solution was identical with that of an authentic sample of trimethylphosphine oxide, prepared by the reaction between phosphoryl chloride and methylmagnesium bromide.

Methyl chloromethylphosphinate (2.6 g, 20.2 mmoles) in ether (20 ml) was slowly added to a solution of phenylmagnesium bromide in ether (30 ml of 3 *N* solution) at −10°. The reaction mixture was stirred for 20 hr. The ether was evaporated and the residue was decomposed by the addition of 2 *N* hydrochloric acid (50 ml). The ether layer was separated and the aqueous layer was extracted with ether (two 200-ml portions). The combined ether extracts were evaporated under reduced pressure. The semisolid residue was subjected to vacuum sublimation. The white crystalline solid (mp 66–68°) obtained below 80° at 10^{-2} mm was identified, by infrared spectroscopy and by mixture melting point with an authentic sample, as biphenyl (1.5 g, 10.0 mmoles). The white solid, obtained on heating the residue at 120–150° (10^{-3} mm), was recrystallized from 100–110° petroleum ether to give methyldiphenylphosphine oxide (1.1 g, 5.1 mmoles), mp 112–113° (mixture melting point with an authentic sample, 112–113°).

Methyldiphenylphosphine oxide was prepared by heating methyltriphenylphosphonium iodide with aqueous sodium hydroxide solution.[12] The product was recrystallized from 100–110° petroleum ether and had mp 113°.

Reaction between Methyl Chloromethylphosphinate and Sodium Thiophenoxide. A solution obtained by adding 0.5 g (21.7 mg-atoms) of sodium to 50 ml of thiophenol was cooled to 0° and methyl chloromethylphosphinate (2.8 g, 22.0 mmoles) was slowly added with stirring. The mixture was allowed to stand at room temperature for 2 hr. The precipitate of sodium chloride was then filtered off and the filtrate was concentrated *in vacuo*. The product, a viscous liquid, was identified by its infrared and nmr spectra as methyl phenylthiomethylphosphinate (4.0 g, 20.0 mmoles, 91%).

Anal. Calcd for $C_8H_{11}O_2PS$: C, 47.5; H, 5.5. Found: C, 46.7; H, 5.4. The compound decomposed when distillation was attempted.

Preparation of Methyl Chloromethylphosphinate-P-*d*. Methanol-*d* was prepared by hydrolyzing dimethyl carbonate with D_2O. Methyl chloromethylphosphinate-P-*d* was prepared by the method previously described for methyl choromethylphosphinate, but using methanol-*d* in place of methanol The areas of the PH peaks in the ^1H nmr spectrum of the product showed that it contained less than 5% of methyl chloromethylphosphinate.

Reaction of Methyl Chloromethylphosphinate-P-*d* with Sodium Methoxide. Methyl chloromethylphosphinate-P-*d* (1.3 g, 10.1 mmoles) was slowly added to a solution of sodium methoxide (0.5 g, 10.0 mmoles) in methanol (25 ml). The usual work-up procedure was followed, and dimethyl methylphosphonate (0.8 g, 6.5 mmole, 65%) was isolated. The ^1H nmr spectrum of the product showed δ_{CH_3} = 1.42 ppm, with J_{HCP} = 18.0 cps, relative area 1.0, and δ_{CH_3O} = 3.67 ppm, with J_{HCOP} = 11.0 cps, relative area 2.1.

Reactions with Phenylmagnesium Bromide. Experiment 1. Methyl chloromethylphosphinate-P-*d* (1.3 g, 10.1 mmoles) in ether (10 ml) was slowly added to a solution of phenylmagnesium bromide in ether (20 ml of 3 *N* solution). The ether was distilled off and the residue was decomposed with water (40 ml). Methyldiphenylphosphine oxide was isolated using the method described previously.

The ethereal distillate was analyzed using an Autoprep Mode A-700 glpc apparatus with a 20-m SE/30 column operating at 80°. Two major fractions were obtained and were identified as ether and benzene. The proportion of benzene to ether was determined by comparison of the peak areas with those of known mixtures of benzene and ether.

The quantity of benzene already present in the phenylmagnesium bromide solution used was determined similarly. The quantity of benzene produced in the reaction was then calculated and was found to be 0.28 g, 3.6 mmoles

Experiment 2. Methyl chloromethylphosphinate (1.3 g, 10.1 mmoles) in ether (10 ml) was slowly added to a solution of phenylmagnesium bromide in ether (20 ml of 3 *N* solution). The ether was distilled off and the residue was decomposed with D_2O (40 ml). Methyldiphenylphosphine oxide was isolated by the usual method. Benzene (0.29 g, 3.8 mmoles) was identified in the ethereal distillate.

Experiment 3. A sample of pure methyldiphenylphosphine oxide (1.5 g) in ether (50 ml) was added to phenylmagnesium bromide solution (20 ml of 3 *N* solution). The ether was evaporated off and the residue was hydrolyzed with D_2O (40 ml); the methyldiphenylphosphine oxide was isolated by the usual procedure.

The amount of deuterium incorporated in the methyldiphenylphosphine oxide obtained from experiments 1, 2, and 3 was determined by ^1H nmr spectroscopy. The results are summarized in Table I.

Secondary Valence Force Catalysis. III. The Apparent Abnormal Reactivity of Anionic Nucleophilic Reagents toward Acyl-Activated Esters[1,2]

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Abstract: Second-order rate constants for reaction of a variety of charged and uncharged nucleophilic reagents with *p*-nitrophenyl chloroacetate, phenyl dichloroacetate, and 2,4-dinitrophenyl acetate have been measured in water at 25° and ionic strength 1.0. The Brønsted plot for the last substrate qualitatively resembles that for *p*-nitrophenyl acetate while those for the first two substrates are reminiscent of that for acetylimidazolium ion. That is, anions are abnormally reactive, compared to a series of uncharged amines, toward esters possessing an electron-withdrawing substituent in the acyl portion of the molecule. This finding is *tentatively* ascribed to electrostatic stabilization of the transition state resulting from ion–dipole or dipole–dipole interactions between acyl-activated substrate and anionic nucleophilic reagent.

An increase in the rate of an organic reaction resulting from noncovalent interactions between two reactants or a reactant and a catalyst is termed secondary valence force catalysis. Weak interactions may influence rates either by serving to approximate and orient appropriate reacting groups, largely an entropy effect, or by directly affecting ground and/or transition state stabilities, largely an enthalpy effect. Rather little attention has been directed toward examination of rate alterations which result from weak interactions. Available evidence does indicate that rather substantial rate effects may result from charge transfer interactions,[4–6] London dispersion forces,[7] and electrostatic effects. Many pertinent cases have been compiled and critically reviewed by Jencks.[8]

Of particular relevance to the present communication are those examples of secondary valence force catalysis that involve electrostatic interactions. A number of studies has revealed that the incorporation of substrates into or onto micelles formed from ionic detergents frequently results in considerable rate accelerations or retardations.[9–13] Similarly, the effects of certain organic anions, cations, and detergent salts on the rate of reaction of methyl 1-naphthoate with hydroxide ion apparently result from electrostatic factors.[14] Such effects may also account for the abnormal reactivity of anions toward acetylimidazolium ion[15] and for the abnormal reactivity of cationic nucleophilic reagents toward the *p*-nitrophenyl phosphate dianion,[16] isopropyl methylphosphonofluoridate,[17] and the *o*-nitrophenyl oxalate anion.[18] Finally, it has been argued that the rates of reaction of anionic nucleophilic reagents with *ortho*-substituted phenacyl chlorides are augmented by ion–dipole interactions in the transition state.[19]

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(2) For paper II in this series, see M. T. A. Behme, J. G. Fullington, R. Noel, and E. H. Cordes, *J. Am. Chem. Soc.*, **87**, 266 (1965).

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